16.1.9 *Documentation of Statistical Methods*

The following document is provided in this appendix:

Statistical Analysis Plan	Date
Statistical Analysis Plan	30 May 2019

Statistical Analysis Plan

Sponsor:	Dompé Farmaceutici s.p.a.
Protocol No:	REP0114
Protocol Version / Date:	Final Version 7.0 / 01-Dec-2017
Title	A randomized, double-blind, placebo-controlled phase 2 study of paclitaxel in combination with reparixin compared to paclitaxel alone as front-line therapy for Metastatic Triple-Negative Breast Cancer (FRIDA)
CRF Version No. / Date	6.1 / 07-May-2018
PRA Project ID:	DGEREP14-REP114
SAP Version No. / Date:	2 / 30 May 2019

APPROVALS

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Dompé Farmaceutici s.p.a. Protocol No. REP0114.

This SAP should be read in conjunction with the study protocol and case report forms (CRF). This version of the plan has been developed using the protocol final version 7.0 dated 01 Dec 2017 and CRF version 6.1 dated 07 May 2018. Any further changes to the protocol or CRF may necessitate updates to the SAP. In the case of discrepancies between the SAP and the study protocol, the SAP will take precedence over the study protocol.

The SAP is to be developed in two stages. The purpose is to "finalize" a SAP so that programming can begin earlier in the process. Versions of the SAP up to initial sponsor approval will be known as SAP1. Changes following approval of SAP1 will be tracked in the SAP Change Log and a final version of the SAP, known as SAP2, will be issued for sponsor approval prior to database lock.

2. STUDY OBJECTIVES

Primary Objective

The primary objective of the study is to evaluate Progression-Free Survival (PFS) (defined as the the number of days between the date of randomization and the date of clinical disease progression (PD) according to RECIST criteria version 1.1, as assessed by Independent Radiology Review, or death for any cause, whichever occurs first) in patients with metastatic triple negative breast cancer (TNBC) treated with the combination of paclitaxel and orally administered reparixin compared to paclitaxel alone.

Secondary Objectives

- To determine Overall Survival (OS)
- To evaluate Objective Response Rates (ORR)
- To determine median PFS (mPFS To assess the safety of the combination of paclitaxel and orally administered reparixin (referred to as combination treatment)).

Exploratory Objectives

- To determine median Time To New Metastasis (TTM) (new lesions at existing or new sites)
- To determine proportion of patients progressing with new metastatic lesions
- To compare the incidence and severity of peripheral neuropathy between the two treatment groups
- Evaluation of Cancer Stem Cells (CSCs) in metastatic tissue.

3. STUDY DESIGN

3.1 DESIGN OVERVIEW

This is a two arm, phase 2 study to evaluate the efficacy of the combination of paclitaxel and reparixin compared to paclitaxel and placebo in metastatic TNBC patients.

Patients will be assessed for eligibility and will have the following procedures done: medical history, physical examination, laboratory assessments, chest x-rays and/or computed tomography (CT) scans, including a CT scan or magnetic resonance imaging (MRI) of the brain. A sample of tumor tissue will be collected for analysis.

There will be two groups:

Group 1: paclitaxel 80 mg/m^2 intravenous (i.v.) (Days 1, 8, and 15 of 28-day cycle) + reparixin oral tablets 1200 mg t.i.d. continuing from Day 1 to Day 21

Group 2: paclitaxel 80 mg/m^2 i.v. (Days 1, 8, and 15 of 28-day cycle) + placebo oral tablets 1200 mg t.i.d. continuing from Day 1 to Day 21

Study drug (reparixin/placebo) will be administered orally every six to ten hours t.i.d. for 21 consecutive days during each cycle with seven days off treatment between each cycle.

Paclitaxel will be administered in combination with study drug (reparixin/placebo) as an i.v. infusion on Days 1, 8, and 15 of each 28-day cycle.

Combination treatment will continue until disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1, withdrawal of consent, or unacceptable toxicity, whichever occurs first.

Tumor response and/or progression assessments will be performed and documented every 8 weeks according to RECIST criteria version 1.1.

Metastatic tissue samples will be analyzed for evaluation of CD24-CD44+ and ALDH+ CSCs.

It is planned that approximately 60 centers located in the USA and Europe will participate in the study.

During study participation and while the patient is receiving study treatment, the patient will continue to be followed with physical examinations, review of concomitant medications and adverse events (AEs), laboratory assessments, and scans (CT, MRI, etc.). The patient will also complete a diary to record intake of study medication.

After completion of study treatment, the patient will be followed for 30 days to assess safety and then followed every 3 months for 1 year thereafter to assess disease status, new treatments, and survival status.

Please refer to Table 1 Study Flow Chart for full details on the schedule of assessments.

Table 1. Study Flow Chart

Procedure	Pre-Study[1]	Treatment Cycles[14]				OTV[15]	Long term Follow up[16]
		D1	D8	D15	D21		
Eligibility criteria	X						
Demographic data/tumor characteristics	X						
Tumor history surgery, radiotherapy, systemic therapies	X						
Medical history	X						
Disease status	X[2,3]	Every 8 weeks[4]				X[3]	
Physical examination	X	X[5]				X	
Vital signs (BP, pulse)[6]		X				X	
Chest X-ray (if not already performed to follow tumor. Thoracic CT scan may substitute chest X-ray)	X					X	
ECG	X						
Zubrod Performance Status	X					X	
Urinalysis	X[7]	As clinically indicated				X[7]	
Hematology	X[8]	X[8]	X[8]	X[8]		X[8]	
Clinical chemistry	X[9]	X[9]				X[9]	

D1 = Day 1 etc, OTV = off-treatment visit

1 **All pre-study examinations should be performed within 14 days (± 1day window) of beginning study treatment unless otherwise specified. Informed consent should be signed before any study specific procedures are performed (with the exception of routine laboratory tests).**

2 **Pre-study disease evaluation should be obtained within 28 days of study treatment initiation.**

3 **Disease evaluations and a brain CT or MRI will be performed at pre-study. The scans (with exception of brain scans) will be repeated every eight weeks until documented PD. A brain scan will be repeated if patient presents with symptoms of brain metastases or progressive disease of baseline lesions. At study end, a Best Overall Response (BOR) assessment will be made: the disease assessments do not need to be repeated if done within four weeks prior to the off-treatment visit. Copies of all scans (CT, MRI of chest, abdomen, pelvis etc.) will be submitted to the central radiology vendor for review at each time point.**

4 **For tumor assessment (i.e. scans) beginning at Week 8, a ± 3-day window will be allowed.**

5 **Physical examination, including weight will be performed at pre-study and Day 1 of each cycle beginning with cycle 2. Pretreatment signs and symptoms, height, and BSA will also be collected at the pre-study visit only.**

6 **Vital signs must be performed within 24 hours prior to the first study drug (reparixin/placebo) administration, and then on Day 1 of subsequent cycles.**

7 **pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocytes and urobilinogen (by dipstick or in laboratory) at pre-study, as clinically indicated, and at off-treatment visit. Laboratory tests performed within 14 days screening period even if before ICF signed are acceptable.**

8 **Hematology tests: hemoglobin, white blood cell (WBC) and differential WBC, platelets at pre-study and on Days 1, 8 and 15 of each cycle and at the off-treatment visit. Routine laboratory tests performed within 14 days screening period even if before ICF signed are acceptable.**

9 **Clinical chemistry tests: sodium, potassium, calcium, serum creatinine, total protein, albumin, asparate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea, total bilirubin at pre-study, on Day 1 of treatment cycles and as clinically indicated and at the off-treatment visit (OTV). Laboratory tests performed within 14 days screening period even if before ICF signed are acceptable.**

Procedure	Pre-Study[1]	Treatment Cycles[14]				OTV[15]	Long term Follow up[16]
		D1	D8	D15	D21		
Urine or serum pregnancy test	X[10]	X[10]				X[10]	
Record concomitant treatments	X	Throughout study				X	
AE monitoring		Throughout study				X	
Peripheral neuropathy monitoring	X	Throughout study				X	
Reparixin/Placeboadministration[11]		Continuously days 1 to 21					
Paclitaxel administration		X	X	X			
Dispense diary card[12]		X				X[review only]	
Tumor tissue (archival or new biopsy)[13]	X						
Date of progression and documentation of additional cancer therapy (if not off study due to progressive disease) and Survival Status							X

10 **Urine or serum pregnancy test required for women of childbearing potential only**

11 **Study drug (reparixin/placebo) administered orally every 6 to 10 hours t.i.d. for 21 consecutive days during each cycle with seven days off treatment between each cycle**

12 **Patients will be given a diary card to record information about date, time, and dose taken. At each scheduled visit before the start of a new cycle of dose administration and at OTV, the diary should be reviewed with the patient for completeness.**

13 **Tumor tissue will be sampled within 28 days of study treatment initiation, to confirm recurrence of metastatic breast cancer, confirm TNBC, and to conduct the following correlative studies: evaluation of CD24-CD44+CSC, ALDH+CSC.**

14 **During Cycle 1, a ± 1-day window will be allowed for study visits. After Cycle 1, a ± 2-day window will be allowed for study visits.**

15 **Off-treatment Visit to be performed 14 to 28 days following the last dose of study drug. Patients with ongoing treatment - related AEs still present in the 30 days after treatment discontinuation should continue to be followed until recovery or assessment of chronicity or as instructed by the medical monitor. Patients off treatment without documented progressive disease should continue to have disease assessments every 8 weeks until progressive disease or another anticancer therapy is initiated, whichever comes first.**

16 **Following PD, survival status will be collected every 3 months until death or until last patient off treatment, whichever occurs first.**

An independent Data Monitoring Committee (DMC) is established and is responsible for safeguarding the interests of trial participants and for enhancing the integrity and credibility of the trial. The DMC is assessing the safety of the treatments during the trial and is monitoring the overall conduct of the clinical trial. The DMC will provide recommendations to Dompé about stopping or continuing the trial.

3.2 RANDOMIZATION

This is a randomized, double-blind, placebo-controlled phase 2 study. Patients are randomized in a 1:1 fashion between paclitaxel and reparixin versus paclitaxel and placebo using an Interactive Response Technology (IRT). Randomization is stratified between the two sub-populations, newly diagnosed metastatic patients and patients that have relapsed following a prior (neo)adjuvant chemotherapy regimen. Patients enrolled under the original Protocol or under Protocol Amendment 1 were not subject to stratification and per these versions of the protocol are all expected to be relapsed following a prior (neo)adjuvant chemotherapy regimen.

The randomization groups are generated with a computer procedure by the method of randomly permuted blocks. The treatment codes are also accessible to an Independent Statistician (liaison between the Contract Research Organization [CRO] database and DMC Biostatistician) who generates the reports for the DMC's evaluation.

3.3 SAMPLE SIZE CONSIDERATIONS

The trial is designed to provide 80% statistical power to detect an improvement in PFS from 5 months with paclitaxel monotherapy in patients with metastatic TNBC to 8 months with the addition of reparixin, corresponding to a hazard ratio 0.625, when using a logrank statistic having (one-sided) 0.025 false positive error rate. This requires 142 PFS events and the approximate sample size will be 156 randomized patients (78 patients per group).

Due to extreme enrollment difficulties during the first 6 months of 2018, enrollment to the study was terminated early (30 July 2018) and the final sample size is equal to 123 randomized patients. Based on current data, at least 113 out of 123 enrolled patients have had observed PFS events.

If an analysis of PFS were to be conducted with 114 PFS events, statistical significance (at the level of a one-sided 2.5% false positive error rate) would be achieved with an estimated PFS HR < 0.6927. This would correspond approximately to an estimated 2-month improvement in PFS of 4.5 vs 6.5 months.

The targeted number of PFS events is therefore 114.

4. STUDY VARIABLES

4.1 PRIMARY VARIABLE

The primary variable of the study is PFS, defined as the time from randomization to first documentation of disease progression according to RECIST 1.1, or to death due to any cause, whichever occurs first, as assessed by Independent Radiology Review.

4.2 SECONDARY AND EXPLORATORY VARIABLES

4.2.1 Efficacy Variables

Secondary efficacy variables are:

- OS
- ORR
- mPFS

4.2.2 Safety Variables

- Number and percentage of TEAEs, overall and by grade
- Serious adverse events (SAEs)
- Fatal AEs
- Concomitant medications
- Vital sign parameters (pulse rate, systolic and diastolic blood pressure [BP])
- Hematology parameters (hemoglobin, WBC and differential count, and platelets)
- Clinical chemistry parameters (sodium, potassium, calcium, serum creatinine, total protein, albumin, AST, ALT, ALP, urea, and total bilirubin)
- Urinalysis parameters (pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocytes and urobilinogen (by dipstick or in laboratory)

4.2.3 Exploratory Variables

Exploratory endpoints of this study are:

- Median TTM
- Proportion of patients progressing with new metastatic lesions
- Extent of peripheral neuropathy
- CSCs in metastatic tissue

Correlative studies performed on paraffin-embedded metastatic tumor tissue:

- CD24-CD44+CSC (by Immunohistochemistry (IHC))
- ALDH+CSC (by IHC)

5. DEFINITIONS

Adverse Drug Reaction

An adverse drug reaction (ADR) is defined as an adverse experience which is reasonably likely to have been caused by the drug. Any AE reported in the study having a possible, probable, or highly probable relationship to study drug will be considered as an ADR.

Age

The following SAS® code will be used to calculate patient age (years):

Age = floor ((intck('month', birth date, IC date) - (day(IC date) < day(birth date))) / 12),

where intck is a SAS® function counting integer days, birth date is the database variable BRTHDT, and informed consent (IC) date is the database variable INFCDT. In cases where a subject rescreened and has more than one date of IC, the later IC date will be used to derive age.

Baseline, Change from Baseline

Baseline is defined as the last non-missing value before the initial administration of the study drug.

Change from baseline will be defined as (value at post-baseline visit – value at baseline).

Post-baseline values for tabulations generally will exclude unscheduled visit values. For tumor response evaluations only (investigator and independently assessed), post-baseline values at unscheduled visits will be analyzed. For unscheduled visits, the following visit windowing will be used.

Timepoint	Window	Target Day
Cycle 2 Day 1	Day 2-56	29
Cycle 3 Day 1	Day 57-84	57
Cycle 4 Day 1	Day 85-112	95
Cycle 5 Day 1	Day 113-140	113
Cycle 6 Day 1	Day 141-168	141
Cycle 7 Day 1	Day 169-196	169
Cycle 8 Day 1	Day 197-224	197
Cycle 9 Day 1	Day 225-252	225
Cycle 10 Day 1	Day 253-280	253
Cycle 11 Day 1	Day 281-308	281
Cycle 12 Day 1	Day 309-336	309
Cycle 13 Day 1	Day 337-364	337
Cycle 14 Day 1	Day 365-392	365

Cycle 15 Day 1	Day 393-420	393
Cycle 16 Day 1	Day 421-448	421
Cycle 17 Day 1	Day 449-476	449
Cycle 18 Day 1	Day 477-504	477
Cycle 19 Day 1	Day 505-532	505
Cycle 20 Day 1	Day 533-560	533
Cycle 21 Day 1	Day 561-588	561
Cycle 22 Day 1	Day 589-616	589
Cycle 23 Day 1	Day 617-644	617
Cycle 24 Day 1	Day 645-672	645
Cycle 25 Day 1	Day 673-700	673

If two assessments fall into one window, then the assessment closest to the target day will be used for analysis. If two assessments were done on the same day, then the worst response of the two will be used for analysis. If one result is NE, NA or Unknown and the other is non-missing, then the non-missing value will be used for analysis. If both results are NE, NA or Unknown, then NE will be used for analysis.

Concomitant Medications

Concomitant medications will be defined as any medications ongoing at the date of first dose of the study drug, reparixin/placebo, or with a start date on or after the date of first dose of the study drug (but not after the last study drug dose date), or with a stop date on or after the date of the first study drug dose. In the case of missing or partial medication start and end dates, medications will be assumed to be concomitant if they could have started or ended between first and last study drug dose date. Please follow section 10.2 to impute the missing or partial dates. A single medication may be both concomitant and prior. (See prior medications in this section.) Concomitant medications will be collected on the concomitant medications page of the CRF and are coded using WHO Drug Dictionary version 2014MAR01 DDE (Enhanced).

Compliance of study drug (Reparixin or Placebo)

Treatment compliance (%) is defined as (the number of tablets taken divided by the expected number of tablets)*100, where number of tablets taken = number of tablets dispensed minus the number of tablets returned collected via the Study Drug Accountability CRF page. If number of returned tablets is missing, doses will be assumed to follow dose regimen in protocol for that visit. Number of tablets expected = 6 tablets / day * 21 days/cycle * number of cycles.

CTCAE Grading for Laboratory Data

Laboratory abnormalities will be given a Common Terminology Criteria for Adverse Events (CTCAE; Version 4.03) grade for severity (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening or disabling) for parameters which only have numeric CTCAE guidelines (i.e., not requiring clinical assessments) by programing. Those tests and their grading algorithms are listed in the table below:

Table 2. CTCAE Grading for Laboratory Data

Test name displayed in table	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin High	Increase in > 0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in > 4 gm/dL above ULN or above baseline if baseline is above ULN	-
Hemoglobin Low (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Platelet Low	<LLN - 75,000/mm^3; <LLN -75.0 x 10e9/L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10e9/L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x 10e9/L	<25,000/mm^3; <25.0 x 10e9/L
Neutrophil Low	<LLN - 1500/mm^3; <LLN - 1.5 x 10e9/L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10e9/L	<1000 - 500/mm^3; <1.0 - 0.5 x 10e9/L	<500/mm^3; <0.5 x 10e9/L
Lymphocyte Low	<LLN - 800/mm^3; <LLN - 0.8 x 10e9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10e9/L	<500 - 200/mm^3; <0.5 - 0.2 x 10e9/L	<200/mm^3; <0.2 x 10e9/L
Lymphocyte High	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3	-
White blood cell Low	<LLN - 3000/mm^3; <LLN - 3.0 × 10^9/L	<3000 - 2000/mm^3; <3.0 - 2.0 × 10^9/L	<2000 - 1000/mm^3; <2.0 - 1.0 × 10^9 /L	<1000/mm^3; <1.0 × 10^9/L
Albumin Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
ALP High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

AST High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Creatinine High	>1 - 1.5 × baseline; >ULN - 1.5 × ULN	>1.5 - 3.0 × baseline; >1.5 - 3.0 × ULN	>3.0 baseline; >3.0 - 6.0 × ULN	>6.0 x ULN
Total bilirubin High	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Calcium High	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences
Calcium Low	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences
Potassium Low	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Potassium High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Sodium Low	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences
Sodium High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences

*Note: CTCAE grade will be only based on value range in programming. No clinical assessment criteria will be used.

Off-Treatment

A patient who is off treatment will be captured in the Reason Off-Treatment CRF page with a Date of Last Dose of Study Medication as well as Reason Off-Treatment.

Enrolled Patient

An enrolled patient will be one who signs IC through the registration form.

Duration of Exposure (days)

Duration of exposure to study medication (reparixin/placebo) in days will be defined as the (last study medication dose date – first study medication dose date + 1).

Duration of exposure to paclitaxel will be defined as the (last paclitaxel dose date – first paclitaxel dose date + 1).

Total Exposure

Total exposure to study medication or paclitaxel will be defined as the total mg of study medication or paclitaxel taken during the study.

Total exposure to study medication will be calculated by cycle and overall according to study medication administration and study medication diary data. Total exposure to study medication will be calculated as [(total # of tablets dispensed - total # of tablets returned) * 600 mg/tablet]. Any subject that does not return the dispensed randomized study medication kit for the pill count will be assumed for exposure and compliance (see definition of compliance in this section) calculation purposes to have taken the required number of pills corresponding to the number of days the subject was on study after the last dispensation.

Total exposure to paclitaxel will be calculated as sum of total dose administered in mg for each cycle (by cycle) or across all cycles (overall).

Geometric Coefficient of Variation

The geometric coefficient of variation (CV), a percentage, is calculated as follows:

$100 \times \sqrt{\exp(x^2) - 1}$, where x is the standard deviation (std) of the ln-transformed (i.e., natural log) parameter values.

Prior Medications

Prior medications will be defined as any medications taken prior to initiation of study medication (reparixin/placebo) dosing. In the case of missing or partial medication start and end dates, medications will be assumed to be concomitant and not prior if they could have started or ended between first and last study drug dose date. Please follow section 10.2 to impute the missing or partial dates. A single medication may be both concomitant and prior. (See also concomitant medications in this section.)

Protocol Deviation, Important Protocol Deviation

Potential protocol deviations noted during clinical monitoring will be documented by category: inclusion criteria, exclusion criteria, study drug, assessment of safety, assessment of efficacy, laboratory assessment, visit window, IC, or other. All protocol deviationss will be reviewed, categorized, designated important or not important, and finalized prior to database lock. Important protocol deviationss will be defined as potentially impacting safety or efficacy assessment following regulatory guidance criteria (ICH E3). Protocol deviationss for the safety population will be imported into SAS® for inclusion in a table and a data listing.

Study Day

Study day is defined relative to the date of the first administration of study drug, reparixin/placebo, per Clinical Data Interchange Standards Consortium (CDISC) Standard Data Tabulation Model (SDTM) conventions. For assessments that occur after this visit date, study day is calculated as (assessment date – study drug first dose date + 1). For assessments that occur prior to study drug first dose date, study day will be calculated as (assessment date – study drug first dose date); there is no Study Day 0.

Study Drug/Medication

In this study, study drug/medication will refer to reparixin or placebo, the only investigational product. Paclitaxel will not be referenced as a study drug/medication.

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are those which first occur or increase in severity or relationship to study drug after the first dose of study drug and before 30 days after the last dose of study treatment, reparixin/placebo. In the case of missing or partial dates, any AE that could have started on or after first dose date will be assumed to be treatment-emergent. In the case of missing or partial dates, imputed dates (see section 10.1 AE date imputation) will be used.

Efficacy Definition

Best Overall Response

BOR is defined as the best response among all overall responses (in the order complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) recorded from the start of reparixin or placebo until disease progression/recurrence or end of treatment, or death, whichever comes first. The status of BOR of PR or CR needs to be confirmed by repeat tumor assessment within no less than 4 weeks according to RECIST version 1.1. If the status of CR or PR cannot be confirmed by repeat tumor assessment, the best overall response of unconfirmed CR and PR will be PR and SD, respectively. No confirmation measurement is needed for a BOR of SD. Best overall response of SD can only be made when the measurements that have met the SD criteria at least after 8 weeks of study entry (1st dose date of study drug).

BOR by investigator assessment is recorded on the "Best Overall Disease Response" CRF page.

Complete Response

CR is defined as the disappearance of all target lesions and disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis). No new lesions may be present.

Duration of (Overall) Response

Duration of overall response (DOR) in days for the investigator assessments is measured from the time response criteria are first met for CR or PR (whichever is first recorded on the "Disease Response" page on the CRF) until either death or the first date that recurrent or PD is objectively documented (on the "Disease Response" page on the CRF or the Follow-Up Disease Evaluation page indicates disease progression and there is supporting information in the Disease Status pages) per RECIST version 1.1.

If a patient is lost to follow-up with no documentation of PD, DOR will be censored at the last evaluable tumor assessment. DOR will be calculated only for responding patients (PR or CR) as recorded on the CRF page "Disease Response" based upon the RECIST version 1.1. Duration of overall response will be calculated only for patients with confirmed CR or PR.

Independent assessment responses will follow the same approach but based on independently adjudicated data rather than CRF data.

Duration of Stable Disease

Duration of stable disease in days for the investigator assessments is measured from the date of randomization until the time of death or the first documentation of PD (as assessed by "Disease Response" page on the CRF or the Follow-Up Disease Evaluation page indicates disease progression and there is supporting information in the Disease Status pages) per RECIST version 1.1.

If a patient is lost to follow-up with no documentation of PD, duration of stable disease will be censored at the date of the last evaluable tumor assessment. Duration of stable disease will be calculated only for patients with best overall response of SD or better.

Independent assessment responses will follow the same approach but based on independently adjudicated data rather than CRF data.

Measurable (Target) Lesions, Non-Measurable (Non-Target) Lesions

Measurable lesions are those that, at baseline, can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) as ≥ 10 mm by CT scan, ≥ 10 mm by caliper measurement by clinical examination, or ≥ 20 mm by chest X-ray. A minimum of one and a maximum of five measurable lesions (2 per organ) will be defined as target lesions for the purpose of the study. All other measurable lesions, including small lesions (LD < 10 mm or pathological lymph nodes with ≥ 10 mm to < 15 mm for the short axis) as well as truly

non-measurable lesions will be considered non-target lesions (see Section 9.1.1 in the protocol for further details).

Partial Response

PR is defined as at least a 30% decrease in the sum of longest diameters of target lesions, relative to the sum of longest diameters at baseline, per the investigator's assessment. Persistence of one or more non-target lesion may be present. No new lesions may be present.

Progression-Free Survival

PFS in days will be measured from the date of randomization until the date of PD according to RECIST 1.1 or death, whichever occurs first. If a patient is lost to follow-up with no documentation of PD, PFS will be censored at the date of the last evaluable tumor assessment. In the event that the date of tumor assessment is unavailable (i.e., there is no tumor assessment after randomization) or the patient did not receive study treatment, Day 1 (based on randomization) will serve as the censoring date instead. Please see Table 3.1 for further details on censoring.

Progressive Disease

PD is defined as at least a 20% increase in the sum of longest diameters of target lesions relative to the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm to qualify as PD. Unequivocal progression of existing non-target lesions or appearance of one or more new lesions is also considered progression.

Stable Disease

SD is defined as, for the sum of longest diameters of target lesions, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, relative to the smallest sum of longest diameters while on study. Persistence of one or more non-target lesion may be present. No new lesions may be present.

Sum of Target Lesion Diameters

Sum of target lesion diameters is the sum of the longest diameter of non-nodal measurable lesions and the shortest axis of pathological lymph nodes.

Time to New Metastasis

Time to new metastasis is defined as the interval (days) between randomization and the date of the first observation that the new lesion was detected at existing or new sites.

6. ANALYSIS POPULATIONS

6.1 INTENT-TO-TREAT POPULATION

The intent-to-treat (ITT) population will consist of all patients who are randomized and will be based upon the randomized treatment, regardless of the treatment actually received. Patients will be in the ITT analysis whether or not they receive study drug. The primary and secondary efficacy analyses will be presented primarily for the ITT Population.

6.2 RESPONSE EVALUABLE POPULATION

The response evaluable population will consist of all patients who have completed at least one cycle of treatment and have baseline assessment and have undergone at least one post-baseline disease assessment.

6.3 SAFETY POPULATION

The safety population will consist of all patients who have taken at least one dose of the study treatment and will be based upon the treatment they actually receive. Patients who were randomized to Group 2 (paclitaxel + placebo) but who received at least one dose of reparixin will be counted in Group 1 (paclitaxel + reparixin).

7. INTERIM ANALYSIS AND REPORTING MILESTONES

7.1 INTERIM ANALYSIS

There will be no interim analysis for this study.

7.2 REPORTING MILESTONES

There are two reporting milestones for this trial: Primary Analysis and Follow-up Analysis.

7.2.1 Primary Analysis Reporting

All primary analyses set out in this analysis plan will be generated from a data base cut that occured on 20 Feb, 2019. This analysis will take place while less than 5 subjects are still on treatment. Once the database is locked, the study will be unblinded, so that the primary results can be obtained based on the analyses of these unblinded data.

Since some subjects will still be on treatment when unblinding takes place, they will be unblinded prematurely.

7.2.2 Follow-up Analysis Reporting

Overall survival and selected safety, demographics and disposition will be reported at this milestone. This analysis will take place when all subjects have completed the study. The accompanying document of TFL shells specifies which outputs will form part of this analysis. This analysis will be for descriptive purposes only.

8. DATA MANAGEMENT

8.1 DATA HANDLING AND TRANSFER

The data management of this study will be performed by PRA Health Sciences. PRA Health Sciences will perform data processing according to approved procedures including database specifications, CRF tracking, central laboratory data reconciliation, SAE reconciliation, and dictionary coding and data validation. A quality control of site responses to data queries will also be performed on this study.

Data will be entered by investigational sites into a clinical database built with DataLabs version 4 and exported as SAS® version 9.4 or higher datasets (SAS Institute, Inc., Cary, NC). Converted datasets will be created using SAS® and following CDISC SDTM (version 1.2, implementation guide version 3.1.2) conventions. Derived analysis datasets will be generated using SAS® and following standard CDISC Analysis Dataset Model (ADaM) conventions. Data analyses including summary tables, figures, and listings (TFLs) will be produced using SAS®.

Medical history and AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) to assign a system organ class (SOC) and preferred term (PT) to each AE. Prior and concomitant medications will be coded to preferred drug names using the World Health Organization Drug Dictionary Enhanced (WHODRUG DDE, 2014Mar01). Anatomic therapeutic classification coding will not be included. PRA's data handling and transfer procedures will be documented separately in the study specific Data Management Plan.

8.2 DATA SCREENING

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets and TFLs provides additional data screening. Presumed data issues will be output into SAS® logs identified by the word “Problem” and sent to Data Management for review.

Review of a pre-freeze TFL run and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The post-freeze TFLs will be discussed with the sponsor in a data review meeting to identify any final data issues and seek corrections prior to database lock. The PRA statistician and the sponsor must approve database lock.

9. STATISTICAL METHODS

All analyses will use SAS® version 9.4 or higher. Summary tables will be organized by treatment group. All available scheduled data for the safety population will be used in the analyses, and important CRF data will be included in data listings, sorted by treatment group, patient, and, when appropriate, by study day or time point within patient.

Unless otherwise noted, categorical data will be presented using counts and percentages, with the number of patients in the analysis population by treatment group as the denominator for percentages. Percentages will be rounded to one decimal place, except 0% and 100% will be displayed without any decimal places. Continuous data, unless otherwise noted, will be summarized using the number of observations (n), mean, standard deviation, median, minimum, and maximum. Minima and maxima will be presented to the precision of the original value, and means, medians, and 95% confidence intervals (CIs) will be rounded to one more decimal place than the original value. Standard deviation will be rounded to two more decimal places than the original value, up to a maximum of three decimal places.

Any hypothesis testing will be performed with a 2-sided level of $\alpha = 0.05$.

Partial dates for adverse event, death, and dosing records will be imputed. Imputation rules for partial and missing dates are described in Section 10.

Patients who have missing randomized sub-population stratification due to enrollment under earlier versions of the protocol will be assigned to the "Relapsed" sub-population. Patients who otherwise have missing randomized sub-population stratification will be assigned to the sub-population derived from their medical history data.

9.1 PATIENT DISPOSITION

Patient disposition data will be summarized for all enrolled patients. A table will be presented that includes the number of patients enrolled and number of patients in each analysis population. The number and percentage of patients who are off-treatment, and a breakdown of the corresponding reasons for off-treatment, will also be presented. Denominators for percentages will be based on the number of patients in the safety population. In addition, the number of patients who are discontinued from the study follow-up will be summarized by reason for termination; the only valid reasons that patients should be discontinued from study follow-up would be death or formal withdrawal of consent.

Another table will summarize the number and percentage of patients by region/country and study site. This summary will be presented for the safety population.

9.2 PROTOCOL DEVIATIONS

Per PRA processes, protocol deviation data will be entered into PRA's Clinical Trials Management System (CTMS). The study team and Dompé will conduct ongoing reviews of the protocol deviation data from CTMS throughout the study, adjusting the protocol deviation criteria as appropriate. Protocol deviations for enrolled patients will be imported into SAS® and

important deviations will be summarized and all protocol deviations will be presented in a listing.

9.3 TREATMENTS

9.3.1 Extent of Study Drug Exposure

Reparixin and paclitaxel exposure, including duration of exposure, total exposure, and total exposure by cycle, number of cycles and overall compliance will be tabulated for the safety population. Information regarding patients' dosing regimen will be presented in a listing.

9.3.2 Concomitant Medications and Concomitant Therapies

Prior medications, concomitant medications, and concomitant therapies will be tabulated separately for the safety population by treatment group and preferred drug name using counts and percentages. The number and percentage of patients using at least one medication or therapy within each treatment group will also be displayed. See Section 5 for definitions of concomitant medications. Prior and concomitant medications will be included in a patient data listing.

9.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic data, including age, ethnicity, race, weight, height, body surface area, and number of target lesion, will be summarized for all patients in the safety population. Patient population will be summarized (newly diagnosed and relapsed), for both as stratified value and actual value. Medical history, tumor history, surgery, physical exam, x-rays and/or CT scans, including a CT scan or MRI of the brain data, will be listed but not tabulated.

9.5 POOLING OF SITES

All analyses will pool sites, since the numbers of patients enrolled at individual sites will be too small for separate analyses.

9.6 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will be presented primarily for the ITT population. The randomization for this trial is stratified based on two patient sub-groups, newly diagnosed metastatic patients and patients that have relapsed following a prior (neo)adjuvant chemotherapy regimen. In few cases, subjects may be randomized into a category incorrectly. All efficacy analyses will be conducted using the randomized stratification factors. Sensitivity analysis will be conducted on actual sub-population.

9.6.1 Primary Efficacy Analysis

PFS is defined as the number of days between the date of randomization and the date of clinical PD according to RECIST criteria version 1.1, or death for any cause, whichever occurs first. Disease progression will be based on the Independent Radiology Review assessments. The date of documented disease progression will be defined as either the date of radiological or symptomatic disease progression as assessed by Independent Radiology Review. If a patient has neither progressed nor died, then progression-free survival will be censored as follows:

Table 3.1 details the primary PFS analysis.

Table 3.1 PFS

Situation	Date of Progression or Censoring	Outcome
No tumor assessment after randomization	Randomization date	Censored
No treatment received	Randomization date	Censored
Progression documented	Date of progression	Progressed
Treatment ongoing with no progression	Date of last adequate radiological assessment of measured lesions	Censored
Treatment discontinuation with no progression either pre or post treatment discontinuation.	Earliest of: • Date of last adequate radiological assessment of measured lesions • Start date of new anticancer treatment from the Long Term Follow up disease evaluation CRF page	Censored
Death without previous progression or any previous situation in this table	Date of death	Progressed

For each treatment group, the Kaplan-Meier estimates for PFS using the ITT population, along with median and the first and third quartiles will be presented. Greenwood's formula will be used to calculate the standard error of the estimates from the Kaplan-Meier curve.

As primary analysis: PFS will be compared between treatment arms using a stratified log-rank test, with randomized sub-group as stratifying factor.

As supportive analysis: in the ITT population, an estimate of the treatment hazard ratio will be obtained based on a Cox proportional model stratified by randomized sub-group, and also will be obtained within sub-groups of newly diagnosed vs relapsed patients. The corresponding CIs will be provided.

Sensitivity analyses can be helpful in determining whether the PFS analysis is robust [2]. The following two tables describe examples of two different sensitivity analyses. Table 3.2 represents a sensitivity analysis that includes well documented and verifiable progression events.

Table 3.2 PFS 1 (includes documented progression only)

Situation	Date of Progression or Censoring	Outcome
No tumor assessment after randomization	Randomization date	Censored
No treatment received	Randomization date	Censored
Progression documented at a scheduled visit	Date of progression	Progressed
Progression documented between scheduled visits	Earliest of: • Date of radiological assessment showing new lesion (if progression is based on new lesion); or • Date of progression by radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Treatment ongoing with no progression	Date of last radiological assessment of measured lesions	Censored
Treatment discontinuation with no progression either pre or post treatment discontinuation.	Earliest of • Date of last radiological assessment of measured lesions • Start date of new anticancer treatment from the Long Term Follow up disease evaluation CRF page	Censored
Death before first PD assessment	Date of death	Progressed
Death between assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last radiological assessment of measured lesions	Censored

The sensitivity analysis in Table 3.3 corrects for potential bias in follow-up schedules for tumor assessment by assigning the dates for censoring and events only at scheduled visit dates.

Table 3.3 PFS 2 (uniform progression and assessment dates)

Situation	Date of Progression or Censoring	Outcome
No tumor assessment after randomization	Randomization date	Censored
No treatment received	Randomization date	Censored
Progression documented at a scheduled visit	Date of progression	Progressed
Progression documented between scheduled visits	Date of next scheduled visit	Progressed
Treatment ongoing with no progression	Date of last scheduled visit with radiological assessment of measured lesions	Censored
Treatment discontinuation	Date of last scheduled visit with radiological assessment of measured lesions	Censored
New anticancer treatment started with no progression	Date of last scheduled visit with radiological assessment of measured lesions	Censored
Death before first PD assessment	Date of death	Progressed
Death between assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last scheduled visit with radiological assessment of measured lesions	Censored

9.6.2 Secondary Efficacy Analysis

The primary and secondary endpoints will be assessed hierarchically. Using two-sided 0.05 level tests to define statistical significance, the hierarchical ordering will be the primary endpoint, PFS, followed (in order) by OS and ORR.

Overall Survival

Overall survival is defined as the time from randomization until death due to any cause. For patients who do not die, time of death will be censored at the date of last contact.

Overall survival will be summarized in the ITT population using Kaplan-Meier curves and compared between treatment arms using a stratified log-rank test.

For each treatment group, the Kaplan-Meier estimates will be used to estimate the median overall survival time, and the first and third quartiles will be presented. Greenwood's formula will be used to calculate the standard error of the estimates from the Kaplan-Meier curve.

Objective Response Rate

The ORR is defined as the percentage of patients achieving CR or PR in the evaluable population. The response rate will be calculated from the independently reviewed assessment best response. In case of PR or CR, only confirmed cases are responses.

Patients with unknown or missing response, including response of "not all evaluated" or "unable to determine", will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentages.

Exact 95% CI for objective response rate in each arm will be calculated.

Objective response rates will be compared between treatment arms using Cochran-Mantel-Haenszel (CMH) test. Estimated common odds ratio and corresponding exact 95% CI will be calculated. Zelen's test for homogeneity of the odds ratios across all strata will be performed as a measure of validation.

Overall tumor response rate based on the investigator assessments will also be summarized in the same way as that described for the independently reviewed response.

All data relating to response from the investigator and independent reviews will be listed (including lesion measurements, response assessment, and best response) and the independent review best response assessments will be cross-tabulated with the investigator best response assessments.

A listing of patients with a discrepancy between the investigator and independent review best response will be provided.

The disease response by IRR (disease status up to PD) at pre-study (baseline) and every eight weeks until the end of the study based on RECIST version 1.1 criteria will be summarized by counts, percentages and 95% CIs and by treatment and stratification group. 95% CIs are calculated using either normal approximation method or exact binomial method, depending on if there are sufficient numbers of response or not.

Median Progression Free Survival

For each treatment group, the Kaplan-Meier estimates for the median PFS time, the first and third quartiles will be presented, along with approximate 95% CIs if there are a sufficient number of progressions or deaths.

Duration of Response

Duration of response (Duration of response) will be summarized similarly to PFS. For each treatment group, duration of response will be summarized descriptively using the K-M estimates, for the response-evaluable population.

9.6.3 Exploratory Analysis

For each treatment group, the Kaplan-Meier estimates for the TTM, and the median and the first and third quartiles will be presented, along with approximate 95% CIs if there are a sufficient number of progressions with new metastatic lesions among ITT population.

The proportion of patients progressing with new metastatic lesions is defined as the percentage of patients who at progression display new lesions at existing or new sites. The proportion of patients progressing with new metastatic lesions will be summarized and evaluated using a CMH test for response evaluable population.

The incidence of peripheral neuropathy will be summarized by treatment group. The incidence and severity of peripheral neuropathy will be also presented in a listing.

The CSC markers (CD24-CD44+CSC and ALDH+CSC assessed by IHC) will be summarized by descriptive statistics.

9.6.4 Sub–group Analyses

Descriptive analyses of multiple subgroups will be performed based on at least the following covariates:

1. a) Newly diagnosed metastatic triple negative breast cancer

   b) Breast cancer relapsing to metastatic triple negative breast cancer after neoadjuvant or adjuvant treatment
2. a) No previous treatment with a taxane

   b) Previous treatment with taxane
3. a) Age $\leq$ 40 years

   b) Age > 40 years
4. a) Visceral disease

   b) No visceral disease
5. Presence of markers of CSC (CD44/CD24 or ALDH+) in metastatic tumor tissue correlated with PFS

Previous treatment with a taxane and visceral disease will be determined based on a manual medical review of the verbatim terms for prior therapies and lesions sites as appropriate.

9.7 SAFETY ANALYSES

9.7.1 Adverse Events

Information on all AEs will be collected from IC signature throughout the study until resolution of the event. Only TEAEs for the safety population will be summarized for this study.
An overall summary of TEAEs, including the number of events reported, the number and percentage of patients reporting at least 1 TEAE, the number and percentage of patients discontinuing due to a TEAE, the number and percentage of patients with at least one serious TEAE, and the number and percentage of deaths will be presented by treatment group and overall. See Section 5 for TEAE definition.

A breakdown of the number and percentage of patients reporting each TEAE, categorized by SOC and PT, will be presented by treatment group and overall. Note that counting will be by patient not event, and patients are only counted once within each SOC or PT. A similar tabulation will be produced for those TEAEs related to study drug (i.e., "suspected" per CRF). Missing relationship to study drug will be counted as related.

A summary of reported TEAEs, categorized by severity (i.e., Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening or disabling, Grade 5 = death per CRF), will be provided by treatment group and overall. Patients with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that body system or preferred term. For a given patient, if the severity grade is missing for all TEAEs with the same preferred term, the TEAEs will be counted only once for that term under the "Missing" severity category. For a patient who has both missing and non-missing severity grades for adverse events with the same preferred term, the TEAE will be counted under the highest non-missing severity category. This summary will also be presented for treatment-related TEAEs.

A summary of TEAEs leading to discontinuation will be provided, grouped by body system and preferred term by treatment group and overall. A similar tabulation will be produced for treatment related TEAEs. A number of additional summaries by SOC and PT will be provided for the safety population by treatment group and overall:

- TEAE with outcome of death
- Treatment related TEAE with outcome of death
- Serious TEAE
- Treatment related serious TEAE
- Non-fatal serious TEAE

All AEs will be listed for patients in the safety population.

A summary of ADRs will be presented in tables. ADRs continuing across more than one treatment cycle without complete resolution and reported more than once in CRF to reflect changes in CTCAE grade, will be reported in this table as single ADRs with worst CTCAE

grade. ADRs occurring more than once per patient but not continuing (i.e. with clear break between one occurrence and the next) will be reported in this table as separate ADRs.

ADRs related to reparixin and ADRs related to paclitaxel will be summarized in separate tables.

9.7.2 Serious Adverse Events

A summary of SAEs and treatment-related SAEs for the safety population will be provided by treatment group and overall, grouped by SOC and PT.

9.7.3 Laboratory Data

Hematology laboratory tests will be performed locally at the study sites at pre-study, on Days 1, 8 and 15 of each cycle, and at the OTV. Chemistry laboratory tests will be measured pre-study, on Day 1 of each treatment cycle, as clinically indicated, and at the OTV. Urinalysis parameters will be at pre-study, throughout each cycle if clinically indicated, and at the OTV.

Laboratory data will include parameter values, normal ranges, and out-of-range flags. In addition, laboratory abnormalities will be assigned a CTCAE (Version 4.03) grade for severity (1= mild, 2 = moderate, 3 = severe, 4 = life-threatening or disabling) for analyses that have numeric CTCAE guidelines only (i.e., not requiring clinical assessments) (see section 5 for detail). Laboratory parameters are listed in Table 4 below, and will be sorted by their order in the table. Laboratory test results will be converted and reported in International System of Units (SI) units.

Clinical laboratory data summaries for safety analyses will include the following tables by treatment group for the safety population:

- Hematology and chemistry results and changes from baseline by cycle and study day
- CTCAE shifts from baseline to worst post-baseline result for hematology and chemistry
- Urinalysis results and changes from baseline for continuous variables
- Hematological toxicity evaluations of thrombocytopenia, neutropenia, and leukopenia based on CTCAE grading.

For change from baseline tables, descriptive statistics will be shown for baseline, specific scheduled post-baseline time points, and the change from baseline to each of these post-baseline time points.

Table 4. List of Laboratory Tests

Hematology:
• Hemoglobin (Hgb)
• Platelets
• WBC count with differential including:
  ○ Neutrophils
  ○ Lymphocytes
  ○ Monocytes
  ○ Eosinophils
  ○ Basophils
 	
Urinalysis:
• Glucose
• Ketones
• pH
• Protein
• Bilirubin
• Blood
• Nitrite
• Leukocyte
• Specific gravity
	Serum Chemistry:
	• Albumin
	• ALP
	• ALT
	• AST
	• Blood urea nitrogen (BUN)
	• Calcium (Ca)
	• Serum Creatinine
	• Potassium (K)
	• Sodium (Na)
	• Total bilirubin
	• Total protein
	• Urea

9.7.4 Vital Signs

Vital signs will be assessed at Day 1 of each cycle (within 24 hours prior to the first study drug (reparixin/placebo) administration for the first cycle) and at the OTV. Vital sign parameters will include pulse rate and systolic and diastolic BP.

A change from baseline summary by cycle will be displayed for vital signs parameters for the safety population. Descriptive statistics will be shown for baseline, scheduled visits, and the change from baseline to these visits. Vital sign parameters will be sorted by their order on the CRF. Vital signs data will also be listed by patient.

9.7.5 Physical Examinations and Electrocardiograms

Physical examination will be assessed at pre-study, on Day 1 of each cycle starting from Cycle 2, and at the OTV. Body systems assessed for physical examination include skin, head/eyes/ears/nose/throat, cardiovascular, respiratory, abdominal (including liver and kidneys), musculoskeletal, neurological, gastrointestinal, genitourinary, endocrine, lymph nodes, and other. Each body system will be assessed as normal, abnormal, or not performed, with abnormalities documented. The number and percentage of patients assessed as normal, abnormal, or not performed for each body system will be summarized at each scheduled visit for the safety population.

Zubrod Performance Status will be summarized at pre-study and at the OTV for safety population. Data will also be listed by patient.

Electrocardiograms (ECGs) will be performed locally at the study sites at screening. Overall ECG impression will be assessed by the investigator as normal, abnormal, and clinically significant or not clinically significant if abnormal. The number and percentage of patients assessed as normal and abnormal (clinically significant or not clinically significant) will be summarized by visit for the safety population. ECGs data will also be listed by patient

10. HANDLING OF MISSING DATA

10.1 TUMOR DATA

In order to evaluate the potential effect of missing tumor data, two sensitivity analyses will be performed. See Section 9.6.1 for more details.

10.2 SURVIVAL DATA

For patients not known to have died prior to the end-of-study date:

- All events with a start date before or on the end-of-study date, and with a missing end date will be reported as “continuing at the end-of-study date”. This approach applies in particular to AEs and concomitant medications. For these events, the end date will not be imputed and therefore will not appear in the listings.

For patients known to have died:

- All events with a start date before or on the end-of-study date, and with a missing end date will have the end date imputed to the death date. This approach applies in particular to AEs and concomitants. For these events, the imputed end date will not appear in the listings.

10.3 AE DATE IMPUTATION

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing dates for AEs will be handled according to rules specified below. A partial date is simply an incomplete date (e.g., DDOCT2001); the days are missing from this DDMMMYYYY date.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**
- Partial/missing AE **end dates**

The following Table 5 explains the abbreviations used.

Table 5. AE / Treatment Date Abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

The following Table 6 describes the possible combinations and their associated imputations. The upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 6. AE Partial Date Imputation Algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain	NC Uncertain	NC Uncertain	NC Uncertain
AEY < TRTY	(D) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD	(C) Before TRTSTD
AEY = TRTY	(B) Uncertain	(C) Before TRTSTD	(B) Uncertain	(A) After TRTSTD
AEY > TRTY	(E) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD	(A) After TRTSTD

The following is the legend to the above table.

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 7 gives a few examples.

Table 7 AE Imputation Example Scenarios

Partial AE start date	Treatment start date	Relationship	Imputation Calculation	Imputed Date
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

10.4 INCOMPLETE DATE FOR CONCOMITANT MEDICATION

If dates are missing or incomplete for concomitant medication, the following algorithm will be used for imputation:

Table 7 Imputation Rules for Partial or Missing Start Dates

Start Date		Stop Date: Complete: yyyymmdd <1st dose	Complete: yyyymmdd ≥1st dose	Partial: yyyymm <1st dose yyyymm	Partial: yyyymm ≥1st dose yyyymm	Partial: yyyy <1st dose yyyy	Partial: yyyy ≥1st dose yyyy	Missing
Partial: yyyymm	= 1st dose yyyymm	2	1	n/a	1	n/a	1	1
	≠ 1st dose yyyymm		2	2	2	2	2	2
Partial: yyyy	= 1st dose yyyy	3	1	3	1	n/a	1	1
	≠ 1st dose yyyy		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute as the date of first dose
2 = Impute as the first of the month
3 = Impute as January 1 of the year
4 = Impute as January 1 of the stop year

Note: If the start date imputation leads to a start date that is after the stop date, then there is a data error and do not impute the start date.

Imputation rules for partial or missing stop dates:

1. Initial imputation
    a. For partial stop date “mmyyyy”, impute the last of the month.

b. For partial stop date "yyyy", impute December 31 of the year.

c. For completely missing stop date, do not impute.

2. If the stop date imputation leads to a stop date that is after the death date or date of off treatment visit, then impute the stop date as the earlier date between the death date and date of off treatment visit.

11. VALIDATION

PRA's quality control procedures will be documented separately in the study-specific quality control plan.

12. REFERENCES

[1] National Cancer Institute, US National Institutes of Health. Response Evaluation Criteria In Solid Tumors (RECIST). http://www.eortc.be/recist/

[2] Food and Drug Administration, US Department of Health and Human Services. Guidance for Industry – Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. http://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

13. APPENDIX 1: GLOSSARY OF ABBREVIATIONS

ADaM	Analysis Dataset Model
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BOR	Best Overall Response
BP	Blood Pressure
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSC	Cancer Stem Cell
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
IC	Informed Consent
IHC	Immunohistochemistry
IRT	Interactive Response Technology
ITT	Intent-to-Treat
i.v.	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mPFS	Median Progression Free Survival
MRI	Magnetic Resonance Imaging
ORR	Objective Response Rates
OS	Overall Survival
OTV	Off-Treatment Visit
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SDTM	Standard Data Tabulation Model

SI	International System (of Units)
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures, and Listings
TNBC	Triple Negative Breast Cancer
TTM	Time to New Metastasis
TTP	Time to Tumor Progression
WBC	White Blood Cell

14. APPENDIX 2: LIST OF IN-TEXT TABLES, FIGURES, AND LISTINGS

A list of in-text TFLs will be finalized after SAP1 is approved.

15. APPENDIX 3: SHELLS FOR IN-TEXT TABLES, FIGURES, AND LISTINGS

Shells for in-text TFLs will be finalized after SAP1 is approved.

16. APPENDIX 4: LIST OF POST-TEXT TABLES, FIGURES, AND LISTINGS

See accompanying document of TFL shells.

17. APPENDIX 5: SHELLS FOR POST-TEXT TABLES, FIGURES, AND LISTINGS

See accompanying document of TFL shells.