Document Cover Page

Official 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 (Protective 1)

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Study Phase:	2/3
Sponsor:	BeyondSpring Pharmaceuticals, Inc. 28 Liberty Street, 39th Floor New York, New York 10005

Confidentiality Statement

SUMMARY OF CHANGES TO PROTOCOL BPI-2358-105

SUMMARY OF AMENDMENT 1

Changes found in Amendment 1.0 Protocol BPI-2358-105 have been made to respond to FDA's Information Request dated 12 January 2017. In addition, headers and footers were changed to reflect the amendment number and dates.

Changes to the protocol are shown as follows:

- General changes to terms, abbreviations, spelling, and formatting have been made for consistency throughout the document and are not detailed here.
- In response to FDA's first information request, protocol pages 5, 9, 37, 43 and 48 the following language was added to the Rescue Treatment sections:
  "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"
- In response to FDA's second information request, protocol pages 5, 44 and 50 the following language was revised:
  From "(with the exception of hypertension and neutropenia)",
  To language in this Amendment 1 version "(with the exception of neutropenia)".
- In response to FDA's third information request, protocol page 6 Protocol Inclusion criteria format for item 3 was corrected by exchanging bullet points for item numbers.
- The protocol title on page 1 includes the short title (Protective 1).
- The protocol title page includes "Amendment 1 17 January 2017".
- Page 45 section 11.1.2 and page 46 section 11.2 the following sentence was added:
  "Instructions for pharmacy drug preparation can be found in the study Pharmacy Manual."
- Page 64 section 12.5.2 was changed:
  From "Hepatitis B/C serologic markers and viral load",
  To "Hepatitis B/C serologic markers".

SUMMARY OF AMENDMENT 2

Changes found in Amendment 2.0 Protocol BPI-2358-105 have been made primarily to present separate analyses for Phase 2 and 3 (rather than pooled analysis of both phases). In addition, headers and footers were changed to reflect the amendment number and dates.

Changes to the protocol are shown as follows:

- General changes to terms, abbreviations, spelling, and formatting have been made for consistency throughout the document and are not detailed here.
- Specific secondary objectives for Phase 2 (related to pharmacokinetics, exposure-response relationships, and exposure-safety relationships) have been added.
- Efficacy objectives that we previously assigned as being for Phase 2 and 3 combined are now assigned to Phase 3 alone.
- Endpoint sections amended in line with changes to objectives detailed above.
- Sample size for Phase 3 increased from 130 to 150 patients; sample size rationale amended.
- Timing of plinabulin dose relative to docetaxel dose clarified.
- Definition of intent-to-treat analysis amended, such that it includes only patients that have received at least one dose of study medication (previously it included all randomized patients, regardless of whether they had received treatment or not).
- Analysis sections restructured to separate Phase 2 and 3 analyses where they were previously combined into a pooled analysis.
- Added details of type of analysis for primary endpoint.
- Section on pharmacokinetic and pharmacodynamics analyses added for Phase 2.
- Interim analyses section has been completely revised to allow stopping of the study (was previously for sample size adjustment).
- Additional pharmacokinetic sample added for Day 2 at 24 hours post-Day 1 dose in Phase 2.
- Day 2 electrocardiogram (ECG) added for Phase 2, and additional ECG time points added for Phase 3 to match those of Phase 2.
- Clarified the timing and methods for vital signs, and resolved inconsistencies in the study assessment flow charts.
- Study assessment flow charts also amended to add ECOG performance status and Day 2 pharmacokinetic samples, other minor clarifications made.
- Noted that analysis of CD34+ can only be performed in selected countries.
- In the overview section (Section 7.1), a figure presenting absolute neutrophil count nadir levels has been added.
- Clarified when central laboratory will be used for analysis.
- Throughout, amended ‘platinum therapy’ to ‘platinum-based therapy’.

SUMMARY OF AMENDMENT 3

Changes found in Amendment 3.0 Protocol BPI-2358-105 have been made primarily to change the Phase 2 portion to open label, to remove all Day 5 assessments, to change semi-continuous blood pressure and ECG monitoring from 6 hours to 4.5 hours after the start of plinabulin/placebo infusion, to reduce the time from the start of docetaxel infusion to start of plinabulin infusion to 30 minutes, and to clarify inconsistent wording.

In addition, headers and footers were changed to reflect the amendment number and dates.

Changes to the protocol are as follows:

- Phase 2 portion of the study changed to open label.
- Matching placebo removed from Phase 2 portion.
- Latin America added to list of countries (Latin America, North America, Europe, Asia Pacific, and Australia).
- Pharmacodynamic endpoint definitively identified as duration of severe neutropenia
- Quality of life and disease progression data collection added as exploratory objectives.
- All Day 5 assessments removed.
- A Day 6 assessment added for CD34+.
- In the Phase 2 portion, bone pain assessment on days 2 and 3 of Cycle 2 removed.
- In the Phase 3 portion, breast cancer eligibility changed to reflect that patients without previous chemotherapy for recurrent cancer are eligible
- For Cycles 2 to 4, serum chemistry added to Day 8.
- Body weight is now included as a separate assessment (and not as part of the physical examination) in the schedules of assessment; for Cycle 1, additional measurements have been added, on Days 2 and 6.
- Requirement for rescue kit for FN removed. If FN develops on cycle 1, blinding is broken (if Phase 3), and plinabulin patients treated with pegfilgrastim.
- Semi-continuous blood pressure and ECG collection to last 4.5 hours.
- Inclusion criterion 8 clarified to confirm prothrombin time (PT) and International Normalized Ratio (INR) should be assessed.
- Exclusion criteria 3 and 4 amended for clarity.
- Exclusion criterion 11 wording in main body amended to be consistent with synopsis wording.
- Reference to an ICON Safety Manual removed.
- Quality of life appendices updated with versions without watermarks.
- Sections 13.1.1.2 and 13.2.2.1 changed to reflect updated adverse event reporting procedures.
- IVRS removed.
- Reduced the time from the start of docetaxel infusion to start of plinabulin infusion to 30 minutes.
- Added 5-minute window to duration of docetaxel dosing.
- Clarified timing of neutrophil count, vital signs, and ECG assessments.
- Clarified in the text that CD34+, urinalysis, and height assessments are performed at screening (not at baseline).
- Added a window up to 18 days less than 1 year to exclusion criterion related to history of

myocardial infarction or ischemic heart disease within 1 year.

- Timing of follow-up made consistent throughout protocol.
- Amended instructions regarding anti-emetic prophylaxis and diarrhea.
- Pharmacokinetic sample moved from 6 hours to 4.5 hours after the start of plinabulin/placebo infusion.
- Clarified that docetaxel/pegfilgrastim will only be supplied by the Sponsor if not available at study sites.
- Language on replacement of withdrawals modified.
- References to prostate cancer removed from schedule of assessments for Phase 2.
- Reduced some duplication regarding follow-up to report of a serious adverse event in Section 13.2.2.1.
- Instructions for the preparation of prescribed doses replaced by reference to Pharmacy Manual.
- Section 'Other Statistical Issues' has been removed.
- Clarified that DSMB will review (but not perform) interim statistical analysis.
- Removed mention of sample size re-estimation from interim analysis.
- Removed some repetition in the protocol, for example text relating to rescue treatment.

SUMMARY OF AMENDMENT 4

At the time of implementation of Amendment 4.0, all patients recruited into the Phase 2 portion had completed the study under a previous version of the protocol. Therefore changes found in Amendment 4.0 that relate to the operation of the study primarily apply to the Phase 3 portion.

Changes to the protocol are as follows:

- EudraCT number added to the title page.
- IND serial number updated.
- Footers were changed to reflect the amendment number and date.
- Latin America and Australia removed and South America and Central America added to the list of investigational sites.
- Part of inclusion criterion 3 revised for Phase 3 from *"*[patients with] *advanced or metastatic NSCLC after failing platinum-based therapy*" to *"*[patients with] *advanced or metastatic NSCLC who have previously received platinum based therapy and have either disease progression, are intolerant of platinum-based therapy, or in the opinion of the investigator, would benefit from docetaxel chemotherapy*".
- For Phase 3 only, pain inventory (short version) removed and patient bone pain scale and pain medication assessment added at Days 1 to 8 for Cycle 1.
- For Phase 3, secondary objectives/endpoints separated into those to be assessed in Cycle 1 and

those to be assessed in Cycles 1 to 4.

- Mean bone pain score and change in bone pain score added as secondary objectives/endpoints for Phase 3; statistical methodology updated accordingly.
- Incidence of Grade 4 neutropenia in Cycle 1 added as a Cycle 1 secondary objective/endpoint for Phase 3; statistical methodology updated accordingly.
- Incidences of use of pegfilgrastim or filgrastim as treatment for neutropenia removed from the Phase 3 secondary objectives/endpoints .
- Area under the curve using the trapezoidal quadrature method for bone pain, from Day 1 through Day 8 in Cycle 1, proportion of patients who needed bone pain medication, and time to first use of bone pain medication added as exploratory objectives/endpoints for Phase 3; statistical methodology updated accordingly.
- Incidence of Grade 4 neutropenia on any of the Days 8 and 15 in Cycle 1 and on Day 8 in Cycles 2 to 4 moved from a secondary objective/endpoint to an exploratory objective/endpoint for Phase 3.
- For Phase 2, safety objective/endpoint to assess the "incidence, occurrence and severity of bone pain" updated to "incidences of bone pain".
- For Phase 3, safety objective/endpoint to assess the incidence, occurrence and severity of bone pain removed.
- "Systemic tolerance" amended to "safety and tolerability" in the Phase 2 and Phase 3 safety objectives/endpoints.
- Section added detailing the rationale for the assessment of bone pain.
- Updated to specify a fixed 40 mg dose as the Recommended Phase 3 Dose (RP3D) following the Phase 2 pharmacokinetic/pharmacodynamic analysis and rationale for the selection of the RP3D added.
- Definition of febrile neutropenia (FN) updated in line with CTCAE version 4.03
- A non-interventional post-treatment assessment has been added, to collect data on time to next treatment.
- Neutrophil(s) count replaced with absolute neutrophil count at first use and ANC thereafter.
- Window for the safety follow-up amended from ±7 days to ±2 days after the last dose of study drug and text added to clarify that "If, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until completion of the safety follow-up visit (in this instance, the safety follow-up visit will be Cycle 4 Day 21)".
- Exclusion Criterion 17 updated to include specific serology testing. Serology tests updated to include hepatitis C antibody, hepatitis B surface antigen (HBsAg), and hepatitis B surface antibody (anti-HBs).
- Clarified that hepatitis serology can be performed by local laboratory or by the central laboratory if local testing is not available.
- "Should" replaced with "must" in the following statement: "If a patient was originally assigned to the pegfilgrastim arm, patients should be treated at a lower dose of docetaxel, or taken off study at the discretion of the investigator".

- Table 3 updated to add ±5 minute window for the timing of plinabulin/placebo matching plinabulin in relation to the end of the docetaxel infusion
- Removal of the requirement for vital signs to be checked every 15 minutes during docetaxel infusion.
- Updated to state that all patients **must** be pre-medicated with oral corticosteroids (previously should be pre-medicated)
- Aprepitant added as an acceptable prophylactic anti-emetic.
- Tropisetron added as an acceptable substitute 5HT3 receptor agonist.
- Text relating to hematopoietic growth factors or transfusion and the initiation of hematological support updated for clarity.
- Text to state that "Milk and milk products should be avoided, and other appropriate dietary interventions should be advised to patients" removed.
- Table 4 (Dose Modifications for Docetaxel): Action for AST, ALT and AP abnormalities updated from "reduce docetaxel by 20%" to "withhold docetaxel until the abnormality returns toward normal and then resume at 55 mg/m^2" .
- "X" added to Day 1 for pregnancy text row in Table 7.
- "X" added to Screening for disease status evaluation row in Table 7.
- In Phase 3, all patients who discontinue will complete the End of Treatment assessments; Early Discontinuation visit removed from Table 7 and any references to an early discontinuation visit for Phase 3 removed from text.
- Definition of End of Treatment revised to "the last assessment for the protocol-specified treatment post Cycle **X** (Day 22 [+ 7 days]) of the study **for an individual patient, regardless at what time the patient discontinues the study (changes shown in bold).**
- Updated to state that confirmatory serum pregnancy testing can be performed by a local or central laboratory and that additional testing may be performed at the discretion of the investigator.
- Added that HIV testing is at the discretion of the investigator and if performed the test will be conducted at the local site.
- Added that "assessments for UDP glucuronosyltransferase (UGT) 1A1 genotyping and total bilirubin, conjugated bilirubin, and unconjugated bilirubin may be performed at the discretion of the investigator".
- Added that "Disease progression or deterioration of the malignancy under study (including new sites of metastasis due to disease progression) will be recorded as part of the subject's disease status and should not be reported as an AE/SAE".
- Added that "The sponsor will collect all deaths on study regardless of its potential relationship to disease progression and up to 30 days after the last dose of plinabulin on an SAE form".
- Country specific fax numbers for the reporting of serious adverse events (SAEs) removed.
- Additional clinical laboratory test parameters added (MCV, MCH, MCHC, glucose, creatine phosphokinase).
- ECG assessment changed from 30 (+ 15) minutes after the start of the infusion to 60 (± 5) minutes after the start of the infusion for Phase 3.

- Updated Section 11.8 (Pharmacokinetics) to present docetaxel sampling before plinabulin sampling; numbering for Tables 13 and 14 switched.
- Possible temperature reading locations updated to include axillary.
- Clarification regarding when to report an elevated temperature as an adverse event added.
- Removed specific details of the vendor to be used for PK/PD analyses.
- Sections of text providing an overview of the analyses removed and full details of statistical analyses added after each of the study endpoints.
- Clarified that the PK analysis set will include all patients who had pre-dose sample collection and at least 1 PK sample collected postdose.
- Confirmed that the plinabulin and docetaxel PK sampling schedules for Phase 2 will be followed for Phase 3.
- Pharmacokinetic and pharmacodynamic analyses updated.
- Appendix A (EORTC QLQ-C30), Appendix B (Patient Bone Inventory [Short Form]) and Appendix D (EQ-5D-5L) removed.
- Other minor edits were made to correct typographical errors, enhance the readability of the text, to provide further clarity, to update minor inconsistencies, and to update formatting.

SUMMARY OF AMENDMENT 5

At the time of Amendment 5.0, a total of 105 patients had been enrolled in the Phase 3 portion under Amendment 4.0 and 55 patients had completed the Phase 2 portion, under Amendments 1.0, 2.0 and 3.0.

All changes to objectives are reflected throughout the protocol in the appropriate sections, including the statistical endpoints sections.

Changes to the protocol are as follows. In addition, minor edits have been made for internal consistency and clarity.

- The Phase 2 exploratory objectives were updated to include:
  - For selected countries only: to investigate the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8.
- The Phase 3 primary objective was amended from "[patients with]… *advanced or metastatic non-small cell lung cancer (NSCLC) who have previously received platinum based therapy and have either disease progression, are intolerant of platinum-based therapy, or in the opinion of the investigator, would benefit from docetaxel chemotherapy…*" to "[patients with] …***locally** advanced or metastatic non small cell lung cancer (NSCLC) **after platinum therapy failure**…*"
- The Phase 3 secondary and exploratory objectives were amended following preliminary results from the Phase 2 portion of the study, to include new objectives regarding healthcare utilization and to re-order for hierarchical analysis.

- Secondary efficacy objectives were amended to evaluate:
  1. Change in platelet count from baseline in Cycle 1
  2. The proportion of patients with neutrophil-to-lymphocyte ratio > 5 during Cycle 1
  3. Area under the concentration-time curve using the trapezoidal quadrature method for bone pain, from Day 1 through Day 8 (pegfilgrastim will be administered on Day 2) in Cycle 1, based on the pain score from the patient bone pain scale
  4. Change in estimated mean bone pain in Cycle 1
  5. The proportion of patients with thrombocytopenia (all grade) in Cycles 1 to 4
- Exploratory efficacy objectives (Cycle 1) were amended to evaluate:
  - The proportion of patients in Cycle 1 with:
    - Thrombocytopenia (all grade)
    - Grade 4 neutropenia (absolute neutrophil count [ANC] < 0.5×10^9/L)
    - Grade 3 neutropenia (ANC < 1×10^9/L)
    - Grade 3 (ANC < 1×10^9/L) and Grade 4 neutropenia (ANC < 0.5×10^9/L)
    - Bands > 0 after Day 7 through Day 15
    - Promyelocytes plus myelocytes > 0 after Day 7 through Day 15
    - Lymphocyte-to-monocyte ratio < 3.2 after Day 7 through Day 15
    - Platelet-to-lymphocyte ratio > 200 after Day 7 through Day 15
    - At least 1 day of bone pain
    - At least 2 days of bone pain
    - At least 3 days of bone pain
    - At least 4 days of bone pain
    - At least 5 days of bone pain
    - At least 6 days of bone pain
    - At least 7 days of bone pain
    - At least 8 days of bone pain
  - The proportion of patients who needed bone pain medication in Cycle 1
  - The time (in days) to first use of bone pain medication between the treatment groups

- Duration of severe neutropenia (DSN) in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure
- To assess DSN in Cycle 1 in patients with hormone refractory prostate cancer (HRPC)
- To assess DSN in Cycle 1 in patients with advanced or metastatic breast cancer who have failed < 5 prior lines of chemotherapy
- DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure or HRPC
- Platelet count at least 30% change from baseline at any time during Cycle 1
- ANC nadir during Cycle 1
- For selected countries only: to investigate the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF alpha, IL-2, FLT-3 ligand, and IL-8.

– Exploratory efficacy objectives (Cycles 1 to 4) were amended to evaluate:
  - The proportion of patients in Cycles 1 to 4 with:
    - Febrile neutropenia (FN) (ANC <1.0 × 109/L AND a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour).
    - Grade 4 neutropenia (ANC < 0.5 × 109/L).
  - The following healthcare utilization objectives:
    - Incidence of 30-day rehospitalizations - all cause.
    - Incidence of all cause hospitalizations
    - Duration of all cause hospitalizations
    - Incidence of all cause emergency room (ER) visits
    - Incidence of all cause intensive care unit (ICU) stays
    - Duration of all cause ICU stays
    - Incidence of all cause docetaxel dose delay (≥7 days), dose reduction (≤85%), or dose discontinuation
    - Incidence of platelet transfusions
    - Incidence of antibiotics use
  - Data on disease progression
  - Health-related quality of life questionnaire evaluated with European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L

- It was clarified that cytokine panel testing will be done using plasma samples collected at the pharmacokinetic (PK) time points and that reconsenting of the patients will be required before analysis is performed.
- It was specified that unused samples (urine/serum plasma) will also be saved for future potential biomarker research, with patient consent.
- Timings were included for the new endpoints associated with new objectives (eg healthcare utilization).
- The following statement was added: "*In order to facilitate balanced treatment arms with respect to cancer type, once either arm reaches at least 1/3 (of total) of patients with that cancer type, it will be closed to that cancer type and enrollment will continue for patients with the other cancer types, up to the planned maximum number of patients.* "
- It was clarified throughout the protocol that patients who withdraw for progressive disease and who will continue to another chemotherapy regimen will complete the end of treatment (EOT) visit at Cycle X Day 21. They then continue to another chemotherapy regimen and do not need to have the safety follow-up visit (where X is the last cycle prior to progression, and is 4 or less). Additionally, if, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until completion of the EOT visit (in this instance, the EOT visit will be Cycle 4 Day 21).
- It was clarified throughout the protocol that patients without progressive disease at the EOT visit will undergo a follow-up visit every 2 months until the occurrence of either disease progression or death. The visits may be conducted per telephone or other means.
- Inclusion Criterion 7 was amended to include a footnote as follows "*Results are from the central laboratory. Local laboratory results may be accepted on a case by case basis after discussion with the Medical Monitor, however in this case central laboratories must also be taken within the screening time window*"
- Exclusion Criterion 17 was revised from "*Active Hepatitis B virus (HBV) infection which requires antiviral treatment or the patient has detectable Hepatitis B surface Antigen (HBsAg)* "*...*to "*Active Hepatitis B virus (HBV) infection which requires antiviral treatment. Patients with detectable Hepatitis B surface Antigen (HBsAg) may be eligible provided the patient has a negative viral load. Patients with a positive HBsAg must have a negative viral load before each chemotherapy administration...* "
- It was clarified throughout the protocol that new NSAIDs are prohibited but patients already receiving NSAIDs are allowed to continue taking treatment as long as the dose remains stable.
- It was clarified that if a patient develops a positive viral load during the study, chemotherapy should be held for a maximum of 21 days. If the viral load returns to zero treatment can be restarted, otherwise the patient should be withdrawn from the study.

- Throughout the protocol, the following text was added to clarify the PK analysis for plinabulin "*Plinabulin PK will be characterized using the population PK approach. Population PK parameter estimates, and individual PK parameters, including AUC and C_{max} will be summarized*."
- It was clarified that the interim analysis will be performed by an independent statistician.
- The requirement to document vital signs (position selected, arm, and blood pressure cuff used) and temperature location on the vital signs CRF was removed.
- A ± 15 minute window was included for the standard cuff vital sign measurements.
- The use of hospitalization or prolongation of hospitalization as an indicator of the seriousness of the AE was clarified.
- Additional references were included to support the information provided.

SUMMARY OF AMENDMENT 6

- The formula for calculating the propotion of relative dose intensity =< 85% was clarified
- Calculation method for EORTC QLQ C30 was clarified
- Additional anyalysis for EORTC QLQ C30 using EORTC QLQ C30 method was added
- Calculation method for EQ 5D-5L 'Your Health Today' was clarified
- Calculation of EQ 5D-5L utitility measures was added
- Statistical method for bone pain measurements was updated
- Statistical method for QoL endpoints was updated
- DSN definition is updated
- Statistical method for tesing difference of proportions is changed to be Barnard's test
- Definition of Grade 3 Neutrpenia is updated
- Imputation rule of missing data of primary and key secondary efficacy endpoints is changed
- Definition of intent-to-treat analysis set and safety analysis set is changed
- Statistical method of laboratory parameters is updated
- Shift table for vital signs parameters is removed

SUMMARY OF AMENDMENT 7

Changes found in Protocol BPI-2358-105 Amendment 7.0 have been made based on the EOP2 Meeting recommendations, the Agency recommended that the Sponsor capture safety data for a minimum of year one and ideally up to five years from Study 105. The Agency recommended that the Sponsor consider follow-up telephone calls and queries of treating physicians or designee health care provider to ascertain safety information on secondary malignancies or tumor progression as well as other potential safety findings/concerns. Subjects who receive at least one dose of plinabulin or pegfilgrastim will be followed up.

In addition, headers and footers were changed to reflect the amendment number and dates.

- Changes to the protocol are as follows:Section 11.8.1 Long-term Safety Follow-up (up to 5 years)
- Safety endpoints to be collected include;
  - Disease progression
  - Disease relapse (local, regional or distant)
  - Second primary tumors
  - Health status check, including autoimmune and hematological disorders
  - Any further anti-cancer treatment information
  - Reporting of medical problems, including information on unexpected hospitalizations and medications (including SAEs)
  - Death (including autopsy report, if available)

- Table 7 (Phase 3) updated to include a column for the Post-study Long-term Safety Follow-up and Exploratory Biomarker Analysis CD34+ and Haptoglobin Assessments

- Secondary Efficacy Objectives (Cycle 1 and Cycles 1 to 4) Updated as follows:
  - To assess DSN in Cycle 1 with only mature neutrophils
  - To assess the incidence of infections in Cycles 1 to 4

- Secondary Efficacy Endpoints (Cycle 1 and Cycles 1 to 4) Updated as follows:
  - DSN in Cycle 1 with only mature neutrophils. The NBR model, on the integer number of days of severe neutropenia, will be used to analyze the DSN endpoint during the fixed time window outlined above, with the treatment arm as the only covariate. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
  - Incidence of infections in Cycles 1 to 4. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.Synopsis and Section 7.2 Phase 3 Objectives (Exploratory Efficacy Objectives, Cycle 1)

- The following Objectives were added to assess the proportion of patients in Cycle 1 with

the following:

- Grade 4 neutropenia (ANC<0.5 x10^9/L) for mature neutrophils only
- Promyelocytes, myelocytes, metamyelocytes and bands >0 after Day 7 through Day 15
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure for mature neutrophils only
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure for mature neutrophils only
- To assess DSN in Cycle 1 in patients with advanced or metastatic breast cancer who have failed < 5 prior lines of chemotherapy for mature neutrophils only
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure or HRPC for mature neutrophils only
- To assess CD34+ at Day 1 pre-dose, Day 2 pre-dose, Day 6, 7, 8, 9, 10, and 15, Day 1 Cycle 2 pre-dose

- Synopsis and Section 14.1.2 Phase 3 Endpoints
  - Exploratory Efficacy Endpopints (Cycle 1) updated to align to addition of Phase 3 Objectives above:
    - Grade 4 neutropenia (ANC<0.5 x10^9/L) for mature neutrophils only. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
    - Promyelocytes, myelocytes, metamyelocytes and bands >0 after Day 7 through Day 15. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
    - DSN in Cycle 1 with only mature neutrophils in patients with locally advanced or metastatic NSCLC after platinum failure. The analysis will be done as per the primary endpoint.
    - DSN in Cycle 1 with only mature neutrophils in patients with with HRPC. The analysis will be done as per the primary endpoint.
    - DSN in Cycle 1 with only mature neutrophils in patients with advanced or metastatic breast cancer who have failed <5 prior lines of chemotherapy. The analysis will be done as per the primary endpoint.
    - DSN in Cycle 1 with only mature neutrophils in patients with locally advanced or metastatic NSCLC after platinum failure or HRPC. The analysis will be done as per the primary endpoint.
    - CD34+ at pre-dose on Day 1, pre-dose on Day 2, Days 6, 7, 8, 9, 10, and 15 in Cycle 1, and pre-dose on Day 1 in Cycle 2. A repeated measure mixed linear model with the pre-dose on day 1 cycle 1 value and treatment arm as covariates will be used to analyze this endpoint.

- Synopsis and Section 7.2 Phase 3 Objectives (Exploratory Objectives, Cycles 1-4)
  - The following Objectives were added to assess maximum change and difference from baseline for CD34+ and haptoglobin:
    - To assess the maximum change from baseline in CD34 + counts in each treatment arm
    - To assess the maximum difference between treatment arms in CD34+ counts
    - To assess the maximum change from baseline in haptoglobin levels in each treatment arm
    - To assess the maximum difference between treatment arms in haptoglobin levels
- Synopsis and Section 14.1.2 Phase 3 Endpoints
  - Exploratory Efficacy Endpopints (Cycles 1-4) updated to align to addition of Phase 3 Objectives above:
    - Maximum change from baseline in CD34+ counts in each arm. A Wilcoxon signed-rank test will be used to analyze this endpoint. The UNIVARIATE procedure in SAS version 9.4 or later will be used for the analysis.
    - Maximum difference between treatment arms in CD34+ counts. The Wilcoxon Rank Sum test will be used to analyze this endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
    - Maximum change from baseline in haptoglobin level in each arm. A Wilcoxon signed-rank test will be used to analyze this endpoint. The UNIVARIATE procedure in SAS version 9.4 or later will be used for the analysis.
    - Maximum difference between treatment arms in haptoglobin level. The Wilcoxon Rank Sum test will be used to analyze this endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Table 12 Clinical Laboratory Tests
- Under Hematology, reticulocyte count added
- Synopsis (Pharmacokinetics) Updated language as follows:
  - Phase 2 and Phase 3: Pharmacokinetic parameters (e.g., Cmax, time to reach Cmax [Tmax], AUC0-t, AUC0-∞, terminal half-life [t1/2], volume of distribution in the terminal elimination phase [Vz], and clearance [CL]) will be derived, where calculable, from plasma concentration-time data of plinabulin and docetaxel. Plinabulin concentration-time data will be pooled with data from other studies in a population PK analysis. Details of this analyses will be summarized in the Pharmacometrics Analysis Plan and may be reported outside of the main clinical study report.
- Pharmacokinetic Analysis Set Updated as follows:
  - All patients who received at least 1 dose of plinabulin or docetaxel and had at least 1

PK sample collected postdose 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.

- Synopsis: South America and Central America deleted from Number of Sites
- Section 6.2.2 Rationale Updated as follows:
    - Total ANC is comprised of mature and immature neutrophils. Immature neutrophils have reduced functional capacity compared to mature neutrophils to enable optimal innate immunity. Compared to mature neutrophils, immature neutrophils exert reduced ROS production leading to reduced microbicidal activity, reduced phagocytic activity, reduced granularity, reduced ability to create NETs (Mackay G et al, Frontiers in Immunology 2019; Mortaz E et al Frontiers in Immunology 2018). Therefore an additional analysis will be made with mature neutrophils only.
- Section 10.5 Dose Interruptions and Modifications updated to reflect Long Term Safety Follow up as follows:
    - Patients included after November 2019 will have a long term FU approximately every 6 months up to 5 years to monitor long term safety of plinabulin. These visits may be conducted per telephone or other means. Updated References added
- Updated References added

1. PROTOCOL SYNOPSIS

Compound No.: BPI-2358 (Formerly NPI-2358)

Name of Active Ingredient(s): plinabulin

Study Protocol 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

Number of Sites

Investigational sites (to be determined) in North America, , Europe, or Asia Pacific.

Study Period and Phase of Development

Patients will be on study for approximately 5 months, including screening, on treatment, and follow-up.

Phase 2/3

Objectives

Phase 2 (Open Label) Objectives

Plinabulin pharmacokinetic (PK) and pharmacodynamic (PD) assessments will be made to enable a PK/PD analysis.

Primary objective:

- To establish the Recommended Phase 3 Dose (RP3D) based on PK/PD analysis.

Primary efficacy pharmacodynamic (PD) objective:

- To assess duration of severe neutropenia (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). Severe (Grade 4) neutropenia is an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L. ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15 (pre-dose on dosing days; times equivalent to pre-dose on other days)

Primary Safety Pharmacodynamic 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).

Secondary Objectives

- To characterize the pharmacokinetic profile of plinabulin and docetaxel
- To characterize the exposure-response relationships between measures of plinabulin exposure and the pharmacodynamic endpoint DSN
- To characterize the exposure-safety relationships between measures of plinabulin exposure and safety events of interest

Exploratory Objectives:

- To assess CD34+ at screening, and on Days 2, 6, 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
- For selected countries only: to investigate the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8

Safety Objectives

- Incidence, occurrence, and severity of adverse events (AEs)/serious adverse events (SAEs)
- Incidences of bone pain
- Safety and tolerability (physical examination and safety laboratory assessments)

Phase 3 (Double Blind) Objectives

Primary Efficacy Objective (Cycle 1):

- To assess DSN in treatment Cycle 1 in patients with advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy; locally advanced or metastatic non small cell lung cancer (NSCLC) after platinum therapy failure; or hormone refractory (androgen independent) metastatic prostate cancer (HRPC) treated with docetaxel (75 mg/m^2) + plinabulin (40 mg) (Arm 2) versus docetaxel (75 mg/m^2) + pegfilgrastim (6 mg) (Arm 1). ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15. Blood draws for ANC will be taken approximately the same time as the time of the pre-dose sample on Day 1, and will be taken by preference in the morning. DSN should be calculated as the number of consecutive days from the first day when a patient's ANC is below 0.5 x l09/L until the patient reaches an ANC> 0.5 x 109/L, in Cycle 1. For patients who do not experience any severe neutropenia in Cycle 1, the DSN is set to 0. For patient's experiencing several episodes, the number of days of DSN will be summed up.

Secondary Efficacy Objectives (Cycle 1 and Cycles 1 to 4):

- To assess DSN in Cycle 1 with only mature neutrophils.
- Platelet count in Cycle 1: maximum decrease from baseline (prior to Cycle 1 docetaxel dose)
- Proportion of patients with neutrophil-to-lymphocyte ratio (NLR) > 5 after Day 7 through Day 15 in Cycle 1
- Area under the concentration-time curve (AUC) using the trapezoidal quadrature method for bone pain, from Day 1 through Day 8 (pegfilgrastim will be administered on Day 2) in Cycle 1, based on the pain score from the patient bone pain scale
- Change in estimated mean bone pain score from pre-dose Day 1 through Day 8 in Cycle 1
- Proportion of patients with thrombocytopenia (all grade) in Cycles 1 to 4
- To assess the incidence of infections in Cycles 1 to 4

Exploratory Efficacy Objectives (Cycle 1):

- To evaluate the proportion of patients in Cycle 1 with:
  - Thrombocytopenia (all grade)
  - Grade 4 neutropenia (ANC < 0.5 × 10^9/L)
  - Grade 4 neutropenia (ANC<0.5 x10^9/L) for mature neutrophils
  - Grade 3 neutropenia (ANC < 1 × 10^9/L)
  - Grade 3 (ANC < 1 × 10^9/L) and Grade 4 neutropenia (ANC < 0.5 × 10^9/L)
  - Bands > 0 after Day 7 through Day 15
  - Promyelocytes plus myelocytes > 0 after Day 7 through Day 15
  - Promyelocytes, myelocytes, metamyelocytes and bands >0 after Day 7 through Day 15Lymphocyte-to-monocyte ratio (LMR) < 3.2 after Day 7 through Day 15
  - Platelet-to-lymphocyte ratio (PLR) > 200 after Day 7 through Day 15
  - At least 1 day of bone pain
  - At least 2 days of bone pain
  - At least 3 days of bone pain
  - At least 4 days of bone pain
  - At least 5 days of bone pain

- At least 6 days of bone pain
- At least 7 days of bone pain
- At least 8 days of bone pain

- To compare the proportion of patients who needed bone pain medication (defined as any medication reported on pain medication assessment from Day 1 through Day 8) in Cycle 1
- To compare the time (in days) to first use of bone pain medication between the treatment groups
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure for mature neutrophils only
- To assess DSN in Cycle 1 in patients with HRPC
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure for mature neutrophils only
- To assess DSN in Cycle 1 in patients with advanced or metastatic breast cancer who have failed < 5 prior lines of chemotherapy
- To assess DSN in Cycle 1 in patients with advanced or metastatic breast cancer who have failed < 5 prior lines of chemotherapy for mature neutrophils only
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure or HRPC
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure or HRPC for mature neutrophils only
- Platelet count at least 30% change from baseline at any time during Cycle 1
- ANC nadir during Cycle 1
- To assess CD34+ at Day 1 pre-dose, Day 2 pre-dose, Day 6, 7, 8, 9, 10, and 15, Day 1 Cycle 2 pre-dose
- For selected countries only: to investigate the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8.

Exploratory Efficacy Objectives (Cycles 1 to 4):

- To evaluate the proportion of patients in Cycles 1 to 4 with:
- Febrile neutropenia (FN) (ANC $<1.0 \times 10^9$/L AND a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour).
- Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L).
- To assess the maximum change from baseline in CD34 + counts in each treatment arm
- To assess the maximum difference between treatment arms in CD34+ counts
- To assess the maximum change from baseline in haptoglobin levels in each treatment arm
- To assess the maximum difference between treatment arms in haptoglobin levels
- To evaluate the following healthcare utilization objectives:
  - Incidence of 30-day rehospitalizations - all cause
  - Incidence of all cause hospitalizations
  - Duration of all cause hospitalizations
  - Incidence of all cause emergency room (ER) visits
  - Incidence of all cause intensive care unit (ICU) stays
  - Duration of all cause ICU stays

- Incidence of all cause docetaxel dose delay (≥7 days), dose reduction (≤85%), or dose discontinuation
- Incidence of platelet transfusions
- Incidence of antibiotics use

- To collect data on disease progression
- To evaluate the following QoL objective:
  - Health-related QoL questionnaire evaluated with European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L

Safety Objectives:

- Incidence, occurrence, and severity of adverse events (AEs)/serious adverse events (SAEs)
- Safety and tolerability (physical examination and safety laboratory assessments)

Study Design

This is a multicenter, randomized study with an open label phase 2 portion and a double blind phase 3 portion. Approximately 190 patients will be enrolled in this study.

The decision to complete the Phase 2 portion of the study as open label was made to reduce the unnecessary complexities of study conduct (such as placebo infusions and injections). All patients will receive docetaxel at a dose of 75 mg/m^2.

In Phase 2, only patients with advanced or metastatic NSCLC after failing platinum-based therapy will be enrolled.

In Phase 3, patients with one of the following diagnosis will be enrolled: advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy; locally advanced or metastatic NSCLC after platinum therapy failure; or HRPC.

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

Phase 2 (Open Label):

Approximately 40 patients with advanced or metastatic NSCLC will be enrolled. Patients are randomly assigned with approximately 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)

The study will be temporarily closed to enrollment when 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 RP3D. The PK/PD analysis will be done by an independent party at the time 40 patients in Phase 2 have completed at least Cycle 1.

Phase 3 (Double Blind):

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.

A fixed dose of 40 mg has been selected as the RP3D following the Phase 2 PK/PD analysis (details of dose selection are provided in Section 6.2.3).

Approximately 150 patients are planned to be enrolled in the Phase 3 with one of the following diagnosis: advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy; locally advanced or metastatic NSCLC after platinum therapy failure; or HRPC. Each eligible patient will be stratified according to his or her tumor type (breast cancer, NSCLC or HRPC) and region (Asia, non-Asia). Patients will be randomly assigned within each stratum (diagnosis) with equal probability (1:1 ratio) or 75:75, with the arm designation and planned intervention as follows:

Arm 1: Docetaxel (75 mg/m^2) + pegfilgrastim (6 mg) + placebo matching plinabulin

Arm 2: Docetaxel (75 mg/m^2) + plinabulin (40 mg) + placebo matching pegfilgrastim

In order to facilitate balanced treatment arms with respect to cancer type, once either arm reaches at least 1/3 (of total) of patients with that cancer type, it will be closed to that cancer type and enrollment will continue for patients with the other cancer types, up to the planned maximum number of patients.

Data from all patients receiving the RP3D plinabulin dose in Phase 2 and Phase 3 will not be pooled for assessing the primary and secondary study endpoints, but analyzed separately.

Treatments Administered:

Both Phase 2 and Phase 3, Cycles 1 to 4, will consist of docetaxel 75 mg/m^2 administered by intravenous (IV) infusion on Day 1 over 60 minutes (±5 minutes) every 21 days. In the phase 2 portion, 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 get a single intravenous infusion of plinabulin at their assigned dose over 30 minutes (± 5 minutes). Thus, the wait time between end of docetaxel infusion and start of the plinabulin infusion is approximately 30 minutes. On Day 2 of each cycle, ≥24 hours after completing chemotherapy, patients assigned to pegfilgrastim (arm 1) will receive a single dose of pegfilgrastim (6 mg) (subcutaneous injection).

In the Phase 3 portion, 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 will get a single dose of plinabulin or placebo intravenously over 30 minutes (± 5 minutes). On Day 2 of each cycle, ≥24 hours after completing chemotherapy, patients will receive a single dose of pegfilgrastim (6 mg) or 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 (refer to Section 10.5) occurs during the cycle, the dosage of docetaxel may be reduced 20% in the next cycle. Only one docetaxel dose reduction is allowed (refer to Taxotere® (Prescribing Information). 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 (± 2 days) after the last dose of study drug. Patients who withdraw for progressive disease and who will continue to another chemotherapy regimen will complete the End of Treatment (EOT) visit at Cycle X Day 21. They then continue to another chemotherapy regimen and do not need to have the safety follow-up visit (where X is the last cycle prior to progression, and is 4 or less). If, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until completion of the EOT visit (in this instance, the EOT visit will be Cycle 4 Day 21). Follow-up visits will be required to monitor for ongoing treatment-related AEs. All patients experiencing drug-related toxicities of ≥ Grade 2 at the EOT 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 study drug 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.

Patients without progressive disease at the EOT visit will undergo a follow-up visit every 2 months until the occurrence of either disease progression or death. These visits may be conducted per telephone or other means.

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 screening only. CD34+ counts will be established through a fluorescence-activated cell sorting (FACS) method as described in Table 6.

Stopping Rules

During the phase 2 study if at any given cohort, 3 patients or more have Grade 4 or 5 toxicity not related to underlying disease (with the exception of neutropenia), accrual to that cohort will be halted and the study will be continued at the lower dose cohorts in phase 2 (for example if 3 patients at the 20 mg/m^2 cohort develop Gr. 4 toxicity the accrual to that cohort will be stopped and the study will continue as planned with the accrual of the two remaining open cohorts). Interactive web response system (IWRS) will be utilized to assign patients to a lower dose cohort in phase 2. Study sites will be instructed to call IWRS when a Grade 4 or 5 toxicity event occurs.

Number of Patients

Approximately 40 patients will be enrolled in Phase 2 and approximately 150 patients are planned to be enrolled in Phase 3.

Inclusion Criteria

1. At least ≥ 18 years of age (male or female) at the time of signing the informed consent form.
2. ECOG performance status of 0 or 1.
3. Patients with:
   ***Phase 2 only*:**
   - Advanced or metastatic NSCLC failing platinum-based therapy

   Phase 3 only:
   - Advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy (Note that study treatment may be the first chemotherapy treatment for advanced or metastatic cancer)
   - Locally advanced or metastatic NSCLC after platinum therapy failure
   - HRPC (Note that study treatment may be the first chemotherapy treatment).
4. Pathology confirmation of cancer is required.
5. Patients with ≥1 of the following risk factors, at the initiation of docetaxel chemotherapy, that would require neutropenia prophylaxis per National Comprehensive Cancer Network (NCCN) guidelines (version 2, 2016) Myeloid Growth Factors (refer to Appendix A):
   a. Prior chemotherapy or radiation treatment
   b. Bone marrow involvement by tumor
   c. Surgery and/or open wounds within 4 weeks of first administration of study drug
   d. Age > 65 years of age and receiving full chemotherapy dose intensity
6. Life expectancy of 3 months or more.
7. The following laboratory results assessed within 14 days prior to study drug administration:[1]
   - Hemoglobin ≥ 9 g/dL independent of transfusion or growth factor support
   - ANC ≥ 1.5 x 10^9/L independent of growth factor support
   - Serum total bilirubin ≤ 1.5 times the upper limit normal (ULN), unless the patient has a diagnosis of Gilbert's disease in which case direct bilirubin ≤ 1.5 times ULN of the direct bilirubin.
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN (≤ 1.5 x ULN if alkaline phosphatase is > 2.5 x ULN)
   - Serum creatinine ≤ 1.5 x ULN
8. Prothrombin time (PT) and International Normalized Ratio (INR) ≤ 1.5 × upper limit of normal (ULN), activated partial thromboplastin time (PTT) ≤ 1.5 × ULN, based on central laboratory results.[1]
9. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had

[1] Results are from the central laboratory. Local laboratory results may be accepted on a case by case basis after discussion with the Medical Monitor; however in this case central laboratories must also be taken within the screening time window.

any evidence of menses in the past 12 months. However, women who have been amenorrhoeic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.

- Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.
- Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner.
- For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception during the treatment period and for at least 3 months after the last dose of study drug.

Exclusion Criteria

1. History of myelogenous leukemia, myelodysplastic syndrome or concomitant sickle cell disease.
2. Received chemotherapy within 4 weeks prior to the first dose of study drug.
3. Received prior docetaxel, except adjuvant docetaxel given > 1 year prior to first dose of study drug.
4. Phase 3 only: Received ≥ 5 lines of cytotoxic chemotherapy for advanced or metastatic breast cancer (adjuvant chemotherapy will count as one line of chemotherapy, and any hormonal or biological, non-conjugate therapy [e.g., trastuzumab] will not count as a line of therapy).
5. Current use of strong cytochrome P450 (CYP) 3A4 inhibitors, within 3 days of the first administration of study drug, and 7 days after treatment with taxanes OR requires use of strong CYP3A4 inhibitors (refer to Section 10.6.2).
6. Received an investigational agent or tumor vaccine within 2 weeks before the first dose of study drug; patients must have recovered from toxicity of prior treatment and have no > Grade 1 treatment emergent AEs.
7. Receiving any concurrent anticancer therapies.
8. Received a prior bone marrow or stem cell transplant.
9. Has a co-existing active infection or received systemic anti–infective treatment within 72 hours before the first dose of study drug.
10. Prior radiation therapy within the 4 weeks before the first dose of study drug.
11. Prior use of pegfilgrastim or filgrastim within 4 weeks before the first dose of study drug.
12. Presence of any serious or uncontrolled illness including, but not limited to: uncontrolled diabetes, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, uncontrolled arterial thrombosis, symptomatic pulmonary embolism, or psychiatric illness that would limit compliance with study requirements, or any other conditions that would preclude the patient from study treatment as per the discretion of the Investigator.
13. Significant cardiovascular history:
    - History of myocardial infarction or ischemic heart disease within 1 year (within a window of up to 18 days less than 1 year) before first study drug administration;
    - Uncontrolled arrhythmia;
    - History of congenital QT prolongation;
    - Electrocardiogram (ECG) findings consistent with active ischemic heart disease;
    - New York Heart Association Class III or IV cardiac disease;
    - Uncontrolled hypertension: blood pressure consistently >150 mm Hg systolic and > 100 mm Hg diastolic in spite of antihypertensive medication.

14. History of hemorrhagic diarrhea, inflammatory bowel disease, or active uncontrolled peptic ulcer disease. (Concomitant therapy with ranitidine or its equivalent and/or omeprazole or its equivalent is acceptable). History of ileus or other significant gastrointestinal disorder known to predispose to ileus or chronic bowel hypomotility.
15. Any other malignancy requiring active therapy.
16. Known human immunodeficiency virus (HIV) seropositivity.
17. Active Hepatitis B virus (HBV) infection which requires antiviral treatment. Patients with detectable Hepatitis B surface Antigen (HBsAg) may be eligible provided the patient has a negative viral load. Patients with a positive HBsAg must have a negative viral load before each chemotherapy administration. Hepatitis B surface antibody (anti HBs) without detectable HBsAg does NOT exclude patients from the study. Hepatitis C infection (Hepatitis C antibody reactive) which requires treatment also excludes patients from the study.
18. Female subject who is pregnant or lactating.
19. Unwilling or unable to comply with procedures required in this protocol

Study Treatments

Phase 2 (approximately 10 patients per arm with advanced or metastatic NSCLC after failing platinum-based therapy):

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)

Phase 3 (a planned 75 patients per arm with advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy; locally advanced or metastatic NSCLC after platinum therapy failure; or HRPC):

Arm 1: Docetaxel (75 mg/m^2) + pegfilgrastim (6 mg) + placebo matching plinabulin

Arm 2: Docetaxel (75 mg/m^2) + plinabulin (40 mg) + placebo matching pegfilgrastim

All patients must be pre-medicated 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® (Prescribing Information)). For hormone-refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the docetaxel infusion (refer to Taxotere® (Prescribing Information)).

Rescue Treatment:

Patients who experience an FN event in Cycle 1 should be discussed with the medical monitor. The blinding will be broken (if Phase 3), and patients assigned to plinabulin will receive pegfilgrastim in subsequent cycles. If a patient was originally assigned to the pegfilgrastim arm, patients must 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 (refer to Section 10.6.1). If a patient is hospitalized, the procedure for reporting Serious Adverse Events (Section 13.2) should also be followed.

Duration of Treatment

Patients will receive treatment with study drug for up to 4 cycles in this study, a treatment cycle is 21 days; thereafter, patients may continue receiving docetaxel and pegfilgrastim at the Investigator's discretion. After completion of 4 cycles, patients will complete a safety follow-up visit 30 days (± 2 days) after the last dose of study drug (see Table 6 and Table 7 Study Assessments and Procedures Schedule). If, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until completion of the EOT visit (in this instance, the EOT visit will be Cycle 4 Day 21). Patients with progressive disease requiring another treatment will also complete the EOT visit at Cycle X Day 21

and can then continue on another chemotherapy regimen (where X is the last treatment cycle prior to progression, and is 4 or less).

Treatment up to 4 cycles of study drug in this study will continue until any 1 of the following occurs:

- Dose limiting toxicity or critical adverse event as described in the docetaxel package insert (Taxotere® (Prescribing Information))
- Need for a protocol-prohibited dose reduction or study drug delay greater than 21 days
- Initiation of a protocol-prohibited concomitant medication or non-protocol chemo/biological therapy for treatment of his or her disease
- Development of a AE/SAE, illness, or condition that may interfere with the patient's participation or require treatment discontinuation
- Investigator opinion
- Sponsor decision
- Voluntary withdrawal of consent

Concomitant Drug/Therapy

Institutional guidelines should be followed in the event of infusion/hypersensitivity reaction. Diphenhydramine and dexamethasone infusion may be administered in the event of infusion reaction.

All patients must be premedicated with oral corticosteroids (see below for HRPC) such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day before the docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (refer to Taxotere® (Prescribing Information)).

For HRPC, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg at 12 hours, 3 hours, and 1 hour before docetaxel infusion (refer to Taxotere® (Prescribing Information)).

The prophylactic use of antibiotics is allowed at the discretion of the Investigator. The use of antibiotics will be recorded by patient and summarized by treatment arm (refer to Table 5).

Corticosteroids (except as described for premedication) and new non-steroidal anti-inflammatory drugs (NSAIDs) are prohibited except for the treatment of AEs and as premedication. Patients already receiving NSAIDs are allowed to continue taking treatment as long as the dose remains stable.

The use of strong CYP3A4 inhibitors as concomitant medications will be prohibited because docetaxel exposure increases by approximately 2-fold (Section 10.6.2) with the use of strong CYP3A4 inhibitors.

Docetaxel is low emetic risk (10% to 30% frequency of emesis) and appropriate anti-emetic prophylaxis should be given prior to study medication per institutional policy. In this study, dexamethasone is used as anti-emetic prophylaxis as well as to minimize docetaxel associated fluid retention.

If "breakthrough" emesis (e.g. emesis and nausea after Day 1) occurs, the general strategy is to add one agent from a different drug class to the "rescue" anti-emesis regimen. Useful anti-emetic agents for rescue include the benzodiazepines, cannabinoids (e.g. dronabinol or nabilone), haloperidol, metoclopramide, scopolamine, the phenothiazines (e.g. prochlorperaxine or promethazine) and 5HT3 receptor agonists. If a 5HT3 receptor agonist is needed, palonosetron (which is not known to prolong QT/QTc intervals) is safest and must be chosen over other 5HT3 receptor agonists. Tropisetron is an acceptable substitute 5HT3 receptor agonist (Yavas et al, 2008).

Because of the potential interference with QT/QTc interval, in Cycle 1 between Day 1 and Day 2, the 5HT3 receptor agonists ondansetron, granisetron and dolenasetron, and the atypical antipsychotic olanzapine, are prohibited until the triplicate ECGs are completed. After Cycle 1, triplicate ECGs are not obtained, and therefore no restrictions in the use of anti-emetics apply in those cycles, thus any 5HT3 receptor agonist can be used.

If nausea and /or vomiting of Grade 2 and higher occurs, it must be treated with "rescue" anti-emetics during mid-cycle, and on subsequent cycles, the prophylactic anti-emetic regimen should be modified. Aprepitant is an acceptable prophylactic anti-emetic in this situation [Marbury et al, 2009]).

If diarrhea of Grade 1 and higher occurs, it must be treated. Grade 1 diarrhea is less than 4 bowel movements a days without any signs of hypotention, dehydration.

Antidiarrheals such as loperamide (or diphenoxylate/atropine) must be prescribed for diarrhea. Suggested loperamide use: 4 mg orally after first loose stool, then 2 mg after each stool not to exceed 16 mg in 24 hours.

The use of anti-emetics and anti-diarrheals will need to be recorded on the CRF.

Patients who have FN should receive antibiotics per standard of care (refer to Rescue Treatment section and Table 5 for prohibited medications). The use of granulocyte colony-stimulating factor (G-CSF) as a treatment option during hospitalization for FN is strongly discouraged, since G-CSF is not approved for the treatment of FN, and is not likely to be effective. If, however, G-CSF treatment for FN is considered, the Investigator should contact the Medical Monitor prior to its use. FN is defined ANC $< 1.0 \times 10^9$/L AND a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour (as per CTCAE v4.03).

Pharmacokinetics

Phase 2 and Phase 3: Pharmacokinetic parameters (e.g., Cmax, time to reach Cmax [Tmax], AUC0-t, AUC0-∞, terminal half-life [t1/2], volume of distribution in the terminal elimination phase [Vz], and clearance [CL]) will be derived, where calculable, from plasma concentration-time data of plinabulin and docetaxel. Plinabulin concentration-time data will be pooled with data from other studies in a population PK analysis. Details of this analyses will be summarized in the Pharmacometrics Analysis Plan and may be reported outside of the main clinical study report.

Patients in Phase 3 will follow the plinabulin and docetaxel PK sampling schedules from Phase 2.

Pharmacodynamics

Patients in phase 2 will participate in the PD assessments. The PD assessments include blood pressure, DSN, and area over the neutropenia curve (AOC) in cycle 1 of the phase 2 portion of the study.

Exploratory Markers

Phase 2 only: A blood sample for exploratory marker evaluation will be collected for CD34+ which will be established by FACS. This test will be performed in selected countries participating in the study, via central laboratory.

Phase 2 and Phase 3: Plasma cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, GCSF, GMCSF, IFN alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8 analysis. This test will be performed in selected countries participating in the study, using unused plasma samples collected at PK time points.

Statistical Methods

Note: Patients in Phase 3 will be stratified based on his or her tumor type (breast cancer, NSCLC, HRPC) and region (Asia, non-Asia).

Study Endpoints and Analyses

Phase 2 (Open Label)

Plinabulin pharmacokinetic (PK) and pharmacodynamic (PD) assessments will be made to enable a PK/PD analysis.

Primary Endpoint:

- The primary endpoint is to establish the Recommended Phase 3 Dose (RP3D) based on PK/PD analysis

Primary Efficacy Pharmacodynamic Endpoint

- 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). ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15 (pre-dose on dosing days; times equivalent to pre-dose on other days). The Negative Binomial Regression (NBR) model, on the integer number of days of severe neutropenia, will be used to analyze the DSN endpoint during the fixed time window outlined above, with the treatment arm as the only covariate.

  The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used. Contrasts for pairwise comparisons between

Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.

Primary Safety Pharmacodynamic Endpoint

- 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). See the Pharmacometrics Analysis Plan for the analysis methods.

Secondary Endpoints:

- To characterize the pharmacokinetic profile of plinabulin and docetaxel. See the Pharmacometrics Analysis Plan for the analysis methods.
- To characterize the exposure-response relationships between measures of plinabulin exposure and the pharmacodynamic endpoint DSN. Robust linear regression (Bablok et al, 1988) with DSN as the dependent variable and plinabulin exposure as the independent variable. The method will also be used to construct point estimates and confidence intervals. The NCSS version 12 statistical software will be used.
- To characterize the exposure-safety relationships between measures of plinabulin exposure and safety events of interest. Robust linear regression (Bablok et al, 1988) with the number of safety events as the dependent variable and plinabulin exposure as the independent variable. The method will also be used to construct point estimates and confidence intervals. The NCSS version 12 statistical software will be used.

Exploratory Endpoints

- To assess CD34+ at screening, and on Days 2, 6 and 8 in Cycle 1 and Day 1 in Cycle 2. A repeated measures mixed linear model with the Day 1 value and treatment arm as covariates will be used to analyze this endpoint. 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. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.
- Health-related QoL questionnaire evaluated with EORTC QLQ-C30 and EQ-5D-5L. The Wilcoxon Rank Sum test will be used to analyze the responses to the individual questions. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.
- Data collection on disease progression. The log-rank test (LIFETEST procedure in SAS) will be used to compare time to disease progression between the treatment groups. The method will also be used to construct point estimates and confidence intervals. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.
- CD34+ at pre-dose on Day 1, pre-dose on Day 2, Days 6, 7, 8, 9, 10, and 15 in Cycle 1, and pre-dose on Day 1 in Cycle 2. A repeated measure mixed linear model with the pre-dose on day 1 cycle 1 value and treatment arm as covariates will be used to analyze this endpoint.
- For selected countries only: to investigate the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8.

Safety Endpoints

- Incidence, occurrence, and severity of AEs/SAEs. These endpoints will be presented descriptively in tables and listings.

- Incidences of bone pain. The NBR model will be used to analyze the endpoint during the fixed time window from pre-dose Day 1 through Day 8 in Cycle 1, with the treatment arm as the only covariate. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.
- Safety and tolerability (physical examination and safety laboratory assessments). These endpoints will be presented descriptively in tables and listings.

Phase 3 (Double Blind)

Primary Efficacy Endpoint (Cycle 1):

- DSN in Cycle 1 in patients treated with docetaxel (75 mg/m^2) + plinabulin (40 mg) (Arm 2) compared with patients treated with docetaxel (75 mg/m^2) + pegfilgrastim (6 mg) (Arm 1). ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15. Blood draws for ANC will be taken approximately the same time as the time of the pre-dose sample on Day 1, and will be taken by preference in the morning. The NBR model, on the integer number of days of severe neutropenia, will be used to analyze the DSN endpoint during the fixed time window outlined above, with the treatment arm as the only covariate. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.

Secondary Efficacy Endpoints (Cycle 1 and Cycles 1 to 4):

- DSN in Cycle 1 with only mature neutrophils.The NBR model, on the integer number of days of severe neutropenia, will be used to analyze the DSN endpoint during the fixed time window outlined above, with the treatment arm as the only covariate. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
- Maximum decrease from baseline (prior to docetaxel dose) in platelet count for each patient in Cycle 1. The Wilcoxon Rank Sum test will be used. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Proportion of patients with NLR > 5 after Day 7 through Day 15 in Cycle 1. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- AUC using the trapezoidal quadrature method for bone pain, from Day 1 through Day 8 in Cycle 1, based on the bone pain score from the patient bone pain scale. The Wilcoxon Rank Sum test will be used. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Estimated mean pain score from the patient bone pain scale from pre-dose Day 1 through Day 8 in Cycle 1. A repeated measures mixed linear model with the pre-dose Day 1 value and treatment arm as covariates will be used to analyze this endpoint. 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.
- Proportion of patients with thrombocytopenia (all grade) in Cycles 1 to 4. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- Incidence of infections in Cycles 1 to 4. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.

Exploratory Efficacy Endpoints (Cycle 1):

- Proportion of patients in Cycle 1 with:
  - Thrombocytopenia (all grade). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 3 (ANC < 1×10^9/L) and ANC >= 0.5×10^9/L) and Grade 4 neutropenia (ANC < 0.5×10^9/L). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 4 neutropenia (ANC < 0.5 × 109/L). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 4 neutropenia (ANC<0.5 x10^9/L) for mature neutrophils only. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 3 neutropenia (ANC < 1 × 109/L) and ANC >= 0.5 × 109/L). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Bands > 0 after Day 7 through Day 15. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Promyelocytes plus myelocytes >0 after Day 7 through Day 15. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Promyelocytes, myelocytes, metamyelocytes and bands >0 after Day 7 through Day 15. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - LMR < 3.2 after Day 7 through Day 15; time course of percentage of patients with LMR < 3.2 over time in Cycle 1. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - PLR > 200 after Day 7 through Day 15; time course of percentage of patients with PLR > 200 over time in Cycle 1. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - For the below bone pain measurements The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
    - At least 1 day of bone pain
    - At least 2 days of bone pain
    - At least 3 days of bone pain
    - At least 4 days of bone pain

- At least 5 days of bone pain
- At least 6 days of bone pain
- At least 7 days of bone pain
- At least 8 days of bone pain

- Proportion of patients in Cycle 1 who needed bone pain medication (defined as any medication reported on the pain medication assessment from Day 1 through Day 8). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- Time (in days) to first use of bone pain medication. The log-rank test (LIFETEST procedure in SAS) will be used to compare time to first use of bone pain medication between the treatment groups. Separate analyses will be made with respect to narcotic and non-narcotic analgesics.
- DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum failure. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 with only mature neutrophils in patients with locally advanced or metastatic NSCLC after platinum failure. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 in patients with HRPC. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 with only mature neutrophils in patients with with HRPC. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 in patients with advanced or metastatic breast cancer who have failed < 5 prior lines of chemotherapy. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 with only mature neutrophils in patients with advanced or metastatic breast cancer who have failed <5 prior lines of chemotherapy. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum failure or HRPC. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 with only mature neutrophils in patients with locally advanced or metastatic NSCLC after platinum failure or HRPC. The analysis will be done as per the primary endpoint.
- Platelet count at least 30% change from baseline at any time during Cycle 1. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- ANC nadir during Cycle 1. The Wilcoxon Rank Sum test will be used to analyze the endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- For selected countries only: maximum change from baseline in the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8. The Wilcoxon Rank Sum test will be used to analyze the endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.

Exploratory Efficacy Endpoints (Cycles 1 to 4):

- Proportion of patients in Cycles 1 to 4 with:
  - FN (ANC $<1.0 \times 10^9$/L AND a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.

- Maximum change from baseline in CD34+ counts in each arm. A Wilcoxon signed-rank test will be used to analyze this endpoint. The UNIVARIATE procedure in SAS version 9.4 or later will be used for the analysis.
- Maximum difference between treatment arms in CD34+ counts. The Wilcoxon Rank Sum test will be used to analyze this endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Maximum change from baseline in haptoglobin level in each arm. A Wilcoxon signed-rank test will be used to analyze this endpoint. The UNIVARIATE procedure in SAS version 9.4 or later will be used for the analysis.
- Maximum difference between treatment arms in haptoglobin level. The Wilcoxon Rank Sum test will be used to analyze this endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Healthcare utilization endpoints:
  - Incidence of 30-day rehospitalizations - all cause. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
  - Incidence of all cause hospitalizations. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
  - Duration of all cause hospitalizations. The Wilcoxon Rank Sum test will be used. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
  - Incidence of all cause ER visits. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
  - Incidence of all cause ICU stays. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
  - Duration of all cause ICU stays. The Wilcoxon Rank Sum test will be used. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
  - Incidence of all cause docetaxel dose delay, dose reduction, or dose discontinuation. The NBR model will be used to analyze the endpoints, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used:
    - Docetaxel dose delays > 7 days
    - Regimen switching
    - Treatment discontinuation
  - Proportion of Relative dose intensity (RDI) ≤ 85% where the RDI is defined as

$$\text{RDI} = \frac{\text{Cumulative dose of administered docetaxel (mg/m}^2\text{)}}{\text{Number of weeks from Day1 Cycle 1 to Day 1 Cycle 4 plus 3 weeks}}$$

Total calculated doses/12 weeks

The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis

- Incidence of transfusions due to thrombocytopenia. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
- Incidence of antibiotics use. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.

- Data collection on disease progression. The log-rank test (LIFETEST procedure in SAS version 9.4 or later) will be used to compare time to disease progression between the treatment groups. The method will also be used to construct point estimates and confidence intervals.
  - QoL endpoints will be analyzed in safety analysis set:
    - Health-related QoL questionnaire evaluated with EORTC QLQ-C30 Item 30 (response to question "How do you rate your overall quality of life during the past week") in Cycle 1 to 4 will be analyzed using linear mixed model for repeated measures (MMRM) with the Cycle 1 Day 1 value and treatment arm as covariates. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS v9.4 or later will be used for the analysis. The summary statistics in terms of counts, means, standard deviations, medians, minimums, and maximums for individual questions will be summarized in a tabular format.
    - Health-related QoL questionnaire evaluated with EORTC QLQ-C30 will also be analyzed with the summary scores. The EORTC QLQ-C30 scoring method combines the 30 questions from the questionnaire into 15 scores: global health state/QoL, functional scale (5 items), and symptoms scale (9 items) (Fayers et al, 2001). Three summary measures will be constructed: the QLQ-C30 Summary Score, which combined the symptom and functional scales (excluding the financial difficulties item), the symptom summary score (excluding the financial difficulties item), and the functional summary score (Hinz et al, 2012). The symptom summary score will be analyzed using linear mixed model for repeated measures (MMRM) with the Cycle 1 Day 1 value and treatment arm as covariates. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS v9.4 or later will be used for the analysis. The summary statistics in terms of counts, means, standard deviations, medians, minimums, and maximums for the 15 scores, the QLQ-C30 summary score, symptom score and the functional summary score will be summarized in a tabular format.
    - The response to the question "Your Health Today" from EQ-5D-5L in Cycle 1 to 4 will be analyzed using linear mixed for model repeated measures (MMRM) with the Cycle 1 Day 1 value and treatment arm as covariates. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS v9.4 or later will be used for the analysis. The summary statistics in terms of counts, means, standard deviations, medians, minimums, and maximums for the question "Your Health Today" will be summarized in a tabular format.
    - The EQ-5D-5L data will be converted into a health utility score using the interim EQ-5D-5L crosswalk value set for the United States (van Hout et al, 2012) unless a validated EQ-5D-5L value set for the United States becomes available. The EQ-5D-5L health utility score in Cycle 1 to 4 will be analyzed using linear mixed model for repeated

measures (MMRM) with the Cycle 1 Day 1 value and treatment arm as covariates. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS v9.4 or later will be used for the analysis. The summary statistics in terms of counts, means, standard deviations, medians, minimums, and maximums for the health utility score will be summarized in a tabular format.

Safety Endpoints

- Incidence, occurrence, and severity of AEs/SAEs. These endpoints will be presented descriptively in tables and listings.
- Safety and tolerability (physical examination and safety laboratory assessments). These endpoints will be presented descriptively in tables and listings.

Primary efficacy endpoint will be imputed by multiple imputation method as sensitivity analysis.

Analysis Sets Phase 2

Intent-to-Treat Analysis Sets

The intent-to-treat analysis set for Phase 2 is comprised of all Phase 2 patients that have been randomized in the study and have received at least one dose of study medication.
The analysis of all endpoints, unless noted otherwise, will be conducted on the intent-to-treat analysis set.

Safety Analysis Set

The safety analysis set will be the same as the intent-to-treat analysis set for Phase 2.

Pharmacokinetic Analysis Set

All patients who received at least 1 dose of plinabulin or docetaxel and had at least 1 PK sample collected postdose 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.

Pharmacodynamic Analysis Set

All patients who had blood pressure and DSN collected at any time during the study will be included in the PD analysis set.

Analysis Sets Phase 3

Intent-to-Treat Analysis Sets

The intent-to-treat (ITT) analysis set for Phase 3 is comprised of all Phase 3 patients that have been randomized in the study. The analysis of all endpoints, unless noted otherwise, will be conducted on the intent-to-treat analysis set.

Safety Analysis Set

The safety analysis set is comprised of all Phase 3 patients that have been randomized in the study and have received at least one dose of study medication.

Efficacy Analyses Considerations

Primary efficacy analysis considerations

DSN was not measured in the previous Phase 2 study ([Study NPI-2358-101] in which patients received treatment with either plinabulin (30 mg/m^2 [n=50] or 20 mg/m^2 [n=40] + docetaxel or docetaxel alone [n=73]). DSN was obtained using the following methods (described below) for generation of ANC data and the observed neutrophil values on Day 8/Cycle 1 in the Phase 2 study. Day 8 neutrophil values were shown to approximately coincide with the nadir of ANC after docetaxel treatment (Blackwell et al, 2015). The study will assume that the shape of the time/neutrophil recovery curve in plinabulin-treated patients is indistinguishable from the time/neutrophil recovery curve for filgrastim and its biosimilars.

In a study with filgrastim and its biosimilar, time course of ANC in Cycle 1 for the Per Protocol dataset was published by Blackwell et al, 2015. Mean values and standard deviations of ANC during the 21-day follow-up

period were readily available. This information was used to write a computer simulation program that would generate random ANC data that asymptotically has the same means and standard deviations for the 21-day follow-up period as the publication. The simulation would then also generate the projected number of days with severe neutropenia, (i.e., the DSN).

Deming regression (Deming, 1943) was used to calculate the linear relationship between simulated nadir and DSN. The rank correlation between simulated nadir and DSN was used to calculate the DSN with plinabulin (+ docetaxel) and docetaxel alone. In the Phase 2 study, ANCs were obtained on Day 8, which approximately coincides with the time that the neutrophil nadir occurs after docetaxel administration. The observed Day 8 neutrophil (nadir) values were computed into the linear relationship (Deming regression), mentioned above to calculate DSN for each patient. Using these methods, calculated mean DSN was 0.065 days for the plinabulin+ docetaxel arm, and 1.076 days for the docetaxel alone. Based on published data with filgrastim in patients receiving docetaxel (Alexopoulos K et al, 1999), the assumption is that Grade 4 neutropenia in Cycle 1 would occur in a 2 times higher frequency with G-CSF+docetaxel versus plinabulin+docetaxel, resulting in a presumed mean DSN of 0.13 days for the G-CSF+ docetaxel combination.

This non-inferiority trial design will utilize a difference (arm 2 minus arm 1) of 0.65 days (non-inferiority margin) in DSN in Cycle 1 as the largest acceptable difference between plinabulin and pegfilgrastim. The non-inferiority test will evaluate the null hypothesis H0: true difference (arm 2 minus arm 1) ≥ 0.65 against the alternative hypothesis H1: true difference (arm 2 minus arm 1) < 0.65. Plinabulin will be considered non-inferior to pegfilgrastim if in Cycle 1, the upper limit of the 2-sided 95% confidence interval for the true difference in mean duration of Grade 4 neutropenia was < 0.65 days. A sample size of patients was based on sample size considerations as outlined.

Data suggest (http://www.neulastahcp.com/risk/duration-of-severe-neutropenia/) that FN is correlated with DSN. The frequency of FN with docetaxel monotherapy (100 mg/m^2) + G-CSF was reported to be 1% in Cycle 1. FN frequency in Cycle 1 with docetaxel combined with doxorubicin and G-CSF was ~ 3 % (Aarts M et al, 2013), which would translate into a DSN of 1 day according to Holmes FA, et al, 2002. Based on these data, it is assumed that the median DSN for docetaxel monotherapy + G-CSF will be approximately 1 day.

The frequency of FN with docetaxel monotherapy (without G-CSF) has been reported to be 11% in Cycle 1 (17% over all cycles) docetaxel dose of 100 mg/m^2 (Vogel et al, 2005) and 19.8% over all cycles at a lower docetaxel dose of 60 mg/m^2 (Yoh K et al, 2016). Hanna N et al, 2004 reported an FN percentage of 12.7% with 75 mg/m^2 docetaxel. Based on this range of FN, the relationship established by Meza et al, 2002 between FN and DSN, we make the assumption that, with docetaxel monotherapy at a dose of 75 mg/m2 without G-CSF, the median DSN is estimated to be 4-5 days.

In the Zarxio® briefing document, 2015, the margin was selected based on the fact that Taxotere/Adriamycin/cyclophosphamide (TAC) chemotherapy is known to induce a median DSN of 7 days in breast cancer patients receiving no G-CSF treatment (Nabholtz, 2001), while G-CSF treatment reduces the mean DSN for this chemotherapy to 1.4 days (95% CI: 1.07 - 1.69) as shown in pegfilgrastim (Neulasta®) Study 20020778 (Kaufman et al, 2004). Based on this a non-inferiority limit of 1 day was derived.

As an extension of this reasoning, it is argued for our study, a non-inferiority margin of 0.65 would be reasonable and correspond to approximately a median of 4.5 days of DSN, as a ratio of 1 day to 7 days of DSN in the Zarxio® briefing document, 2015.

A non-inferiority margin of 0.65 days can also be justified, because a difference of 0.65 days is not considered to be clinically meaningful.

Pharmacokinetic and Pharmacodynamic Analyses Considerations

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.

Exposure-Neutropenia Relationship

A sequential population PK/PD modeling approach will be used to characterize the exposure neutropenia relationship. The semi-physiological model described by Friberg (2003) will be used to characterize the time course of neutropenia in the exposure-neutropenia model.

The developed exposure-response models will be used to simulate ANC profiles for the computation of key PD endpoints such as DSN, DMSN, and area over the ANC curve (AOC). The latter will be calculated as the area below the threshold of $<0.5 \times 10^9$ cells/L and above ANC-time response curve in a chemotherapy cycle.

Exposure-Blood Pressure Analysis
A sequential PK-PD model analysis will be performed. Since the ambulatory blood pressure measurements (ABPM) are subject to circadian variations, ABPM will be modeled to describe the circadian rhythm in blood pressure over the 4.5-hour observation period. The diurnal rhythm in the AMBP data will be described with the cosine function (Hempel 1998) in the exposure ABPM models.
Exposure-QTc Analysis
Either a direct or sequential PK-PD model analysis will be performed. The choice of the modeling approach will be informed by the matching or non-matching of PK sampling times with ECG observation times. QT measurements corrected with the Fridericia formula will be used in the exposure-QTc analysis.

Interim Analyses

The study design is group sequential with 1 interim analysis (after 50 patients in each treatment arm have completed at least 1 cycle in each of the treatment arms docetaxel + plinabulin (40 mg) versus docetaxel + pegfilgrastim, with matching placebos) and 1 final analysis at the completion of the study. These results assume that 2 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries.

If non-inferiority is determined from the statistical testing, then also the hypothesis of superiority will be tested, and if it is concluded that the plinabulin treatment is superior to the pegfilgrastim treatment, with respect to DSN, then the study will be stopped. Since the design allows for stopping for inferiority, it might be decided at that occasion that the study will be stopped. Since this is a hierarchical testing procedure no penalty with respect to overall significance will be paid.

The statistical testing will be performed by an independent statistician and will be reviewed by the Data Safety Monitoring Board at the interim analysis.

Sample Size Rationale

Phase 2 (Open Label)

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

Phase 3 (Double blind)

Approximately 150 patients are planned to be enrolled with 1 of the following diagnoses: advanced or metastatic breast cancer, NSCLC, or HRPC. A sample size of 75 patients in each of the treatment arms docetaxel + plinabulin (40 mg) versus docetaxel + pegfilgrastim, with matching placebos achieve at least a 90% power to reject the null hypothesis of 0.65 day of inferiority in DSN between the treatment means with standard deviations of 0.75, at a significance level (alpha) of 0.05 two-sided two-sample zero-inflated Poisson model.

The software PASS version 15.0.1 has been used for the calculations referencing Chow et al. 2003, Lan and DeMets 1983, O'Brien and Fleming 1979.

Timing of Statistical Analysis

	Number of Patients in Phase 2	
Arm 1: Docetaxel + Pegfilgrastim 6 mg	10	
Arm 2: Docetaxel + Plinabulin 20 mg/m^2	10	
Arm 3: Docetaxel + Plinabulin 10 mg/m^2	10	
Arm 4: Docetaxel + Plinabulin 5 mg/m^2	10	
	PK/PD Analysis (to determine RP3D)	
	Number of patients in Phase 3	
Arm 1: Docetaxel + Pegfilgrastim 6 mg	50	75
Arm 2: Docetaxel + Plinabulin (40 mg)	50	75
	Interim Analysis	**Final Analysis**

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure measurement
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-HBs	Hepatitis B surface antibody
AOC	Area over the curve
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BSA	Body surface area
BOCF	Baseline observation carried forward
CBC	Complete blood count
CI	Confidence intervals
CRF	Case report form
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
D5W	Dextrose 5% in distilled water
DEHP	di(2-ethylhexyl)phthalate
DMSN	Duration of moderate and severe neutropenia
DSMB	Data safety monitoring board
DSN	Duration of severe neutropenia
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
ER	Emergency Room
FACS	Fluorescence-activated cell sorting
FDA	Food and Drug Administration
FN	Febrile neutropenia
G-CSF	Granulocyte colony-stimulating factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus

Abbreviation	Definition
HRPC	Hormone refractory prostate cancer
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IEC	Institutional Ethical Committee
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
IWRS	Interactive web response system
JSCO	Japanese Society of Clinical Oncology
LMR	Lymphocyte-to-monocyte ratio
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NBR	Negative Binomial Regression
NCI	National Cancer Institute
NLR	Neutrophil-to-lymphocyte ratio
NSAID	Non-steroidal anti-inflammatory drug
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
PAP	Pharmacometrics Analysis Plan
PD	Pharmacodynamic
PK	Pharmacokinetic
PLR	Platelet-to-lymphocyte ratio
PT	Prothrombin Time, preferred term
PTT	Partial thromboplastin time
PVC	Polyvinyl chloride
QoL	Quality of Life
RBC	Red blood cell
RP2D	Recommended Phase 2 dose
RP3D	Recommended Phase 3 dose
SAE	Serious adverse events
SAP	Statistical Analysis Plan

Abbreviation	Definition
SOC	System organ class
SOP	Standard Operating Procedure
TAC	Taxotere/Adriamycin/cyclophosphamide
TEAE	Treatment emergent adverse event
UGT	UDP glucuronosyltransferase
ULN	Upper limit of normal
US	United States
WHO	World Health Organization
WOCF	Worst observation carried forward

4. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

4.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements before the study is initiated at a study center in that country.

4.2. Investigator Responsibilities

4.2.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, South Africa, and Edinburgh) or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" International Council on Harmonisation (ICH) Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the United States (US) or under US Investigational New Drug Application (IND), the Investigator will additionally ensure that the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Patients", and part 56, "Institutional Review Boards", are adhered to.

In other countries where "Guideline for Good Clinical Practice" exists the Sponsor and the Investigators will strictly ensure adherence to the stated provisions.

4.2.2. Ethical Conduct of the Study and Ethics Approval

This Protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the patient, will be submitted by the Investigator to an Institutional Review Board (IRB)/Institutional Ethics Committee (IEC). Approval from the Committee must be obtained before starting the study, and should be documented in a letter to the Investigator specifying the date on which the committee met and granted the approval.

Any modifications made to the Protocol after receipt of the IEC approval must also be submitted by the Investigator to the Committee in accordance with local procedures and regulatory requirements.

When no local review board exists, the Investigator is expected to submit the Protocol to a regional committee. If no regional committee exists, the Sponsor will assist the Investigator in submitting the Protocol to an appropriate Ethics Review Committee.

It is the understanding of the Sponsor that this Protocol (and any modifications) as well as appropriate consent procedures will be reviewed and approved by an IRB. This board must operate in accordance with the current Federal Regulations. A letter or certificate of approval

will be sent by the Investigator to the Sponsor before initiation of the study, and also whenever subsequent modifications to the Protocol are made.

4.2.3. Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written informed consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, or unable to understand due to language barriers, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the study, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The Case Report Forms (CRFs) for this study contain a section for documenting informed patient consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information, given a copy of the revised form and give consent to continue in the study. No study related activities should be conducted on a patient until after obtaining informed consent.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be conducted at sites (to be determined) in North America, Europe, or Asia Pacific.

The name, telephone and fax numbers of the medical monitor and other contact personnel at the Sponsor are listed in the regulatory binder provided to each site.

6. INTRODUCTION

6.1. Overview

Myelosuppression is the primary toxicity of many chemotherapy regimens which often limits applicability. Both the duration of Grade 4 neutropenia and the depth of the neutrophil nadir have been correlated to severe and life-threatening infections (Pizzo et al, 1993; Holmes FA, et al, 2002; Crawford et al, 2004). As a result, the prevention of neutropenia is a major goal for oncology practitioners for both safety and cost-efficiency (Green et al, 2004; Aarts et al, 2013; Dinan et al, 2015).

Neutropenia is a frequent and potentially life-threatening complication of cytotoxic myelosuppressive chemotherapy. Research has shown that patients who develop neutropenia are more susceptible to infections which often required treatment with antibiotics and in severe cases require hospitalization (Kawatkar et al, 2017). Moreover, severe neutropenia often necessitates modification of the chemotherapy regimen, thereby compromising the ultimate success of the anticancer treatment plan (Waller et al, 2010).

Febrile neutropenia (FN) is a potentially life-threatening condition characterized by the development of fever (a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour) in addition to chemotherapy-induced Grade 3 or 4 neutropenia (absolute neutrophil count [ANC] < 1.0×10^9/L).

The risk of severe neutropenia including FN is mitigated by reducing chemotherapy dosages or extending the dosing interval of the agents. However, research has shown these measures are directly correlated to lower long-term survival rates because of the relative reduction in the dose intensity of the chemotherapy (Zhang et al, 2018). Therefore, granulocyte colony-stimulating factor (G-CSF) also known as filgrastim (Neupogen®) or pegfilgrastim (Neulasta®), is given as standard of care to manage chemotherapy-induced severe neutropenia and to allow chemotherapy to be administered more effectively. Guidelines for the use of G-CSF based on the risk of FN have been established by several groups worldwide such as the National Cancer Institute (NCI) Network, American Society of Clinical Oncology, National Comprehensive Cancer Network (NCCN), European Organization for Research and Treatment of Cancer, and Japanese Society of Clinical Oncology (JSCO). According to these guidelines, prophylactic G-CSF use is recommended for patients at significant risk of FN based on the chemotherapy regimen and patient specific risk factors (Kosaka et al, 2015). However, the prophylactic use of G-CSF has some significant limitations in terms of safety, cost and convenience of use. Treatment should not be administered within 14 days of chemotherapy initiation. Moreover, G-CSF therapy cannot be initiated until 24 hours after the last dose of chemotherapy for each treatment cycle and is generally administered once per chemotherapy cycle (requires baseline complete blood count [CBC] and platelet count during therapy). The concern with administering G-CSF on the day of chemotherapy is that increasing growth of myeloid cells may increase sensitivity to cytotoxic chemotherapy agents. Since cytotoxic chemotherapy causes the most damage to rapidly growing cells, giving an agent that causes myeloid cells to grow faster while chemotherapy is present may cause more toxicity. Duration of G-CSF therapy is to attenuate chemotherapy-induced neutropenia and is dependent on the myelosuppressive potential of chemotherapy regimen employed. Patients are required to either self-administer the drug or return to the center for treatment and evaluation which is often difficult and costly for the patient.

Cost constraints in health care have been reported to be factor in access to filgrastim and pegfilgrastim for some patients. In countries in which patients are required to contribute to treatment costs, high drug prices have resulted in reduced compliance. In Europe, the availability of filgrastim biosimilars (which are more cost effective) have been accompanied by increased use suggesting physicians are more likely to use a cost-effective product (Blackwell et al, 2015).

Warnings and precautions for pegfilgrastim include splenic rupture, acute respiratory distress syndrome, allergic reactions including anaphylaxis, fatal sickle cell crisis, glomerulonephritis, capillary leak syndrome, and leukocytosis. The most common adverse reactions are bone pain and pain in an extremity which occurred in 31% and 9% of patients, respectively. Additional notable adverse events include acute febrile neutrophilic dermatosis, cutaneous vasculitis and injection site reactions (Neulasta® Package Insert).

Plinabulin has the potential to offer a new treatment option that would ameliorate chemotherapy-related severe neutropenia (including FN) as well as have a better safety profile (much less bone pain) and be more convenient for the patient by reducing the number of required patient visits and potentially also reducing the burden to the healthcare system. Most importantly, plinabulin can be given 1 hour after a chemotherapy cycle as opposed to 24 hours after the completion of the cycle (as prescribed by pegfilgrastim).

Two clinical studies with plinabulin have been conducted to date, a Phase 1 monotherapy study (Study NPI-2358-100) and a Phase 1/2 combination study (Study NPI-2358-101) with docetaxel. A total of 141 patients with solid tumors received plinabulin. Laboratory data did not uncover any clinically significant deleterious changes in hematology or chemistry laboratory parameters; however, there was a significantly lower incidence of neutropenia in patients receiving plinabulin plus docetaxel compared with the docetaxel monotherapy arm.

Plinabulin (BPI-2358) is a synthetic, low molecular weight, new chemical entity originally developed (previous name NPI-2358) by Nereus Pharmaceuticals, Inc., and now by BeyondSpring Pharmaceuticals, Inc. It belongs to the diketopiperazine class of compounds.

The chemical name of plinabulin is 2, 5-piperazinedione, 3-[[5-(1,1-dimethylethyl)-1H-imidazol-4-yl]methylene]-6-(phenylmethylene)-,(3Z,6Z).

Plinabulin is a yellow to orange solid and the clinical drug product is supplied as a solution in 40% Kolliphor HS 15 (formerly known as polyoxyl 15 hydroxystearate, or Solutol HS-15)®/60% propylene glycol in an amber vial containing 80 mg in 20 mL (4 mg/mL). Each vial is designated for single use.

Plinabulin is intended for intravenous (IV) infusion and is diluted with dextrose 5% in distilled water (D5W) and given over 30 minutes (± 5 minutes) at an initial dose of 30 mg/m^2.

Plinabulin which inhibits the polymerization of tubulin monomers, also has multiple mechanisms of action that inhibit tumor growth. Plinabulin targets angiogenesis and the existing tumor vasculature and also directly induces cancer cell apoptosis via the JNK pathway (Nicholson et al, 2006; Singh et al, 2011; Kennedy et al, 2003). Plinabulin stimulates the tumor-related immune system by means of dendritic cell maturation and enhances the antitumor activity of checkpoint inhibitors in an immune-competent mouse model (Lloyd et al, 2016). Based on the nonclinical and clinical studies conducted to date, plinabulin has several advantages compared to agents that

target existing tumor vasculature, including inhibition of angiogenesis, induction of tumor cell apoptosis, sustained suppression of tumor growth after treatment, inhibition of tubulin dimerization and thus new microtubule formation without alteration of microtubule dynamic instability (reducing the risk of peripheral neuropathies associated with taxanes) (Gornstein, 2014). The safety profile of plinabulin appears to be superior to that of other agents with immune-oncology effects, such as checkpoint inhibitors (e.g., nivolumab), providing a major advantage in cancer therapy. Thus, plinabulin may prove to be efficacious in the management of cancers such as advanced non-small cell lung cancer (NSCLC). A Phase 3 global trial with plinabulin in combination with docetaxel is underway in NSCLC patients. (Study NPI-2358-103).

The mechanism by which plinabulin exerts its beneficial effect in neutropenia is still under investigation. Preclinical evidence shows that plinabulin induces maturation of dendritic cells, resulting in the release of the cytokines interleukin (IL)-1β, IL-6 and IL-12 from monocytes/dendritic cells (Lloyd et al, 2016). In particular IL-6 is mediated in the prevention of neutrophil apoptosis (Asensi et al, 2004) and IL-1β with increased neutrophil count (Dinarello, 2011).

Phase 1 (Study NPI-2358-100) and Phase 1/2 (Study NPI-2358-101) studies with plinabulin have been completed. Study NPI-2358-100 was a Phase 1, open-label, dose-escalation study to determine the maximum-tolerated dose and/or recommended Phase 2 dose (RP2D) of plinabulin monotherapy in patients with advanced solid tumor malignancies or lymphoma, whose disease had progressed after treatment with standard approved treatments. Plinabulin was administered once per week as an IV infusion for 3 successive weeks in repeating 4-week cycles. Doses ranged from 2 to 30 mg/m^2. A total of 38 patients received plinabulin monotherapy.

Study NPI-2358-101 was a Phase 1/2, open-label study to evaluate plinabulin in combination with docetaxel in patients with advanced NSCLC that had progressed after treatment with at least 1 chemotherapy regimen. In the Phase 1 part of the study, patients received escalating doses of plinabulin (13.5 mg/m^2 to 30 mg/m^2) in combination with a standard dose of docetaxel (75 mg/m^2). No drug-drug interaction was detected between plinabulin and docetaxel. The RP2D of plinabulin administered with docetaxel was determined to be 30 mg/m^2.

In the Phase 2 part, patients were randomized to receive either docetaxel in combination with plinabulin or docetaxel alone (active control group). A docetaxel dose of 75 mg/m^2 was administered to all patients. The study was stratified into 2 segments. A stratum that compared plinabulin 30 mg/m^2 plus docetaxel (study arm DN) to docetaxel alone (study arm D) followed by a second stratum of plinabulin 20 mg/m^2 plus docetaxel (DN arm) to docetaxel alone (D arm). Study drug was administered by IV infusion on Day 1 (docetaxel plus plinabulin) and Day 8 (plinabulin) of each 3-week cycle. A total of 103 patients receive plinabulin plus docetaxel and 73 patients received docetaxel alone.

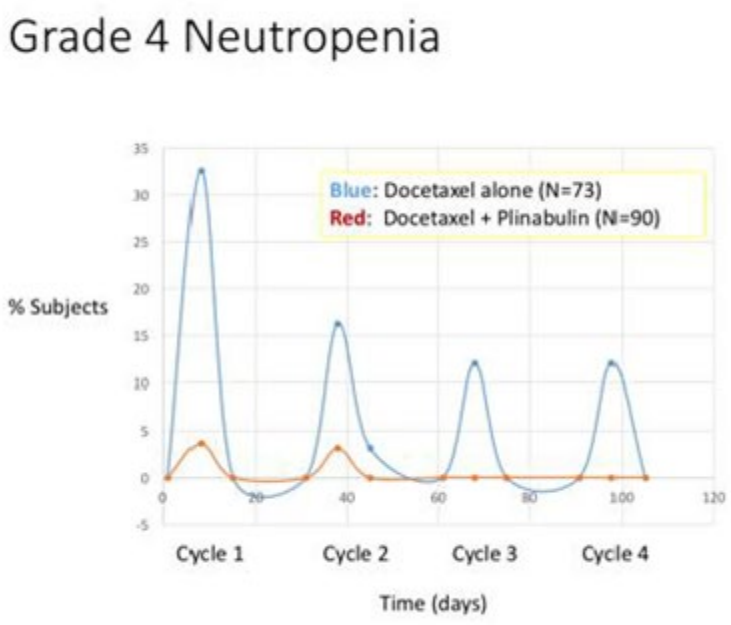
Improvement in Neutropenia

In the Phase 2 clinical trial, patients were randomized to receive docetaxel 75 mg/m^2 alone (n=73) or docetaxel 75 mg/m^2 followed by plinabulin (Study NPI-2358-101) at 30 mg/m^2 (n=50) or at 20 mg/m^2 (n=40), repeated every 3 weeks (clinicaltrials.gov NCT00630110). Plinabulin was given by a 30-minute intravenous (IV) infusion, starting 1 hour after administration of docetaxel. The primary efficacy endpoint was median overall survival. Secondary endpoints

included safety assessments, such as complete blood count measurements, on Days 1, 8, and 15 of each cycle.

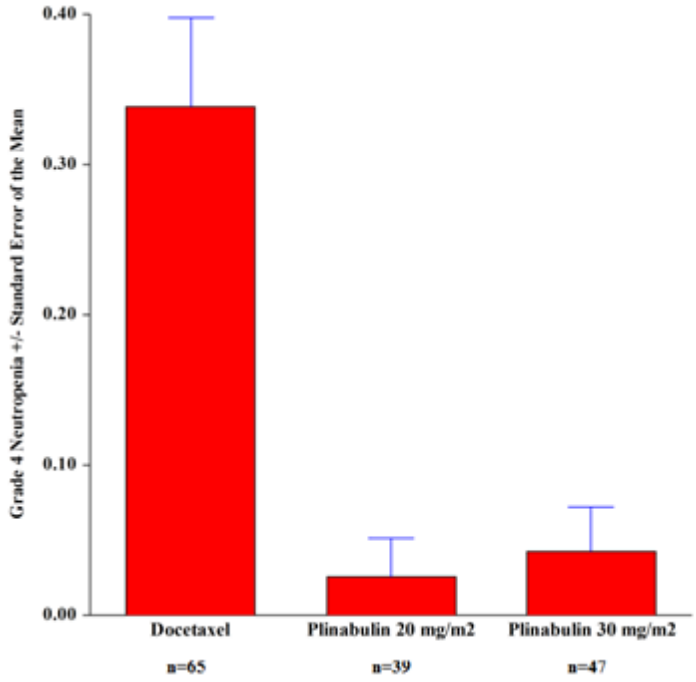
In Figure 1, plinabulin and docetaxel combination has a much lower incidence of Grade 4 neutropenia versus docetaxel alone (4% versus 33% in the first cycle, based on hematological laboratory values) for both the 20 mg/m^2 and 30 mg/m^2 plinabulin cohorts combined, and a benefit in neutropenia prevention was maintained over Cycles 2, 3, and 4.

Figure 1: Grade 4 Neutropenia for Docetaxel Plus Plinabulin and Docetaxel Alone by 21-day Cycles (NPI-2358, Phase 2)



In Figure 2, the percentage of patients with Grade 4 neutropenia (ANC < 0.5 x 10^9/L) on Day 8 of Cycle 1, in the patients receiving docetaxel monotherapy without plinabulin ("Docetaxel"), docetaxel +20 mg/m^2 plinabulin, and docetaxel+ 30 mg/m^2 plinabulin are shown. The reduction in Grade 4 neutropenia with either plinabulin dose was statistically highly significant, and this reduction was comparable for the 20 and 30 mg/m^2 plinabulin dose.

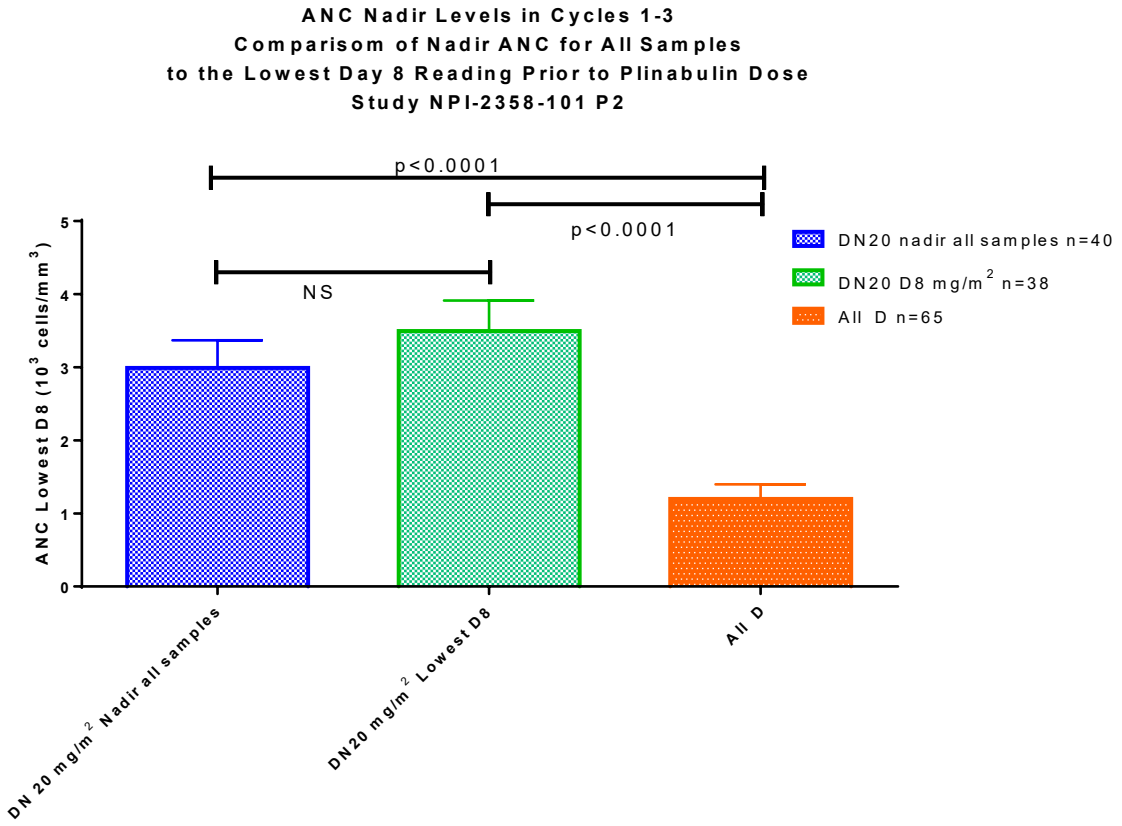
Figure 2: Grade 4 Neutropenia on Cycle 1 Day 8



Docetaxel (n=65) vs plinabulin 20 mg/m^2 (n=39): p = 0.00026
Docetaxel (n=65) vs plinabulin 30 mg/m^2 (n=47): p = 0.00018
Plinabulin 20 mg/m^2 (n=39) vs plinabulin 30 mg/m^2 (n=47): p = 0.68

The benefit in Grade 4 neutropenia reduction on Day 8 in Cycle 1 was observed prior to patients receiving their plinabulin dose on Day 8, which provides evidence that a single plinabulin dose per cycle, given on Day 1 after docetaxel administration, is sufficient to achieve the neutropenia benefit. Further evidence that a single 20 mg/m^2 dose of plinabulin after each dose of docetaxel is sufficient to prevent myelosuppressive regimens-induced neutropenia is demonstrated in Figure 3 in which the nadir following a single dose (measured on Day 8 prior to the second dose of plinabulin) is similar to that measured in all blood samples in a cycle.

Figure 3: Absolute Neutrophil Count at Day 8 Only (Prior to the Second Dose of Plinabulin) After a Single Dose of 20 mg/m^2 Plinabulin per Cycle and Absolute Neutrophil Count Nadir Observed in all Samples Taken in Cycles 1 to 3



Abbreviations: ANC = absolute neutrophil count; D = docetaxel; DN = docetaxel plus plinabulin.

There were 10% of patients (5 of 50 patients) in the plinabulin 30 mg/m^2 plus docetaxel treatment arm who required docetaxel dose reductions and 18.2% of patients (10 of 55 patients) in the docetaxel arm who required dose reductions. In the 20 mg/m^2 cohort, similar findings were observed, in which a lower proportion of patients required docetaxel dose reductions when treated with the combination (2.5%) than the companion docetaxel arms (22.2%) (refer to Table 1).

Table 1: Summary of Docetaxel Dose Reductions and G-CSF Use (NPI-2358-101, Phase 2

	30 mg/m^2 Cohort		20 mg/m^2 Cohort	
	DN arm N=50	**D arm N=55**	**DN arm N=40**	**D arm N=18**
Docetaxel dose reductions (n [%])	5 (10.0%)	10 (18.2%)	1 (2.5%)	4 (22.2%)
G-CSF use (n [%])	7 (14%)	16 (29.1%)	2 (5%)	6 (33.3%)

Abbreviations: D = docetaxel; DN = docetaxel plus plinabulin; G-CSF = granulocyte colony stimulating factor.
Note: G-CSF included the following concomitant medications: pegfilgrastim, filgrastim, Neupogen, and Neulasta.
P = 0.0013 (G-CSF use % in combined DN arm versus combined D arm).

The Phase 2 data suggest that a single dose of 20 mg/m^2 plinabulin per cycle is highly effective in preventing docetaxel-induced neutropenia, and that the 20 mg/m^2 plinabulin dose appears equally effective as the 30 mg/m^2 group for the prevention of docetaxel-induced neutropenia. Consistent with the benefit of neutropenia prevention, in the plinabulin groups fewer patients required G-CSF treatment, and fewer patients required docetaxel dose reductions.

Safety Conclusions

The safety profile of plinabulin was consistent with what has been reported in earlier Phase 1 studies. The combination appeared to have a similar adverse event (AE) profile as single-agent docetaxel. Increases in both systolic and diastolic blood pressure were seen in 20% to 30 % of patients. The incidence of hypertension in the 20 mg/m^2 (9 patients, 22.5%; 5% with Grade 3) and 30 mg/m^2 (16 patients, 32.0%; 20% with grade 3) cohorts was higher compared with the docetaxel group (1 patient 5.6% and 2 patients, 3.6%), respectively. These events typically resolved within 2 hours after plinabulin infusion. No events of Grade 4 hypertension had occurred. Grade 3 hypertension had occurred in 2 cases with the 20 mg/m^2 dose and 7 cases with the 30 mg/m^2 dose. In both cases, the patients had a previous medical history of hypertension, which makes a causal relationship with plinabulin unlikely. In the 30 mg/m^2, there were 7 cases with Grade 3 hypertension, of which 4 cases had a prior medical history of hypertension; a causal relationship with plinabulin could not be determined in these 4 cases. Hypertension typically resolved within 2 hours after the plinabulin infusion. Ileus and intestinal obstruction were also reported as AEs. It was not clear if they were a direct effect of plinabulin or caused by some concomitant medications such as opioids.

Overall, plinabulin + docetaxel appeared to have a more favorable safety profile at the 20 mg/m^2 plinabulin dose versus the 30 mg/m^2 plinabulin dose, as demonstrated by a smaller proportion of patients who discontinued treatment due to a treatment emergent adverse event ([TEAE] 3 patients, 7.5% versus 11 patients, 22.0%) and a smaller proportion experienced 1 or more serious adverse events ([SAEs] 14 patients, 35.0% versus 31 patients, 62.0%).

The proportion of patients in the plinabulin plus docetaxel 20 mg/m^2 arm who discontinued treatment due to a TEAE and experienced 1 or more SAEs was similar to that reported for the combined docetaxel alone arms (4 patients, 5.5% and 23 patients, 31.5%, respectively), thus the 20 mg/m^2 plinabulin dose appears to represent a safe plinabulin dose.

Laboratory data did not uncover any clinically significant deleterious changes in hematology or chemistry laboratory parameters; however, there was a lower incidence of neutropenia in patients

in the DN 30 mg/m^2 and 20 mg/m^2 arm compared with its companion docetaxel arm as discussed above.

Adverse events of concern were atrial fibrillation, ileus/intestinal obstruction, and reversible posterior leukoencephalopathy syndrome (see current Investigator Brochure).

In specific therapeutic settings as described by the NCCN guidelines, docetaxel is an accepted treatment regimen for breast cancer, NSCLC, and hormone refractory prostate cancer (HRPC) (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site).

6.1.1. Pharmacokinetics and Drug Disposition in Humans

The pharmacokinetics (PK) of plinabulin was evaluated in a Phase1 monotherapy clinical study in advanced solid tumor malignancies or lymphoma. Compartment-independent PK analysis revealed a linear increase in systemic exposure (are under the curve $[AUC]_{tot}$) with increasing dose of plinabulin. Inter-patient variability in AUC_{tot} was large, suggesting individual differences in metabolism of the parent drug. Maximal plasma concentration was observed at the end of infusion for most patients. Distributive volumes (Vz and Vss) were similar for all patients, and were indicative of the drug reaching deep compartments or being stored in peripheral compartments.

There was no evidence of any interaction between plinabulin and docetaxel with regard to plasma levels in the Phase 1b portion of Study NPI-2358-101.

Pharmacokinetic analysis of plinabulin indicated C_{max} and AUC were dose proportional over the range of 2 to 30 mg/m^2 without evidence of drug accumulation. The mean $t_{½}$ is 6.35 hours, the mean CL is 31 L/hour, and the mean Vz is 208 L for plinabulin as a single agent.

6.2. Study Rationale

6.2.1. Rationale for the Assessment of Bone Pain

Generalized bone pain is a risk associated with the use of G-CSF and is correlated with the mechanism of action (Lambertini et al, 2014). A meta-analysis of 5 controlled trials indicates that the overall incidence of bone pain with G-CSF can range from 20% to 50% (Lambertini et al, 2014; Kubista et al, 2003). The overall incidence of mild-to-moderate bone pain attributed to G-CSF is approximately 24%, and overall incidence of severe bone pain can range from 1% to 5% of patients (Lambertini et al, 2014; Kubista et al, 2003). The G-CSF-induced bone pain can lead to the discontinuation of this growth factor, which in turn can reduce the chemotherapy dose intensity (Kirshner et al, 2012).

Generally, bone pain with pegfilgrastim reached its peak at Day 3 after dosing with pegfilgrastim on a scale of 1 to 10 (Kirshner et al, 2012). An AUV analysis of bone pain over at least 5 days after dosing with pegfilgrastim was previously employed to evaluate bone pain with pegfilgrastim (Kirshner et al, 2012).

G-CSFs mobilize hematopoietic progenitor cells from the bone marrow into the systemic circulation (Lambertini et al, 2014). This progenitor-cell-mobilizing effect is an important reason why G-CSFs should wait 24 hours after the chemotherapy, and if administered sooner (ie, on the same day of chemotherapy), G-CSFs are known to lead to a paradoxical worsening of the

neutropenia (Burris et al, 2010). The possible biologic explanation for the increase in FN observed with same-day pegfilgrastim dosing, relates to G-CSFs release of bone marrow-derived hematopoietic progenitor cells, and that the stimulation of these myeloid progenitor cells by G-CSFs makes these progenitor cells more sensitive to the effects of cytotoxic chemotherapy (Burris et al, 2010). Therefore, pegfilgrastim is not recommended to be administered on the same day but on the next day of chemotherapy (Burris et al, 2010).

A therapeutic intervention that is effective though a mechanism that is independent from mobilization of progenitor cells from the bone marrow has the potential to have superior efficacy over G-CSFs, as this therapeutic intervention can be administered on the same day, shortly after the chemotherapy. Since no bone marrow effects are involved, this agent should therefore also not cause bone pain.

The absence of an effect on neutrophil counts with plinabulin monotherapy (in the absence of chemotherapy), and the relative absence of bone pain with plinabulin, is indicative of differential mechanisms of action between plinabulin and G-CSF in the prevention of chemotherapy induced neutropenia. In addition, in contrast to G-CSFs, plinabulin has anti-cancer effect, which potentially represents an important advantage over G-CSFs, which do not have anti-cancer effects, or may even promote cancer growth, being a growth factor.

Based on the bone pain data from the completed Phase 2 study NPI-2358-101 in 90 patients on plinabulin (at the dose of 30 or 20 mg/m^2), a significant bone pain benefit is expected with plinabulin compared to G-CSF, while having an at least comparable benefit on chemotherapy-induced neutropenia.

The patient reported outcome bone pain is included as a secondary endpoint in the Phase 3 portion of the present study.

6.2.2. Rationale for the use of Plinabulin in the Prevention of Chemotherapy Induced Neutropenia

Plinabulin is a small molecule with tumor-inhibiting and immune-enhancing effects. Plinabulin induces dendritic cell maturation and cytokines interleukin-1β (IL-1β), IL-6, and IL-12 production, all of which are important in neutrophil survival. In preclinical studies, plinabulin prevented docetaxel- or cyclophosphamide-induced neutropenia via a mechanism of action different from that of G-CSF analogues. In Phase 1 and 2 solid tumor trials of plinabulin, which included >140 patients, routine safety laboratory assessments revealed an unexpected protective effect against neutropenia.

Compared to docetaxel treatment alone, the addition of plinabulin to docetaxel significantly ($p < 0.0003$) reduced the proportion of patients with Grade 4 neutropenia from 33.3% to 4.6% in Cycle 1. Figure 2 shows the proportions of patients with Grade 4 neutropenia (ANC < 0.5 x 10^9/L) on Day 8, the approximate day after docetaxel administration corresponding to the largest reduction in ANC (Blackwell et al, 2015). Plinabulin also reduced the clinical sequelae associated with docetaxel-induced neutropenia (sepsis, infections, hospitalizations, need for docetaxel dose reductions, and G-CSF use). Bone pain was reported in 4% of patients receiving plinabulin. Plinabulin had a favorable safety profile; the most prominent finding was Grade 3 transient hypertension in 20% and 5% of patients receiving 30 mg/m^2 and 20 mg/m^2 plinabulin, respectively (Blayney D, et al, 2016).

Total ANC is comprised of mature and immature neutrophils. Immature neutrophils have reduced functional capacity compared to mature neutrophils to enable optimal innate immunity. Compared to mature neutrophils, immature neutrophils exert reduced ROS production leading to reduced microbicidal activity, reduced phagocytic activity, reduced granularity, reduced ability to create NETs (Mackay G et al, Frontiers in Immunology 2019; Mortaz E et al Frontiers in Immunology 2018). Therefore an additional analysis will be made with mature neutrophils only.

Plinabulin is a novel small molecule that is being developed for the mitigation of chemotherapy-induced neutropenia. Administered by IV infusion on the same day of (approximately 1 hour after) chemotherapy, plinabulin will be given in a single dose to be determined per cycle. Plinabulin has the potential to be an effective, safe (with much less bone pain), cost-effective, and convenient alternative to G-CSF for the prevention of chemotherapy-induced neutropenia (Kuderer et al, 2006).

6.2.3. Rationale for the Selection of the Recommended Phase 3 Dose

A model-based approach was used to characterize the effect of plinabulin on docetaxel-induced neutropenia. The population pharmacokinetic/pharmacodynamic model developed was used to perform simulations. Daily sampling for neutrophils was implemented to enable accurate delineation of the efficacy metrics, duration of severe neutropenia (DSN; number of days with an ANC of $< 0.5 \times 10^9$/L), duration of moderate and severe neutropenia (DMSN; number of days with an ANC of $< 1.0 \times 10^9$/L), and area over the curve (AOC), which measure the duration and severity of neutropenia. The results were summarized by dose groups 5, 10, and 20 mg/m^2 studied in the Phase 2 portion of the present study.

Based on AOC, DMSN, and DSN, 20 mg/m^2 of plinabulin performed better than the 5 and 10 mg/m^2 doses, and was therefore the recommended dose for the Phase 3 study. In recommending the dose, the minimal dose-independent effect of plinabulin on ambulatory blood pressure monitoring, and negligible effect on QT interval are taken into account.

Simulations were also performed to determine the fixed dose of plinabulin that is similar to the body surface area (BSA)-based dose of 20 mg/m^2. Simulations were performed with plinabulin fixed doses of 20, 40, 60, and 80 mg and compared with the selected BSA-based dose of 20 mg/m^2 as the reference, assuming a similar population as that studied in the Phase 2 portion of the study and used in the BSA-based dosing simulations. The 40 mg fixed dose yielded similar peak concentration and AUC as the body surface area-based dose of 20 mg/m^2, indicating that subjects are not predicted to be at any risk of over or under exposure to plinabulin at this dose.

The efficacy performance of the 40 mg fixed dose is predicted to be similar to that of the BSA-based dose of 20 mg/m^2. The 60 and 80 mg fixed doses yielded results similar to the 40 mg fixed dose. Thus, a fixed plinabulin dose of 40 mg is predicted to yield a similar efficacy as a BSA-based dose of 20 mg/m^2.

7. STUDY OBJECTIVES

7.1. Phase 2 (Open Label) Objectives

Plinabulin pharmacokinetic (PK) and pharmacodynamic (PD) assessments will be made to enable a PK/PD analysis.

Primary objective:

- To establish the Recommended Phase 3 Dose (RP3D) based on PK/PD analysis.

Primary efficacy pharmacodynamic 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). Severe (Grade 4) neutropenia is an absolute neutrophil count (ANC) $<0.5 \times 10^9$/L ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15 (pre-dose on dosing days; times equivalent to pre dose on other days).

Primary safety pharmacodynamic 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).

Secondary objectives:

- To characterize the pharmacokinetic profile of plinabulin and docetaxel
- To characterize the exposure-response relationships between measures of plinabulin exposure and the pharmacodynamic endpoint DSN
- To characterize the exposure-safety relationships between measures of plinabulin exposure and safety events of interest

Exploratory objectives:

- To assess CD34+ at screening, and on Days 2, 6, 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
- For selected countries only: to investigate the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8.

Safety objectives:

- Incidence, occurrence, and severity of AEs/SAEs
- Incidences of bone pain

- Safety and tolerability (physical examination and safety laboratory assessments)

7.2. Phase 3 (Double Blind) Objectives

Primary Efficacy Objective (Cycle 1):

To assess DSN in treatment Cycle 1 in patients with advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy; locally advanced or metastatic non small cell lung cancer (NSCLC) after platinum therapy failure; or hormone refractory (androgen independent) metastatic prostate cancer (HRPC) treated with docetaxel (75 mg/m^2) + plinabulin (40 mg) (Arm 2) versus docetaxel (75 mg/m^2) + pegfilgrastim (6 mg) (Arm 1). ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15. Blood draws for ANC will be taken approximately the same time as the time of the pre-dose sample on Day 1, and will be taken by preference in the morning. DSN should be calculated as the number of consecutive days from the first day when a patient's ANC is below 0.5 x l09/L until the patient reaches an ANC> 0.5 x 109/L, in Cycle 1. For patients who do not experience any severe neutropenia in Cycle 1, the DSN is set to 0. For patient's experiencing several episodes, the number of days of DSN will be summed up.

Secondary Efficacy Objectives (Cycle 1 and Cycles 1 to 4):

- To assess DSN in Cycle 1 with only mature neutrophils
- Platelet count in Cycle 1: maximum decrease from baseline (prior to Cycle 1 docetaxel dose)
- Proportion of patients with neutrophil-to-lymphocyte ratio (NLR) > 5 after Day 7 through Day 15 in Cycle 1
- AUC using the trapezoidal quadrature method for bone pain, from Day 1 through Day 8 (pegfilgrastim will be administered on Day 2) in Cycle 1, based on the pain score from the patient bone pain scale
- Change in estimated mean bone pain score from pre-dose Day 1 through Day 8 in Cycle 1
- Proportion of patients with thrombocytopenia (all grade) in Cycles 1 to 4
- To assess the incidence of infections in Cycles 1 to 4

Exploratory Efficacy Objectives (Cycle 1):

- To evaluate the proportion of patients in Cycle 1 with:
  - Thrombocytopenia (all grade)
  - Grade 4 neutropenia (ANC < 0.5×10^9/L)
  - Grade 4 neutropenia (ANC<0.5 x10^9/L) for mature neutrophils
  - Grade 3 neutropenia (ANC < 1×10^9/L)
  - Grade 3 (ANC < 1×10^9/L) and Grade 4 neutropenia (ANC < 0.5×10^9/L)
  - Bands > 0 after Day 7 through Day 15

  - Promyelocytes plus myelocytes > 0 after Day 7 through Day 15
  - Promyelocytes, myelocytes, metamyelocytes and bands >0 after Day 7 through Day 15
  - Lymphocyte-to-monocyte ratio (LMR) < 3.2 after Day 7 through Day 15
  - Platelet-to-lymphocyte ratio (PLR) > 200 after Day 7 through Day 15
  - At least 1 day of bone pain
  - At least 2 days of bone pain
  - At least 3 days of bone pain
  - At least 4 days of bone pain
  - At least 5 days of bone pain
  - At least 6 days of bone pain
  - At least 7 days of bone pain
  - At least 8 days of bone pain
- To compare the proportion of patients who needed bone pain medication (defined as any medication reported on pain medication assessment from Day 1 through Day 8) in Cycle 1
- To compare the time (in days) to first use of bone pain medication between the treatment groups
- To assess DSN in treatment Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure for mature neutrophils only
- To assess DSN in treatment Cycle 1 in patients with HRPC
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure for mature neutrophils only
- To assess DSN in treatment Cycle 1 in patients with advanced or metastatic breast cancer who have failed < 5 prior lines of chemotherapy
- To assess DSN in Cycle 1 in patients with advanced or metastatic breast cancer who have failed < 5 prior lines of chemotherapy for mature neutrophils only
- To assess DSN in treatment Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure or HRPC
- To assess DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum therapy failure or HRPC for mature neutrophils only
- Platelet count at least 30% change from baseline at any time during Cycle 1.
- ANC nadir during Cycle 1

- To assess CD34+ at Day 1 pre-dose, Day 2 pre-dose, Day 6, 7, 8, 9, 10, and 15, Day 1 Cycle 2 pre-dose
- For selected countries only: to investigate the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8.

Exploratory Efficacy Objectives (Cycles 1 to 4):

- To evaluate the proportion of patients in Cycles 1 to 4 with:
  - Febrile neutropenia (FN) (ANC $<1.0 \times 10^9$/L AND a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour).
  - Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L).
- To assess the maximum change from baseline in CD34 + counts in each treatment arm
- To assess the maximum difference between treatment arms in CD34+ counts
- To assess the maximum change from baseline in haptoglobin levels in each treatment arm
- To assess the maximum difference between treatment arms in haptoglobin levels
- To evaluate the following healthcare utilization objectives:
  - Incidence of 30-day rehospitalizations - all cause
  - Incidence of all cause hospitalizations
  - Duration of all cause hospitalizations
  - Incidence of all cause emergency room (ER) visits
  - Incidence of all cause intensive care unit (ICU) stays
  - Duration of all cause ICU stays
  - Incidence of all cause docetaxel dose delay (≥7 days), dose reduction (≤85%), or dose discontinuation
  - Incidence of platelet transfusions
  - Incidence of antibiotics use
- To collect data on disease progression
- To evaluate the following QoL objective:
  - Health-related QoL questionnaire evaluated with European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L

Safety Objectives:

- Incidence, occurrence, and severity of adverse events (AEs)/serious adverse events (SAEs)

- Safety and tolerability (physical examination and safety laboratory assessments)

8. STUDY DESIGN

8.1. Summary of Study Design

This is a multicenter, randomized study with an open label phase 2 portion and a double blind phase 3 portion. Approximately 190 patients will be enrolled in this study.

The decision to complete the Phase 2 portion of the study as open label was made to reduce the unnecessary complexities of study conduct (such as placebo infusions and injections).

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

In Phase 2, patients only with advanced or metastatic 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; locally advanced or metastatic NSCLC after platinum therapy failure; or hormone refractory (androgen independent) metastatic prostate cancer.

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

Phase 2 (Open Label):

Approximately 40 patients with advanced and metastatic NSCLC will be enrolled. Patients are randomly assigned, with approximately 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)

The study will be temporarily closed to enrollment when 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 RP3D. The PK/PD analysis will be done by an independent party at the time 40 patients in Phase 2 have completed at least Cycle 1.

Phase 3 (Double Blind):

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.

A fixed dose of 40 mg has been selected as the RP3D following the Phase 2 PK/PD analysis (details of dose selection are provided in Section 6.2.3).

Approximately 150 patients are planned to be enrolled in the Phase 3 with one of the following diagnosis: advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy; locally advanced or metastatic NSCLC after platinum therapy failure; or hormone refractory (androgen independent) metastatic prostate cancer. Each eligible patient will be

stratified according to his or her tumor type (breast cancer, NSCLC, or HRPC) and region (Asia, non-Asia). Patients will be randomly assigned with equal probability (1:1 ratio) or 75:75, with the arm designation and planned intervention as follows:

Arm 1: Docetaxel (75 mg/m^2) + pegfilgrastim (6 mg) + placebo matching plinabulin

Arm 2: Docetaxel (75 mg/m^2) + plinabulin (40 mg) + placebo matching pegfilgrastim

In order to facilitate balanced treatment arms with respect to cancer type, once either arm reaches at least 1/3 (of total) of patients with that cancer type, it will be closed to that cancer type and enrollment will continue for patients with the other cancer types, up to the planned maximum number of patients.

Data from all patients receiving the RP3D plinabulin dose in Phase 2 and Phase 3 will not be pooled for assessing the primary and secondary study endpoints, but analyzed separately.

Treatment Administration:

In Phase 2 and Phase 3, Cycles 1 to 4 will consist of docetaxel 75 mg/m^2 administered by IV infusion on Day 1 over 60 minutes (±5 minutes) every 21 days.

In the phase 2 portion, 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 get a single intravenous infusion of plinabulin at their assigned dose over 30 minutes (± 5 minutes). Thus the wait time between end of docetaxel infusion and start of the plinabulin infusion is approximately 30 minutes. On Day 2 of each cycle, ≥24 hours after completing chemotherapy, patients assigned to pegfilgrastim (arm 1) will receive a single dose of pegfilgrastim (6 mg) (subcutaneous injection).

In the phase 3 portion, 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 will get a single dose of plinabulin or placebo intravenously over 30 minutes (± 5 minutes). On Day 2 of each cycle, ≥24 hours after completing chemotherapy, patients will receive a single dose of pegfilgrastim (6 mg) or 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 one docetaxel dose reduction is allowed (refer to Taxotere® (Prescribing Information)). 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 (± 2 days) after the last dose of study drug. Patients who withdraw for progressive disease and who will continue to another chemotherapy regimen will complete the EOT visit at Cycle X Day 21. They then continue to another chemotherapy regimen and do not need to have the safety follow-up visit (where X is the last cycle prior to progression, and is 4 or less).

If, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until completion of the EOT visit (in this instance, the EOT visit will be Cycle 4 Day 21). Follow-up visits will be required to monitor for ongoing treatment-related AEs. All patients experiencing drug-related toxicities of ≥ Grade 2 at the EOT 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 study drug 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.

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 screening only.

Post-Treatment Assessment

For both Phase 2 and Phase 3, once a patient has completed all cycles of study treatment they will enter a post-treatment (non-interventional) assessment phase. On a monthly basis, the patients will be contacted to assess whether they have started to receive another anti-cancer therapy, which could be cytotoxic chemotherapy, a programmed death-ligand 1 (PD-L1) inhibitor, radiation therapy, or other therapy. This assessment will continue until the patient starts another anti-cancer therapy, the patient chooses to have no further therapy, the patient dies, or the patient becomes lost to follow-up. This information will be used to analyze the time to next treatment.

This will be performed in addition to any follow up for monitoring of ongoing treatment-related AEs, as described above.

Patients without progressive disease at the EOT visit will undergo a follow-up visit every 2 months until the occurrence of either disease progression or death. These visits may be conducted per telephone or other means.

For patients included into the Phase 3 part of the study after November 2019, there will be a long-term safety follow-up through patient contacts by phone calls, letters or electronic means; or medical records reviews will be conducted to all subjects approximately every 6 months up to 5 years to monitor long term safety of plinabulin. Follow-up telephone calls and queries of treating physicians or designee health care provider to ascertain safety information on secondary malignancies or tumor progression as well as other potential safety findings/concerns. Subjects who receive at least one dose of plinabulin or pegfilgrastim will be followed up.

The schedule of assessments is presented in Table 6 and Table 7.

9. STUDY POPULATION

9.1. Inclusion Criteria

Patients may be entered in the study only if they meet all of the following criteria:

1. At least ≥ 18 years of age (male or female) at the time of signing the informed consent form.
2. ECOG performance status of 0 or 1.
3. Patients with:

   Phase 2 only:

   – advanced or metastatic NSCLC failing platinum-based therapy

   Phase 3 only:

   – advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy (Note that study treatment may be the first chemotherapy treatment for advanced or metastatic cancer)

   – locally advanced or metastatic NSCLC after platinum therapy failure

   – HRPC (Note that study treatment may be the first chemotherapy treatment)
4. Pathology confirmation of cancer is required.
5. Patients with ≥ 1 of the following risk factors, at the initiation of docetaxel chemotherapy, that would require neutropenia prophylaxis per NCCN guidelines (version 2, 2016) (refer to Appendix A):

   a. Prior chemotherapy or radiation treatment
   b. Bone marrow involvement by tumor
   c. Surgery and/or open wounds within 4 weeks of first administration of study drug
   d. Age > 65 years of age and receiving full chemotherapy dose intensity
6. Life expectancy of 3 months or more.
7. The following laboratory results assessed within 14 days prior to study drug administration[2]:

   – Hemoglobin ≥ 9 g/dL independent of transfusion or growth factor support

   – ANC ≥ 1.5 x 10^9/L independent of growth factor support

   – Serum total bilirubin ≤ 1.5 times the upper limit normal (ULN), unless the patient has a diagnosis of Gilbert's disease, in which case direct bilirubin less than or equal to 1.5 x ULN of the direct bilirubin.

   – AST and ALT ≤ 2.5 x ULN (≤ 1.5 x ULN if alkaline phosphatase is > 2.5 x ULN)

[2] Results are from the central laboratory. Local laboratory results may be accepted on a case by case basis after discussion with the Medical Monitor, however in this case central laboratories must also be taken within the screening time window.

- Serum creatinine ≤ 1.5 x ULN

8. Prothrombin time (PT) and International Normalized Ratio (INR) ≤ 1.5 × ULN, activated partial thromboplastin time (PTT) ≤ 1.5 × ULN, based on central laboratory results. [2]
9. Female subjects of childbearing potential have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrhoeic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.
   - Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.
   - Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 3 months after their last dose of study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (e.g., oral, injectable, implant, transdermal) plus one barrier method; (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner.
   - For male patients who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception during the treatment period and for at least 3 months after the last dose of study drug.

9.2. Exclusion Criteria

Patients will not be entered in the study if they meet any of the following criteria:

1. History of myelogenous leukemia, myelodysplastic syndrome, or concomitant sickle cell disease.
2. Received chemotherapy within 4 weeks prior to the first dose of study drug.
3. Received prior docetaxel, except adjuvant docetaxel given > 1 year prior to first dose of study drug.
4. Phase 3 only: Received ≥ 5 lines of cytotoxic chemotherapy for advanced or metastatic breast cancer (adjuvant chemotherapy will count as one line of chemotherapy, and any hormonal or biological, non-conjugate therapy [e.g. trastuzumab] will not count as a line of therapy).
5. Current use of strong cytochrome P450 (CYP) 3A4 inhibitors, within 3 days of the first administration of study drug, and 7 days after treatment with taxanes OR requires use of strong CYP3A4 inhibitors (refer to Section 10.6.2)

6. Received an investigational agent or tumor vaccine within 2 weeks before the first dose of study drug; patients must have recovered from toxicity of prior treatment and have no > Grade 1 CTCAE (v4.03) treatment emergent adverse events.
7. Receiving any concurrent anticancer therapies.
8. Received a prior bone marrow or stem cell transplant.
9. Has a co-existing active infection or received systemic anti–infective treatment within 72 hours before the first dose of study drug.
10. Prior radiation therapy within the 4 weeks before the first dose of study drug.
11. Prior use of pegfilgrastim or filgrastim within 4 weeks before the first dose of study drug.
12. Presence of any serious or uncontrolled illness including, but not limited to: uncontrolled diabetes, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, uncontrolled arterial thrombosis, symptomatic pulmonary embolism, or psychiatric illness that would limit compliance with study requirements, or any other conditions that would preclude the patient from study treatment as per the discretion of the Investigator.
13. Significant cardiovascular history:
    - History of myocardial infarction or ischemic heart disease within 1 year (within a window of up to 18 days less than 1 year) before first study drug administration;
    - Uncontrolled arrhythmia;
    - History of congenital QT prolongation;
    - Electrocardiogram (ECG) findings consistent with active ischemic heart disease;
    - New York Heart Association Class III or IV cardiac disease;
    - Uncontrolled hypertension: blood pressure consistently >150 mm Hg systolic and > 100 mm Hg diastolic in spite of antihypertensive medication
14. History of hemorrhagic diarrhea, inflammatory bowel disease, or active uncontrolled peptic ulcer disease. (Concomitant therapy with ranitidine or its equivalent and/or omeprazole or its equivalent is acceptable). History of ileus or other significant gastrointestinal disorder known to predispose to ileus or chronic bowel hypomotility.
15. Any other malignancy requiring active therapy.
16. Known human immunodeficiency virus (HIV) seropositivity.
17. Active Hepatitis B virus (HBV) infection which requires antiviral treatment. Patients with detectable Hepatitis B surface Antigen (HBsAg) may be eligible provided the patient has a negative viral load. Patients with a positive HBsAg must have a negative viral load before each chemotherapy administration. Hepatitis B surface antibody (anti-HBs) without detectable HBsAg does NOT exclude patients from the study. Hepatitis C infection (Hepatitis C antibody reactive) which requires treatment also excludes patients from the study.
18. Female subject who is pregnant or lactating.

19. Unwilling or unable to comply with procedures required in this protocol.

9.3. Removal of Patients from Therapy or Assessments

Patients will receive treatment with study drug up to 4 cycles in this study; thereafter patients may continue receiving docetaxel and pegfilgrastim at the Investigator's discretion. Patients will complete a safety follow-up visit 30 days (± 2 days) after the last dose of study drug. If, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until completion of the EOT visit (in this instance, the EOT visit will be Cycle 4 Day 21). The safety follow-up visit does not need to be performed in this case. The same situation applies for patients with progressive disease who need another chemotherapy treatment, they also will perform the EOT visit at Cycle X Day 21 and continue to the next chemotherapy regimen (where X is the last cycle prior to progression, and is 4 or less). The safety follow-up visit is not applicable in these cases.

If a patient develops a positive viral load during the study, chemotherapy should be held for a maximum of 21 days. If the viral load returns to zero treatment can be restarted, otherwise the patient should be withdrawn from the study.

Treatment up to 4 cycles of study drug in this study will continue until any 1 of the following occurs:

- Dose limiting toxicity or critical adverse events as described in the docetaxel package insert (refer to Taxotere® (Prescribing Information) and Table 4).
- Need for a protocol-prohibited dose reduction or study drug delay greater than 21 days
- Initiation of a protocol-prohibited concomitant medication or non-protocol chemo/biological therapy for treatment of his or her disease
- Development of an AE/SAE, illness or condition that may interfere with the patient's participation or require treatment discontinuation
- Investigator opinion
- Sponsor decision
- Voluntary withdrawal of consent

10. STUDY TREATMENTS

10.1. Study Treatment

The study drugs under evaluation are plinabulin and pegfilgrastim. Placebo-matching plinabulin and pegfilgrastim will also be used as part of the study design.

10.1.1. Treatments Administered

Patients will be included in either Phase 2 or Phase 3 parts of the study (Table 2 and Table 3):

Phase 2 (Open Label) (approximately 10 patients per arm with advanced or metastatic NSCLC after failing platinum-based therapy):

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)

In the phase 2 portion, 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 get a single intravenous infusion of plinabulin at their assigned dose over 30 minutes (± 5 minutes). Thus the wait time between end of docetaxel infusion and start of the plinabulin infusion is approximately 30 minutes. On Day 2 of each cycle, ≥24 hours after completing chemotherapy, patients assigned to pegfilgrastim (arm 1) will receive a single dose of pegfilgrastim (6 mg) (subcutaneous injection).

Phase 3 (Double Blind) (a planned 75 patients per arm with advanced or metastatic breast cancer, who have failed < 5 prior lines of chemotherapy; locally advanced or metastatic NSCLC after platinum therapy failure; or hormone refractory [androgen independent] metastatic prostate cancer):

Arm 1: Docetaxel (75 mg/m^2) + pegfilgrastim (6 mg) + placebo matching plinabulin

Arm 2: Docetaxel (75 mg/m^2) + plinabulin (40 mg) + placebo matching pegfilgrastim

All patients with HRPC also are given prednisone 5 mg orally twice daily continuously in addition to docetaxel (see Taxotere® (Prescribing Information) as well as other assigned study drugs.

In the phase 3 portion, 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 will get a single dose of plinabulin or placebo intravenously over 30 minutes (± 5 minutes). On Day 2 of each cycle, ≥24 hours after completing chemotherapy, patients will receive a single dose of pegfilgrastim (6 mg) or placebo (subcutaneous injection).

Rescue Treatment:

Patients who experience an FN event in Cycle 1 should be discussed with the medical monitor. The blinding will be broken (if Phase 3), and patients assigned to plinabulin will receive pegfilgrastim in subsequent cycles. If a patient was originally assigned to the pegfilgrastim arm,

patients must 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 (refer to Section 10.6.1). If a patient is hospitalized, as a result of a Serious Adverse Event, the procedure for reporting Serious Adverse Events (Section 13.2) should also be followed.

Treatments Administered:

Table 2: Treatments Administered for Phase 2

	Cycles 1 to 4, Day 1 of each 21 Day Cycle **Docetaxel**	**Cycles 1 to 4, Day 1 of each 21 Day Cycle 30 minutes after the end of the docetaxel infusion** **Plinabulin**	**Cycles 1 to 4, Day 2 of each 21 Day Cycle ≥ 24 hours post docetaxel** **Pegfilgrastim**
Arm 1	docetaxel (75 mg/m^2) 60-minute IV infusion		pegfilgrastim (6 mg) SC single dose
Arm 2	docetaxel (75 mg/m^2) 60-minute IV infusion	plinabulin (20 mg/m^2) 30-minute IV infusion	
Arm 3	docetaxel (75 mg/m^2) 60-minute IV infusion	plinabulin (10 mg/m^2) 30-minute IV infusion	
Arm 4	docetaxel (75 mg/m^2) 60-minute IV infusion	plinabulin (5 mg/m^2) 30-minute IV infusion	

Abbreviations: IV = intravenous; SC = subcutaneous

Table 3: Treatments Administered for Phase 3

	Cycles 1 to 4, Day 1 of each 21 Day Cycle **Docetaxel**	**Cycles 1 to 4, Day 1 of each 21 Day Cycle** **30 (±5) minutes after the end of the docetaxel infusion** **Plinabulin or Placebo**	**Cycles 1 to 4, Day 2 of each 21 Day Cycle** **≥ 24 hours after the end of the docetaxel infusion** **Pegfilgrastim or Placebo**
Arm 1	docetaxel (75 mg/m^2) 60-minute (±5 minutes) IV infusion	placebo matching plinabulin 30-minute (±5 minutes) IV infusion	pegfilgrastim (6 mg) SC single dose
Arm 2	docetaxel (75 mg/m^2) 60-minute (±5 minutes) IV infusion	plinabulin (40 mg) 30-minute (±5 minutes) IV infusion	placebo matching pegfilgrastim SC single dose

Abbreviations: IV = intravenous; SC = subcutaneous

Dose modifications for docetaxel for specific Grade 3/4 AEs are provided in Section 10.5, Table 4.

Stopping Rules

During the phase 2 study if at any given cohort, 3 patients or more have Grade 4 or 5 toxicity not related to underlying disease (with the exception of neutropenia), accrual to that cohort will be halted and the study will be continued at the lower dose cohorts in phase 2 (for example if 3 patients at the 20 mg/m^2 cohort develop Gr. 4 toxicity the accrual to that cohort will be stopped and the study will continue as planned with the accrual of the two remaining open cohorts). Interactive web response system (IWRS) will be utilized to assign patients to a lower dose cohort in phase 2. Study sites will be instructed to call IWRS when a Grade 4 or 5 toxicity event occurs.

10.1.2. Identity of Study Drugs

The Sponsor will supply plinabulin during the study treatment. If docetaxel/pegfilgrastim is not available at study sites, this will be supplied by the Sponsor.

Refer to Taxotere® (Prescribing Information) and Neulasta® Package Insert for details on docetaxel and pegfilgrastim.

Details are provided for plinabulin below.

Instructions for pharmacy drug preparation can be found in the study Pharmacy Manual.

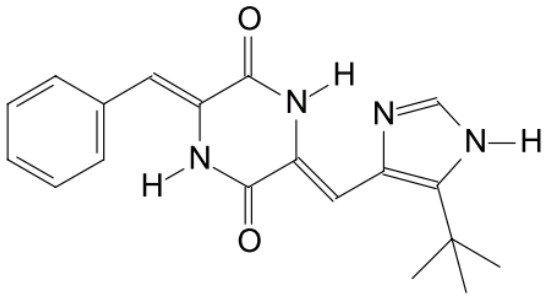
Plinabulin

Plinabulin (BPI-2358) is a synthetic, low molecular weight, new chemical entity originally developed (previous name NPI-2358) by Nereus Pharmaceuticals, Inc., and now by BeyondSpring Pharmaceuticals, Inc. It belongs to the diketopiperazine class of compounds. Plinabulin is being developed as an anti-cancer agent for use in combination with docetaxel as a second-line and third-line treatment for patients with recurrent NSCLC and for the prevention of

severe neutropenia in patients with non-myeloid malignancies receiving docetaxel monotherapy. Investigator-initiated clinical trial of plinabulin with nivolumab in recurrent NSCLC has been initiated.

Chemical Name, Structural Formula of Plinabulin

- Study drug code: BPI-2358 (previous name NPI-2358)
- Generic name: Plinabulin
- Chemical name: 5-Piperazinedione, 3-[[5-(1,1-dimethylethyl)-1H-imidazol-4-yl]methylene]-6-(phenylmethylene)-, (3Z,6Z)
- Molecular formula: $C_{19}H_{20}N_4O_2$
- Molecular Weight: 336.4 g/mol
- Structural Formula:



10.2. Study Drug Preparation and Dispensation

Details are provided for plinabulin only. Refer to the Taxotere® (Prescribing Information) and Neulasta® Package Insert for details on docetaxel and pegfilgrastim.

Instructions for pharmacy drug preparation can be found in the study Pharmacy Manual.

10.2.1. Packaging and Labeling

Plinabulin is supplied as a solution in 40% Kolliphor HS 15 (formerly known as polyoxyl 15 hydroxystearate or Solutol HS-15®)/60% propylene glycol in amber vials containing 80 mg in 20 mL (4 mg/mL). Each vial is designated for single use. The labeled storage condition for the drug product is stored between 15° and 25°C (59° and 77°F). Vials contain 80 mg drug in 20 mL (4 mg/mL) and are labeled with other information as per local regulatory requirements.

The contents of the label will be in accordance with all applicable regulatory requirements.

10.2.2. Handling and Storage

The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures.

Vials of plinabulin should be stored at room temperature (between 15°C and 25°C [59° F and 77°F]) and must be protected from light. Protection from light must be maintained throughout the drug administration process.

The stability of the drug meets all specifications under controlled room temperature storage conditions (25°C, 60% relative humidity). Using a previous manufacturing process, drug product stability was demonstrated for up to, and including, 48 months. Maintenance of plinabulin purity, potency, and impurity profile has been demonstrated at 6 months at elevated temperature and humidity (40°C/75% relative humidity) and after freeze-thaw cycles.

Instructions for the preparation of prescribed doses are provided in the Pharmacy Manual.

10.2.3. Compliance and Accountability

Plinabulin will be provided by an agent of the Sponsor and shipped directly to the Investigator or the designated pharmacist. If docetaxel/pegfilgrastim is not available at study sites, this will be supplied by the Sponsor.

The Investigator or designated pharmacist will acknowledge receipt of the shipment and note content and condition of the shipment on the clinical material shipping form. The Sponsor or its representatives will supply the appropriate forms.

The pharmacist or person responsible for dispensing the study drug at the site will maintain an accurate and current record of all drug supplies received from the repository and dispensed to study patients. The dispensing record should contain the protocol number and information regarding the amount/vial(s) dispensed; date dispensed, lot #, patient identifier number, patient initials, and the initials of the person dispensing the medication.

10.2.4. Disposal and Destruction

All partially used or empty vial drug counts should be verified by the Sponsor's monitor. The site will contact and discuss with the Sponsor the method of study drug destruction to determine whether the study drug will be shipped to a designated facility contracted by the Sponsor or destroyed at the study center according to the site's Standard Operating Procedures (SOP). If it is determined that the study drug will be destroyed on site, written confirmation of vial destruction and a copy of the institutional SOP must be provided to the Sponsor or its representative.

At the end of the study, all expired or unused medication will be returned to the contract repository with an inventory of returned clinical materials or destroyed on site according to site procedures. The Sponsor will be notified before shipment or destruction.

10.3. Patient Numbering and Treatment Assignment

10.3.1. Patient Numbering

Patients will be identified by a patient number.

10.3.2. Treatment Assignment

Patients in Phase 3 will be stratified based on his or her tumor type (breast cancer, NSCLC, HRPC) and region (Asia, non-Asia). Patients will be randomized using IWRS to 1 of the following treatment groups:

Phase 2 (approximately 10 patients in each 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)

Phase 3 (75 patients enrolled in each arm):

Arm 1: Docetaxel (75 mg/m^2) + placebo matching plinabulin + pegfilgrastim (6 mg)

Arm 2: Docetaxel (75 mg/m^2) + plinabulin (40 mg) + placebo matching pegfilgrastim

10.3.3. Treatment Allocation

Phase 2 Open Label:

During randomization, patients and all personnel involved in the conduct of the study and interpretation of results, including investigators, site personnel, and sponsor staff will be notified of treatment allocation. A master list of all treatments and the patient numbers associated with the treatments will be maintained by the clinical supply vendor, the IWRS vendor, and the sponsor.

Phase 3 Double Blind:

During randomization, patients and all personnel involved with the conduct and interpretation of the study, including Investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or contract research organization (CRO) and accessible only to authorized persons.

A master list of all treatments and the patient numbers associated with the treatments will be maintained in a sealed envelope by the clinical supply vendor, the IWRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IWRS. Emergency procedures for revealing drug codes are provided in the study manual. If possible, before breaking the blind, the Investigator should consult with the sponsor to ascertain the necessity of breaking the code.

10.4. Dosage and Administration

10.4.1. Plinabulin or Matching Placebo

In the Phase 2 portion, plinabulin will be administered at a dose of 5 mg/m^2, 10 mg/m^2, and 20 mg/m^2. In the Phase 3 portion of the study, plinabulin will be administered at a fixed dose of 40 mg and the study matching placebo of plinabulin will be administered in an equal volume.

10.4.2. Pegfilgrastim or Matching Placebo

In the Phase 2 portion, pegfilgrastim will be administered at a dose of 6 mg as a single dose syringe. In the Phase 3 portion, pegfilgrastim will be administered at a dose of 6 mg as a single dose syringe and the study matching placebo of pegfilgrastim will be administered in an equal volume.

The Investigator and study site staff should be experienced in the use of pegfilgrastim and familiar with the pegfilgrastim prescribing information provided by the manufacturer. Pegfilgrastim should be obtained from the institutional pharmacy and prepared per institutional protocol. United States Food and Drug Administration (US FDA) approved source of pegfilgrastim is required for use in this study. The recommended dosage of pegfilgrastim is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle in adults. Do not administer pegfilgrastim between 14 days before and 24 hours after administration of cytotoxic chemotherapy. Pegfilgrastim or matching placebo will be administered 24 hours after completing chemotherapy. Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer pegfilgrastim if discoloration or particulates are observed. NOTE: The needle cover on the single-use prefilled syringe contains dry natural rubber (latex); persons with latex allergies should not administer this product. Follow institutional guideline/practice for prevention/assessment/management of hypersensitivity/infusion reaction with pegfilgrastim administration (refer to Neulasta® Package Insert for further details).

10.4.3. Docetaxel

Docetaxel will be administered at a dose of 75 mg/m^2.

As a standard approved chemotherapy agent, the Investigator and study site staff should be experienced in the use of docetaxel and familiar with the docetaxel prescribing information provided by the manufacturer. Docetaxel should be obtained from the institutional pharmacy and prepared per institutional protocol. US FDA approved source of docetaxel is required for use in this study. Docetaxel may be provided by a distributer in some regions by agreement with the Sponsor. Administration should be carried out with a 1-hour IV infusion per institutional protocol at the dose prescribed by this clinical study protocol (75 mg/m^2). Dexamethasone (16 mg per day administered as 8 mg twice daily, or as per institution standard) will be given on the day before, the day of (Day 1), and the day following docetaxel infusion (Day 2). Follow institutional guideline/practice for prevention/assessment/management of hypersensitivity/infusion reaction with docetaxel administration (refer to Taxotere® (Prescribing Information) for further details).

Docetaxel when given on a standard regimen (e.g., 75 mg/m^2 IV every 3 weeks in non-small cell lung cancer) has an intermediate (10%-20%) risk of causing febrile neutropenia. The NCCN guidelines recommend that physicians consider (but do not mandate) myeloid growth factor support in patients with ≥1 risk factor with docetaxel treatment (see below). Patients without risk factors may be observed for their initial treatment cycle. If the patient experiences an episode of febrile neutropenia or a dose limiting neutropenic event (a nadir or a day of treatment count impacting the planned dose of chemotherapy) during the previous treatment cycle, the patient should continue on study, and have dose adjustments as specified in Sections 10.5 and 10.6.1.

Patient risk factors for developing febrile neutropenia when receiving docetaxel at the dose and schedule used in the protocol are per NCCN guidelines (Version 2.2016, refer to Appendix A).

10.5. Dose Interruptions and Modifications

All adverse events should be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, v4.03). In the event of multiple toxicities, dose delays and modifications should occur in accordance with the highest adverse events observed.

All patients, including patients who withdraw from the study early, will complete a safety follow-up visit 30 days (± 2 days) after the last dose of study drug. Patients who withdraw for progressive disease and who will continue to another chemotherapy regimen will complete the EOT visit at Cycle X Day 21. They then continue to another chemotherapy regimen and do not need to have the safety follow-up visit (where X is the last cycle prior to progression, and is 4 or less).

If, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until completion of the EOT visit (in this instance, the EOT visit will be Cycle 4 Day 21). Follow-up visits will be required to monitor for ongoing treatment-related AEs. All patients experiencing drug-related toxicities of ≥ Grade 2 at the EOT 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 study drug 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.

Patients without progressive disease at the EOT visit will undergo a follow-up visit every 2 months until the occurrence of either disease progression or death. Patients included after November 2019 will have a long term FU approximately every 6 months up to 5 years to monitor long term safety of plinabulin. These visits may be conducted per telephone or other means.

As described in Table 4, the occurrence of specific Grade 3 or 4 AEs during chemotherapy will require a dose reduction, delay, or discontinuation. Only one docetaxel dose reduction is allowed (refer to Taxotere® (Prescribing Information) for further details). If a chemotherapy cycle is delayed by more than 3 weeks, the patient will be withdrawn from the study.

No dose reductions are allowed with plinabulin or pegfilgrastim.

Docetaxel

Dose reduction and treatment delay for docetaxel will follow guidance described in docetaxel prescribing information as summarized in Table 4.

Hematologic support, such as erythropoietin, darbopoetin, granulocyte colony-stimulating factor (Neupogen® or Neulasta®), or red blood cell or platelet transfusions prior to 4 weeks of the first dose of study drug in order to meet entry criteria is not permitted.

Patients may receive hemopoietic support or transfusions during the study as clinically indicated. Please note the special instructions regarding Neupogen® or Neulasta® use during study treatment in Section 10.6.1.

Any delay of docetaxel dosing will result in the delay of plinabulin administration. For each cycle, the dose of plinabulin is always administered 30 minutes after the docetaxel infusion. If docetaxel is discontinued, plinabulin will also be discontinued.

Table 4: Dose Modifications for Docetaxel

Condition	Action
Febrile neutropenia or ANC < 0.5 x 10^9/L for > 1 week or Grade 4 thrombocytopenia	withhold docetaxel until ANC > 1.5 x 10^9/L and platelets > 100 x 10^9/L, then resume at 55 mg/m^2
Grade 3/4 skin reactions	withhold docetaxel until resolution and then resume at 55 mg/m^2
Grade 3/4 non-hematologic docetaxel related toxicities	withhold docetaxel until resolution and then resume at 55 mg/m^2
Grade 3/4 peripheral neuropathy	discontinue docetaxel
AST and/or ALT > 2.5 to ≤ 5 x ULN, or AST and/or ALT > 1.5 to ≤ 5 x ULN and AP > 2.5 to ≤ 5 x ULN	withhold docetaxel until the abnormality returns toward normal and then resume at 55 mg/m^2
AST and/or ALT or AP > 5 x ULN	discontinue docetaxel

ALT=alanine aminotransferase; AP=alkaline phosphatase; AST=aspartate aminotransferase; ULN=upper limit of normal

Dexamethasone

If the patient has trouble sleeping, anxiety, stomach upset, nausea, vomiting, diarrhea, headache or swelling, they have the option to skip the 3rd day of dexamethasone (or steroid equivalent) dosing, on the day after the day of docetaxel infusion. On the day before and on the day of docetaxel infusion, the patient must take their dexamethasone (or steroid equivalent) as per institution standard.

Stopping Rules

During the phase 2 study if at any given cohort, 3 patients or more have Grade 4 or 5 toxicity not related to underlying disease (with the exception of neutropenia), accrual to that cohort will be halted and the study will be continued at the lower dose cohorts in phase 2 (for example if 3 patients at the 20 mg/m^2 cohort develop Gr. 4 toxicity the accrual to that cohort will be stopped and the study will continue as planned with the accrual of the two remaining open cohorts).IWRS will be utilized to assign patients to a lower dose cohort in phase 2. Study sites will be instructed to call IWRS when a Grade 4 or 5 toxicity event occurs.

10.5.1. Criteria for Premature Withdrawal

Patients have the right to withdraw from the study at any time for any reason. The Investigator also has the right to withdraw patients from the study if it is in the best interest of the patient.

The sponsor may also decide to withdraw a patient. All efforts should be made to complete and report the observations as thoroughly as possible as described in Section 11.7.

Every reasonable effort should be made to determine as completely as possible the reason for the withdrawal, including contacting the patient either by telephone or through a personal visit, or contacting a responsible relative. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will also be recorded on the eCRF.

Patients with clearly documented progressive disease will be taken off treatment.

10.6. Concomitant Medications and Non-drug Therapies

10.6.1. Permitted Medications

Institutional guidelines should be followed in the event of infusion/hypersensitivity reaction. Diphenhydramine and dexamethasone infusion may be administered in the event of infusion reaction.

All patients must be premedicated with oral corticosteroids (see below for HRPC) such as dexamethasone 16 mg per day (e.g., 8 mg twice daily) for 3 days starting 1 day before docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (refer to Taxotere® (Prescribing Information)). If the patient has trouble sleeping, anxiety, stomach upset, nausea, vomiting, diarrhea, headache or swelling, they have the option to skip the 3rd day of Dexamethasone (or steroid equivalent) dosing, on the day after the day of docetaxel infusion. On the day before and on the day of docetaxel infusion, the patient must take their dexamethasone (or steroid equivalent) as per institution standard.

For HRPC, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg at 12 hours, 3 hours and 1 hour before docetaxel infusion (refer to Taxotere® (Prescribing Information).

The prophylactic use of antibiotics is allowed per discretion of the treating physician. The use of antibiotics will be recorded per treatment arm (refer Table 5 for prohibited medications).

Corticosteroids (except as described for premedication) and new non-steroidal anti-inflammatory drugs (NSAIDs) are prohibited except for the treatment of AEs and as premedication as described above. Patients already receiving NSAIDs are allowed to continue taking treatment as long as the dose remains stable.

The use of strong CYP3A4 inhibitors as concomitant medications will be prohibited because docetaxel exposure increases by approximately 2-fold (Section 10.6.2) with the use of strong CYP3A4 inhibitors.

Patients who have FN should receive antibiotics per standard of care (refer to Section 10.1.1 and Table 5 for prohibited medications). The use of G-CSF as a treatment option during hospitalization for FN is strongly discouraged, since G-CSF is not approved for the treatment of FN, and is not likely to have efficacy. If, however, G-CSF treatment for FN is considered, the

Investigator should contact the Medical Monitor prior to its use. FN is defined as ANC <1.0 × 10^9/L AND a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour (as per CTCAE v4.03).

10.6.2. Prohibited Medications

Corticosteroids (except as described in Section 10.6.1) and new NSAIDs are prohibited except for the treatment of AEs. Patients already receiving NSAIDs are allowed to continue taking treatment as long as the dose remains stable.

Table 5: Strong Inhibitors of CYP3A4, as Docetaxel Exposure Increases by Approximately 2-fold

Class/Therapeutic Area	Drugs/Agents
Antibiotics	clarithromycin, telithromycin
Antidepressant	nefazodone
Antifungals	itraconazole, ketoconazole, posaconazole, voriconazole
Antiretroviral	ritonavir/lopinavir, ritonavir, saquinavir, ,
Antiviral	boceprevir, telaprevir
Miscellaneous[a]	conivaptan, grapefruit juice, mibefradil

[a] Topical formulations of prohibited medication(s) are permitted.
[b] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. studies have shown that it can be classified as a "strong CYP3A4 inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A4 inhibitor" when another preparation was used (e.g., low dose, single strength).
[c] Withdrawn from the US market.
CYP = cytochrome P450

Strong CYP3A4 inhibitors are not permitted as they may alter docetaxel exposure; consider therapeutic substitutions for these medications. Approval from the Medical Monitor is required in these situations. Please contact the Sponsor for review and approval if questions on any concomitant medication before patient enrollment or during the study treatment.

10.6.3. Anti-emetics, Antidiarrheals, and Bowel Maintenance Regimens

Docetaxel is low emetic risk (10% to 30% frequency of emesis) and appropriate anti-emetic prophylaxis should be given prior to study medication per institutional policy. In this study, dexamethasone is used as anti-emetic prophylaxis as well as to minimize docetaxel associated fluid retention.

If "breakthrough" emesis (e.g. emesis and nausea after Day 1) occurs, the general strategy is to add one agent from a different drug class to the "rescue" anti-emesis regimen. Useful anti-emetic agents for rescue include the benzodiazepines, cannabinoids (e.g. dronabinol or nabilone), haloperidol, metoclopramide, scopolamine, the phenothiazines (e.g. prochlorperaxine or promethazine) and 5HT3 receptor agonists. If a 5HT3 receptor agonist is needed, palonosetron

(which is not known to prolong QT/QTc intervals) is safest and must be chosen over other 5HT3 receptor agonists. Tropisetron is an acceptable substitute 5HT3 receptor agonist (Yavas et al, 2008).

Because of the potential interference with QT/QTc interval, in Cycle 1 between Day 1 and Day 2, the 5HT3 receptor agonists ondansetron, granisetron and dolenasetron, and the atypical antipsychotic olanzapine, are prohibited until the triplicate ECGs are completed. After Cycle 1, triplicate ECGs are not obtained, and therefore no restrictions in the use of anti-emetics apply in those cycles, thus any 5HT3 receptor agonist can be used.

If nausea and /or vomiting of Grade 2 and higher occurs, it must be treated with "rescue" anti-emetics during mid-cycle, and on subsequent cycles, the prophylactic anti-emetic regimen should be modified. Aprepitant is an acceptable prophylactic anti-emetic in this situation [Marbury et al, 2009]).

Diarrhea:

If diarrhea of Grade 1 and higher occurs, it must be treated. Grade 1 diarrhea is less than 4 bowel movements a days without any signs of hypotention, dehydration.

Antidiarrheals such as loperamide (or diphenoxylate/atropine) must be prescribed for diarrhea. Suggested loperamide use: 4 mg orally after first loose stool, then 2 mg after each stool not to exceed 16 mg in 24 hours.

Patients should also be cautioned to avoid dehydration, and of the importance of drinking water and electrolyte containing fluids throughout the day when diarrhea occurs. If IV fluids are needed, their administration must be recorded on the CRF.

In patients who develop diarrhea, use of a motility enhancing agent such as metoclopramide as part of the anti-emetic regimen in subsequent treatment cycles should be avoided.

Prophylaxis with bowel motility agents should follow institutional practice as applied to drugs such as vincristine, including the use of agents such as stool softeners, bulking agents, stimulating agents and/or dopamine antagonists. The use of opiates should be limited to when clearly indicated and prophylaxis for opiate induced constipation with agents such as methylnaltrexone should be administered. If significant constipation develops, it should be managed immediately and plinabulin administration should be delayed until resolution. Careful observance for signs of ileus and early diagnostic evaluation with radiographic and/or ultrasound studies is recommended.

The use of anti-emetics and anti-diarrheals will need to be recorded on the CRF.

10.6.4. Other Concomitant Medications

If an increase in systolic blood pressure to > 160 mmHg is observed after administration of plinabulin or placebo, oral amlodipine 10 mg or an equivalent calcium channel blocker should be administered before each subsequent dose. Increases in systolic blood pressure above 200 mmHg should be managed with nitroprusside or similar regimen per institutional practice. If hypertension can be successfully managed, patient can continue in the study at the discretion of the investigator. The Investigator should be experienced in the use of docetaxel and familiar with the docetaxel prescribing information provided by the manufacturer. According to the prescribing information for docetaxel, there have been no formal clinical studies to evaluate the

drug interactions of docetaxel with other medications. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by CYP3A4, (refer to Table 5 for further details). These medications should be avoided when patients receive docetaxel as there is a potential for a significant interaction. For patients receiving these medications before the study entry, these medications must be discontinued before docetaxel administration and sufficient time for drug clearance must be provided.

Any other medication which is considered necessary for the patient's welfare including bisphosphonates, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator.

All medications will be recorded in an appropriate section of the CRF.

No other cancer therapies or investigational agents are permitted during the entire duration of the study treatment (from 21 days before the first administration until the End of Treatment evaluation).

11. STUDY ASSESSMENTS

11.1. Study Flow and Visit Schedule

The study-specific assessments and procedures for Phase 2 and Phase 3 are shown in Table 6 and Table 7.

Table 6: Study Assessments and Procedures Schedule for Phase 2 (Open-Label)/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 Discontinuation[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 (+7days)**	**(± 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																

Period	**Screening Period**	**Treatment Period for Phase 2/Cycle 1**										**Treatment Period for Phase 2 Cycle 2, 3 and 4**					**EOT[a]**	**Early Discontinuation[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 (+7days)**	**(± 21 days)**	**± 7 days**
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 ONLY, 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 Table 13 and Table 14 (see Section 11.9). During the phase 2 open label portion of the study patients randomized to pegfilgrastim will not have samples collected for plinabulin PK analysis. Cytokine panel testing will be done using unused plasma samples collected at the PK time points; reconsenting of the patients will be required before analysis is performed.

q. Investigator opinion of progression (yes/no) at End of Treatment (EOT) recorded in CRF. For example if the patient completes two 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”. Patients without progressive disease at the EOT visit will undergo a follow-up visit every 2 months until the occurrence of either disease progression or death. These visits may be conducted per telephone or other means.

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 must 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.
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.

Table 7: Study Assessments and Procedures Schedule for Phase 3 (Double Blind)/Cycles 1 through 4, End of Treatment, 30 Day Safety Follow-up, Post-study Long-term Safety Follow-up, and Early Termination Visits

Period	**Screening Period**	**Treatment Period for Phase 3/Cycle 1**									**Treatment Period for Phase 3 Cycle 2, 3 and 4**					**EOT[a]**	**30 Day Safety Follow-up[b]**	**Post-study Long term safety follow-up**
Cycle Day	**-28 to -1**	**1**	**2**	**3, 4, 5**	**6**	**7**	**8**	**9**	**10**	**15**	**-1**	**1**	**2**	**3**	**8**	**Post Cycle X on Day 22 (+ 7 days)**	**± 2 days**	**Once every 6 months for up to 5 years after EOT**
Cycle Week		**1**					**2**			**3**	**1**				**2**			
Informed consent	X																	
Inclusion/Exclusion	X																	
Demographics[c]	X																	
Medical History/ Baseline Characteristics[d]	X																	
Vital Signs[e]	X	X	X		X	X	X	X	X	X		X			X	X	X	
ECOG Performance Status	X																	
Temperature[f]	X	X	X		X	X	X	X	X	X		X			X	X	X	
Physical examination[g]	X	X										X						
Body weight	X	X	X		X							X				X		
12-lead ECG[h]	X	X	X													X	X	
Hematology[i]	X	X	X		X	X	X	X	X	X		X			X	X	X	
Serum Chemistry[i]	X	X										X			X	X		
PT, INR, PTT[j]	X																	
Urinalysis[j]	X																	

Period	**Screening Period**	**Treatment Period for Phase 3/Cycle 1**									**Treatment Period for Phase 3 Cycle 2, 3 and 4**					**EOT[a]**	**30 Day Safety Follow-up[b]**	**Post-study Long term safety follow-up**
Cycle Day	**-28 to -1**	**1**	**2**	**3, 4, 5**	**6**	**7**	**8**	**9**	**10**	**15**	**-1**	**1**	**2**	**3**	**8**	**Post Cycle X on Day 22 (+ 7 days)**	**± 2 days**	**Once every 6 months for up to 5 years after EOT**
Hepatitis B/C testing[k]	X																	
HIV[l]	X																	
Pregnancy test[m]	X	X																
Randomization[n]	X	X																
PK sample collection[o]		X	X															
Haptoglobin		X[y]	X[y]		X	X	X	X	X	X		X[z]			X[aa]			
Exploratory Biomarker Analysis CD34+		X[y]	X[y]		X	X	X	X	X	X		X[z]			X[aa]			
Disease status evaluation[p]	X		Assessments of disease progression will be performed in accordance with standard medical practice per institution standard													X		
Docetaxel Pre-Medication		X[q]	X[q]								X[q]	X[q]	X[q]					
Docetaxel treatment[r]		X										X						
Plinabulin or placebo[r]		X										X						
Pegfilgrastim or placebo[r]			X										X					
Patient bone pain scale & pain medication assessment[s]		X[t]	X[t,u]	X	X	X	X											
Health-related QoL EORTC QLQ-C30 and EQ 5D-5L questionnaire[v]		X					X					X			X	X		
Concomitant medications[w]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events[x]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	

Period	**Screening Period**	**Treatment Period for Phase 3/Cycle 1**									**Treatment Period for Phase 3 Cycle 2, 3 and 4**					**EOT[a]**	**30 Day Safety Follow-up[b]**	**Post-study Long term safety follow-up**
Cycle Day	**-28 to -1**	**1**	**2**	**3, 4, 5**	**6**	**7**	**8**	**9**	**10**	**15**	**-1**	**1**	**2**	**3**	**8**	**Post Cycle X on Day 22 (+ 7 days)**	**± 2 days**	**Once every 6 months for up to 5 years after EOT**
Post-study contact patients or access to patient's medical records																		X

Abbreviations: ANC = absolute neutrophil count; 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 X (Day 22 [+ 7 days]) of the study for an individual patient, regardless at what time the patient discontinues the study.

b. All patients, (including those who discontinued from the study) will complete a safety follow-up visit 30 (±2) days after the last dose. Patients who withdraw for progressive disease and who will continue to another chemotherapy regimen will complete the EOT visit at Cycle X Day 21 (where X is the last cycle prior to progression, and is 4 or less). They then continue to another chemotherapy regimen and do not need to have the safety follow-up visit. If, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until completion of the EOT visit (in this instance, the EOT visit will be Cycle 4 Day 21). 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.

c. Demographic data will include gender, date of birth (or age), and race/ethnicity

d. 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

e. 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.
A standard cuff will be used to measure blood pressure (heart rate will also be measured), with a ±15 minute window:
   - Cycle 1: On Day 1 at pre-dose docetaxel, pre-dose plinabulin, 30 min, 1 hour, 2 hours post-infusion with plinabulin or placebo, and on Days 2, 6, 7, 8, 9, 10, and 15 (once, prior to blood draw).
   - Cycles 2 to 4: On Day 1 at pre-dose docetaxel, pre-dose plinabulin, 30 min,1 hour, 2 hours post-infusion with plinabulin or placebo and on Day 8

f. Temperature is to be taken every time a blood draw is taken for ANC. The same temperature location selected for a patient (ear, oral, or axillary) should be used throughout the study for each patient.

g. Physical examination will include height (cm) at screening.

h. A single 12-lead ECG will be performed at screening, EOT, 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/placebo infusion, 5-minutes before end of plinabulin/placebo infusion, 60 minutes and 4.5 hours after start of infusion with plinabulin/placebo. In Cycle 1 Day 2, ECG will be performed in triplicate prior to pegfilgrastim/placebo injection.

i. 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, ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose), on Days 1, 2, 6, 7, 8, 9, 10, and 15. Blood draws for ANC will be taken approximately the same time as the time of the pre-dose sample on Day 1, and will be taken by preference in the morning. If Grade 4 neutropenia is observed in a patient, absolute neutrophil count will be evaluated daily (central and local laboratories) during the first cycle, until Grade 4 neutropenia is resolved.

j. Analyzed at a central laboratory.

k. Hepatitis C antibody, hepatitis B surface antigen (HBsAg), viral load at local laboratory if HBsAg is positive, hepatitis B surface antibody (anti-HBs). Hepatitis serology can be performed using laboratory standard methodology, by local laboratory or by the central laboratory if local testing is not available.

l. If HIV testing is done (at the discretion of the investigator), the test will be conducted at the local site.

m. 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 (either on Day -1 or prior to infusion on Day 1). Confirm with serum testing (local or central laboratory) if urine sample is positive. Additional testing may be performed at the discretion of the investigator.

n. Patients can be randomized on Cycle 1 Day -1 or Cycle 1 Day 1, to allow site flexibility to dispense pre-medication treatment.

o. Plasma samples (5 mL each) for plinabulin and docetaxel PK. All patients will be sampled for PK via a central laboratory. Patients in Phase 3 will follow the plinabulin and docetaxel PK sampling schedules from Phase 2. For PK collection schedule refer to Table 13 and Table 14 (see Section 11.9). Cytokine panel testing will be done using unused plasma samples collected at the PK time points;

p. Investigator opinion of progression (yes/no) at End of Treatment (EOT) recorded in CRF. For example if the patient completes two 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." Patients without progressive disease at the EOT visit will undergo a follow-up visit every 2 months until the occurrence of either disease progression or death. These visits may be conducted per telephone or other means.

q. Docetaxel infusion: 75 mg/m^2 docetaxel will be administered via IV infusion over 1 hour on Day 1 of each cycle. All patients must be premedicated with oral corticosteroids (see below for prostate cancer) 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). For hormone-refractory metastatic prostate cancer, given the concurrent use of prednisone, the recommended premedication regimen is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the docetaxel infusion (refer to Taxotere® Package Insert).

r. 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 or placebo intravenously over 30 minutes (± 5 minutes) 30 minutes after the end of the docetaxel infusion. On Day 2 of each cycle ≥ 24 hours after completing chemotherapy, patients will receive a single dose of pegfilgrastim (6 mg) or placebo (subcutaneous injection).

s. The bone pain scale and pain medication assessment should be completed on Day 1 prior to docetaxel infusion and on each remaining day through Day 8 at approximately the same time (Moore et al, 2017). On Days 2, 6, 7, and 8 the patient will complete the bone pain scale and pain medication assessment at the investigational site

t. Bone pain assessment to be completed pre-dose.

u. On Day 2 the patient will be provided with a further copy of the assessment to be completed at home on Day 3, Day 4, and Day 5 and returned to the study center at the next visit (Day 6).

v. Health-related QoL questionnaire evaluated with EORTC QLQ-C30 and EQ 5D-5L will be collected on Day 1 (prior to the infusion) and on Day 8 of each cycle (Giesinger et al, 2014).
w. All concomitant medicines (dose, schedule, and duration of treatment) and in particular analgesics as well as antibiotics should be entered in the eCRF.
x. All hospitalizations should be entered in the eCRF. Adverse events will be collected at all study visits starting with the first dose of study drug. Serious adverse events are collected from the time of signing the informed consent form and up to 30 days following the last dose of the study drug.
y. Collected at pre-dose only.
z. Pre-dose Cycle 2 only
aa. All Cycles, Day 8

11.2. General Study Procedures

11.2.1. Demographics

Demographic data will include gender, date of birth (or age), and race/ethnicity.

11.2.2. Medical History

Medical history findings (i.e., previous diagnoses, diseases, or surgeries) not pertaining to the study indication, started before signing the informed consent, and considered relevant for the patient's study eligibility will be collected and captured in the eCRF.

11.2.3. Baseline Characteristics

Baseline characteristics will include a history of disease and current disease status, staging, bone marrow involvement, sites of disease, prior anticancer therapies, and prior medications/significant non-drug therapies will be collected.

Information will also be collected regarding child-bearing potential and any other assessments that are done for the purpose of eligibility for inclusion into the study (physical examination, vital signs, hematology and blood chemistry, urinalysis, pregnancy test, and ECG). For further details on eligibility assessments, see Table 6 and Table 7.

11.2.4. Vital Signs

The following measurements for vital signs must be performed: systolic/diastolic blood pressure, heart rate, and respiratory rate. The patient must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. 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 the same throughout the study.

Two methods will be used to collect blood pressure.

- Method 1: using blood pressure devices provided by the sponsor (SpaceLabs 90217 ambulatory blood pressure monitor) to measure blood pressure (heart rate will also be measured)
- Method 2: using a standard cuff to measure blood pressure (heart rate will also be measured)

Vital assessments will be performed as detailed in Table 8, with a ± 15 minute window for the standard cuff measurements.

Table 8: Vital Signs Assessments

Cycle	Day	Time Point(s)	Method
Phase 2			
-	Screening	-	2 (standard cuff)
Cycle 1 (all arms)	Day 1	Pre-docetaxel dose	2 (standard cuff)
Cycle 1 (Arm 1)	Day 1	Semi-continuously starting at 15 minutes after completion of docetaxel infusion, and at every 15 minutes thereafter for 4.5 hours	1 (ambulatory)
Cycle 1 (Arms 2 to 4)	Day 1	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	1 (ambulatory)
Cycle 1 (all arms)	Days 2, 6, 7, 8, 9, 10, and 15	Time approximately equivalent to pre-dose on Day 1, before blood draws	2 (standard cuff)
Cycles 2 to 4 (Arm 1)	Day 1	Pre-dose docetaxel	2 (standard cuff)
Cycles 2 to 4 (Arms 2 to 4)	Day 1	Pre-dose docetaxel, pre-dose plinabulin, 30 min, 1 hour, 2 hours post-infusion with plinabulin	2 (standard cuff)
Cycles 2 to 4 (all arms)	Day 8	Time approximately equivalent to pre-dose on Day 1, before blood draws	2 (standard cuff)
Phase 3			
-	Screening	-	2 (standard cuff)
Cycle 1 (Arms 1 and 2)	Day 1	Pre-dose docetaxel, pre-dose plinabulin, 30 min, 1 hour, 2 hours after end of infusion with plinabulin or placebo	2 (standard cuff)
Cycle 1 (Arms 1 and 2)	Days 2, 6, 7, 8, 9, 10, and 15	Time approximately equivalent to pre-dose on Day 1, before blood draws	2 (standard cuff)
Cycles 2 to 4 (Arms 1 and 2)	Day 1	Pre-dose docetaxel, pre-dose plinabulin, 30 min, 1 hour, 2 hours after end of infusion with plinabulin or placebo	2 (standard cuff)
Cycles 2 to 4 (Arms 1 and 2)	Day 8	Time approximately equivalent to pre-dose on Day 1, before blood draws	2 (standard cuff)
Phase 2			
All cycles	End of Treatment, Early Discontinuation, and 30-Day Safety Follow-up	-	2 (standard cuff)

Cycle	Day	Time Point(s)	Method
Phase 3			
All cycles	End of Treatment, and 30-Day Safety Follow-up	-	2 (standard cuff)

11.2.5. Temperature

The temperature location (ear,oral, or axillary) selected for a patient should be the same throughout the study.

If abnormalities are found and they are considered an AE, record on the AE summary page. If an isolated elevated temperature is not clinically significant, it should not be reported as an AE. If an elevated temperature is part of an AE that is reported elsewhere, elevated temperature (fever) should not be reported as an AE.

11.2.6. Physical Examinations, Height, and Weight

Physical examinations (comprehensive [including neurological examination] or symptom directed) will be performed as described in Table 6 and Table 7. A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the screening Visit will be recorded on the CRF. Changes from the screening physical examination findings that meet the definition of an AE will be recorded on CRF.

Height will be measured in centimeters once at screening. Weight will be measured in kilograms at screening, prior to Day 1 dosing in all cycles and at the end of treatment (EOT) visit. For Cycle 1, body weight will also be measured on Days 2 and 6. The body weight measurements are made to enable the calculation of the plinabulin dose and to monitor for potential weight increase due to the docetaxel pre-medication. Both measurements will be performed without the patient wearing shoes.

11.2.7. Performance Status

Patients will be graded according to the ECOG Performance Status scale and criteria as described in Table 9.

Table 9: ECOG Performance Status

ECOG Scale	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., office work or light house work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours

ECOG Scale	
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot perform any self-care; totally confined to bed or chair

11.2.8. Electrocardiogram

A single 12-lead ECG will be performed at screening and triplicate ECGs will be taken for Phase 2 (Table 10) and Phase 3 (Table 11).

ECGs are to be performed using a standardized method before blood draws or any other procedures. The patient must be in a supine position in a rested and calm state for at least 5 minutes before the ECG assessment is conducted. If the patient is unable to be in the supine position, the patient should be in most recumbent position as possible.

In Phase 2 and Phase 3, single safety ECGs will be obtained during screening, at the EOT, Early Discontinuation (Phase 2 only), and at 30-day safety follow-up visit for **all** patients. ECG in triplicate with 2-3 minutes between measurements will be obtained in Phase 2 (Arms 2 to 4 only) and Phase 3 on Cycle 1 Day 1 (in both arms) before docetaxel infusion, immediately before plinabulin infusion, 5 minutes before end of plinabulin infusion, 60 minutes (30 minutes in Phase 2) and 4.5 hours after start of infusion with plinabulin or matching placebo. On Cycle 1 Day 2, ECG in triplicate will be obtained prior to blood draws in Arms 2 to 4 (Phase 2) or prior to pegfilgrastim/placebo injection in both arms (Phase 3).

For Arm 1 of Phase 2, the triplicate ECGs will not be obtained; so the only assessments will be the single ECGs at screening, end of treatment, early discontinuation, and follow-up.

The ECG must include the following measurements: heart rate, QRS, QT, and PR intervals.

Table 10: Schedule for ECG Collection (Phase 2)

Screening Day −28 to −1 (All arms)	**Cycle 1 Day 1 Before docetaxel infusion (up to 1-hour window) (Arms 2 to 4)**	**Cycle 1 Day 1 Immediately before plinabulin infusion (-5 minutes window; must be before plinabulin infusion starts) (Arms 2 to 4)**	**Cycle 1 Day 1 5-minutes before End of plinabulin infusion (Arms 2 to 4)**	**Cycle 1 Day 1 Post-plinabulin infusion**		**Cycle 1 Day 2 Pre-blood draws (Arms 2 to 4)**	**End-of Treatment, Early Discontinuation, and 30 Day Safety Follow-up (All arms)**
				30 minutes after start of infusion* (+ 15 minutes window) (Arms 2 to 4)	**4.5 hours after start of infusion** (+ 15 minutes window) (Arms 2 to 4)**		
Single	Triplet#	Triplet#	Triplet#	Triplet#	Triplet#	Triplet#	Single

* ECG measurement after the end of the infusion with plinabulin.

** ECG measurement approximately 4 hours after the end of the infusion with plinabulin.

Triplicate ECGs not performed for Arm 1 in Phase 2.

Table 11: Schedule for ECG Collection (Phase 3)

Screening Day −28 to −1	Cycle 1 Day 1 Before docetaxel infusion (up to 1-hour window)	Cycle 1 Day 1 Immediately before plinabulin/ placebo infusion (-5 minutes window; must be before plinabulin/ placebo infusion starts)	Cycle 1 Day 1 5-minutes before End of plinabulin/ placebo infusion	Cycle 1 Day 1 Post-plinabulin/placebo infusion		Cycle 1 Day 2 Pre-pegfilgrastim/ placebo injection	End-of Treatment and 30 Day Safety Follow-up
				60 minutes after start of infusion* (± 5 minutes window)	4.5 hours after start of infusion** (± 15 minutes window)		
Single	Triplet	Triplet	Triplet	Triplet	Triplet	Triplet	Single

* ECG measurement 30 minutes (± 5 minutes window) after the end of the 30-minute infusion with plinabulin/placebo.

** ECG measurement 4 hours (± 15 minutes window) after the end of the 30-minute infusion with plinabulin/placebo.

11.2.9. Health-Related Quality of Life Questionnaire Evaluated with EORTC QLQ-C30 and EQ-5D-5L

Health-related QoL questionnaire evaluated with EORTC QLQ-C30 and EQ-5D-5L is a validated questionnaire developed to assess the QoL of cancer patients.

It is a copyrighted instrument, which has been translated and validated in over 90 languages and used in more than 3,000 studies worldwide.

Refer to the study manual for specific module and how to administer.

11.2.10. Bone Pain Inventory (Short Form) (Phase 2 Only)

The incidences of bone pain will be recorded through a validated questionnaire. 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

11.2.11. Patient Bone Pain Scale and Pain Medication Assessment (Phase 3 only)

The incidences, occurrences, and severity of bone pain will be recorded through a patient bone pain scale during Cycle 1, at the times presented in Table 7.

The bone pain scale will be based upon the validated Wong Baker Faces® Pain Rating Scale (http://wongbakerfaces.org).

The bone pain scale and pain medication assessment should be completed on Day 1 prior to docetaxel infusion and on each remaining day through Day 8 at approximately the same time. On Days 2, 6, 7, and 8 the patient will complete the bone pain scale and pain medication assessment at the investigational site. If the patient is discharged from hospital prior to Day 8, the bone pain scale and pain medication assessment pages for the remaining days will be handed to the patient

with the date field completed by the site personnel for each of the remaining days. The patient will be instructed to fill in the documents at home, approximately at the same time as on Day 1. On each day following the patient's discharge from the hospital when the patient returns to the site for study procedures, they will return any available completed assessments.

Increases of bone pain severity are assessed as an objective during Phase 3 of the study, using the bone pain scale ("*Please rate your bone pain by circling the one number below the faces that best describes your pain at its worst in the last 24 hours*"). The severity of pain is marked on a scale from 0 ('no hurt') to 10 ('hurt worst').

Concomitant pain medication use will be recorded via a pain medication assessment. Information recorded for concomitant pain medication use will include date, name of medication, route of administration, dosage, total taken in one day, and reason medication was taken.

11.3. Efficacy

Efficacy assessments and the time when they will be performed are presented in Table 6 and Table 7.

11.3.1. Disease Progression

Patients will be evaluated for disease progression in accordance with institutional practice. For example, the investigator may identify target lesions at screening, and at the EOT visit will assess the patient's response to the docetaxel and study drug. This will be designated the patient's treatment response. If no reliable target lesions are identifiable (e.g. patients with bone-only cancer metastases), institutional response criteria will be used for recording disease progression.

Investigators should exercise their clinical judgment in performing studies (including computed tomography and positron emission tomography scans) to assess disease progression, and can end study treatment if a patient is clearly having disease progression prior to the completion of the planned 4 cycles of chemotherapy. If a patient is taken off-study prior to completing 4 cycles of docetaxel and study drug, the screening and end of study images, when clinically indicated, will be performed. If the patient completes four cycles of docetaxel and study drug, and there is not disease progression and the docetaxel is continued, then the EOT assessment of disease progression will be recorded as "no."

The investigator will submit supporting documentation for the treatment response determination, which could include reports from cross-sectional imaging, laboratory values, and performance status estimates (before and at the end of study treatment), and this data will support the investigator's determination in the CRF as disease progression "yes" or "no". Source documents supporting the investigator's judgment of disease progression will be reviewed, but images (such as CT scan, MRI etc.) or other documents will not be collected for central review. The disease progression will be judged by the investigator.

The assessment of disease progression during the follow-up period for patients assessed as non-progressive at the EOT visit does not need to be reported, only the determination of disease progression will be collected.

(Note: a requirement for a target lesion or for "measurable disease" is not required for study entry.)

11.4. Safety

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Table 6 and Table 7.

11.4.1. Adverse Events

Adverse events observed by the Investigator or reported by the patient will be collected at all study visits starting with the first dose of study drug.

Serious adverse events are collected from the time of signing the informed consent form and up to 30 days following the last dose of the study drug.

All AEs, SAEs, treatment emergent AEs, treatment emergent SAEs, and treatment emergent deaths regardless of the relationship to the study drug, will be collected.

Disease progression or deterioration of the malignancy under study (including new sites of metastasis due to disease progression) will be recorded as part of the subject's disease status and should not be reported as an AE/SAE. If death is determined to be due to disease progression, the SAE form will attribute the death to disease progression and document that disease progression was determined to have caused the event(s). These events will not be included in the safety analysis.

The Sponsor will collect all deaths on study regardless of its potential relationship to disease progression and up to 30 days after the last dose of plinabulin on an SAE form.

All hospitalizations should be documented in the eCRF.

11.4.2. Concomitant Medications

All concomitant medications and in particular all analgesics, pain medications, and antibiotics should be recorded with date of onset and discontinuation, dose, and frequency will be entered into the eCRF.

11.5. Healthcare Resource Utilization

Information on all cause hospitalizations (including ICU) and ER visits will be collected at all visits to the study center and throughout the study, at end of study and during any follow-up post study (except for FU visits for patients without disease progression at the EOT visit).

11.6. Laboratory Evaluations

Chemistry, coagulation tests, hematology, and urinalysis will be performed using a central laboratory and serum pregnancy testing and hepatitis serology will be performed using a local or central laboratory; results will be used to determine docetaxel dosing. 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 safety (e.g. protocol specified) blood samples as per the schedule of assessments (refer to Table 6 and Table 7) 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.

The Sponsor or the central laboratories will supply containers for sample collection, preparation, packaging, and shipping. Detailed instructions for sample collection, processing, and shipping are provided in the central laboratory manual and/or the Sponsor will provide training materials. The date and time of sample collection will be recorded in the source documents at the site.

Table 12 outlines the specific analytes that will be assessed during the study at time points outlined in the Schedule of Assessments (Table 6 and Table 7).

Table 12: Clinical Laboratory Tests (Central Laboratory)

Category	Parameters
Hematology	Haptoglobin, hematocrit, hemoglobin, platelets, MCV, MCH, MCHC, RBC count, WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC and reticulocyte count
Chemistry	
Electrolytes	Bicarbonate, chloride, magnesium, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine, Creatinine Clearance
Pregnancy test	Subject must have a negative urine pregnancy test documented within the 24-hour period prior to the first infusion. Confirm with serum testing (local or central laboratory) if urine sample is positive. Additional testing may be performed at the discretion of the investigator.
Coagulation	PT, INR, PTT
Other	Albumin, amylase, calcium, lactate dehydrogenase, lipase, phosphorus, total protein, uric acid, glucose, creatine phosphokinase, hepatitis B/C testing (local or central laboratory): hepatitis C antibody, HBsAg, anti-HBs
Urinalysis	glucose, ketones, pH, protein, RBCs, specific gravity
Exploratory Biomarker	
	CD34+ (Phase 2 and Phase 3, in selected countries) cytokine panel (in selected countries)

Abbreviations: ANC= absolute neutrophil count, anti-HBs = hepatitis B surface antibody, β hCG = beta-human chorionic gonadotropin, HBsAg = hepatitis B surface antigen, INR = International Normalized Ratio, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, PT = prothrombin time, PTT = partial thromboplastin time, RBC = red blood cells, WBC = white blood cells

Assessments for UDP glucuronosyltransferase (UGT) 1A1 genotyping and total bilirubin, conjugated bilirubin, and unconjugated bilirubin may be performed at the discretion of the investigator.

11.6.1. Pregnancy Testing

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 (local or central laboratory) if urine sample is positive. Additional testing may be performed at the discretion of the investigator.

11.6.2. Hepatitis B/C Testing

Hepatitis B/C serologic markers (hepatitis C antibody, HBsAg, viral load in case HBsAG is positive and anti-HBs) will be tested. If HBsAg is positive but viral load is negative, the patient should be tested prior to each treatment cycle to ensure that viral load remains negative.

Hepatitis (hepatitis C antibody, HBsAg, viral load and anti-HBs) serology can be performed using laboratory standard methodology, by local laboratory or by the central laboratory if local testing is not available (not for viral load).

11.7. End of Treatment Assessment

EOT is defined as the last assessment for the protocol-specified treatment post Cycle X (Day 22 [+ 7 days]) of the study for an individual patient, regardless at what time the patient discontinues the study.

11.7.1. Exploratory Markers

Phase 2 only: a blood sample for exploratory marker evaluation will be collected for CD34+ which will be established by FACS. This test will be performed in selected countries participating in the study, via central laboratory.

Phase 2 and Phase 3: Plasma cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, GCSF, GMCSF, IFN alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8 analysis. This test will be performed in selected countries participating in the study, using unused plasma samples collected at PK time points.

Unused samples (urine/serum plasma) will also be saved for future potential biomarker research, with patient consent.

11.7.2. HIV Testing

If HIV testing is done (at the discretion of the investigator), the test will be conducted at the local site using standard methodology.

11.8. Safety Follow-up/End of Study Assessment

All patients, including patients who withdraw from the study early, should complete a safety follow-up visit 30 (± 2) days after the last dose (refer to Table 6 and Table 7). Patients who withdraw for progressive disease and who will continue to another chemotherapy regimen will complete the EOT visit at Cycle X Day 21. They then continue to another chemotherapy regimen and do not need to have the safety follow-up visit (where X is the last cycle prior to progression, and is 4 or less). If, in the opinion of the investigator, the patient will benefit from more than 4 cycles of docetaxel and open label pegfilgrastim, then the fifth cycle will not start until

completion of the EOT visit (in this instance, the EOT visit will be Cycle 4 Day 21). Follow-up visits will be required to monitor for ongoing treatment-related AEs. All patients experiencing drug-related toxicities of ≥ Grade 2 at the EOT 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.

Patients without progressive disease at the EOT visit will undergo a follow-up visit every 2 months until the occurrence of either disease progression or death. These visits may be conducted per telephone or other means.

The assessment of disease progression during the follow-up period for patients assessed as non-progressive at the EOT visit does not need to be reported, only the determination of disease progression will be collected.

11.8.1 Long-term Safety Follow-up (up to 5 years)

The long-term safety follow-up through patient contacts by phone calls, letters or electronic means; or medical records reviews will be conducted to all subjects approximately every 6 months up to 5 years to monitor long term safety of plinabulin. Follow-up telephone calls and queries of treating physicians or designee healthcare provider to ascertain safety information on secondary malignancies or tumor progression as well as other potential safety findings/concerns. Subjects from each treatment arm will be followed up. Subjects who receive at least one dose of plinabulin or pegfilgrastim will be followed up.

Safety endpoints to be collected include;

- Disease progression
- Disease relapse (local, regional or distant)
- Second primary tumors
- Health status check, including autoimmune and hematological disorders
- Any further anti-cancer treatment information
- Reporting of medical problems, including information on unexpected hospitalizations and medications (including SAEs)
- Death (including autopsy report, if available)

11.9. Pharmacokinetics

All patients in Phase 2 and Phase 3 will participate in the PK assessments.

Docetaxel Sampling

All patients in Phase 2 and Phase 3 will have samples taken for docetaxel PK on Cycle 1 Day 1 for up to 24 hours after the start of the docetaxel infusion.

Table 13: Docetaxel Pharmacokinetic Sampling Schedule (Cycle 1, Day 1)

Day	**Day 1**			**Day 2**
Time	**End-of infusion** (+/- 5 min)	**1.5 hours after start of infusion*** (+/- 5 min)	**6.0 hours after start of infusion**** (+/- 15 min)	**24 hours after start of infusion on Day 1** (+/- 6 hr)

* Sample to be taken 30 minutes after the end of the 60-minute docetaxel infusion.

** Sample to be taken 5 hours after the end of the 60-minute docetaxel infusion. Sample can be taken at the same time as the plinabulin 4.5 hour sample.

Plinabulin Sampling

All patients randomized to a plinabulin treatment arm in Phase 2 and Phase 3 will have samples taken for plinabulin PK on Cycle 1 for up to 24 hours after the start of the plinabulin infusion. Patients in Phase 2 randomized to pegfilgrastim during open label treatment will not have samples collected for plinabulin PK. Cytokine panel testing will be done using unused plasma samples collected at the PK time points.

Table 14: Plinabulin Pharmacokinetic Sampling Schedule (Cycle 1)

Day	**Day 1**				**Day 2**
Time	**Immediately before infusion starts**	**End-of infusion** (+/- 5 min)	**60 minutes after start of infusion*** (+/- 5 min)	**4.5 hours after start of infusion**** (+/- 15 min)	**24 hours after start of infusion on Day 1** (+/- 6 hr)

* Sample to be taken 30 minutes after the end of the 30-minute infusion.

** Sample to be taken 4 hours after the end of the 30-minute infusion.

11.10. Appropriateness of Measurements

All safety assessments used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant, either in clinical practice or specifically in cancer patients. Health-related QoL questionnaire evaluated with EORTC QLQ-C30 and EQ-5D-5L is validated for use in this population.

The patient bone pain scale will be based upon a validated pain rating scale (the Wong-Baker Faces® Pain Rating Scale (http://wongbakerfaces.org).

12. DATA HANDLING AND QUALITY ASSURANCE

Data management will be the responsibility of the Sponsor. CRFs and edit checks will be designed and validated based on protocol requirements for data collection and with input from the statistical, data management and clinical operations staff.

12.1. Data Collection

Data will be captured by using an online Electronic Data Capture (EDC) system. Data collected in patient source documents will be entered onto the eCRFs by site study staff, and subject to an audit trail of changes made to the eCRF. For each patient enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. The investigator should ensure the accuracy and completeness of the data reported to the sponsor/ CRO in the eCRFs. Data will be stored in files that can be accessed through listing exports.

12.2. Data Management/Coding

A CRO will be responsible for data management, including quality checking of the data. During the data entry and verification process, edit check programs will identify data discrepancies and, automatically generate queries. Query reports will be sent to sites or to laboratories for resolution. The sites will correct the data as needed to resolve the queries. Any data captured electronically (such as laboratory results) will be transferred to the database electronically and edit checks will be programmed to search for missing and out of range data. For electronically transferred data, the laboratory is expected to re-send the data transferred with the correction applied. Per Sponsor's or designee's operating procedures, an audit trail will be maintained.

Throughout the study, the Study Management Team will review data according to the Edit Specifications Document as described in the Data Management Plan.

12.3. Quality Assurance

The database will be audited for quality assurance by an outside vendor based on a predefined study audit plan to ensure acceptable accuracy and completeness.

13. SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

13.1. Adverse Events

13.1.1. Definitions and Reporting

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions, which worsen during a study, are to be reported as AEs.

All AEs encountered during the clinical study, irrespective of the likelihood that the event is related to disease progression, will be reported on the AE page of the CRF.

13.1.1.1. Assessment of Severity

Whenever possible, the intensity of clinical AEs will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) (v 4.03) grading system. Adverse events not listed on the NCI-CTCAE grading system will be graded on a 5-point scale (mild, moderate, severe, life-threatening, and death) as described below, and reported in detail as indicated on the CRF (Study Manual).

Severity Grading for AEs not listed in NCI-CTCAE (v4.03)

Grade 1: **Mild** – Transient or mild discomfort; no medical intervention or therapy required.

Grade 2: **Moderate** – Moderate discomfort or limitation in activity – some assistance may be needed or minimal medical intervention or therapy required.

Grade 3: **Severe** – Marked limitation in activity, some assistance required; medical intervention or therapy required; hospitalization possible.

Grade 4: **Life Threatening** – Extreme limitation in activity; significant assistance required; significant medical intervention or therapy required; hospitalization probable.

Grade 5: **Death**

13.1.1.2. Relationship to Study Drug

The investigator will assess the possible relationship of a AE or SAE to the use of study drug. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The following grading of causality will be used for this study:

- **Related:** There is a reasonable causal relationship between the study drug and the event, and the event occurred within a plausible time relationship to drug administration, and the event cannot be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event responds to withdrawal of study drug (dechallenge) and recurs with rechallenge (if clinically feasible to rechallenge).
- **Probable:** There is reasonable causal relationship between the event and the study drug, the event occurred within plausible time relationship to drug administration, the event is unlikely to be attributed to the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. The event follows a clinically reasonable response on withdrawal of study drug.
- **Possible:** There is a reasonable causal relationship between the event and study drug, the event occurred within a plausible time relationship to study drug administration, but the event could also possibly be explained by the condition under study, concurrent disease, other drugs or chemicals, or other circumstances. Dechallenge information is lacking or unclear.
- **Unlikely:** There is a temporal relationship of the event to study drug but not a reasonable causal relationship, or there is no temporal relationship to study drug administration or the condition under study, concurrent disease, other drugs or chemicals, or other circumstances provide a plausible explanation for the event.
- **Unrelated:** There is no temporal relationship between the event and study drug administration (too early or late or study drug not administered). There is no reasonable causal relationship between the event and the study drug. The condition under study, concurrent disease, other drugs or chemicals, or other circumstances provides a plausible explanation for the event.

For the purposes of regulatory reporting a causality assessment of related, probable, or possible, will be treated as related.

If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF and report such an assessment in accordance with the SAE reporting requirements.

13.1.1.3. Follow-Up of Adverse Events and Serious Adverse Events

For the purpose of this study, AEs irrespective of causality will be collected from first study drug administration (Study Day 1) and all SAEs irrespective of causality will be collected from the time the Informed Consent Form is signed. AEs and SAEs will be collected until 30 days after the last infusion of study treatment or initiation of another anti-cancer therapy. Thereafter, all SAEs which are considered to be drug-related should be reported, regardless of time elapsed since the last dose of study drug (even if the study has stopped).

13.1.2. Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the eCRF. Laboratory test value abnormalities as such should not be reported on the AE page of the CRF as AEs unless they result in a clinically significant condition as judged by the investigator.

13.2. Serious Adverse Events

13.2.1. Definitions

The definition and reporting requirements of International Council on Harmonisation (ICH) Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited reporting, Topic E2 will be adhered to.

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. With respect to human clinical experience, this includes any experience which:

- is fatal,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is considered medically significant by the investigator or requires intervention to prevent 1 or other of the outcomes listed above,

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the Sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. The term severe is a measure of intensity, thus an SAE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

Hospitalization or prolongation of hospitalization is used as an indicator of the seriousness of the AE and should ONLY be submitted as an SAE where the event truly fits this definition (see regulatory definition above) and NOT for hospitalizations associated with non serious reasons for hospitalization or prolongation of hospitalization. If a patient is hospitalized or hospitalization is prolonged due to planned procedures such as administration of scheduled IV therapy or minor treatment such as hydration; administration of growth factors; elective surgery; social reasons and respite care; or economic reasons in the absence of any deterioration in the patient's general condition, these hospitalizations do not meet the criteria of seriousness from a medical perspective and do not need to be reported as SAEs. Hospitalizations or prolonged hospitalizations that are required for an SAE but also include a portion of hospitalization for

nonmedical reasons should be reported as an SAE. However, AEs that do not meet criteria for serious should be entered into the EDC and all hospitalizations should be entered into EDC with the reason for hospitalization identified.

All relevant information, either initial or follow-up, has to be reported on the SAE report forms.

For serious and all other AEs, the following must be assessed and recorded on the AE page of the CRF: event, intensity, relationship to test substance, action taken, and outcome to date.

The Investigator must notify the Ethics Review Committee/IRB of such an event in writing as soon as is practical and in accordance with international and local laws and regulations.

13.2.2. Reporting

13.2.2.1. Timeframes for Submitting Serious Adverse Events

ANY CLINICAL AE OR ABNORMAL LABORATORY TEST VALUE THAT IS SERIOUS (INCLUDING DEATH OR CONGENITAL ANOMALY) OCCURRING DURING THE COURSE OF THE STUDY, IRRESPECTIVE OF THE TREATMENT RECEIVED BY THE PATIENT, MUST BE REPORTED TO THE SPONSOR OR DESIGNEE WITHIN ONE WORKING DAY OF THE SITE LEARNING OF THE EVENT (EXPEDITED REPORTING).

Please contact the sponsor or designee to report all SAEs within 24 hours of learning of the SAE.

- Please complete an SAE Report Form and scan the form and any supporting documentation (which includes laboratory data, hospital records and the results of relevant tests). The form and supporting documentation must be e-mailed to:

  ICON-Safety-CentralReceipt@iconplc.com **within 24 hours.**

- The preferred method for receiving SAEs is via email. In cases where submission through email is not possible, the site may report the SAEs through the following alternative number:

  Fax No.: +44 (0)208 100 5005

- If an ongoing SAE changes in intensity or causal relationship to the investigational product, or if new information becomes available, a follow-up SAE report should be sent to ICON within 24 hours using the same procedure used for transmitting the initial SAE report.

- All SAEs should be followed-up until resolution, improvement, or stabilization.

The definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited reporting, Topic E2 will be adhered to.

13.3. Pregnancies

A female patient of child-bearing potential must be instructed to immediately inform the Investigator if she becomes pregnant during the study. Pregnancies occurring up to 90 days after final administration of study drug must also be reported to the Investigator. The Investigator should report all pregnancies within 24 hours to the Sponsor. The Investigator should counsel

the patient; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Patients who become pregnant while on study will be discontinued from the study treatment and all End of Treatment visit procedures will be performed. If the patient is a man who is capable of fathering a child, he must agree to use adequate birth control beginning immediately after he enrolls on this study until 3 months after his last dose of study drug. Pregnancy occurring in the partner of a patient participating in the study should also be immediately reported to the Investigator and the Sponsor. The partner should be counseled and followed as described above.

Pregnancy is not an SAE; however, the outcome of a pregnancy must be reported to detect a potential SAE (congenital anomaly, premature birth, or birth defect). All pregnancies must be initially reported and follow-up information must be reported on the pregnancy follow-up form. The reporting timeframe to report a pregnancy to the Sponsor is from start of study drug up to 90 days after the last dose of study drug. Procedures and policies at the site and at the Sponsor, regarding pregnancies, will be followed to ensure that the safety and well-being of the study patient and fetus are appropriately followed through the pregnancy to birth. In the event that a pregnancy occurs in the female partner of a male patient, the Investigator will then (and only then) also be required to obtain her consent so that the Sponsor can hold her data on file. If the female partner is unwilling to sign the consent her data may not be held in the safety database. However, this will not affect the ability of the male patient to continue in the study.

13.4. Independent Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) will be assembled and be governed by a DSMB charter, which will specify membership, frequency of meetings, and potential sample size adjustment.

14. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

All statistical analyses will be performed by the sponsor or designee after the study is completed included in a separate statistical analysis plan (SAP).

Patients in Phase 3 will be stratified according to his or her by tumor type (breast cancer, NSCLC, HRPC) and region (Asia, non-Asia).

Data from all patients receiving the RP3D plinabulin dose in Phase 2 and Phase 3, will not be pooled for assessing the primary and secondary study endpoints, but analyzed separately.

14.1. Study Endpoints

14.1.1. Phase 2 Endpoints

Plinabulin pharmacokinetic (PK) and pharmacodynamic (PD) assessments will be made to enable a PK/PD analysis.

Primary Endpoint:

- To establish the Recommended Phase 3 Dose (RP3D) based on PK/PD analysis

Primary Efficacy Pharmacodynamic Endpoint:

- 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). ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15 (pre-dose on dosing days; times equivalent to pre-dose on other days). The Negative Binomial Regression (NBR) model, on the integer number of days of severe neutropenia, will be used to analyze the DSN endpoint during the fixed time window outlined above, with the treatment arm as the only covariate.

  The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.

Primary Safety Pharmacodynamic Endpoint:

- 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). See the Pharmacometrics Analysis Plan for the analysis methods.

Secondary Endpoints:

- To characterize the pharmacokinetic profile of plinabulin and docetaxel. See the Pharmacometrics Analysis Plan for the analysis methods.
- To characterize the exposure-response relationships between measures of plinabulin exposure and the pharmacodynamic endpoint DSN. Robust linear regression (Bablok

et al, 1988) with DSN as the dependent variable and plinabulin exposure as the independent variable. The method will also be used to construct point estimates and confidence intervals. The NCSS version 12 statistical software will be used.

- To characterize the exposure-safety relationships between measures of plinabulin exposure and safety events of interest. Robust linear regression (Bablok et al, 1988) with the number of safety events as the dependent variable and plinabulin exposure as the independent variable. The method will also be used to construct point estimates and confidence intervals. The NCSS version 12 statistical software will be used.

Exploratory Endpoints:

- To assess CD34+ at screening, and on Days 2, 6, and 8 in Cycle 1 and Day 1 in Cycle 2. A repeated measures mixed linear model with the Day 1 value and treatment arm as covariates will be used to analyze this endpoint. 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. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.
- Health-related QoL questionnaire evaluated with EORTC QLQ-C30 and EQ-5D-5L. The Wilcoxon Rank Sum test will be used to analyze the responses to the individual questions. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.
- Data collection on disease progression. The log-rank test (LIFETEST procedure in SAS) will be used to compare time to disease progression between the treatment groups. The method will also be used to construct point estimates and confidence intervals. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard 1999) will be used for the multiple comparisons.
- For selected countries only: to investigate the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8.

Safety Endpoints

- Incidence, occurrence, and severity of AEs/SAEs. These endpoints will be presented descriptively in tables and listings.
- Incidences of bone pain. The NBR model will be used to analyze the endpoint during the fixed time window from pre-dose Day 1 through Day 8 in Cycle 1, with the treatment arm as the only covariate. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used. Contrasts for pairwise comparisons between Arm 1 and the plinabulin arms will be used for the evaluation. A closed testing procedure by Hommel (Hommel 1988, Hommel and Bernhard

1999) will be used for the multiple comparisons.

- Safety and tolerability (physical examination and safety laboratory assessments). These endpoints will be presented descriptively in tables and listings.

14.1.2. Phase 3 Endpoints

Primary Efficacy Endpoint (Cycle 1):

DSN in Cycle 1 in patients treated with docetaxel (75 mg/m^2) + plinabulin (40 mg) (Arm 2) compared with patients treated with docetaxel (75 mg/m^2) + pegfilgrastim (6 mg) (Arm 1). ANC will be assessed at baseline (prior to Cycle 1 docetaxel dose) and during Cycle 1 on Days 1, 2, 6, 7, 8, 9, 10, and 15. Blood draws for ANC will be taken approximately the same time as the time of the pre-dose sample on Day 1, and will be taken by preference in the morning. DSN should be calculated as the number of consecutive days from the first day when a patient's ANC is below 0.5 x l09/L until the patient reaches an ANC> 0.5 x 109/L, in Cycle 1. For patients who do not experience any severe neutropenia in Cycle 1, the DSN is set to 0. For patient's experiencing several episodes, the number of days of DSN will be summed up. The NBR model, on the integer number of days of severe neutropenia, will be used to analyze the DSN endpoint during the fixed time window outlined above, with the treatment arm as the only covariate. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.

Secondary Efficacy Endpoints (Cycle 1 and Cycles 1 to 4):

- DSN in Cycle 1 with only mature neutrophils. The NBR model, on the integer number of days of severe neutropenia, will be used to analyze the DSN endpoint during the fixed time window outlined above, with the treatment arm as the only covariate. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used. Maximum decrease from baseline (prior to docetaxel dose) in platelet count for each patient in Cycle 1. The Wilcoxon Rank Sum test will be used. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Proportion of patients with NLR > 5 after Day 7 through Day 15 in Cycle 1. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- AUC using the trapezoidal quadrature method for bone pain, from Day 1 through Day 8 in Cycle 1, based on the bone pain score from the patient bone pain scale. The Wilcoxon Rank Sum test will be used. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Estimated mean pain score from the patient bone pain scale from pre-dose Day 1 through Day 8 in Cycle 1. A repeated measures mixed linear model with the pre-dose Day 1 value and treatment arm as covariates will be used to analyze this endpoint.

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.

- Proportion of patients with thrombocytopenia (all grade) in Cycles 1 to 4. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- Incidence of infections in Cycles 1 to 4. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.

Exploratory Efficacy Endpoints (Cycle 1):

- Proportion of patients in Cycle 1 with:
  - Thrombocytopenia (all grade). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 3 (ANC >= 0.5 and < 1 × 109/L) and Grade 4 neutropenia (ANC < 0.5 × 109/L). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 4 neutropenia (ANC < 0.5 × 109/L). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 4 neutropenia (ANC<0.5 x10E9/L) for mature neutrophils only. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 3 neutropenia (ANC < 1 × 109/L) and ANC >= 0.5 × 109/L). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Bands > 0 after Day 7 through Day 15. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence

intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.

- Promyelocytes plus myelocytes >0 after Day 7 through Day 15. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- Promyelocytes, myelocytes, metamyelocytes and bands > 0 after Day 7 through Day 15. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- LMR < 3.2 after Day 7 through Day 15; time course of percentage of patients with LMR < 3.2 over time in Cycle 1. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- PLR > 200 after Day 7 through Day 15; time course of percentage of patients with PLR > 200 over time in Cycle 1. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- For the below bone pain measurements, The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis:
  - At least 1 day of bone pain
  - At least 2 days of bone pain
  - At least 3 days of bone pain
  - At least 4 days of bone pain
  - At least 5 days of bone pain
  - At least 6 days of bone pain
  - At least 7 days of bone pain
  - At least 8 days of bone pain

- Proportion of patients in Cycle 1 who needed bone pain medication (defined as any medication reported on the pain medication assessment from Day 1 through Day 8). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided

confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.

- Time (in days) to first use of bone pain medication. The log-rank test (LIFETEST procedure in SAS) will be used to compare time to first use of bone pain medication between the treatment groups. Separate analyses will be made with respect to narcotic and non-narcotic analgesics.
- DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum failure. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 with only mature ANC, thus excluding bands in patients with locally advanced or metastatic NSCLC after platinum failure. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 in patients with HRPC. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 with only mature ANC, thus excluding bands in patients with with HRPC. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 in patients with advanced or metastatic breast cancer who have failed < 5 prior lines of chemotherapy. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 with only mature ANC, thus excluding bands in patients with advanced or metastatic breast cancer who have failed <5 prior lines of chemotherapy. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 in patients with locally advanced or metastatic NSCLC after platinum failure or HRPC. The analysis will be done as per the primary endpoint.
- DSN in Cycle 1 with only mature ANC, thus excluding bands in patients with locally advanced or metastatic NSCLC after platinum failure or HRPC. The analysis will be done as per the primary endpoint.
- Platelet count at least 30% change from baseline at any time during Cycle 1. The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
- ANC nadir during Cycle 1. The Wilcoxon Rank Sum test will be used to analyze the endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- CD34+ at pre-dose on Day 1, pre-dose on Day 2, Days 6, 7, 8, 9, 10, and 15 in Cycle 1, and pre-dose on Day 1 in Cycle 2. A repeated measure mixed linear model with the pre-dose on day 1 cycle 1 value and treatment arm as covariates will be used to analyze this endpoint.

- For selected countries only: maximum change from baseline in the following cytokine panel: IL-1beta, IL-6, IL-12p70, IL-12p40, IL-17A, IL-23, G-CSF, GM-CSF, IFN-alpha, IFN-gamma, TNF-alpha, IL-2, FLT-3 ligand, and IL-8. The Wilcoxon Rank Sum test will be used to analyze the endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.

Exploratory Efficacy Endpoints (Cycles 1 to 4):

- Proportion of patients in Cycles 1 to 4 with:
  - FN (ANC $<1.0 \times 10^9$/L AND a single temperature of >38.3°C or a sustained temperature of ≥38°C for more than 1 hour). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis.
  - Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L). The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and 2-sided confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis
- Maximum change from baseline in CD34+ counts in each arm. A Wilcoxon signed-rank test will be used to analyze this endpoint. The UNIVARIATE procedure in SAS version 9.4 or later will be used for the analysis.
- Maximum difference between treatment arms in CD34+ counts. The Wilcoxon Rank Sum test will be used to analyze this endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Maximum change from baseline in haptoglobin level in each arm. A Wilcoxon signed-rank test will be used to analyze this endpoint. The UNIVARIATE procedure in SAS version 9.4 or later will be used for the analysis.
- Maximum difference between treatment arms in haptoglobin level. The Wilcoxon Rank Sum test will be used to analyze this endpoint. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Healthcare utilization endpoints:
  - Incidence of 30-day rehospitalizations - all cause. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
  - Incidence of all cause hospitalizations. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset

variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.

- Duration of all cause hospitalizations. The Wilcoxon Rank Sum test will be used. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Incidence of all cause ER visits. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
- Incidence of all cause ICU stays. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
- Duration of all cause ICU stays. The Wilcoxon Rank Sum test will be used. The method will also be used to construct point estimates and confidence intervals. The NPAR1WAY procedure in SAS version 9.4 or later will be used for the analysis.
- Incidence of all cause docetaxel dose delay, dose reduction, or dose discontinuation. The NBR model will be used to analyze the endpoints, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used:
  - Docetaxel dose delays > 7 days
  - Regimen switching
  - Treatment discontinuation
- Proportion of Relative dose intensity (RDI) ≤ 85% where the RDI is defined as

$$\text{RDI} = \frac{\text{Cumulative dose of administered docetaxel (mg/m}^2\text{)/ Number of weeks from Day1 Cycle 1 to Day 1 Cycle 4 plus 3 weeks}}{\text{Total calculated doses/12 weeks}}$$

The Barnard's test will be used to evaluate the difference in proportions between the treatment arms. The method will also be used to construct point estimates and confidence intervals. The FREQ procedure in SAS version 9.4 or later will be used for the analysis

- Incidence of transfusions due to thrombocytopenia. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.
- Incidence of antibiotics use. The NBR model will be used to analyze the endpoint, with the treatment arm as the only covariate. An offset variable will be used to account for exposure time. The method will also be used to construct point estimates and confidence intervals. The GENMOD procedure in SAS version 9.4 or later will be used.

- Data collection on disease progression. The log-rank test (LIFETEST procedure in SAS version 9.4 or later) will be used to compare time to disease progression between the treatment groups. The method will also be used to construct point estimates and confidence intervals.
- QoL endpoints will be analyzed in safety analysis set:
  - Health-related QoL questionnaire evaluated with EORTC QLQ-C30 Item 30 (response to question "How do you rate your overall quality of life during the past week") in Cycle 1 to 4 will be analyzed using linear mixed model for repeated measures (MMRM) with the Cycle 1 Day 1 value and treatment arm as covariates. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS v9.4 or later will be used for the analysis. The summary statistics in terms of counts, means, standard deviations, medians, minimums, and maximums for individual questions will be summarized in a tabular format.
  - Health-related QoL questionnaire evaluated with EORTC QLQ-C30 will also be analyzed with the summary scores. The EORTC QLQ-C30 scoring method combines the 30 questions from the questionnaire into 15 scores: global health state/QoL, functional scale (5 items), and symptoms scale (9 items) (Fayers et al, 2001). Three summary measures will be constructed: the QLQ-C30 Summary Score, which combined the symptom and functional scales (excluding the financial difficulties item), the symptom summary score (excluding the financial difficulties item), and the functional summary score (Hinz et al, 2012). The symptom summary score will be analyzed using linear mixed model for repeated measures (MMRM) with the Cycle 1 Day 1 value and treatment arm as covariates. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS v9.4 or later will be used for the analysis. The summary statistics in terms of counts, means, standard deviations, medians, minimums, and maximums for the 15 scores, the QLQ-C30 summary score, symptom score and the functional summary score will be summarized in a tabular format.
  - The response to the question "Your Health Today" from EQ-5D-5L in Cycle 1 to 4 will be analyzed using linear mixed for model repeated measures (MMRM) with the Cycle 1 Day 1 value and treatment arm as covariates. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS v9.4 or later will be used for the analysis. The summary statistics in terms of counts, means, standard deviations, medians, minimums, and maximums for the question "Your Health Today" will be summarized in a tabular format.
  - The EQ-5D-5L data will be converted into a health utility score using the interim

EQ-5D-5L crosswalk value set for the United States (van Hout et al, 2012) unless a validated EQ-5D-5L value set for the United States becomes available. The EQ-5D-5L health utility score in Cycle 1 to 4 will be analyzed using linear mixed model for repeated measures (MMRM) with the Cycle 1 Day 1 value and treatment arm as covariates. The method will also be used to construct point estimates and confidence intervals. The MIXED procedure in SAS v9.4 or later will be used for the analysis. The summary statistics in terms of counts, means, standard deviations, medians, minimums, and maximums for the health utility score will be summarized in a tabular format.

Safety Endpoints

- Incidence, occurrence, and severity of AEs/SAEs. These endpoints will be presented descriptively in tables and listings.
- Safety and tolerability (physical examination and safety laboratory assessments). These endpoints will be presented descriptively in tables and listings.

14.2. Statistical Analysis Considerations

14.2.1. Analysis Sets of Phase 2

14.2.1.1. Intent-to-Treat Analysis Set

The intent-to-treat analysis set for Phase 2 is comprised of all Phase 2 patients that have been randomized in the study and have received at least one dose of study medication.

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

14.2.1.2. Safety Analysis Set

The safety analysis set will be the same as the intent-to-treat analysis set for Phase 2.

14.2.1.3. Pharmacokinetic Analysis Set

All patients who received at least 1 dose of plinabulin or docetaxel and collection and at least 1 PK sample collected postdose will be included in the PK analysis set. These subjects will be evaluated for PK unless significant protocol deviations affect the data analysis or if key dosing, dosing interruption, or sampling information is missing. Patients in Phase 3 will follow the plinabulin and docetaxel PK sampling schedules from Phase 2.

14.2.1.4. Pharmacodynamic Analysis Set

All patients who had blood pressure and DSN collected at any time during the study will be included in the PD analysis set. For phase 3, PD data may be collected with a schedule of collection to be confirmed based on the emerging data to be determined. 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 statistical analysis plan, and may be reported outside of the main clinical study report.

14.2.2. Analysis Sets of Phase 3

14.2.2.1. Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set for Phase 3 is comprised of all Phase 3 patients that have been randomized in the study.

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

14.2.2.2. Safety Analysis Set

The safety analysis set is comprised of all Phase 3 patients that have been randomized in the study and have received at least one dose of study medication.

14.2.2.3. Health Economic and Patient Reported Outcomes

Health economic and patient reported outcomes will be conducted on the safety analysis set, which is the same as the intent-to-treat analysis set for Phase 3.

14.2.3. Patient Disposition

Descriptive summaries will be generated to describe the disposition of all enrolled patients.

14.2.4. Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be described, but no hypothesis testing will be done.

14.2.5. Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization (WHO) Drug dictionary codes.

14.2.6. General Efficacy Analyses Considerations

Data will be tabulated by treatment group, with data listings provided for all data captured in the eCRF as well as laboratory data. On treatment data, will be assessed descriptively as both observed values and as changes from pretreatment. When tabulated, data will be presented using descriptive statistics (e.g., mean, median, standard deviation, and range for continuously scaled parameters, and as number and percent for categorically scaled parameters). Statistical Analysis System Version 9.4 or higher will be used to perform the majority of the analyses; other software (e.g., NCSS) may be utilized to generate graphics or perform other analysis. A detailed statistical analysis plan (SAP) will be written and approved before unblinding the treatment allocation codes. Analyses will be performed based on observed data, and missing values will not be imputed unless otherwise stated in the SAP.

Primary efficacy endpoint will be imputed by multiple imputation method as sensitivity analysis.

Missing pain score data: In the case in which analgesic medication was taken during the treatment period, as sensitivity analyses, the pain scores will be imputed using the last

observation carried forward (LOCF) method, Worst Observation Carried Forward (WOCF), and Baseline Observation Carried Forward (BOCF).

14.2.6.1. Phase 3 Efficacy Analyses Considerations

14.2.6.1.1. Primary Efficacy Analysis Considerations

DSN was not measured in the previous Phase 2 study ([Study NPI-2358-101] in which patients received treatment with either plinabulin (30 mg/m^2 [n=50] or 20 mg/m^2 [n=40] plinabulin + docetaxel or docetaxel alone [(n=73]). DSN was obtained using the following methods (described below) for generation of ANC data and the observed neutrophil values on Day 8 in the Phase 2 study. Day 8 neutrophil values were shown to approximately coincide with the nadir of ANC after docetaxel treatment (Blackwell et al, 2015). The study will assume that the shape of the time/neutrophil recovery curve in plinabulin-treated patients is indistinguishable from the time/neutrophil recovery curve for filgrastim and its biosimilars.

In a study with filgrastim and its biosimilar, time course of ANC in Cycle 1 for the Per Protocol dataset was published by Blackwell et al, 2015. Mean values and standard deviations of ANC during the 21-day follow-up period were readily available. This information was used to write a computer simulation program that would generate random ANC data that asymptotically has the same means and standard deviations for the 21-day follow-up period as the publication. The simulation would then also generate the projected number of days with severe neutropenia (i.e., the DSN).

Deming regression (Deming, 1943) was used to calculate the linear relationship between simulated nadir and DSN. The rank correlation between simulated nadir and DSN was used to calculate the DSN with plinabulin (+ docetaxel) and docetaxel alone. In the Phase 2 study, ANCs were obtained on Day 8, which approximately coincides with the time that the neutrophil nadir occurs after docetaxel administration. These observed Day 8 neutrophil (nadir) values were computed into the linear relationship (Deming regression), mentioned above to calculate DSN for each patient. Using these methods, calculated mean DSN was 0.065 days for the plinabulin+ docetaxel arm, and 1.076 days for the docetaxel alone. Based on published data with filgrastim in patients receiving docetaxel (Alexopoulos K et al, 1999), the assumption is that Grade 4 neutropenia in Cycle 1 would occur in a 2 times higher frequency with G-CSF+docetaxel versus plinabulin+docetaxel, resulting in a presumed mean DSN of 0.13 days for the G-CSF+ docetaxel combination.

This non-inferiority trial design will utilize a difference (arm 2 minus arm 1) of 0.65 days (non-inferiority margin) in DSN in Cycle 1 as the largest acceptable difference between plinabulin and pegfilgrastim. The non-inferiority test will evaluate the null hypothesis H_0: true difference (arm 2 minus arm 1) ≥ 0.65 against the alternative hypothesis H_1: true difference (arm 2 minus arm 1) < 0.65. Plinabulin will be considered non-inferior to pegfilgrastim if in Cycle 1, the upper limit of the 2-sided 95% confidence interval for the true difference in mean duration of Grade 4 neutropenia was < 0.65 days. A sample size of patients was based on sample size considerations as outlined.

Data suggest (http://www.neulastahcp.com/risk/duration-of-severe-neutropenia/) that FN is correlated with DSN. The frequency of FN with docetaxel monotherapy (100 mg/m^2) + G-CSF was reported to be 1% in cycle 1. FN frequency in Cycle 1 with docetaxel combined with

doxorubicin and G-CSF was ~ 3 % (Aarts M et al, 2013), which would translate into a DSN of 1 day according to Holmes FA, et al, 2002. Based on this data, it is assumed that the median DSN for docetaxel monotherapy + G-CSF will be approximately 1 day.

The frequency of FN with docetaxel monotherapy (without G-CSF) has been reported to be 11% in cycle 1 (17% over all cycles) docetaxel dose of 100 mg/m^2 (Vogel et al, 2005) and 19.8% over all cycles at a lower docetaxel dose of 60 mg/m^2 (Yoh K et al, 2016). Hanna et al., 2004 reported a FN percentage of 12.7% with 75 mg/m^2 docetaxel. Based on this range of FN, the relationship established by Meza et al, 2002 between FN and DSN, we make the assumption that, with docetaxel monotherapy at a dose of 75 mg/m^2 without G-CSF, the median DSN is estimated to be 4-5 days.

In the Zarxio® briefing document, 2015, the margin was selected based on the fact that TAC chemotherapy is known to induce a median DSN of 7 days in breast cancer patients receiving no G-CSF treatment (Nabholtz, 2001), while G-CSF treatment reduces the mean DSN for this chemotherapy to 1.4 days (95% CI: 1.07 - 1.69) as shown in pegfilgrastim (Neulasta®) Study 20020778 (Kaufman et al, 2004). Based on this a non-inferiority limit of 1 day was derived.

As an extension of this reasoning, it is argued for our study, a non-inferiority margin of 0.65 would be reasonable and correspond to approximately a median of 4.5 days of DSN, as a margin of 1 day to 7 days of DSN in the Zarxio® briefing document, 2015.

A non-inferiority margin of 0.65 days can also be justified, because a difference of 0.65 days is not considered to be clinically meaningful.

14.2.7. Pharmacokinetic and Pharmacodynamic Analyses Considerations

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.

Plinabulin PK will be characterized using the population PK approach. Population PK parameter estimates, and individual PK parameters, including AUC and C_{max} will be summarized.

Exposure-Neutropenia Relationship

A sequential population PK/PD modeling approach will be used to characterize the exposure-neutropenia relationship. The semi-physiological model described by Friberg (2003) will be used to characterize the time course of neutropenia in the exposure-neutropenia model.

The developed exposure-response models will be used to simulate ANC profiles for the computation of key PD endpoints such as DSN, DMSN, and area over the ANC curve (AOC). The latter will be calculated as the area below the threshold of <0.5 x 10^9 cells/L and above ANC-time response curve in a chemotherapy cycle. Details will be included in the Pharmacometrics Analysis Plan (PAP).

Exposure-Blood Pressure Analysis

A sequential PK-PD model analysis will be performed. Since the ambulatory blood pressure measurements (ABPM) are subject to circadian variations, ABPM will be modeled to describe the circadian rhythm in blood pressure over the 4.5-hour observation period. The diurnal rhythm

in the AMBP data will be described with the cosine function (Hempel 1998) in the exposure-ABPM models. Details will be included in the PAP.

Exposure-QTc Analysis

Either a direct or sequential PK-PD model analysis will be performed. The choice of the modeling approach will be informed by the matching or non-matching of PK sampling times with ECG observation times. QT measurements corrected with the Fridericia formula will be used in the exposure-QTc analysis. Details will be included in the PAP.

14.3. Safety Analyses Considerations

Medical history and AE data will be coded by system organ class (SOC) and preferred term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Concomitant medication data will be coded by drug class and indication, using the WHO Drug dictionary.

All treatment emergent AEs will be graded according to NCI CTCAE version 4.03, and grouped by the MedDRA Preferred Term and System Organ Class, and summarized by worst grade severity per patient.

Treatment emergent AEs are those events that occur after first administration of any study therapy through 30 days post last dose of any study therapy, and/or any treatment-related AEs, regardless of the onset date. Dose delays, dose modifications and/or dose discontinuation of docetaxel due to safety concerns will be summarized for the 2 treatment groups.

Continuous variables and proportions will be analyzed using exact t-tests. Other categorical data will be analyzed using non-parametric statistical methods.

14.3.1. Deaths

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.

14.3.2. Extent of Exposure

Refer to the SAP for details.

14.3.3. Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. AEs will be coded to MedDRA (Version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

14.3.4. Laboratory Analyses

Descriptive summary statistics for laboratory values will be provide as well as the shift table..

14.3.5. Vital Signs

Descriptive statistics tables will be used for the evaluations.

14.3.6. Electrocardiogram

Electrocardiogram assessments will be provided in a listing.

14.4. Sample Size Considerations

14.4.1. Phase 2

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

14.4.2. Phase 3

Approximately 150 patients are planned to be enrolled with 1 of the following diagnoses: advanced or metastatic breast cancer, NSCLC, or HRPC. A sample size of 75 patients in each of the treatment arms docetaxel + plinabulin (40 mg) versus docetaxel + pegfilgrastim, with matching placebos achieve at least a 90% power to reject the null hypothesis of 0.65 day of inferiority in DSN between the treatment means with standard deviations of 0.75, at a significance level (alpha) of 0.05 two-sided two-sample zero-inflated Poisson model.

The software PASS version 15.0.1 has been used for the calculations referencing Chow et al. 2003, Lan and DeMets 1983, O'Brien and Fleming 1979.

14.5. Interim Analysis

The study design is group sequential with 1 interim analysis (after 50 patients in each treatment arm have completed at least 1 cycle in each of the treatment arms docetaxel + plinabulin [40 mg] versus docetaxel + pegfilgrastim, with matching placebos) and 1 final analysis at the completion of the study (Table 15). These results assume that 2 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries.

If non-inferiority is determined from the statistical testing, then also the hypothesis of superiority will be tested, and if it is concluded that the plinabulin treatment is superior to the pegfilgrastim treatment, with respect to DSN, then the study will be stopped. Since the design allows for stopping for inferiority, it might be decided at that occasion that the study will be stopped. Since this is a hierarchical testing procedure no penalty with respect to overall significance will be paid.

The statistical testing will be performed and will be reviewed by an independent DSMB at the interim analysis.

Table 15: Timing of Statistical Analyses

	Number of Patients in Phase 2 (approximate)	
Arm 1: Docetaxel + Pegfilgrastim 6 mg	10	
Arm 2: Docetaxel + Plinabulin 20 mg/m^2	10	
Arm 3: Docetaxel + Plinabulin 10 mg/m^2	10	
Arm 4: Docetaxel + Plinabulin 5 mg/m^2	10	
	PK/PD Analysis (to determine RP3D)	
	Number of patients in Phase 3 (approximate)	
Arm 1: Docetaxel + Pegfilgrastim 6 mg	50	75
Arm 2: Docetaxel + Plinabulin (40 mg)	50	75
	Interim Analysis	**Final Analysis**

14.6. Withdrawal

During the phase 2 and phase 3 portions, randomized patients who withdraw before receiving the first dose will be replaced.

14.7. Independent Data Safety Monitoring Board Interim Safety Review

An independent DSMB will be utilized in this study and will be comprised of individuals who are not members of the clinical study team. At least 2 independent oncologists (external to the sponsor) will serve on the committee. The objective of the DSMB will be to ensure objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. See details in Section 14.5.

15. ADMINISTRATIVE PROCEDURES

15.1. Investigator Reporting Requirements

As indicated in periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

15.2. Confidentiality

The Investigator must assure that patients' anonymity will be maintained and that his or her identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, patients should not be identified by his or her names, but by an identification code. The Investigator should keep a patient enrollment log showing codes, names and addresses. The Investigator should maintain documents not for submission to the Sponsor (e.g., patients' written consent forms, in strict confidence).

15.3. Case Report Forms

For each patient enrolled, an eCRF must be completed and electronically signed by the Principal Investigator or authorized delegate from the study staff. Once a patient has signed informed consent and any study related procedures are performed, an eCRF must be completed. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.

15.4. Drug Accountability

The investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records and returned or destroyed study product.

15.5. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

15.6. Protocol Modifications

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsor and the Investigator. Protocol modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by Chief Medical Officer.

All protocol modifications must be submitted to the appropriate IEC or IRB for information and approval in accordance with local requirements and to Regulatory Agencies if required. Approval must wait before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in Monitor(s), change of telephone number(s).

15.7. Study Report and Publications

The results of this study may be published or presented at scientific meetings. The Investigators agree to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

Because this is a multicenter study, individual investigators may not publish the results of the study based on information from his or her sites until the complete study has been published in full (not abstract) form. If a joint publication has not been submitted within 8 months after the study has been completed or terminated at all sites, then individual sites may publish subject to the requirement to submit to the Sponsor before publication.

The Sponsor will prepare a clinical study report upon completion or termination of the study.

15.8. Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patient's interests.

15.9. Records Retention and Study Files

15.9.1. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 different separate categories 1) Investigator's Study File, and 2) patient clinical source documents.

The Investigator's Study File will contain the Protocol/Amendments, sample CRFs, patient screening and enrollment logs, Independent Ethics Committee/IRB and governmental approval with correspondence, sample informed consent, study-drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed informed consent forms and consultant letters. The Investigator must keep these 2 categories of documents on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, according to local regulations.

Should the Investigator wish to assign the study records to another party or move the study records to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in a sealed container(s) outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for

the continued care of the patient, appropriate copies should be made for storing outside of the site.

15.9.2. Source Documents and Background Data

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected.

15.10. Provision of Study Results and Information to Investigators

When the clinical study report is completed, the sponsor will provide the major findings of the study to the investigator.

15.11. Information Disclosure and Inventions

15.11.1. Access to Information for Monitoring

It is understood that the responsible Sponsor's Monitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (CRFs and other pertinent source data) provided that patient confidentiality is maintained in accord with local requirements.

It will be the Monitor's responsibility to inspect the CRFs at regular intervals throughout the study, to verify the adherence to the Protocol and the completeness, consistency and accuracy of the data being entered on the CRFs. The Monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. The Investigator (or his/her deputy) agrees to cooperate with the Monitor to ensure that any problems detected in the course of these monitoring visits are resolved. Refer to Monitoring Plan for further details.

15.11.2. Access to Information for Auditing or Inspections

The Investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Sponsor, or its designees, or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

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Study NPI-2358-101: A Phase 1/2 study of the Vascular Disrupting Agent NPI-2358 in combination with Docetaxel in patients with Advanced Non-Small cell Lung Cancer.

Study NPI-2358-103: A Randomized Single-Blinded Phase 3 Study of Second- or Third-Line Chemotherapy with Docetaxel + Plinabulin Compared to Docetaxel + Placebo in Patients with Advanced Non-Small Cell Lung Cancer with at Least One Measurable Lung Lesion (DUBLIN-3).

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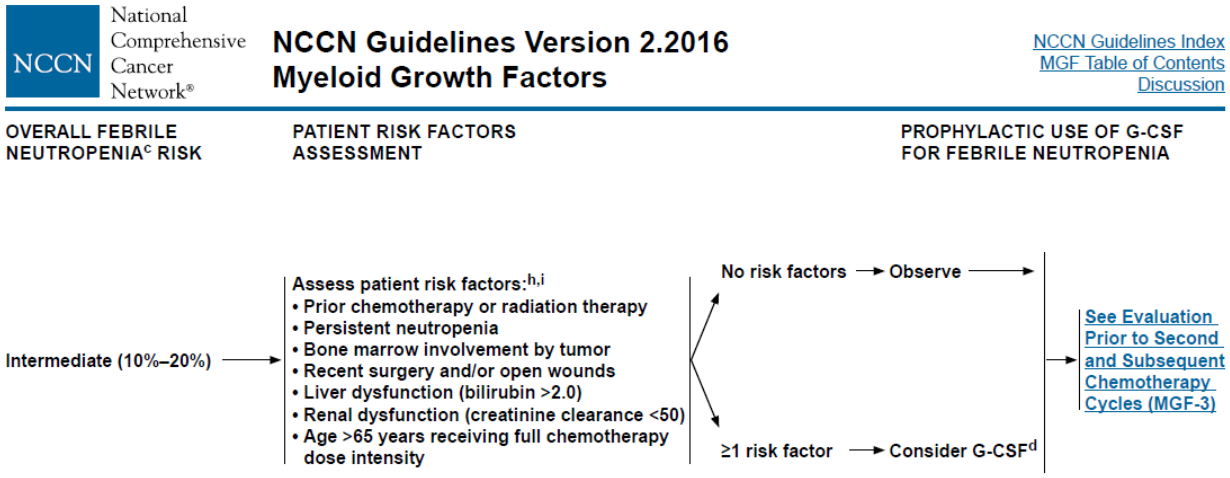
17. APPENDICES

APPENDIX A. NCCN GUIDELINES VERSION 2.2016

NOTE: Persistent neutropenia, liver dysfunction (bilirubin > 2,0) and renal dysfunction (creatinine clearance < 50) intermediate risk factors are not applicable to this study.



[c]Febrile neutropenia is defined as single temperature: ≥38.3°C orally or ≥38.0°C over 1 h; neutropenia: <500 neutrophils/mcL or <1,000 neutrophils/mcL and a predicted decline to ≤500 neutrophils/mcL over the next 48 h. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

[d]G-CSF refers to the following approved agents: filgrastim, filgrastim-sndz, tbo-filgrastim, and pegfilgrastim. See G-CSF for Prophylaxis of Febrile Neutropenia and Maintenance of Scheduled Dose Delivery (MGF-B).

[h]Other possible patient risk factors for febrile neutropenia may include poor performance status or HIV infection (in particular, patients with low CD4 counts).The listed patient risk factors are based on a multivariable risk model using a prospective cohort study of several thousand ambulatory cancer patients receiving chemotherapy. This cohort did not include patients with HIV, acute leukemia, or hematopoetic cell transplant. (Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. Crit Rev Oncol Hematol 2014;90:190-199)

[i]Other factors may warrant the use of G-CSF (eg, chronic immunosuppression in the post-transplant setting, including organ transplant).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MGF-2

APPENDIX B. CTCAE VERSION 4.03

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

18. SIGNATURES

Signature of Investigator

PROTOCOL 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

PROTOCOL NO: BPI-2358-105 Amendment 7

This protocol is confidential

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

Signature of Chief Medical Officer

PROTOCOL TITLE: A Phase 2/3, Multicenter, Randomized, Study to Evaluate Duration of Severe Neutropenia with Plinabulin Versus Pegfilgrastim in Patients with Solid Tumors Receiving Docetaxel Myelosuppressive Chemotherapy

PROTOCOL NO: BPI-2358-105 Amendment 7

Date: 19 December 2019

Sponsor Chief Medical Officer