Document Cover Page

Official Title: A Phase 2, Multicenter, Randomized Study to Evaluate Duration of Severe Neutropenia With Plinabulin Versus Pegfilgrastim in Patients With Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy (Protective-1)

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STATISTICAL ANALYSIS PLAN

PHASE 2 DATA

Study Title:	A Phase 2/3, Multicenter, Randomized, Double Blind, Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastim in Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy
Sponsor	BeyondSpring Pharmaceuticals, Inc. 48 Wall Street, 11th Floor New York, NY 10005
Drug Product:	Plinabulin (NPI-2358)
Protocol Number:	BPI-2358-105
Phase:	Phase 2/3
Analysis Plan Version	Version 2.0
Analysis Plan Date	07 December 2017
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STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURE PAGE

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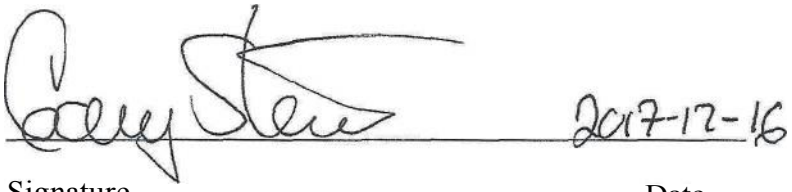

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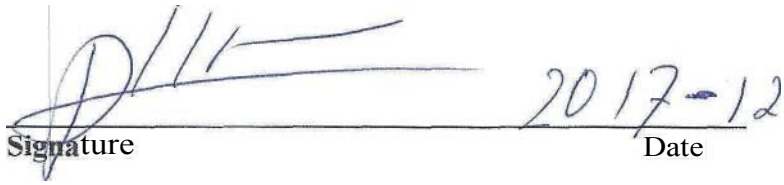

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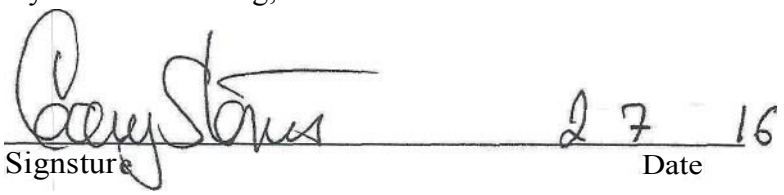

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LIST OF ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Measurements
AE	Adverse Event
ATC	Anatomical Class (from WHODRUG dictionary)
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
DMN	Duration of Moderate Neutropenia; the number of days with a neutrophil count of $<1.0x10^9/L$
DSN	Duration of Severe Neutropenia; the number of days with a neutrophil count of $<0.5x10^9/L$
ECG	Electrocardiogram
FDA	Foos and Drug Administration
FN	Febrile Neutropenia
GCP	Good Clinical Practices
ICH	International Committee for Harmonization
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Affairs
NSCLC	Non-Small Cell Lung Cancer
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QoL	Quality of Life
RP3D	Recommended Phase 3 Dose of Docetaxel (75 mg/m^2) + plinabulin (5, 10 or 20 mg/m^2)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHODRUG	World Health Organization Drug Reference Listing

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of the Phase 2 data collected within the scope of BeyondSpring Pharmaceuticals, Inc. Protocol BPI-2358-105 titled "*A Phase 2/3, Multicenter, Randomized, Double Blind, Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastim in Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy"*.

Analysis of Phase 3 data will be described in a separate Statistical Analysis Plan (SAP).

This SAP was prepared in accordance with BPI-2358-105 Protocol Amendment 3, dated 30 May 2017 and Protocol Amendment 2, dated 10 February 2017. Key differences between the protocol versions are outlined in Section 1.1.

The purpose of this SAP is to provide a framework in which answers to the protocol objectives related to the Phase 2 portion of the study, may be achieved in a statistically rigorous fashion, without bias or analytical deficiencies, following methods identified prior to database lock.

This SAP governs:

1. Tier 1 data from Phase 2, with all patients in Phase 2 having completed Cycle 1
2. Tier 2 data from Phase 2, with all patients in Phase 2 having completed Cycle 1
3. The Phase 2 Clinical Study Report (CSR) with all patients in Phase 2 having completed Cycles 1-4.

The Phase 2 data will be analyzed at the end of the Phase 2 portion of the study as planned per protocol, and additionally at the point when the last patient in the Phase 2 portion has completed Cycle 1, in 2 tiers (Tier 1 and Tier 2), as described below.

Once all patients have completed Cycle 1, the database will be locked and the available data (from all cycles) will be analyzed using a 2-tier approach. Pre-specified data (Tier 1) will be analyzed first, in order to inform dose selection for the Phase 3 portion of the study. This data set will be complete for Cycle 1 only; however, available data from Cycles 2-4 at the time of database lock will also be reported. The data will be summarized and submitted to the Food and Drug Administration (FDA) in the form of a Summary document (Summary of Pharmacokinetic [PK], Pharmacodynamic [PD], Safety and Exploratory Data to Establish RP3D for Phase 3). The focus will be on the PK/efficacy PD endpoints (duration of severe neutropenia [DSN] and duration of moderate neutropenia [DMN]) from Cycle 1 and the

PK/safety PD endpoint (semi-continuous blood pressure) from Cycle 1, as well as other relevant safety data. The remaining data (Tier 2) will be analyzed subsequently.

The Phase 2 portion of the study will continue, and all data will be analyzed as planned per protocol at the end of this part of the study. This complete Phase 2 dataset will be reported in the Phase 2 BPI-2358-105 CSR.

This SAP therefore has the following purposes:

- To prospectively outline the specific types of analyses and presentations of Phase 2 data that will form the basis for conclusions.
- To clearly identify Tier 1 and Tier 2 data.
- To explain in detail how all Phase 2 data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry. Any deviations from these guidelines must be substantiated by sound statistical reasoning and documented in the final CSR.

1.1. Protocol Amendments

This SAP is prepared in accordance with Protocol Amendment 3 (30 May 2017) and Protocol Amendment 2 (10 February 2017), as patients have been enrolled under both versions of the protocol. Minor differences in calculation of the primary PK/PD efficacy and safety endpoints are necessary, and are explained in detail in Section 2.1.1.

The key differences between the protocol versions relating to statistical considerations are summarized below:

Protocol Amendment 2 **10 February 2017**	**Protocol Amendment 3** **30 May 2017**
Plinabulin infusion started 60 minutes after the end of the docetaxel infusion	Plinabulin infusion started 30 minutes after the end of the docetaxel infusion
Phase 2 portion randomized, double-blind with matching placebo	Phase 2 portion changed to open-label, no matching placebo
Assessments performed on Day 5 (including duration of severe neutropenia)	All Day 5 assessments removed
Semi-continuous blood pressure and ECG collection to last 6 hours after start of plinabulin/placebo infusion	Semi-continuous blood pressure and ECG collection to last 4.5 hours after start of plinabulin/placebo infusion
	A Day 6 assessment added for CD34+
	In the Phase 2 portion, bone pain assessment on Days 2 and 3 of Cycle 2 removed

2. OVERVIEW OF STUDY DESIGN

This is a multicenter, randomized study with a Phase 2 portion and a Phase 3 portion. Approximately 190 patients will be enrolled in this study. Per Protocol Amendment 3, the Phase 2 portion will be open label with all patients receiving plinabulin or pegfilgrastim (no placebo will be administered). Prior to this amendment, the Phase 2 portion of the study was double-blind.

All patients will receive docetaxel at a dose of 75 mg/m^2.

In Phase 2, patients only with advanced or metastatic non-small cell lung cancer (NSCLC) after failing platinum-based therapy will be enrolled.

In Phase 3, patients with one of the following will be enrolled: advanced or metastatic breast cancer, who have failed <5 prior lines of chemotherapy; advanced or metastatic NSCLC after failing platinum-based therapy; or hormone refractory (androgen independent) metastatic prostate cancer.

The eligibility of all patients will be determined during a 28-day screening period.

Phase 2:

Approximately 40 patients with advanced and metastatic NSCLC will be enrolled. Patients are randomly assigned, with 10 patients enrolled in each arm, with the arm designation and planned intervention as follows:

- Arm 1: Docetaxel (75 mg/m^2) + pegfilgrastim (6 mg)
- Arm 2: Docetaxel (75 mg/m^2) + plinabulin (20 mg/m^2)
- Arm 3: Docetaxel (75 mg/m^2) + plinabulin (10 mg/m^2)
- Arm 4: Docetaxel (75 mg/m^2) + plinabulin (5 mg/m^2)

Patients enrolled under Protocol Amendment 2 will receive matching placebo to blind for either pegfilgrastim or plinabulin.

The study will be temporarily closed to enrollment when approximately 40 patients have been enrolled and completed at least 1 treatment cycle in each arm in Phase 2. The Sponsor will notify the study sites when this occurs.

Once the study is temporarily closed to enrollment in Phase 2, a PK/PD analysis will be performed to determine the recommended Phase 3 dose (RP3D) of docetaxel (75 mg/m^2) + plinabulin (5, 10 or 20 mg/m^2). The PK/PD analysis will be performed by an independent party (Anoixis Corporation) and will be blinded to the study team. At this point, datasets will

be created for the Tier 1 and Tier 2 data, as further described in Section 6 and listed in Section 14.1.

The Phase 2 portion of the study will continue as planned, and once completed, all data will be analyzed as planned per protocol.

Phase 3:

Phase 3 will not begin until RP3D has been determined based on the Phase 2 PK/PD analysis as mentioned above; the RP3D will be the only plinabulin dose administered in Phase 3.

As previously noted, analysis of the Phase 3 portion of the study will be described in a separate SAP, and therefore this part of the study is not further described in this document.

Phase 2 Study Design:

Cycles 1 to 4 will consist of docetaxel 75 mg/m^2 administered by IV infusion over 60 minutes on Day 1 every 21 days. Administration of other study treatment is dependent on protocol version as follows:

- Per Protocol Amendment 2, on Day 1 of each cycle, 2 hours (±10 minutes) after the start time of docetaxel infusion (i.e., approximately 60 minutes from the end of docetaxel infusion), patients will receive a single dose of plinabulin or placebo intravenously over 30 minutes (±5 minutes), in a double blinded manner.
- Per Protocol Amendment 3, on Day 1 of each cycle, 1.5 hours (±10 minutes) after the start time of docetaxel infusion (i.e., approximately 30 minutes after the end of docetaxel infusion), patients assigned to a plinabulin arm (arms 2-4) will receive a single IV infusion of plinabulin at their assigned dose over 30 minutes (±5 minutes).

On Day 2 of each cycle ≥24 hours after completing chemotherapy, all patients will receive a single dose of pegfilgrastim (6 mg), and if patients are enrolled under Protocol Amendment 2 (but not Amendment 3), patients who will not receive pegfilgrastim on Day 2 will receive matching placebo (subcutaneous injection).

If a chemotherapy cycle is delayed by more than 3 weeks, the patient will be withdrawn from the study. If a critical AE occurs during the cycle, the dosage of docetaxel may be reduced 20% in the next cycle. Only 1 docetaxel dose reduction is allowed. No dose reductions are allowed with plinabulin or pegfilgrastim.

All patients, including patients who withdraw from the study early, will complete a safety follow-up visit 30 days (± 7 days) after the last dose of study drug. Follow-up visits will be required to monitor for ongoing treatment-related adverse events (AEs). All patients experiencing drug-related toxicities of Grade ≥ 2 at the End of Treatment visit should be followed-up at least monthly until the AE(s) resolves to Grade ≤ 1, the event is considered to be chronic, or the patient receives other anti-cancer therapy. The method of follow-up

assessment will be at the Investigator's discretion (for example, patient site visit or telephone call). All deaths which occur within 30 days of plinabulin administration regardless of relationship to the study drug must be reported to the Sponsor immediately and within 24 hours of becoming aware of the event.

Protocol-directed laboratory test results (hematology and serum chemistry) will be collected via a central laboratory. Safety laboratory tests are required prior to treatment on Day 1 of each cycle and can be collected by a local laboratory; however, all other scheduled blood samples as per the schedule assessments and procedure table must also be obtained for central laboratory assessment. Urinalysis will be performed at baseline only. CD34+ counts will be established through a fluorescence-activated cell sorting method.

The schedule of events is provided in Section 13.

Rescue Treatment:

Patients who experience a febrile neutropenia (FN) event in Cycle 1 with plinabulin will receive pegfilgrastim in subsequent cycles. If the patient was orginally assigned to the pegfilgrastim arm, the patient should be treated at a lower dose of docetaxel or taken off study at the discretion of the investigator.

If the patient develops an FN event on subsequent cycles, the patient should be discussed with the medical monitor and either treated with a lower dose of docetaxel, or taken off study at the discretion of the investigator. Febrile neutropenia should be treated with antibiotics per institutional standard of care. If a patient is hospitalized, the procedure for reporting SAEs should be followed.

2.1. Phase 2 Objectives

Plinabulin PK and PD assessments will be made to enable PK/PD analysis.

2.1.1. Primary Objective

To establish the RP3D based on PK/PD analysis.

- **Primary efficacy PD objective:** To assess DSN in treatment Cycle 1 in patients treated with docetaxel (75 mg/m^2) + plinabulin (5, 10 or 20 mg/m^2) or with docetaxel (75 mg/m^2) + pegfilgrastim (6 mg). Neutrophil count will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 5*, 6, 7, 8, 9, 10, 15 (pre-dose on dosing days; times equivalent to pre-dose on other days).
  * Day 5 is included per Protocol Amendment 2 but is omitted per Protocol Amendment 3.
- **Primary safety PD objective:** To assess blood pressure semi-continuously with 15-minute intervals, starting 15 minutes pre-plinabulin dose and lasting 4.5 hours

after start of infusion with plinabulin (Arms 2 to 4) or for 4.75 hours starting 15 minutes after the end of docetaxel infusion (Arm 1). Under Protocol Amendment 2, blood pressure will be measured for 6 hours starting 15 minutes after the end of docetaxel infusion with a matching schedule in Arm 1.

2.1.2. Secondary Objectives

- **Secondary efficacy PD objective:** To assess duration of moderate neutropenia (DMN) in treatment Cycle 1 in patients treated with docetaxel (75 mg/m^2) + plinabulin (5, 10 or 20 mg/m^2) or with docetaxel (75 mg/m^2) + pegfilgrastim (6 mg). Neutrophil count will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 5*, 6, 7, 8, 9, 10, 15 (pre-dose on dosing days; times equivalent to pre-dose on other days).
  * Day 5 is included per Protocol Amendment 2 but is omitted per Protocol Amendment 3.
- To characterize the PK profile of plinabulin and docetaxel.
- To characterize the exposure-response relationships between measures of plinabulin exposure and the PD endpoint DMN.
- To characterize the exposure-response relationships between measures of plinabulin exposure and the PD endpoint DSN.
- To characterize the exposure-safety relationships between measures of plinabulin exposure and safety events of interest.

2.1.3. Exploratory Objectives

- To assess CD34+ at screening, and on Days 2, 5, and 8 in Cycle 1 and Day 1 in Cycle 2.
- Health-related quality of life (QoL) questionnaire evaluated with EORTC QLQ-C30 and EQ-5D-5L.
- To collect data on disease progression.

2.1.4. Safety Objectives

- Incidence, occurrence, and severity of AEs/serious adverse events (SAEs).
- nciIdence, occurrence and severity of bone pain .
- Systemic tolerance (physical examination and safety laboratory assessments).

3. SAMPLE SIZE JUSTIFICATION

In the Phase 2 portion, approximately 40 patients with advanced or metastatic NSCLC will be enrolled, with approximately 10 patients per arm.

4. RANDOMIZATION, STRATIFICATION, BLINDING, AND REPLACEMENT OF PATIENTS

Patients will be identified by a patient number.

Treatment Assignment:

Patients will be randomly assigned by Interactive Response Technology to 1 of the following treatment groups (10 patients per arm):

- Arm 1: Docetaxel (75 mg/m^2) + pegfilgrastim (6 mg)
- Arm 2: Docetaxel (75 mg/m^2) + plinabulin (20 mg/m^2)
- Arm 3: Docetaxel (75 mg/m^2) + plinabulin (10 mg/m^2)
- Arm 4: Docetaxel (75 mg/m^2) + plinabulin (5 mg/m^2)

(Note, patients enrolled under Protocol Amendment 2 will receive matching placebo in a double-blind manner.)

5. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED

5.1. Phase 2 Analysis Sets

5.1.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set for Phase 2 includes all Phase 2 patients that have been randomized in the study and have received at least 1 dose of study medication.

The analysis of all endpoints, unless noted otherwise, will be conducted on the intent-to-treat analysis set.

5.1.2. Safety Analysis Set

The safety analysis set will be the same as the intent-to-treat analysis set.

5.1.3. Pharmacokinetic Analysis Set

All patients who received at least 1 dose of plinabulin or docetaxel and had at least 1 PK sample collected will be included in the PK analysis set. These patients will be evaluated for PK unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption, or sampling information is missing. Population PK modeling will be utilized to analyze the PK data, and informative sampling approaches will be used to determine the PK time points for Phase 3.

5.1.4. Pharmacodynamic Analysis Set

All patients who had blood pressure and DSN and/or DMN collected at any time during the study will be included in the PD analysis set. Exploratory PK/PD and exposure-response analyses will be conducted to evaluate the effects of plinabulin on safety and efficacy endpoints. Details of these analyses will be summarized in the pharmacometrics analysis plan.

6. PHASE 2 STATISTICAL ANALYSIS CONSIDERATIONS

6.1. General Principles

Statistical analyses will be reported using summary tables, figures, and data listings. Continuous variables will be summarized with counts, means, standard deviations, medians, confidence intervals, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of patients.

Formal inferential statistical analyses techniques will be discussed in subsequent sections of this SAP.

Individual patient data obtained from the case report forms (CRFs), electrocardiogram (ECG), core laboratory, PK data and any derived data will be presented in by-patient listings sorted by study center and patient number.

All analyses and tabulations will be performed using SAS Version 9.4 or higher on a PC platform. Table, listings, and figures will be presented in RTF format. Upon completion, all SAS programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated.

6.2. Order of Analysis

As previously described, Phase 2 data will initially be analyzed using a 2-tier approach, after all patients have completed Cycle 1. Appendix 14.1 provides a detailed listing of which data will be included in Tier 1 and Tier 2. Datasets will be created for Tier 1 data, encompassing:

- Demographics
- Baseline characteristics
- Drug exposure (including summarization of the number of patients per cycle (1, 2, 3, and 4) in each treatment arm)
- PK/efficacy PD: DMN (described in pharmacometrics analysis plan)
- PK/efficacy PD: DSN (described in pharmacometrics analysis plan)
- PK/safety PD: Blood pressure (semi continuous) (described in pharmacometrics analysis plan)

- Safety: AEs and SAEs.

These data will be analyzed immediately, in order to inform dose selection for the Phase 3 portion of the study. Other study data (Tier 2) will be analyzed as planned per protocol and all study data will be reported in the Phase 2 CSR.

6.3. Major Protocol Violations

Major protocol violations will be identified by the clinical study team, documented, signed and provided to the Sponsor prior to database lock. A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP). The noncompliance may be either on the part of the patient, the investigator, or the study site staff. Reportable protocol violations will be listed by study center and patient numbers.

6.4. Patient Enrollment and Disposition

Patient enrollment by site will be tabulated by treatment arm and overall and per cycle for each treatment arm.

Patient disposition will be summarized by treatment arm and overall. The summary will include the number and percentage of patients in each of the defined analysis populations in Section 5. In addition, frequency counts and percentages of patients' reported reasons for ending the study will be summarized.

A listing will be presented to describe patient study arm, date of first and last dose, date of last visit or contact, total number of completed cycles, and the reason for ending the study for each patient.

Listings of inclusion/exclusion criteria responses will also be provided.

6.5. Description of Demographic and Baseline Characteristics

A summary of age, gender, race, ethnicity, vital signs, ECOG status, tumor staging, and prior: cancer-specific surgery, radiotherapy, and prior chemotherapy (Yes/No); along with the number of prior chemotherapy regimens will be presented using appropriate descriptive statistics by each treatment arm and overall total. The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). These summaries will include patients in the ITT population.

All demographic and baseline characteristics will be listed by study center, and subject number.

6.6. Medical History

Medical history data will be coded by system organ class and preferred term, using the MedDRA dictionary (2008).

Medical history will be summarized by body system for each study arm in the safety analysis set. The table will be sorted in alphabetic order by system organ class, as well as by incidence and preferred term, and the statistics n and % will be presented by study arm where: n is the number of patients who present at least 1 occurrence of the medical history and % is the percentage of patients. The denominator used for calculating the percentages will be the total number of patients included in the ITT analysis set on each study arm.

6.7. Cancer History

Histology of NSCLC, disease status, cancer-specific surgery, prior chemotherapy regimen, and best response will be summarized using frequency counts and percentage.

6.8. Concomitant Medications

All medication data will be coded by drug class and indication, using the WHO Drug dictionary (2008). All medication taken prior to the first dose of study drug will be classified as prior medication. All medication taken on or after the first dose of study drug will be classified as concomitant medication. Medications with start and stop date that bracket the date of first dose will be summarized as both prior and concomitant medication.

For the purpose of inclusion concomitant medication tables, incomplete medication start and stop date will be imputed as detailed in Section 11. Based on imputed start and stop dates, medications that started on or after date of first dose will be included in the concomitant medications table.

Concomitant medications will be summarized in the safety population by giving the number and percentage of patients by preferred term within each therapeutic class, with therapeutic class and medications in each class sorted in alphabetical order. The total number of drugs in each selected therapeutic class will also be presented, where, for example 2 drugs each belonging to the same class will only contribute once to the presented count.

All prior and concomitant medications, as well as medical procedures will be listed by study center, and patient number.

6.9. Physical Examination

All physical examination findings will be listed by study center and patient number.

6.10. Study Drug Exposure

Study treatment exposure will be summarized in the safety population.

For each treatment arm for each product (doxetaxel, pegfilgrastim, and plinabulin), the following will be summarized using descriptive statistics by study arm and overall:

- Duration of exposure, calculated as (date of last dose – date of first dose+1).
- Number of cycles received per patient.
- Number of cycles with dose modification and (or) dose delay.
- Reasons for dose deviations from planned therapy.

All study drug administration data will be listed by study center and patient number.

6.11. Pharmacokinetic and Pharmacodynamic Analyses

Plasma plinabulin and docetaxel concentrations will be measured using validated methods and PK parameters will be summarized using descriptive statistics. Individual and mean serum plinabulin and docetaxel concentration versus time profiles will be plotted on both linear and logarithmic scales.

Exploratory graphical and statistical techniques, including linear, nonlinear, and logistic regression, etc., will be used to explore potential relationships between pharmacokinetic parameters of interest and efficacy endpoints, pharmacodynamic variables, and safety events of interest. These exposure-response analyses will support the RP3D of plinabulin which will be used during the Phase 3 of study treatment.

The PK/PD analyses are described in Section 6.12 and include:

- PK/Efficacy PD (DMN) from Cycle 1
- K/Efficacy PD (DSN) from Cycle 1
- PK/Safety PD (semi-continous blood pressure) from Cycle 1

Full methodology will be described in the pharmacometrics analysis plan.

6.12. Efficacy Analysis

The PK and PD efficacy and safety endpoints will be analyzed according to the pharmacometrics analysis plan.

6.12.1. Primary Efficacy Pharmacodynamic Analysis

Phase 2 data from Cycle 1 will be subjected to PK/PD analysis to determine the RP3D of plinabulin which will be used during the Phase 3 portion of the study. The primary efficacy pharmacodynamic marker is DSN, defined as the number of days with a neutrophil count of $< 0.5 \times 10^9$ neutrophils/L.

In addition, an exploratory analysis to assess DSN in Treatment Cycle 1 in patients treated with docetaxel (75 mg/m^2) + plinabulin (5, 10 or 20 mg/ m^2) will be performed, using the Jonckheere-Terpstra Test for Ordered Alternatives (Hollander, Wolfe and Chicken, 2013). With this statistical procedure, the null hypothesis of equality among treatment group means will be tested (μ_j's, $j = 2, 3, 4$)

$$H_0: \mu_2 = \mu_3 = \mu_4$$

against the alternative in which order is specified

$$H_1: \mu_2 \geq \mu_3 \geq \mu_4,$$

where at least 1 of the inequalities is strict. The mean indices have the following interpretation: 2 = docetaxel (75 mg/m^2) + plinabulin (5 mg/m^2), 3 = docetaxel (75 mg/m^2) + plinabulin (10 mg/m^2), and 4 = docetaxel (75 mg/m^2) + plinabulin (20 mg/m^2). The statistically significant rejection of the null hypothesis will be interpreted, that there is an ordered alternative of responses as indicated by the alternative hypothesis H_1. If the null hypothesis is rejected, then pair wise Wilcoxon tests will be performed to aid in the assessment of which treatment(s) contributed to the rejection of the null hypothesis.

Since the Jonckheere-Terpstra Test for Ordered Alternatives is a non-parametric test, this will be performed in SAS using PROC FREQ with JT option. The DSN for this analysis is calculated as in Section 6.10, and since this is an exploratory, non-parametric analysis, no adjustment will be made for the potential number of 0 values of the DSN. The non-parametric nature of the test factors these into consideration. Missing ANC values will not be imputed.

6.12.2. Secondary Efficacy Pharmacodynamic Analysis

The secondary efficacy pharmacodynamic marker is DMN, defined as the number of days with a neutrophil count of $< 1.0 \times 10^9$ neutrophils/L.

In addition, an exploratory analysis to assess DMN in Treatment Cycle 1 in patients treated with docetaxel (75 mg/m^2) + plinabulin (5, 10 or 20 mg/ m^2) will be performed as described in Section 6.12.1.

6.12.3. Primary Safety Pharmacodynamic Analyses

A PK/ambulatory blood pressure measurements (ABPM) model will be developed to characterize the exposure-ABPM relationship. Circadian rhythm will be accounted for in the PK/ABPM model, as appropriate. The details of the PK/ABPM are described in the pharmacometrics analysis plan.

6.12.4. Exploratory Efficacy Analyses

An exploratory analysis is to assess CD34+ at screening, and on Days 2, 5, and 8 in Cycle 1 and Day 1 in Cycle 2. These data will be summarized by Cycle and Day and the differences between the treatment arms will be assessed by day using an Analysis of Variance with a term for ARM. Pairwise differences will be assessed using pre-defined contrasts.

DSN and DMN data will be summarized via confidence intervals for the 30 minute and 60 minute wait times, in order to investigate possible effect of changing the timing of dosing in Protocol Amendment 3.

6.13. Safety Analysis

All patients will be evaluable for safety analysis if they receive at least 1 dose of study drug. All patients receiving a dose of study drug will be included in all safety summaries. The safety data will be presented by study arm in individual listings and summary tables, including frequency tables for adverse events and frequency and shift tables for laboratory variables. All AEs and abnormal laboratory variables will be assessed according to the NCI CTCAE (v 4.0) grading system. Descriptive statistics will be used to summarize ECOG performance status. Vital signs will be reported in listings. AEs and SAEs will be reported in combined tables and SAEs will also be in tabulated in a separate table.

All safety information will be listed by study center and subject number.

6.13.1. Adverse Events

Incidences (overall and treatment-emergent) of adverse events will be summarized by system organ class and by preferred terms (MedDRA). AEs will be considered as treatment-emergent adverse events (TEAEs) if onset is on or after the initiation of study treatment. AEs with missing onset dates will be summarized as TEAEs regardless of severity and relationship to study medication.

The incidence of AEs by severity and/or CTCAE adverse events grade (mild, moderate, severe, life threatening or death) and by relationship to study drug will be tabulated similarly. Each AE will be reported by greatest known severity and by strongest relationship to the study drug.

Each patient will be counted only once within a system organ class or a preferred term by using the AEs with the highest severity grade.

All information pertaining to AEs noted during the study will be listed per patient, detailing verbatim, preferred term, system organ class, start date, stop date, severity and relationship to study treatment. AE onset will be shown relative (in number of days) to the day of the first study treatment.

6.13.2. Serious Adverse Events

All SAEs will be listed by study arm and summarized in tabular and graphical form (using TTE methods if data warrant)

6.13.3. Adverse Events Leading to Discontinuation from Study

All AEs leading to discontinuation from study will be listed by study arm and summarized in tabular and graphical form (using time-to-event methods).

6.13.4. Deaths

All deaths within 30 days of last study treatment will be listed by study arm. Treatment emergent deaths are those deaths within 30 days of last dose of any study therapy. Early deaths are those deaths within 60 days of the first dose of study therapy.

Treatment emergent and/or early deaths will be tabulated and summarized by treatment groups using tabular and graphical methods (Time-to-event methods).

6.13.5. Clinical Laboratory Tests

Safety laboratory data will include clinical chemistries, hematology and urinalysis. Safety summaries in the form of shift tables for key laboratory parameters showing the number and percentage of patients who experience changes in laboratory parameters during the course of the study (e.g. change from normal to high, based on the laboratory reference ranges) will be displayed. Also shift tables for changes in CTCAE grades will be summarized by counts and percents.

Descriptive summary statistics (mean, standard deviation, median, minimum, maximum, frequencies, and percentages, as appropriate) for laboratory values will be presented at baseline, the follow-up time points, and change from baseline for each study treatment arm

All laboratory data, values, units, normal reference range, and out-of-range flags collected in the clinical database will be included in by-patient listings for further medical review. Graphs of key parametric clinical lab tests should be presented by group (mean ± standard deviation).

6.13.6. Vital Signs

Vital signs (including temperature, respiratory rate, blood pressure, heart rate, and weight) will be presented descriptively at baseline and for each follow-up time point for each study treatment arm. The number (n), mean, standard deviation, median, range will be presented. Changes from baseline to each time point will also be summarized as well as shifts from normal to abnormal results. Missing blood pressure values will not be imputed.

All vital sign parameters will be included in by-patient listings for further medical review.

6.13.7. ECGs

Patients will be analyzed for QTc prolongation by Fridericia's adjustment to QTc. The average of the 3 replicates will be used and compared to the average of the 3 replicates done just prior to the start of the infusion. The incidence of QTc prolongation by either calculation of >30 and >60 ms will be presented. The incidence of QTc prolongation by either calculation of >480 ms post-infusion will be presented.

All ECGs will be summarized descriptively using N, mean, standard deviation, median, and range for each treatment arm at each visit ECGs are collected (see Section 13). Missing ECG values will not be imputed.

All ECG parameters will be included in by-patient listings for further medical review.

6.13.8. Other Safety Parameters

The health related QOL EORTC QLQ-C30 and the EQ-5D-dL questionnaires will be summarized for each visit performance status was assessed and as changes from the baseline assessment. Differences between treatment arms will be tested using a t-test for each time point where the data is collected.

6.13.9. Population Pharmacokinetic Analysis

Population pharmacokinetic analyses will be conducted to evaluate the effect of intrinsic and extrinsic factors on the PK of plinabulin and its active metabolite(s), if identified, in humans. Intrinsic factors such as gender, age, hepatic or renal impairment, and race and/or ethnicity and extrinsic factors such as concomitant drugs, herbal products will be assessed in relationship to drug exposure according to FDA *Guidance for Industry: Population Pharmacokinetics*.

Further details of PK analysis will be presented in the pharmacometrics analysis plan.

7. INTERIM ANALYSIS

Interim analysis is not planned for Phase 2 of the study.

8. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

None.

9. CONVENTIONS

The precision of original measurements will be maintained in summaries, when possible. Means, medians and standard deviations will be presented with an increased level of precision; means and medians will be presented to 1 more decimal place than the raw data, and the standard deviations will be presented to 2 more decimal places than the raw data.

Summaries of continuous variables that have some values recorded using approximate values (e.g., < or >) will use imputed values. The approximate values will be imputed using the closest exact value for that measurement. For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, if the round-off unit is the ones place (i.e., integers), values ≥XX.5 will be rounded up to XX+1 while values <XX.5 will be rounded down to XX.

Percentages will be based on available data and denominators will generally exclude missing values. For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the patients discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.

For AE incidence tables:

- The order of SOCs presented in tables will be according to the internationally agreed order of SOCs according to MedDRA. Within each SOC, the preferred terms will be shown in alphabetic order.
- Patients who have multiple events in the same SOC and/or preferred term will be counted only once at each level of summation (overall, by SOC, and by preferred term) in the tables. For summaries of AEs by severity, only the highest severity of AE will be counted at each level of summation (overall, by SOC, and by preferred term) in the tables. For summaries of related AEs, patients with more than 1 related AE will be counted only once at each level of summation (overall, by SOC, and by preferred term) in the tables.

10. STANDARD CALCULATIONS

Variables requiring calculation will be derived using the following formulas:

Study day – For a given date (date), study day is calculated as days since the date of first dose of study drug (firstdose):

- Study day = date – firstdose + 1, where date ≥ firstdose
- Study day = date – firstdose, where date < firstdose

Days – Durations, expressed in days between 1 date (date1) and another later date (date2), are calculated using the following formula: duration in days = (date2-date1).

Weeks – Durations, expressed in weeks between 1 date (date1) and another later date (date2), are calculated using the following formula: duration in weeks = (date2-date1)/7.

Months – Durations, expressed in months between 1 date (date1) and another later date (date2), are calculated using the following formula: duration in months = (date2-date1)/30.4.

Years – Durations, expressed in years between 1 date (date1) and another later date (date2), are calculated using the following formula: duration in years = (date2-date1)/365.25.

Minutes – Durations, expressed in minutes between 1 timepoint (time1) and another later timepoint (time2), are calculated using the following formula: duration in minutes = (time2-time1)/60.

Age – The patient's age is calculated as the number of years from the patient's date of birth to the date of randomization into the study:

Age = ([Randomization Date - Date of Birth] / 365.25).

11. IMPUTATION OF DATES

Incomplete Cancer Diagnosis

If day is missing, day will be set to 15th of the month, or date of first dose, whichever is earlier. If month and day are missing, month and day will be set to July 1st, or date of first dose, whichever is earlier.

AE

If onset date is completely missing, onset date is set to date of first dose unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.

If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of first dose, then set month and day to month and day of first dose unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.
- If year < year of first dose, then set month and day to December 31st.
- If year > year of first dose, then set month and day to January 1st.

If month and year are present and day is missing:

- If year=year of first dose and if month = month of first dose then set day to day of first dose date unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.
- If month < month of first dose then set day to last day of month
- If month > month of first dose then set day to 1st day of month
- If year < year of first dose then set day to last day of month
- If year > year of first dose then set day to 1st day of month

For all other cases, set onset date to date of first dose unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.

Concomitant Medications

If start date is completely missing: start date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to January 1.

If year and month are present and day is missing: set day to 1st day of month.

If end date is completely missing: end date will not be imputed.

If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to December 31.

If year and month are present and day is missing: set day to last day of the month.

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2011, 2009). No other imputation of missing data will be performed.

12. REFERENCES

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13. SCHEDULE OF EVENTS FOR PHASE 2

Study Assessments and Procedures Schedule for Phase 2/Cycles 1 through 4, End of Treatment, Safety Follow-up, and Early Termination Visits

Period	**Screening Period**	**Treatment Period for Phase 2/Cycle 1**										**Treatment Period for Phase 2 Cycle 2, 3 and 4**					**EOT[a]**	**Early Discontin-uation[b]**	**30 Day Safety Follow-up[c]**
Cycle Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**6**	**7**	**8**	**9**	**10**	**15**	**-1**	**1**	**2**	**3**	**8**	**Post Cycle 4 on Day 22 (+7 days)**	**(± 21 days)**	**± 7 days**
Cycle Week			**1**					**2**			**3**	**1**				**2**			
Informed consent	X																		
Inclusion/Exclusion	X																		
Demographics[d]	X																		
Medical History/ Baseline Characteristics[e]	X																		
Vital Signs[f]	X		X	X		X	X	X	X	X	X		X			X	X	X	X
ECOG Performance Status	X																		
Temperature[g]	X		X	X		X	X	X	X	X	X		X			X	X	X	X
Physical examination[h]	X		X										X						
Body weight	X		X	X		X							X				X		
12-lead ECG[i]	X		X	X													X	X	X
Hematology[j]	X		X	X		X	X	X	X	X	X		X			X	X	X	X
Serum Chemistry[j]	X		X										X			X	X		
PT, INR, PTT[k]	X																		
Exploratory Biomarker analysis CD34+[l]	X			X		X		X					X[m]						

Urinalysis[k]	X																		
Hepatitis B/C testing[n]	X																		
HIV[k]	X																		
Pregnancy test[o]	X																		
Randomization			X																
PK sample collection[p]			X	X															
Disease progression evaluation[q]		Assessments of disease progression will be performed in accordance with standard medical practice per institution standard															X		
Docetaxel Pre-Medication		X[r]	X[r]	X[r]								X[r]	X[r]	X[r]					
Docetaxel treatment			X										X						
Plinabulin [s]			X										X						
Pegfilgrastim [s]				X										X					
Bone Pain Inventory Short Form[t]	X		X[u]	X[u]	X		X		X				X[v]				X		
Health-related QoL EORTC QLQ-C30 and EQ-5D-5L questionnaire[w]			X										X				X		
Concomitant medications[x]	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Adverse events[y]	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X

Abbreviations: ECG = electrocardiogram, EORTC = European Organization for Research and Treatment of Cancer, HIV = human immunodeficiency virus, QoL = Quality of Life.

a. EOT is defined as the last assessment for the protocol-specified treatment post cycle 4 (Day 22 [+ 7 days]) of the study for an individual patient.
b. If a patient discontinues the study, procedures should be performed within 21 days of the last dose of study drug.
c. All patients, (including patients who withdraw from the study early), will complete a safety follow-up visit 30 (+7) days after the last dose. Follow-up visits will be required to monitor for ongoing treatment-related adverse events. All patients experiencing drug-related toxicities of Grade ≥ 2 at the End of Treatment visit should be followed-up at least monthly until the adverse event(s) resolves to Grade ≤ 1, the event is considered to be chronic or the patient receives other anti-cancer therapy. The method of follow-up assessment will be at the Investigator's discretion (for example, patient site visit or telephone call). All deaths which occur within 30 days of study drug administration regardless of relationship to the study drug must be reported the Sponsor immediately and within 24 hours of becoming aware of the event.
d. Demographic data will include gender, date of birth (or age), and race/ethnicity.
e. Background characteristics will include a history of disease and current disease status, bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies.

f. Patients must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure is assessed. If the patient is unable to be in the supine position, the patient should be in the most recumbent position possible. The position selected for a patient, the same arm, and same blood pressure cuff should be kept the same throughout the study.
Two methods will be used to collect blood pressure.
Method 1 in Phase 2, Cycle 1 Day 1 ONLY, using blood pressure devices provided by the sponsor (SpaceLabs 90217 ambulatory blood pressure monitor):
- Day 1 (Arm 1): Blood pressure and heart rate will be measured semi-continuously starting at 15 minutes after completion of docetaxel infusion, and at every 15 minutes thereafter for 4.5 hours.
- Day 1 (Arms 2 to 4): Blood pressure and heart rate will be measured semi-continuously starting at 15 minutes before plinabulin infusion (15 minutes after completion of docetaxel infusion), and at every 15 minutes thereafter for 4.5 hours after start of infusion with plinabulin.

Method 2 in Phase 2 in Cycles 1, 2, 3, and 4 as follows:
A standard cuff will be used to measure blood pressure (heart rate will also be measured):
- Cycle 1 (Arms 1 to 4): At screening, Day 1 (pre-docetaxel), Days 2, 6, 7, 8, 9, 10, and 15 (once, prior to blood draw).
- Cycles 2 to 4 (Arm 1): Day 1 pre-docetaxel dose, and on Day 8 prior to blood draw
- Cycles 2 to 4 (Arms 2 to 4): On Day 1 at pre-dose, 30 min, 1 hour, 2 hours post-infusion with plinabulin, and on Day 8

g. Temperature is to be taken every time a blood draw is taken for neutrophil count and can be taken orally or in the ear; however, the same method (ear or oral) should be used throughout the study for each patient; thus if the ear method was used the first time for a given patient, the ear method should be used throughout the study for that patient.

h. Height (cm) will be measured at screening.

i. A single 12-lead ECG will be performed at screening, EOT, Early Discontinuation and 30 Day Safety Follow-Up. All other ECGs will be performed in triplicate. In Cycle 1 Day 1, ECG will be collected before docetaxel infusion, immediately before plinabulin infusion, 5-minutes before end of plinabulin infusion, 30 minutes and 4.5 hours after start of infusion with plinabulin. In Cycle 1 Day 2, ECG will be performed in triplicate prior to the blood draws on Day 2 in Arms 2 to 4. For Arm 1, the triplicate ECGs will not be performed.

j. Laboratory test samples (hematology and serum chemistry) will be collected and sent to the protocol central laboratory. Safety laboratory tests are required prior to treatment on Day 1 of each cycle and can be collected by a local laboratory and will be used to determine docetaxel dosing; however, all other safety (e.g. protocol specified) blood samples as per the schedule assessments and procedure table must also be obtained for central laboratory assessment. In addition a central laboratory blood draw needs to be taken on the day of dosing on Day 1 of each cycle, prior to the docetaxel dosing. Neutrophils are to be collected on time points as indicated in this schedule; neutrophils must be collected at pre-dose on day 1 of each cycle. During Cycle 1, neutrophils count will be assessed at baseline (prior to Cycle 1 docetaxel dose), pre-dose on Day 1 and on Days 2, 6, 7, 8, 9, 10, and 15.

k. Analyzed at a central laboratory.

l. CD34+ will be analyzed using FACS via a central laboratory.

m. Samples for CD34+ analysis to be collected at Day 1 Cycle 2 only. Do not collect at cycle 3 and 4 visits.

n. Hepatitis B surface antigen reactive, hepatitis B core antibody, hepatitis B surface antibody, and hepatitis C antibodies

o. Pregnancy tests will be done using urine samples in women of childbearing potential. Subject must have a negative urine pregnancy test documented within the 24-hour period prior to the first infusion. Confirm with serum testing (central laboratory) if urine sample is positive.

p. Plasma samples (5 mL each) for plinabulin and docetaxel PK. All patients will be sampled for PK via a central laboratory. For PK collection schedule refer to Tables 13 and 14 of the Protocol. During the Phase 2 open label portion of the study patients randomized to pegfilgrastim will not have samples collected for plinabulin PK analysis.

q. Investigator opinion of progression (yes/no) at End of Treatment (EOT) recorded in CRF. For example if the patient completes 2 cycles of docetaxel and study drug, and in the opinion of the investigator per institutional practice the cancer is growing and a new treatment is required, then the EOT evaluation will be performed as specified, and the "disease progression" will be scored as "yes." As an another example, if after four cycles of docetaxel and study drug, the cancer is stable or responding, and the patient receives further docetaxel, then the EOT evaluation will be completed as specified, and the "disease progression" will be scored as "no.".

r. Docetaxel infusion: 75 mg/m^2 docetaxel will be administered via IV infusion over 1 hour on Day 1 of each cycle. All patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (e.g., 8 mg bid) for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (refer to Taxotere® Package Insert).

s. Cycles 1 to 4 will consist of docetaxel 75 mg/m^2 administered by IV on Day 1 over 60 minutes (±5 minutes) each 21 day cycle. Patients will get a single dose of plinabulin intravenously over 30 minutes (± 5 minutes) 30 minutes after the end of the docetaxel infusion if in arms 2-4. On Day 2 of each cycle ≥ 24 hours after completing chemotherapy, patients will receive a single dose of pegfilgrastim (6 mg) if in arm 1.
t. The bone pain questionnaire should be completed prior to docetaxel infusion and at the site if possible, if not the questionnaire needs to be returned to the site at the next scheduled visit.
u. Bone pain questionnaire to be completed prior to pegfilgrastim and plinabulin pre dose, Cycle 1
v. Bone pain questionnaire to be collected at Cycle 2: Pre-dose Day 1, only. Do not collect at Cycle 3 and 4 visits.
w. Health-related QoL questionnaire evaluated with EORTC QLQ-C30 and EQ 5D-5L will be collected prior to docetaxel infusion on Day 1 of each cycle (Protocol, Appendices A and D).
x. All concomitant medicines (dose, schedule, and duration of treatment) and in particular analgesics as well as antibiotics should be entered in the eCRF.
y. All hospitalizations should be entered in the eCRF.

14. APPENDICES

14.1. List of Tables, Listings and Figures for Phase 2 Data

Index	Listings	Tables
Tier 1		
1	Listing of Demographic Characteristics	Summary of Demographic Characteristics
2	Listing of Exposure Information	Summary of Exposure by Treatment Group
3	Listing of ECOG	Summary of ECOG by Treatment Group
4	Listing of Pregnancy Information	
5	Listing of Medical History	Summary of Significant Medical History by Treatment Group
6	Listing of Concomitant Medications	
7	Listing of Adverse Events	High Level Summary of Adverse Events by Treatment Group
		Summary of AE by SOC and PT – by Treatment Group – Number of Patients and Number of AE
		Summary of AE by SOC and PT – AE Grade – By Treatment Group– Number of Patients and Number of AE
		Summary of AE by SOC and PT – Serious – By Treatment Group– Number of Patients and Number of AE
8	Listing of Deaths	
9a	Listing of DSN data	Table of the Analysis of DSN
9b	Listing of DMN data	Table of the Analysis of DMN
10	Listing of Vital Signs	Summary and Analysis of Blood Pressure Data
11	Listing of Patient Excluded from any Efficacy Analysis	

PK/PD Tables, Figures and Listings are included in the pharmacometrics analysis plan.

Index	Listings	Tables
Tier 2		
1	Listing of Disposition Data and Discontinued Patients	Summary of Disposition by Treatment Group
2	Listing of Protocol Deviations	
3	Listing of Demographic Characteristics	Summary of Demographic Characteristics
4	Listing of Exposure Information	Summary of Exposure by Treatment Group
5	Listing of ECOG	Summary of ECOG by Treatment Group
6	Listing of Pregnancy Information	
7	Listing of HIV Information	
8	Listing of Hepatitis B/C Information	
9	Listing of Medical History	Summary of Significant Medical History by Treatment Group
10	Listing of PT, INR, PTT	Summary Statistics for PT, INR, PTT by Treatment Group
11	Listing of Urinalysis Results	
12	Listing of Concomitant Medications	
13	Listing of Adverse Events	High Level Summary of Adverse Events by Treatment Group
		Summary of AE by SOC and PT – by Treatment Group – Number of Patients and Number of AE
		Summary of AE by SOC and PT – AE Grade – By Treatment Group– Number of Patients and Number of AE
		Summary of AE by SOC and PT – Serious – By Treatment Group– Number of Patients and Number of AE
14	Listing of Deaths	
15	Listing of Patients with Serious and Significant Adverse Events	
16a	Listing of DSN data	Table of the Analysis of DSN
16b	Listing of DMN data	Table of the Analysis of DMN
17	Listing of Vital Signs	Summary and Analysis of Blood Pressure Data
18	Listing of Physical Examination Results	Summary of Changes in Physical Examinations by Visit and Treatment Group
19	Listing of Laboratory Results	Summary of Laboratory Results by Visit and Treatment Group
		Summary of Changes from Baseline in Laboratory Results by Visit and Treatment Group

continued

Index	Listings	Tables
Tier 2		
20	Listing of Abnormal Laboratory Values	
21	Listing of Laboratory Results for Patients with Grades 3 and 4	Summary of Change in Grades from Baseline by Visit and Treatment Group
22	Listing of CD34 Results	Summary of CD34 Results by Treatment Group
		Summary of CD34 Results changes from Baseline by Treatment Group
23	Listing of Bone Pain Data	Summary of Bone Pain Data – Categorical Yes/No by Treatment Group
		Summary of Bone Pain Data – Individual Questions for Yes by Treatment Group
24	Listing of EORTC-QLQ-C30	Summary of Scored EORTC-QLQ-C30 results by Treatment Group
		Summary of Scored EORTC-QLQ-C30 Changes from Baseline Results by Treatment Group
25	Listing of EQ-5D-5L	Summary of Scored EQ-5D-5L results by Treatment Group
		Summary of Scored EQ-5D-5L Changes from Baseline results by Treatment Group

PK/PD Tables, Figures and Listings are included in the pharmacometrics analysis plan.

STATISTICAL ANALYSIS PLAN

Supplement

Study Title:	A Phase 2/3, Multicenter, Randomized, Double Blind, Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastim in Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy
Sponsor	BeyondSpring Pharmaceuticals, Inc. 28 Liberty Street, 39th Floor New York, NY 10005
Drug Product:	Plinabulin (BPI-2358)
Protocol Number:	BPI-2358-105
Phase:	Phase 2
Analysis Plan Version	Supplement Version 1.0
Analysis Plan Date	January 6, 2019
Author	Shuxin Yin, Ph.D BeyondSpring Pharmaceuticals, Inc. 28 Liberty Street, 39th Floor New York, NY 10005

STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURE PAGE

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Section **Page**

LIST OF ABBREVIATIONS

DSN	Duration of Severe Neutropenia
TEAE	TreatmentEmergent Adverse Event

1. INTRODUCTION

This document outlines the discrepancies of analysis methods between Statisitcal Analysis Plan 2.0 dated on 27 December 2017 and protocol BPI-2358-105, amendment 4 dated on 21 March 2018 and add the analyses which are indicated in protocol amendment 4 but are missing or different from SAP 2.0.

2. DESCRIPTION OF DISCREPANCIES

SAP 2.0	Protocol Amendment 4.0
The primary efficacy endpoint DSN will be analyzed by using Jonckleere-Terpstra test	The primary efficacy endpoint DSN will be analyzed by using Negative Binomial Regression (NBR) model.
Secondary efficacy endpoint is DMN and Jonckleere-Terpstra test will be used.	Secondary efficacy endpoints are PK, exposure-response and exposure-safety and they will be discussed in PAP
CD34+ will be analyzed by using analysis of variance	CD34+ will be analyzed by using repeated measures mixed linear model.
QoL related endpoints will be analyzed by using t-test	QoL related endpoints will be analyzed by using Wilcoxon rank sum test
Time to disease progression is not indicated	Time to disease progression will be analyzed by using log-rank test
Bone pain information will be displayed in listing	Incidence of bone pain will be analyzed by using NBR model
Lab parameters will be summarized in descriptive and/or shift tables	For lab parameters, continuous variables and proportions will be analyzed using exact t-tests. Other categorical data will be analyzed using non-parametric statistical methods.

3. GENERAL CONSIDERTION

All analysis in ITT and SP will be based on actual treatment regardless of assigned treatment. Durations, expressed in days between 1 date (date1) and another later date (date2), are calculated using the following formula: duration in days = (date2-date1+1).

4. EFFICACY ENDPOINTS

DSN

In addition to J-T test, the NBR model will also be used to analyze the DSN endpoint with the treatment arm as the only covariate. The method will also be used to construct point estimates and confidence intervals. The NBREG, GLM and TABSTAT procedures in Stata v11.0 or later will be used.

CD34+

CD34+ will be analyzed by using repeated measures mixed linear model. Analysis of variance is not applicable.

QoL related endpoints

Wilcoxon rank sum test or t-test is not applicable for QoL related endpoints. A repeated measure mixed linear model with the baseline value and treatment arm as covariates will be used to analyze this type of endpoints. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS version 9.4 or later will be used for the analysis.

Time to disease progression

Due to the limit of data, time to disease progression will be only listed.

Incidence of bone pain

Due to the limit of data, incidence of bone pain will be listed and plotted.

5. SAFETY ENDPOINTS

Laboratory parameters

The t-test and non-parametric statistical tests are specified in protocol amendment 4 but they are not applicable to laboratory parameters so they will not be performed.