DISCLOSURE

REDACTED STATISTICAL ANALYSIS PLAN

ABI-007-PST-001

A PHASE 1/2, MULTICENTER, OPEN-LABEL, DOSE-FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF WEEKLY *nab*®- PACLITAXEL IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

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STATISTICAL ANALYSIS PLAN

A PHASE 1/2, MULTICENTER, OPEN-LABEL, DOSE-FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF WEEKLY *nab*®-PACLITAXEL IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

INVESTIGATIONAL PRODUCT (IP): ***nab*®[1]-paclitaxel (ABRAXANE®)**

PROTOCOL NUMBER: **ABI-007-PST-001**

DATE FINAL: **8 August 2017**

DATE AMENDMENT #1 FINAL: **12 January 2018**

Prepared by:

Celgene Corporation

86 Morris Avenue

Summit, NJ 07901

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SIGNATURE PAGE

STATISTICAL ANALYSIS PLAN (SAP) AND SAP AMENDMENT APPROVAL SIGNATURE PAGE	
SAP TITLE	ABI-007-PST-001 Statistical Analysis Plan
SAP VERSION, DATE	Version: Amendment #1, 12 January, 2018
SAP AUTHOR	PPD Printed Name and Title PPD Signature and Date
PROTOCOL TITLE	A PHASE 1/2, MULTICENTER, OPEN-LABEL, DOSE-FINDING STUDY TO ASSESS THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF WEEKLY *nab*®-PACLITAXEL IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS
INVESTIGATIONAL PRODUCT	*nab*®-paclitaxel (ABRAXANE®)
PROTOCOL NUMBER	ABI-007-PST-001
PROTOCOL VERSION, DATE	Amendment # 5.0, 13 July 2016
SIGNATURE STATEMENT	By my signature, I indicate I have reviewed this SAP and find its contents to be acceptable.

Statistical Therapeutic Area Head

Signature PPD

Printed Name _____ Date PPD

Lead Clinical Research Physician / Clinical Research Physician

Signature PPD

Printed Name _____ Date PPD

Lead Product Safety Physician

Signature PPD

Printed Name _____ Date PPD

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophils count
AST (SGOT)	Aspartate amino transferase
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AUC_t	Area under the plasma concentration-time curve
AUC_{24}	Area under the plasma concentration-time curve from time zero to 24 hours
AUC_∞	Area under the plasma concentration-time curve from time zero extrapolated to infinity
BLQ	Below the limit of quantitation
BSA	Body surface area
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CL	Total clearance
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	Diastolic blood pressure
DCR	Disease control rate
DDS	Dose-determining set
DLT	Dose-limiting toxicity

Abbreviation or Specialist Term	Explanation
DoR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EE	Efficacy evaluable
FCBP	Female of child bearing potential
GCP	Good Clinical Practice
IAF	Informed assent form
ICH	International Council for Harmonisation
ICF	Informed consent form
IV	Intravenously
IVRS	Interactive voice recognition system
LVSF	Left ventricular shortening fraction
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	^{123}I-metaiodobenzylguanidine
Min	Minimum
MRT	Maximum residence dose
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PDI	Planned dose intensity
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response

Abbreviation or Specialist Term	Explanation
PT	Preferred term
Q1	First quartile
Q3	Third quartile
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
Rsq	Regression coefficient for calculation of terminal phase rate constant
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems
SBP	Systolic blood pressure
SD	Standard deviation
SJS	Stevens-Johnson syndrome
SMC	Safety monitoring committee
SOC	System organ class
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TLG	Tables, listings, and graphs
t_{max}	Time to maximum observed plasma concentration
$t_{½}$	Terminal phase half-life
V_{ss}	Volume of distribution at steady state
WBC	White blood cells
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
λ_z	Terminal phase rate constant
V_z	Volume of distribution based on the terminal phase

2. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations for Celgene's protocol ABI-007-PST-001 "A Phase 1/2, Multicenter, Open-label, Dose-finding Study to Assess the Safety, Tolerability, and Preliminary Efficacy of Weekly *nab*-paclitaxel in Pediatric Patients with Recurrent or Refractory Solid Tumors", Amendment # 5, dated 13 July 2016. This study was set up with the objective of evaluating the safety profile of *nab*-paclitaxel as monotherapy in recurrent or refractory specific solid tumors in pediatric subjects, in addition to collecting pharmacokinetic (PK) data in this population and evaluating anticancer activity in the specific solid tumors in pediatric subjects. This SAP contains definitions of analysis populations, derived variables, and statistical methods for the analysis of all efficacy, safety, and PK endpoints.

Furthermore, the purpose of this SAP is to specify, prior to database lock, the statistical approaches to the final analysis of study data. This SAP will be finalized and signed prior to the clinical database lock for the final analysis. All analyses detailed in this SAP will be conducted using Statistical Analysis Systems® (SAS®) version 9.2 or higher, except for the PK analysis which will be conducted using PK software (Phoenix WinNonlin 6.4 or higher, and other software as appropriate).

2.1. Summary of Change

There are no major revisions from the 8th August 2017 version to the current version of this SAP. Minor revisions are refined to the addition of reporting of study disposition for scree-fail subjects and of cancer history. Other minor revision are clarifications of definitions and data reporting, and correction of language used.

3. STUDY OBJECTIVES

3.1. Primary Objectives

Phase 1

The primary objectives of Phase 1 of the study are to determine the pediatric maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) and to characterize the safety and tolerability of *nab*-paclitaxel administered intravenously (IV) over approximately 30 minutes on Days 1, 8, and 15 of a 28-day cycle in subjects ≥ 6 months and < 18 years old with recurrent or refractory solid tumors.

Phase 2

The primary objective of Phase 2 of the study is to determine the antitumor activity assessed by the overall response rate (ORR) of *nab*-paclitaxel given at the RP2D in subjects ≥ 6 months and ≤ 24 years old with several discrete recurrent or refractory solid tumor types, including neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma.

3.2. Secondary Objectives

Phase 1

To evaluate PK and to characterize the ORR.

Phase 2

To characterize duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and survival at 1 year. To confirm safety and to evaluate PK.

3.3. Exploratory Objectives

Phase 1

To assess ^{123}I-metaiodobenzylguanidine (MIBG) response in subjects with neuroblastoma.

Phase 1 and Phase 2

To explore the potential utility of biomarkers of response and resistance in this study population. The most recent available tumor tissue sample will be optionally collected at the time of study entry. Biomarkers will be prioritized for analysis in these samples after study completion, as informed by emerging data.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a Phase 1/2 multicenter, open-label, dose-finding study to assess the safety, tolerability, PK, and efficacy of *nab*-paclitaxel administered intravenously to patients ≥ 6 months and < 18 years old in the Phase 1 portion and patients ≥ 6 months and ≤ 24 years old in the Phase 2 portion with recurrent and refractory solid tumors.

Phase 1 is a dose-finding study to determine the MTD/RP2D (rolling-6 design), safety, tolerability, and PK parameters of *nab*-paclitaxel in pediatric subjects with recurrent and refractory solid tumors who have progressed on standard therapy or for whom no standard therapy exists. The decision to dose-escalate or to declare an MTD/RP2D will be determined by the Safety Monitoring Committee (SMC) each time clinical and laboratory safety data for a given dose-determining set (DDS) are available for review. The SMC will also determine the dose(s) appropriate for Phase 2 (or the RP2D) (Figure 1). In addition to DDS data, the SMC may take into consideration the totality of all data, including that of subjects enrolled in previous dose cohorts or enrolled at a dose previously assessed as safe.

Phase 2 will be conducted using the RP2D established in Phase 1 to determine:

- The antitumor activity of *nab*-paclitaxel in several solid tumor types (3 groups: neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma;
- The safety profile and PK of *nab*-paclitaxel administered at the RP2D.

In Phase 2, three disease indications will be studied: neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma, each forming an independent treatment arm. Each disease indication will be studied in the Simon's Minimax Two-stage design, run in parallel to one another (Figure 2).

During Phase 2, the SMC will continue to review safety data regularly and to make recommendations about the study continuation, as appropriate.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

The study will consist of 3 periods: Screening Period, Treatment Period, and Follow-up Period, outlined as follows:

Screening Period

The Screening Period will start from the time of signing the informed consent form (ICF)/informed assent form (IAF) and will last no more than 14 days, at which time the Treatment Period will begin (Cycle 1 Day 1). The subject's screening procedures are to occur during the Screening Period within 14 days prior to dosing on Cycle 1 Day 1; by exception historical tumor scans (and MIBG scans for neuroblastoma) performed ≤ 28 days before the first dose can be used for screening.

Treatment Period

Subjects meeting all eligibility criteria will then enter the Treatment Period and start *nab*-paclitaxel treatment. Subjects must start treatment within 14 days of signing the ICF/IAF. For all subsequent visits, an administrative window of ± 2 days is permitted.

nab-paclitaxel will be administered as monotherapy, IV over approximately 30 minutes, without corticosteroid or antihistamine premedication, weekly on Days 1, 8, and 15 of a 28-day cycle. The treatment will be given until disease progression, the subject begins a new anticancer treatment, withdrawal of parent/guardian/subject consent/assent, parent/guardian/subject refusal, physician decision, toxicity that cannot be managed by dose delay or dose reduction alone, or the study ends for any reason.

If deemed necessary, a dose should be reduced by 1 dose level according to Table 7 in the protocol. A maximum of 2 dose reductions are permitted. If a toxicity requiring dose adjustment occurs after a second dose reduction, further treatment must be discontinued. Treatment modifications are applicable during Phase 1 and Phase 2 of the study, except that dose reductions during Phase 1 Cycle 1 (and during Cycle 2 for subject ≤ 10 kg) are not permitted.

Follow-up Period

Following treatment discontinuation, all subjects will be followed for 28 days from last *nab*-paclitaxel dose date for safety and monitoring of adverse events (AEs). This data will be collected at the 28-day Safety Visit.

Special Monitoring: Neuropathy (eg, motor neuropathy, sensory neuropathy, peripheral neuropathy) AEs present at the time of treatment discontinuation should be followed until 1 of the following are met, but no less than the minimum 28-day safety follow-up:

- Improvement to ≤ Grade 1;
- At least 3 months have elapsed without improvement or worsening;
- The subject initiates any other anticancer therapy during the follow-up.

Follow-up will continue for 1 year after last dose of *nab*-paclitaxel with subjects being followed for survival status and start of any new anticancer therapies.

All subjects who discontinue treatment for reasons other than disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study will be followed for response and new anticancer therapies as specified in Section 6.3 of the protocol.

Figure 1: Phase 1 Study Design

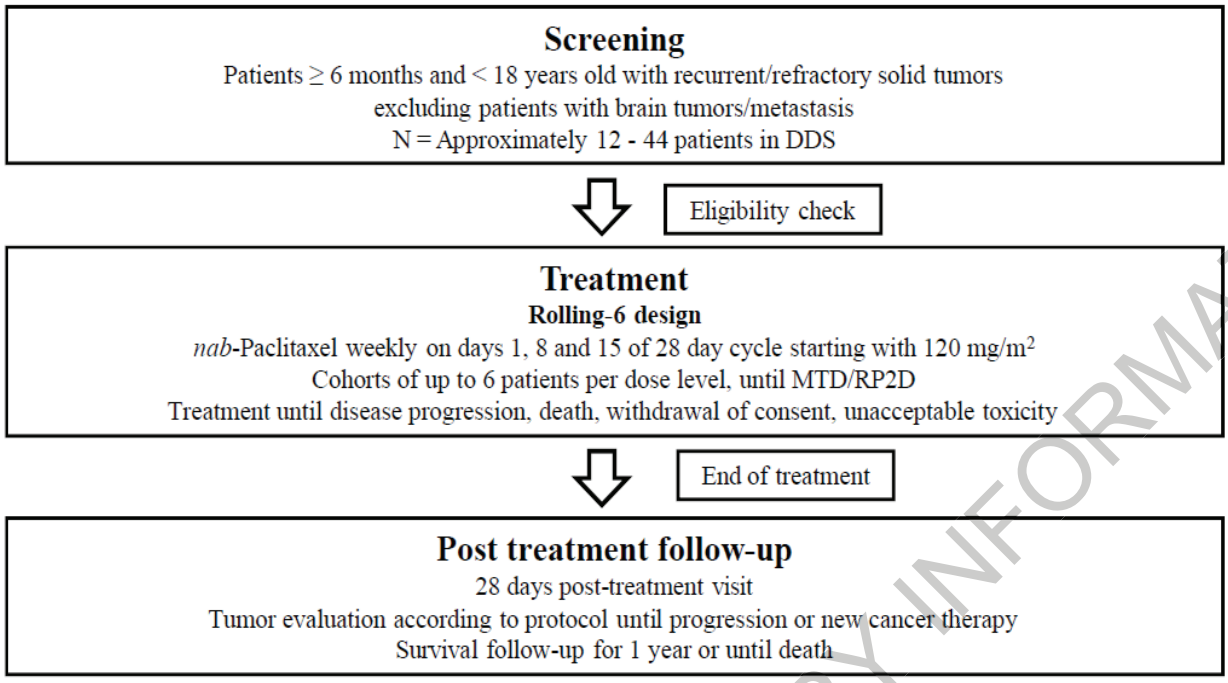
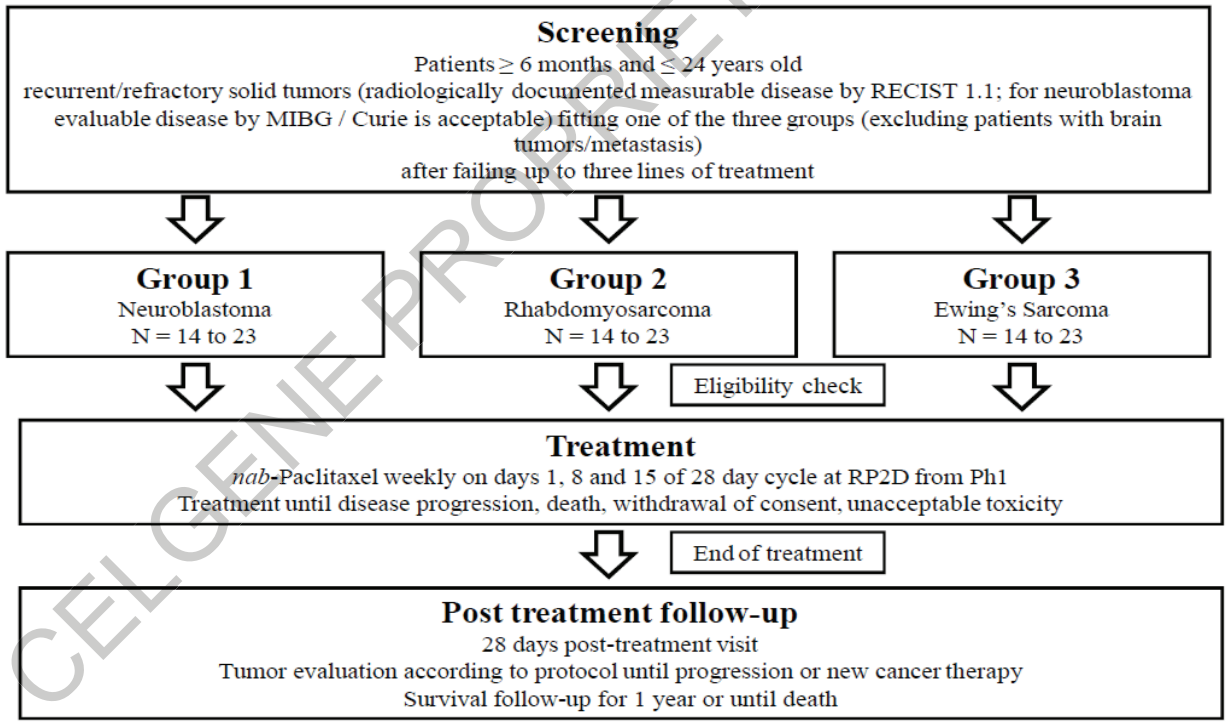


Figure 2: Phase 2 Study Design



4.2. Study Endpoints

4.2.1. Primary Endpoints

Phase 1

The incidence of dose-limiting toxicities (DLTs) (defined in Section 8.2.1.1 of the protocol and Section 12.4 of this SAP) and the incidence of treatment-emergent AEs (TEAEs).

Phase 2

The ORR, which is the combined incidence of complete response (CR) and partial response (PR), confirmed no less than 4 weeks after the criteria for response are first met, based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In the neuroblastoma group, the ORR will be determined by RECIST and/or the Curie score (MIBG response).

4.2.2. Secondary Endpoints

Phase 1

- Pharmacokinetic parameters including the maximum observed plasma concentration (C_{max}), area under the blood concentration-time curve (AUC), clearance (CL) and volume of distribution at steady state (V_{ss});
- Overall response rate.

Phase 2

- Duration of response in subjects with a confirmed objective CR or PR;
- Disease control rate: the percentage of subjects with a confirmed objective CR or PR, or stable disease for at least 16 weeks;
- Progression-free survival based on investigator assessment of response using RECIST 1.1 guidelines. In the neuroblastoma group the PFS will be determined by RECIST and/or the Curie score (MIBG response);
- Survival at 1 year;
- The incidence of TEAEs;
- Population PK parameters (eg, clearance and volume of distribution). Data from Phase 1 and Phase 2 will be analyzed together for this endpoint.

4.2.3. Exploratory Endpoints

Phase 1

- MIBG response using the Curie Score in subjects with neuroblastoma.

Phase 2

- Bone marrow biopsy verification of confirmed complete response in subjects with neuroblastoma.

Phase 1 and Phase 2

- Biomarker analysis prioritized after study completion, as informed by emerging data.

4.3. Stratification, Randomization, and Blinding

This is an open-label, single therapy study. Treatment assignment does not require randomization, blinding, or stratification.

4.4. Sample Size Determination

Phase 1

During Phase 1, a rolling-6 subject dose escalation design will be used to establish the MTD/RP2D, with approximately 64 subjects anticipated to be enrolled depending on the number of dose levels required (approximately 44 considered evaluable for determination of the MTD/RP2D, and about 20 additional subjects at dose levels previously evaluated as safe by the SMC). Subjects who are ineligible for determination of the MTD/RP2D will be replaced at the discretion of the sponsor. Additional subjects may be enrolled at dose levels evaluated as safe by the SMC.

Phase 2

In Phase 2, Simon's Minimax Two-stage design will be employed per disease indication with each incorporating the following parameters: 5% significance level, 80% power and an upper and lower boundary of interest of 10% and 28%, respectively, for the ORR. Each of the disease indications will therefore enroll up to 23 subjects across Phase 2 (14 subjects in stage one and an additional 9 subjects in stage two) meaning a maximum total of 69 subjects evaluable for the primary endpoint.

For purposes of the primary endpoint analysis, the ORR is defined using the maximum likelihood estimator.

For each of the 3 groups in stage one, if < 2 of the 14 evaluable subjects have a response, then enrollment into that disease indication group will be stopped; otherwise enrollment shall continue as planned in stage two. At the final analysis, the study treatment will be concluded with more than a 5% true response rate if ≥ 5 of 23 subjects have a response. The Phase 2 target response rate is therefore 21.74% with 80% power and a 10% significance level.

5. ANALYSIS POPULATIONS

5.1. Informed Consent/Assent Population

The informed consent population includes all subjects who signed informed consent and/or assent, ie, all subjects who entered the Screening Period regardless of later being a screen failure.

5.2. Enrolled Population

The enrolled population includes all subjects enrolled, ie, all subjects who are marked as enrolled in the clinical database regardless of whether they received *nab*-paclitaxel.

5.3. Safety Population

The safety population includes all subjects who received at least 1 dose of *nab*-paclitaxel.

5.4. Efficacy Evaluable Population

Phase 1 Regardless of Disease Indication

All treated subjects who meet eligibility criteria, complete at least 1 dose of *nab*-paclitaxel, and have baseline and either at least 1 postbaseline efficacy assessment, or having discontinued *nab*-paclitaxel due to disease progression or symptomatic deterioration before a postbaseline efficacy assessment could be conducted. Here efficacy assessment means radiological assessment of the tumor or tumor assessment by other appropriate means.

Phase 2 Rhabdomyosarcoma and Ewing's Sarcoma Indications

All treated subjects who meet eligibility criteria relevant to efficacy, complete at least 1 dose of *nab*-paclitaxel, and have baseline and either at least 1 postbaseline efficacy assessment assessed per RECIST 1.1, or having discontinued *nab*-paclitaxel due to disease progression or symptomatic deterioration before a postbaseline efficacy assessment could be conducted. Here efficacy assessment means radiological assessment of the tumor or tumor assessment by any means appropriate.

Phase 2 Neuroblastoma Indication

All neuroblastoma subjects who meet eligibility criteria relevant to efficacy, complete at least 1 dose of *nab*-paclitaxel, and have baseline and either at least 1 postbaseline efficacy assessment assessed per the RECIST 1.1 and/or the Curie score (MIBG response), or having discontinued *nab*-paclitaxel due to disease progression or symptomatic deterioration before a postbaseline efficacy assessment could be conducted. Here efficacy assessment means radiological assessment of the tumor or tumor assessment by any appropriate means.

5.5. Dose-determining Set

The primary endpoint for Phase 1, determination of the MTD/RP2D, will be performed on the DDS for each dose level tested. In subjects weighing > 10 kg, the DDS includes all subjects who experienced a DLT, or received all 3 weekly doses of *nab*-paclitaxel at the cohort planned dose during Cycle 1 and had adequate safety assessments during the DLT assessment period (Cycle 1

including predose assessments on Cycle 2 Day 1). In subjects weighing ≤ 10 kg, the DDS includes all subjects who experienced a DLT, or received all 6 weekly doses of *nab*-paclitaxel at the cohort planned doses during Cycles 1 and 2 and had adequate safety assessments during the DLT assessment period (Cycle 1 and 2 including predose assessments on Cycle 3 Day 1).

5.6. Pharmacokinetic Population

The PK population includes all subjects who received at least 1 dose of *nab*-paclitaxel and had evaluable concentration data.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. Reporting Conventions

The summary tables, listings, and any supportive SAS output will include the explanatory "headers" that indicate, at a minimum:

- protocol number;
- data cutoff date;
- company name (Celgene Corporation);
- page number (Page x of x).

The summary tables, listings, and any supportive SAS output will include the explanatory "footers" that indicate, at a minimum:

- program source (ie, SAS program name, including the path, run date);
- data extraction date;
- data source (ie, list of datasets used for the display).

The purpose of the data extraction date is to link the output to the database, either active or archived, that is write-protected for replication and future reference. The program run date is the output date which will appear on each output page and will indicate the date the output was generated by the analysis program. Individual source listings will display all the relative values supporting corresponding table(s) and figure(s).

In addition, the following reporting conventions will be implemented:

- Data from all study sites will be combined for analysis;
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless otherwise specified;
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the sample size (n), mean, median, standard deviation (SD), minimum (Min), and maximum (Max) for continuous variables;
- All mean and median values will be formatted to 1 more decimal place than the measured value. Standard deviation values will be formatted to 2 more decimal places than the measured value;
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '<0.0001' and p-values that round to 1.000 will be presented as '>0.9999';
- All percentages will be rounded to the nearest whole number. The number and percentage of responses will be presented in the form xx (xx), where the percentage is in the parentheses. In the case the numerator is equal to the denominator, the percentage should be presented as (100) instead of (100.0);

- All listings will be sorted for presentation in order of study phase, dose level (Phase 1 only), study site, subject number, and date of procedure or event. Subjects who are not enrolled will be listed as a non-enrolled group after enrolled subjects;
- All tables will be presented by study phase, and dose/disease indication;
- All analysis and summary tables will have the analysis population sample size for each treatment group in the column heading (ie, number of subjects) where applicable;
- Baseline is defined as the latest value collected on or before the date when the first dose of study treatment is administered. If multiple values are present for the same date, the mean of these values will be used as the baseline, except for laboratory data, where the value with the worst Common Terminology Criteria for Adverse Events (CTCAE) grade will be set as baseline. For subjects who were not treated, the baseline value will be defined as the latest value collected on or prior Day 1 of the Cycle 1 visit, if available;
- The day of first dose of study drug *nab*-paclitaxel will be defined as Day 1. For subjects who are not treated, the Cycle 1 Day 1 visit will be defined as Day 1;
- For tables and figures displaying results by visit, only scheduled visits will be considered beside clinical laboratory evaluations. Unscheduled visits will appear only in listings and could be considered in some derivations;
- All the analyses will be performed separately for Phase 1 and Phase 2 unless specified otherwise.

6.2. Calculation of Treatment Start Dates, Cycles, and Treatment End Dates

Treatment will commence on Day 1 and planned cycle lengths are 28 days. Day 1 of a cycle is defined as day 1 of study drug for the given cycle as recorded on the electronic case report form (eCRF).

Cycle end dates are defined as the day before Day 1 of the following cycle, or if on the last cycle then the last day is the last treatment administration date plus 28 days, i.e. the treatment end date plus 28 days. The treatment end date, and the end date of the last cycle, will be calculated as follows:

- For subjects who discontinue prior to the clinical cutoff date, treatment end date is the date of treatment discontinuation from the treatment disposition page in the eCRF;
- For subjects who are still on treatment at the time of study closure or clinical cutoff, the last date of planned cycle (27 days after first dose of the last cycle) will be used as the treatment end date.

The cycle number for each date of interest, eg, AE start date, will be calculated based on the cycle window set by their start and end dates.

The following rules will be implemented for cycle calculations for TEAEs:

- TEAEs present on or after Day 1 Cycle i but before Day 1 of the subsequent cycle belong to Cycle i (where i stands for cycle number);

- All TEAEs that occur between Day 1 of the last cycle and 28 days after last dose administration date will be included only in the last cycle.

7. SUBJECT DISPOSITION

Tables showing a summary of analysis population will present data by study phase, specifically by dose level and in aggregate (Phase 1) and by disease indication and in aggregate (Phase 2) for the following analysis populations:

- Informed Consent/Assent Population;
- Enrolled Population;
- Safety Population;
- Efficacy Evaluable Population;
- Dose-determining Set;
- Pharmacokinetic Population.

A summary of subjects enrolled by country, and site number/name will be provided.

A summary table showing subjects that did not enroll into the study, and reason for non-enrollment, will be provided. The table will present data for Phase 1 and 2 individually but not by dose level nor disease indication.

Reasons for treatment discontinuation will be summarized overall and by cycle based on the safety population and presented by study phase, specifically by dose level and in aggregate (Phase 1) and by disease indication and in aggregate (Phase 2) and in aggregate across Phase 1 and Phase 2 for the following categories:

- Death;
- Adverse event;
- Pregnancy;
- Progressive disease;
- Withdrawal by subject;
- Withdrawal by parent/guardian;
- Lost to follow-up;
- Study terminated by sponsor;
- Physician decision;
- Protocol violation;
- Symptomatic deterioration;
- Other.

Reasons for discontinuing the study follow-up/study will be collected on the case report form (CRF) and will be summarized for the Informed Consent/Assent Population with the following categories:

- Screen failure;
- Death;
- Adverse event;
- Withdrawal by subject;
- Withdrawal by parent/guardian;
- Lost to follow-up;
- Study terminated by sponsor;
- Other.

Included also is the number and proportion of subjects who completed the study, defined as those completing the 1-year survival follow-up. Summary tables for study discontinuation will present data by study phase, specifically by dose level and in aggregate (Phase 1) and by disease indication and in aggregate (Phase 2) and in aggregate across Phase 1 and Phase 2.

Listings will be provided for study discontinued subjects with reason for treatment discontinuation and for screen failure subjects.

8. PROTOCOL DEVIATIONS/VIOLATIONS

Protocol deviations and protocol violations will be identified and assessed by the sponsor's clinical monitor or designee following company standard operational procedure; these possible deviations and violations are entered into the clinical trial management system by the clinical monitor and are reviewed by the sponsor for confirmation/correction. This adjudicated protocol deviation/violation tracker maintained in an excel file will be used for analysis.

Protocol deviations and violations will be reviewed before database lock to partly determine the EE Population.

It should be noted that not all protocol deviations or violations will result in the exclusion of subjects from the EE Population. Events that could trigger exclusion from the EE Population include certain inclusion/exclusion criteria violations, failure to take the study drug as assigned, and prohibited concomitant medications and procedures.

Protocol violations will be summarized for the Safety Population using frequency tabulations. Moreover, frequencies will be provided for number of subjects with 1, 2, or > 2 protocol violations.

A listing of subjects with protocol violations/deviations in the Enrolled Population will be provided. Summary tables will present data by study phase, specifically by dose level and in aggregate (Phase 1) and by disease indication (Phase 2) and in aggregate for Phase 1 and Phase 2, based upon subjects in the Safety Population.

9. DEMOGRAPHICS AND BASELINE CHARACTERISTICS AND MEDICAL AND TREATMENT HISTORIES

Demographics and baseline characteristics, and medical and treatment histories will be summarized by study phase, specifically by dose level and in aggregate (Phase 1) and by disease indication (Phase 2) and in aggregate Phase 1 and Phase 2 for the Safety Population and EE Population unless specified otherwise. Baseline clinical characteristics are defined as the latest data collected on or before Cycle 1 Day 1, but before start of treatment. Individual subject listings will be provided to support the summary tables.

9.1. Demographics

Age (years), height (cm), and weight (kg) at baseline will be summarized using descriptive statistics (n, mean, SD, median, min and max). Age category (< 2 years, ≥ 2 years to < 12 years, ≥ 12 years to < 18 years, and ≥ 18 years to ≤ 24 years [Phase 2 only]), weight category (≤ 10 kg, > 10 kg), gender, race, ethnicity, and other categorical variables will be summarized by frequency tabulations.

Age will be calculated as follows: age (year) = [(Date of informed consent/assent – Date of Birth + 1) / 365.25]. In the table, age will be presented as an integer. In the listing, age < 2 years will be displayed in month(s), which will be calculated as age (month) = Integer ≤ [(Date of informed consent/assent – Date of Birth + 1) / 30.4375]. Years reached are to be used for categorization.

Within listings, age will be displayed in years and months as computed following directions given in Appendix 1A, Section 2, while within tables summary statistics for age in years will be used. The World Health Organization (WHO) growth chart will be used for infants and children ages 0 to 2 years of age and the Centers for Disease Control and Prevention (CDC) growth chart will be used for children age 2 years and older.

Body surface area (BSA) will not be recalculated for tables, listings, and graphs (TLG) presentation but presented based on BSA as calculated and reported by the site per their institutional practice.

9.2. Baseline Characteristics

The number and percentage of subjects in each of the following categories will be presented:

- Overall interpretation of electrocardiograms (ECG);
- Lansky/Karnofsky performance status at baseline (the 2 performance assessments will be presented separately);
- Tumor type;

The time from initial diagnosis to the first recurrence/progression and time from first recurrence/progression to first dose date will be summarized descriptively.

9.3. Medical History

A summary of medical history will be presented by Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later system organ class (SOC) and preferred term (PT) for the safety population.

Medical and surgical history will be sorted in descending frequency for the SOC based on the overall column and within each SOC; the PTs will be displayed in alphabetical order.

9.4. Cancer History

A summary of cancer history will be presented showing disease diagnosis and stage at initial diagnosis and at time of study screening, and time to and from specified cancer history timepoints including, but not limited to, prior disease progression/reoccurrence to first study treatment dose date.

Information pertaining to baseline lesion status will also be presented, including, but not limited to, lesion diameter, location and assessment method used.

9.5. Prior and Concomitant Medications/Procedures

Medications initiated prior to the start of study treatment and continued after the start of study treatment will be counted as both prior and concomitant medications.

Tables and listings described in this section will use the Safety Population.

9.5.1. Prior Medications and Procedures

Prior medications and procedures, such as surgeries, are defined as medications or procedures that were started before the start of the study treatment and either ended before the start of the study treatment or continued after study treatment.

The number of prior therapies and procedure, such as surgeries, will be summarized for prior radiation therapies, prior cancer surgeries, prior systemic anticancer therapies, prior stem cell transplants and other prior anticancer therapies by frequency tabulations based on the Safety Population. Descriptive statistics may be provided also, if needed. The therapies/surgeries with the same sequence/regimen number are counted as 1 prior therapy/surgery.

Prior anticancer therapies will be summarized, if applicable, based on the WHO Drug Dictionary (WHODD), version March 2015 or later, therapeutic drug class (Anatomical Therapeutic Chemical [ATC] level 1) and preferred name sorted by descending frequency of drug class in the overall column, and by alphabetical order of the preferred name within drug class.

Prior procedures will be summarized, if applicable, based on the MedDRA Version 20.1 or later system organ class (SOC) and preferred term (PT) for the safety population, sorted by descending frequency of SOC in the overall column, and by alphabetical order of the PT within SOC.

9.5.2. Concomitant Medications/Procedures

Concomitant medications and procedures are defined as medications and procedures, such as surgeries, that were either initiated before the first dose of study drug and continued during the study treatment, or initiated on/after the date of the first dose of study drug and on/before 28 days after the end of the study treatment.

A summary showing the number and percentage of subjects who had concomitant medications and a separate summary showing the number and percentage of subjects who had concomitant procedures will be presented by WHO ATC level 1 drug name and preferred name, version WHODD March 2015 or later, sorted by descending frequency of ATC level 1drug name in the overall column, and by alphabetical order of the preferred name within drug class. Summaries will be based on the safety population.

Concomitant procedures will be summarized, if applicable, based on the MedDRA Version 20.1 or later system organ class (SOC) and preferred term (PT) for the safety population, sorted by descending frequency of SOC in the overall column, and by alphabetical order of the PT within SOC.

Individual listings of prior and concomitant medications will be provided to support the tables.

10. STUDY TREATMENTS AND EXTENT OF EXPOSURE

Study treatment and extent of exposure summaries will be provided based on the Safety Population. Descriptive statistics (n, mean, SD, median, min, and max) will be provided for the following *nab*-paclitaxel exposure parameters: treatment duration, cumulative dose, dose exposure, average weekly dose, dose intensity and relative dose intensity. Total number of, and frequency of, cycles administered, number and percentage of subjects dosed at each cycle, number and percentage for maximum number of cycles received per subject, total number of doses administered, and dose reduction/interruption will also be presented.

Tables will present data by study phase, specifically by dose level and in aggregate (Phase 1) and by disease indication (Phase 2) as well as an aggregate for all patients across Phases 1 and 2 treated at the RP2D, and for all subjects included in the Safety Population across Phases1 and 2.

Individual subject listings of exposure to study drug will be provided.

10.1. Treatment Duration

The treatment duration (weeks) is defined as:

[(date of last study drug administration) – (date of first study drug administration) + 7] / 7.

Treatment duration will be presented separately for subjects with weight ≤ 10 kg versus > 10 kg; if no subjects are found within a given weight category then that weight category will not be displayed.

10.2. Cumulative Dose

The cumulative dose (mg/m^2 or mg/kg) is defined as the sum of all doses taken across the Treatment Period. Cumulative dose will be presented separately for subjects with weight ≤ 10 kg versus > 10 kg; if no subjects are found within a given weight category then that weight category will not be displayed.

10.3. Dose Exposure

Dose exposure in days is defined as the total number of actual drug administration days during the Treatment Period. Dose exposure will be presented separately for subjects with weight ≤ 10 kg versus > 10 kg; if no subjects are found within a given weight category then that weight category will not be displayed.

10.4. Average Daily Dose

Average daily dose will be calculated as:

Cumulative Dose / Dose Exposure.

Average weekly dose intensity will be presented separately for subjects with weight ≤ 10 kg versus > 10 kg; if no subjects are found within a given weight category then that weight category will not be displayed. Average daily dose shall be presented in mg/m^2 and calculated as the actual administered dose divided by the reported BSA value.

10.5. Average Dose Intensity

The weekly average dose intensity (mg/m^2/week or mg/kg/week, depending on subject weight) during treatment is calculated as:

Cumulative Dose / Treatment Duration.

Average dose intensity will be presented separately for subjects with weight ≤ 10 kg versus > 10 kg; if no subjects are found within a given weight category then that weight category will not be displayed. Average dose intensity shall be presented in mg/m^2 and calculated as the actual administered dose divided by the reported BSA value.

10.6. Relative Dose Intensity

Relative Dose Intensity is calculated as:

Average Dose Intensity / Planned Dose Intensity.

For *nab*-paclitaxel administrated in Phase 2 to a subject of body weight > 10 kg, the planned dose intensity (PDI) is calculated as (RP2D*3)/7 mg/m^2 per week. For subjects ≤ 10 kg body weight in Phase 2, the PDI is calculated as (RP2D*3)/7 mg/kg per week.

Relative dose intensity will be categorized into ≥ 90%, < 90% to 80%, < 80% to 70%, and < 70%.

10.7. Dose Reduction, Interruption and Escalation

Dose reductions are identified as an actual scheduled dose as recorded on the study drug record CRF page, e.g. > 0 mg/m^2 for subjects > 10 kg in weight / > 0 mg/kg for subjects ≤ 10 kg in weight at the time of administration, while being less than the scheduled dose directly prior to the current administration. Dose changes as a result in change of body weight will not be considered as a dose reduction. Dose reductions will be summarized as follows:

- Number and percentage of subjects with at least 1 dose reduction, reasons for reduction, frequency of reductions;
- Summary statistics (n, mean, median, SD, min, and max) for time to first reduction.

Drug interruption are identified as a non-administered planned dose, e.g. actual dose received = 0 mg/m^2 / 0 mg/kg, while being directly followed with an actual administered dose e.g. actual dose received > 0 mg/m^2 / mg/kg, provided an actual dose had been administered previously. Drug interruption will be summarized as follows:

- Number and percentage of subjects with at least 1 drug interruption, reasons for each interruption, frequency of interruptions;
- Summary statistics (n, mean, median, SD, min, and max) for time to first drug interruption.

During Phase 1, subjects receiving treatment beyond Cycle 1 who had not had any dose reductions may, following approval by the SMC, have their dose level increased, providing that the alternative dose level has been shown to be well tolerated by at least one cohort of other subjects in this study. Once a subjects' dose has been reduced, it could not be increased to the previous level.

Dose escalations are identified as an actual scheduled dose as recorded on the study drug record CRF page, e.g. > 0 mg/m^2 for subjects > 10 kg in weight / > 0 mg/kg for subjects ≤ 10 kg in weight at the time of administration, while being more than the scheduled dose (> 0 mg/m^2 / mg/kg) administered directly prior to the current administration. Dose changes as a result in change of body weight will not be considered as a dose escalation. Dose escalations will be summarized as follows for Phase 1 subjects only:

- Number and percentage of subjects with at least 1 dose escalation, reasons for each interruption, frequency of interruptions;
- Summary statistics (n, mean, median, SD, min, and max) for time to first dose escalation.

11. EFFICACY ANALYSIS

Tables will be provided to describe the efficacy endpoints for both the Safety Population and EE Population. Tables will present data by study phase, specifically by dose level and in aggregate (Phase 1) and by disease indication (Phase 2). A listing will display efficacy data for the Safety Population.

11.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint, ORR, relates to Phase 2 only; in Phase 1 ORR is considered a secondary efficacy endpoint. In Phase 1, the primary endpoint is the incidents of DLTs and TEAEs. The ORR will be displayed by dose level and overall (Phase 1) and disease indication (Phase 2).

11.1.1. Overall Response Rate

Overall response rate is defined as the percentage of subjects that achieve a CR or PR confirmed no less than 4 weeks after the criteria for response are first met, over the total number of subjects available for the analysis within the given population, i.e. subjects contained within the EE Population as outlined within Section 5.2 of this SAP, as well as the Safety Population which is formed of all subjects receiving at least 1 dose of *nab*-paclitaxel as outlined within Section 5.3 of this SAP. The corresponding 2-sided, 95% Clopper-Pearson CI will also be provided.

Complete response is considered confirmed if another CR is observed at least 4 weeks (28 days) after the first CR is observed without another response type identified between assessments.

Partial response is considered confirmed if another PR or a CR is observed at least 4 weeks (28 days) after the first PR is observed without another response type beside CR identified between assessments.

Disease assessments recorded on or after start of a new anticancer therapy will not be considered, nor will disease assessments reported after a progressive disease (PD) has been observed.

In addition, best overall response will be summarized by number and percentage of subject's best response that meets one of the following categories: CR, PR, stable disease, symptomatic deterioration as recorded on the treatment discontinuation and/or the study discontinuation eCRF (for subjects that discontinue treatment/study before a disease assessment can be taken), PD, or not evaluable. Stable disease will additionally show subcategories for SD lasting < 16 weeks or ≥ 16 weeks.

In Phase 1, all subjects will be analyzed regardless of disease indication based on the RECIST postbaseline response assessments (as well as for neuroblastoma subjects only, based on the Curie score [MIBG response] postbaseline response assessments).

In Phase 2, rhabdomyosarcoma and Ewing's sarcoma subjects will be analyzed based on the RECIST postbaseline response assessments. Neuroblastoma subjects will be analyzed based on the RECIST and/or the Curie score (MIBG response) postbaseline response assessments, without crossover between assessment types over time. If both the RECIST and the Curie score have been used and should both response assessments show a similar response (ie, either both are CR or both are PR) then that response shall be considered as the best response for calculation of the

best overall response; should both show a response but different, ie, CR and PR, the PR shall be considered the best overall response; should only one of the response assessments show a response (either a CR or PR) while the other shows a stable disease, then PR shall be considered the best overall response. For the best overall response to be considered a PD, a PD must have been recorded according to at least 1 of the response assessments, see Table 2 for further direction. If only RECIST or the Curie scale was used, a corresponding baseline assessment must have been conducted using the same assessment type method.

Table 2: Best Overall Response Per RECIST and the Curie Scale

Response Assessment Method		Overall Best Response
RECIST	**Curie Score**	
Complete Response	Complete Response	Complete Response
Partial Response	Complete Response	Partial Response
Complete Response	Partial Response	Partial Response
Complete Response	Stable Disease	Partial Response
Stable Disease	Complete Response	Partial Response
Partial Response	Stable Disease	Partial Response
Stable Disease	Partial Response	Partial Response
Stable Disease	Stable Disease	Stable Disease
Complete Response	Disease Progression	Disease Progression
Partial Response	Disease Progression	Disease Progression
Stable Disease	Disease Progression	Disease Progression
Disease Progression	Complete Response	Disease Progression
Disease Progression	Partial Response	Disease Progression
Disease Progression	Stable Disease	Disease Progression
Disease Progression	Disease Progression	Disease Progression

Waterfall plots of best percentage change from baseline in the sum of length (longest diameter) of target lesions will be provided by dose/disease indication. Individual listings of tumor assessment will be provided.

11.2. Analysis of Secondary Efficacy Endpoints

11.2.1. Duration of Response

Duration of response will be presented in weeks and is defined as the time from the date of first observed response, either a confirmed CR or PR, until the date a PD is first observed. Subjects who do not have PD or have not died will be censored at the time of their last disease assessment or at the time of start of new anticancer therapy, whichever occurs first.

In Phase 1 subjects and Phase 2 Ewing's sarcoma and rhabdomyosarcoma subjects, tumor assessments will be based on RECIST 1.1 while in Phase 2 neuroblastoma subjects it will be based on the Curie Score or RECIST 1.1; should a Phase 2 neuroblastoma subject have their response assessment conducted with both RECIST 1.1 and the Curie Score then an overall

response as shown in Table 2: Best Overall Response Per RECIST and the Curie Scale will be used.

For identification of PD for this endpoint, PD is classed as either a PD as observed on the response assessments eCRF (both during the Treatment Period and the Follow-up Period if applicable), or as a PD or symptomatic deterioration as recorded on the treatment discontinuation and/or the study discontinuation eCRF; the first time this occurrence is observed is selected as the PD date.

Duration of response shall be summarized by descriptive statistics for non-censored subjects, and includes n, arithmetic mean, SD, median, min, and max, for each dose/disease indication.

11.2.2. Disease Control Rate

Disease control rate is defined as the percentage of subjects that achieve either a stable disease maintained for ≥ 16 weeks or confirmed CR (confirmed no less than 4 weeks after criteria for response are first met) or confirmed PR (confirmed no less than 4 weeks after criteria for response are first met) over the total number of subjects available for the analysis within the given population, i.e. subjects contained within the EE Population as outlined within Section 5.2 of this SAP, as well as the Safety Population which is formed of all subjects receiving at least 1 dose of *nab*-paclitaxel as outlined within Section 5.3 of this SAP. The corresponding 2-sided, 95% Clopper-Pearson CI will also be provided.

Complete response is considered confirmed if another CR is observed at least 4 weeks (28 days) after the first CR is observed without another response type identified between assessments.

Partial response is considered confirmed if another PR or a CR is observed at least 4 weeks (28 days) after the first PR is observed without another response type beside CR identified between assessments.

Calculation of stable disease duration starts at the time of first dose of *nab*-paclitaxel until the date first observation of PD is recorded, or until the date of the last disease assessment if no PD is recorded; if the difference is ≥ 16 weeks (≥ 112 days) then the SD will be considered as being maintained for ≥ 16 weeks.

Disease assessments recorded on or after start of a new anticancer therapy will not be considered, nor will disease assessments reported after a PD has been observed.

In Phase 1 subjects and Phase 2 Ewing's sarcoma and rhabdomyosarcoma subjects, tumor assessments will be based on RECIST 1.1 while in Phase 2 neuroblastoma subjects it will be based on the Curie Score or RECIST 1.1; should a Phase 2 neuroblastoma subject have their response assessment conducted with both RECIST 1.1 and the Curie Score then an overall response as shown in Table 2: Best Overall Response Per RECIST and the Curie Scale will be used.

11.2.3. Progression Free Survival

Progression-free survival will be presented in weeks and is defined as the time from the date of first *nab*-paclitaxel dose until the date a PD is first observed or date of death (any cause),

whichever occurs first. Subjects who do not have PD or have not died will be censored at the time of their last disease assessment or at the time of start of new anticancer therapy, whichever occurs first.

For the purpose of identification of PD for this endpoint, PD is classed as either a PD as observed on the response assessments eCRF (both during the Treatment Period and the Follow-up Period if applicable), or as a PD or symptomatic deterioration as recorded on the treatment discontinuation and/or the study discontinuation eCRF; the first time this occurrence is observed is selected as the PD date.

In Phase 1 subjects and Phase 2 Ewing's sarcoma and rhabdomyosarcoma subjects, tumor assessments will be based on RECIST 1.1 while in Phase 2 neuroblastoma subjects it will be based on the Curie Score or RECIST 1.1; should a Phase 2 neuroblastoma subject have their response assessment conducted with both RECIST 1.1 and the Curie Score then an overall response as shown in Table 2: Best Overall Response Per RECIST and the Curie Scale will be used.

Progression-free survival will be summarized by median progression-free time along with the corresponding 95% CI, calculated using Kaplan-Meier methods (the estimate of variance will be calculated using Greenwood's formula) (Kaplan and Meier, 1958). The Kaplan-Meier curves for progression-free survival will be presented graphically. The number and percentage of total disease progression/deaths, as well as cause of death, as identified for PFS event will be summarized.

11.2.4. Survival at 1 Year

Overall survival (OS) will be presented in months and is defined as the duration in weeks from the date of first *nab*-paclitaxel dose to the date of death (any cause). Subjects who are alive at the time of analysis will be censored at the last known time that the subject was alive. Overall survival will be summarized by median survival time along with the corresponding 95% CI, calculated using Kaplan-Meier methods (the estimate of variance will be calculated using Greenwood's formula) (Kaplan and Meier, 1958). The Kaplan-Meier curve for survival will be presented graphically. The number and percentage of total deaths, as well as cause of death, will be summarized by dose/disease indication. The survival rate at 1 year, including the corresponding 95% CI, will be provided.

11.3. Subgroup Analysis

No subgroup analysis is planned for efficacy data.

11.4. Analyses of Exploratory Efficacy Endpoints

11.4.1. MIBG Response Using Curie Score

In Phase 1, overall response based on MIBG scan will be analyzed for neuroblastoma subjects only, analyzed in the same way as ORR was analyzed for all subjects in Phase 1 regardless of disease indication.

Individual listing of Curie score and overall response will be provided.

12. SAFETY ANALYSIS

The purpose of this section is to define the safety parameters for the study. All summaries of safety data will be conducted using the Safety Population and will be presented by study phase, and dose/disease indication. Safety measurements will include AEs, clinical laboratory information, vital sign measurements, ECG, left ventricular shortening fraction (LVSF) assessment, pregnancy status, and deaths. Individual subject listings will be provided to support the tables.

Tables will present data by study phase, specifically by dose level and in aggregate (Phase 1) and by disease indication (Phase 2) as well as an aggregate for all subjects across Phases 1 and 2 treated at the RP2D, and for all subjects included in the Safety Population across Phases 1 and 2.

12.1. Adverse Events

Adverse events will be analyzed in terms of TEAEs which are defined as any AEs that begin or worsen on or after the start of study drug through 28 days after the last dose of study drug. Adverse events are documented on the eCRF together with their severity, according to the National Cancer Institute (NCI) CTCAE version 4.0, also referred to as NCI toxicity grading. For the categorization of the adverse events, the MedDRA Version 20.1 or later will be used and TEAEs will be summarized by SOC and PT.

Tables summarizing the incidence of TEAEs will be generated for each of the following:

- All TEAEs;
- Treatment-related TEAEs;
- All TEAEs by cycle of onset;
- Treatment-related TEAEs by cycle of onset;
- All TEAEs by maximum NCI CTCAE grade;
- All TEAEs by dose/disease indication, and maximum NCI CTCAE grade;
- Treatment-related TEAEs by maximum NCI CTCAE grade;
- Treatment-related TEAEs by dose/disease indication, and maximum NCI CTCAE grade;
- All TEAEs with NCI CTCAE grade 3 or 4;
- Treatment-related TEAEs with NCI CTCAE grade 3 or 4;
- Serious TEAEs;
- Treatment-related serious TEAEs;
- TEAEs leading to discontinuation of the study drug;
- Treatment-related TEAEs leading to discontinuation of the study drug;
- TEAEs leading to dose reduction of the study drug;
- Treatment-related TEAEs leading to dose reduction of the study drug;

- TEAEs leading to drug interruption of the study drug;
- Treatment-related TEAEs leading to drug interruption of the study drug;
- TEAEs leading to death;
- Treatment-related TEAEs leading to death;
- All death within 28 days of last dose with cause of death.

The following individual listings will be provided:

- AE listings by subject;
- Listing of serious TEAEs;
- Listing of TEAEs leading to discontinuation of the study drug;
- Listing of TEAEs with outcome of death.

Dose limiting toxicities will be summarized by dose cohort for Phase 1 only.

The incidence of TEAEs will be summarized by MedDRA SOC and PT. System organ classes will be sorted by descending order of frequency, and by alphabetical and then descending order of frequency of PT within SOC, according to the overall column.

Relationship of AEs to *nab*-paclitaxel treatment is documented on the eCRF as well. A treatment-related TEAE is defined as a TEAE which was suspected by the investigator to be related to the study drug.

If a subject experiences the same TEAE more than once with different toxicity grade, then the event with the highest grade will be tabulated in "by grade" tables. If a subject experiences multiple TEAEs under the same PT (or SOC), then the subject will be counted only once for that PT (or SOC). In addition, TEAEs with a missing intensity will be presented in the summary table as an intensity category of "Missing".

Treatment emergent adverse events, treatment-related TEAEs, TEAEs of Grade 3 or 4, treatment-related TEAEs of Grade 3 or 4, serious TEAEs and treatment-related serious TEAEs will also be analyzed within the following age subgroups:

- Age category (< 2 years, ≥ 2 years to < 12 years, ≥ 12 years to < 18 years, and ≥ 18 years to ≤ 24 years [Phase 2 only].

12.2. Adverse Events of Special Interest

The following AE of interest categories and PTs include, but are not limited to:

- General myelosuppression;
- Neutropenia;
- Anemia;
- Thrombocytopenia;
- Peripheral neuropathy;
- Cranial nerve palsies;

- Hypersensitivity reactions;
- Pneumonitis;
- Clinically severe infections, specifically sepsis;
- Gastrointestinal events;
- Myalgia and arthralgia;
- Cardiotoxicity, including congestive heart failure/left ventricular dysfunction;
- Cystoid macular edema;
- Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN);
- Infusion site reactions/extravasation;
- Hepatic toxicity (drug-induced liver injury);
- Acute renal failure and hemolytic-uremic syndrome;
- Drug-induced lupus erythematosus;
- Skin toxicity.

The following summaries will be provided for above-mentioned TEAEs of special interest:

- TEAEs;
- Treatment-related TEAEs;
- Grade 3 or 4 TEAEs;
- Treatment-related Grade 3 or 4 TEAEs;
- Serious TEAEs;
- TEAEs leading to treatment discontinuation;
- TEAEs leading to dose reduction;
- TEAEs leading to drug interruption;
- TEAEs leading to death.

In addition, the following tables will be presented to further investigate the corresponding TEAEs of interest:

- Time to first occurrence of NCI CTCAE Grade 2 or higher treatment-emergent peripheral neuropathy;
- Time to first occurrence of NCI CTCAE Grade 3 or higher treatment-emergent neutropenia;
- Time to first occurrence of NCI CTCAE Grade 2 or higher, and Grade 3 or higher treatment-emergent skin toxicity;
- Time to first occurrence of NCI CTCAE Grade 3 or higher treatment-emergent thrombocytopenia;

- Time to improvement of NCI CTCAE Grade 2 or higher treatment-emergent peripheral neuropathy to Grade 1 or better.

Listing of subjects with TEAEs of special interest will be provided.

12.3. Deaths

Deaths will be coded according to MedDRA Version 20.1 or later.

Tables summarizing the frequency and percentage of deaths by primary cause of death will be generated, sorted by descending frequency of primary cause in the overall column, by dose level (Phase 1) and disease indication (Phase 2) for each of the following:

- All deaths;
- All death during the Treatment Period (defined as deaths from first *nab*-paclitaxel dose date to 28 days after the last dose of *nab*-paclitaxel);
- All death after 28 days after end of treatment.

12.4. The incidence of deaths will be shown in subject listings showing MedDRA SOC and PT. Dose-limiting Toxicities

The treatment-related DLTs as per NCI CTCAE version 4.0 will be summarized for subjects in Phase 1 in the DDS analysis population by dose level.

A subject listing of subjects with DLT in the DDS analysis population will also be provided.

The DLT assessment period will be as follows:

- For subjects > 10 kg: the first cycle including Cycle 2 Day 1 predose evaluations;
- For subjects ≤ 10 kg: the first 2cycles including Cycle 3 Day 1 predose evaluations.

A DLT is defined as a *nab*-paclitaxel-related AE occurring during the DLT assessment period that leads to treatment discontinuation or meets one of the following criteria:

- Grade 3 or 4 nonhematologic toxicity (excluding transient transaminitis);
- Grade 3 or 4 nausea or vomiting that persists > 5 days despite maximal anti-emetic treatment;
- Grade 4 thrombocytopenia or anemia that persists > 7 days or requires transfusion > 7 days;
- Grade 3 thrombocytopenia with bleeding;
- Grade 4 uncomplicated neutropenia lasting > 7 days;
- Febrile neutropenia with confirmed bacterial infection;
- Grade 3 hematologic toxicity requiring treatment delay > 21 days.

12.5. Pregnancies

Listings of subjects with data from the "Pregnancy Status Female Child Bearing Potential (FCBP)" and "Pregnancy Status Pregnancy Test" eCRF pages will be provided.

12.6. Clinical Laboratory Evaluations

Clinical laboratory values from local laboratories will be graded per NCI CTCAE (version 4.0, May 2009) or later for applicable tests. Clinical laboratory values will be summarized by dose level (Phase 1) and disease indication (Phase 2).

Laboratory results by visit and change from baseline will be summarized using descriptive statistics. Maximum postbaseline values, minimum postbaseline values, and corresponding change from baseline will be summarized as well. Additionally, the worst result observed across all unscheduled visit samples taken while the subject is receiving *nab*-paclitaxel treatment up to 28 days post last *nab*-paclitaxel dose, will be summarized and presented under the time visit 'Unscheduled', after each planned cycle visit and end of treatment visit.

Baseline grade and worst grade during the Treatment Period for each gradable laboratory parameter will be summarized.

Frequency distributions for shift from baseline to the worst grade during the Treatment Period will be presented by dose level (Phase 1) and disease indication (Phase 2).

Normal ranges will be used to determine the categories of high, low, and normal for lab tests that have no severity grade.

Listings of clinical laboratory data from local laboratories with abnormal flags will be provided by subject and tests.

12.6.1. Hematology

The following parameters will be reported for this study:

- Hemoglobin (g/L);
- White blood cell (WBC) count (10^9/L);
- Platelets count (10^9/L);
- Neutrophils (10^9/L or %);
- Lymphocytes (10^9/L or %).

In case of differential counts of white blood cells (ie, neutrophils, lymphocytes, monocytes, eosinophils, and basophils) reported in percentage of WBC, a conversion rule will be applied to report these differential counts in absolute count (10^9/L).

To investigate the worst grade, the NCI-CTCAE grade for absolute neutrophil count (ANC), absolute lymphocyte count, WBC count, platelet count, and hemoglobin will be derived.

12.6.2. Clinical Chemistry

The following parameters will be reported for this study:

- Sodium (mmol/L);
- Potassium (mmol/L);
- Calcium (mmol/L);

- Phosphorus (mmol/L);
- Creatinine (µmol/L);
- Uric acid (µmol/L);
- Glucose (mmol/L);
- Alkaline phosphatase (U/L);
- Alanine aminotransferase (ALT; SGPT) (U/L) ;
- Aspartate aminotransferase (AST; SGOT) (U/L);
- Total bilirubin (µmol/L).

To investigate the worst grade, the NCI CTCAE grade for sodium (hypo/hypernatremia), potassium (hypo/hyperkalemia), calcium (hypo/ hypercalcemia), magnesium (hypo/ hypermagnesemia), phosphorus (hypophosphatemia), uric acid (hyperuricemia), glucose (hypo/ hyperglycemia), albumin (hypoalbuminemia), alkaline phosphatase, ALT (SGPT), AST (SGOT), total bilirubin, and creatinine will be derived.

Nongradable hematology and clinical chemistry parameters will be compared with the relevant laboratory ranges in SI units (Gregory's Pediatric Anesthesia, 2012) and categorized as:

- Low: Below the lower limit of the laboratory reference range;
- Normal: Within the laboratory reference range (upper and lower limit included);
- High: Above the upper limit of the laboratory reference range.

12.6.3. Urinalysis

Neuroblastoma subject will have urinalysis laboratory samples taken and the parameters (homovanillic acid and vanillylmandelic acid) presented in listings.

12.7. Vital Sign Measurements

Vital sign values by visit and change from baseline will be summarized using descriptive statistics (n, mean, SD, median, min, and max). Maximum postbaseline values, minimum postbaseline values, and corresponding change from baseline will be summarized. Shift tables demonstrating the changes (low/normal/high) from baseline to worst postbaseline will be displayed in cross-tabulations.

Individual subject listings will be provided to support the summary tables.

Temperature in Fahrenheit will be converted to Celsius with the following formula:

- Temperature in Celsius = (temperature in Fahrenheit – 32) * 5/9;

For each vital sign parameter, the baseline grade and the worst grade postbaseline will be determined for each subject classified in below, within, and above the normal ranges. Subjects may show both with normal and missing results for the vital sign, provided no abnormal (low or high) results will be reported. Low and high categories will be presented separately. Normal ranges are reported in Table 3.

Table 3: Normal Range of Vital Sign Measurements

Test	Age Group (years) [a]	Normal Range (Unit)
Diastolic Blood Pressure	< 2	[34,66] (mmHg)
	2-5	[34,74] (mmHg)
	6-8	[35,80] (mmHg)
	9-13	[37,87] (mmHg)
	14-16	[40,91] (mmHg)
	≥ 17	[40,89] (mmHg)
Systolic Blood Pressure	< 2	[58,112] (mmHg)
	2-5	[60,125] (mmHg)
	6-8	[65,131] (mmHg)
	9-13	[68,141] (mmHg)
	14-16	[76,153] (mmHg)
	≥ 17	[70,139] (mmHg)
Pulse Rate	1-2	[95, 178] (bpm)
	3-7	[62, 124] (bpm)
	8-15	[48, 110] (bpm)
	≥ 16	[60, 100] (bpm)
Temperature	All	[35, 38] (°C)

[a] Years reached at the time of the assessment.

12.8. Electrocardiograms

Electrocardiogram observed values (local review) and change from baseline will be summarized by predetermined schedule of ECG evaluation using descriptive statistics. Postbaseline abnormal corrected QT (QTc) interval (both QTcF and QTcB) values by local review will be summarized using frequency tabulations for the following 5 categories separately: QTc > 450 msec; QTc > 480 msec; QTc > 500 msec; QTc increase from baseline > 30 msec; QTc increase from baseline > 60 msec.

The overall ECG interpretation will be summarized using the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant' by predetermined schedule of ECG evaluation. Shift from baseline to the worst postbaseline in the overall ECG interpretation ('Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant') will be displayed in cross–tabulations, using investigator interpretation.

Listings of ECG data will be provided.

12.9. Left Ventricular Shortening Fraction Assessment

Left ventricular shortening fraction (LVSF) (echocardiogram [ECHO] or multi-gated acquisition [MUGA] scan) values by predetermined schedule of LVSF evaluation and change from baseline will be summarized using descriptive statistics. Shift from baseline to worst postbaseline in the

overall LVSF interpretation ('Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant') will be displayed in cross–tabulations for each dose/disease indication.

Listings of LVSF data will be provided.

12.10. Survival

Listings of subjects with data from "Survival" and "Survival Information" eCRF pages will be provided.

12.11. Lansky/ Karnofsky Performance status

Performance status will be measured using the Karnofsky (Karnofsky, 1948) or Lansky (Lanksy, 1987) performance status score, whichever is the most applicable for the subject. Performance status by cycle and change from baseline will be summarized using descriptive statistics. Maximum postbaseline values, minimum postbaseline values, and corresponding change from baseline during the treatment period will be summarized for the Safety Population. Lansky and Karnofsky performance status will be presented both separately and combined. A listing of performance status will be provided.

12.12. Other Safety Assessments

Data collected for other safety assessments, including chest x-ray, will be listed.

13. PHARMACOKINETIC ANALYSIS

The PK population will be used for all PK analysis tables and figures.

13.1. Pharmacokinetic Sampling

Pharmacokinetic blood samples will be collected for the first dose (Cycle 1 Day 1) from all subjects in both Phase 1 and Phase 2 of the study to analyze paclitaxel concentrations in plasma.

Samples will be collected from all subjects enrolled in Phase 1 of the study using a dense PK sampling strategy as specified in Table 4.

Samples will be collected from all remaining subjects enrolled in the study using a sparse PK sampling strategy as specified in Table 5, or if optionally consented using a dense PK sampling strategy.

Table 4: Dense Pharmacokinetic Sampling

Sample Number	Sample Time (hours)	Subjects ≥ 6 Years Old	Subjects < 6 Years Old
1	1-2 minutes prior to the end of infusion (no window, must be collected before end of infusion)	X	X
2	15 minutes after end of infusion (± 5 minutes)	X	X
3	1 hour after end of infusion (± 5 minutes)	X	
4	3 hours after end of infusion (± 10 minutes)	X	X
5	5 hours after end of infusion (± 10 minutes)	X	X
6	8 hours after end of infusion (± 1 hour, recommended[a])	X	
7	24 hours after end of infusion[b] (± 3 hours)	X	X
8	48 hours after end of infusion[c] (± 3 hours)	X	
9	72 hours after end of infusion[d] (± 3 hours, recommended[e])	X	

[a] Recommended sample at 8 hours after infusion should be performed in any site where the subject can remain to have the sample drawn. Subjects who are being treated as an out-patient may omit this sample.
[b] 24- hour sample may occur on study Day 2, depending on the timing.
[c] 48-hour sample may occur on study Day 3, depending on the timing.
[d] 72-hour sample may occur on study Day 4, depending on the timing.
[e] Recommended sample at 72 hours after infusion should be performed in subjects who live close enough to the center to return on the third day. Subjects living far from the center may omit this sample.

Table 5: Sparse Pharmacokinetic Sampling

Sample Number	Sample Time (hours)	Subjects ≥ 6 Years Old	Subjects < 6 Years Old
1	15 minutes after end of infusion (± 5 min)	X	X
2	3 hours after end of infusion (± 10 minutes)	X	X
3	24 hours after end of infusion (± 3 hours)[a]	X	X

[a] 24-hour sample may occur on study Day 2 depending on the timing.

13.2. Handling of *nab*-paclitaxel Concentration Data

Predose concentrations that are below the limit of quantitation (BLQ) or missing will be assigned a numerical value of zero for PK analysis. Postdose concentrations that are BLQ and occur before the first quantifiable concentration will also be treated as zero for PK analysis. Postdose concentrations that are BLQ but occur after the first quantifiable concentration will be treated as missing for PK analysis.

Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics. A concentration value of zero will be excluded from the computation of geometric coefficient of variation mean (geometric CV%). Aberrant concentration data will be excluded from PK analysis and summary statistics but they will be included in the concentration listing.

In tables and listings for the derived PK data, there should be 4 decimal places for numerical values below 1, 3 decimal places for numeric values below 10 but above 1, and 2 decimal places for numeric values above 10. However, the listings of raw data should not have more decimal places than the actual data.

13.3. Noncompartmental Pharmacokinetic Parameters

Noncompartmental PK analysis will be performed using the plasma concentration versus time data obtained from subjects participating in dense PK sampling. Actual sampling times will be used in the calculations of *nab*-paclitaxel PK parameters.

The following noncompartmental PK parameters will be included, but not limited to:

- λ_z: terminal phase rate constant, determined by linear regression of the terminal portion of the log-concentration versus time curve in plasma. Visual assessment may be used to identify the terminal linear phase of the concentration versus time profile. A minimum of 3 data points will be used for calculation. λ_z will not be estimated if the terminal phase of the log-concentration versus time profile does not exhibit a linear decline phase or has a regression coefficient (Rsq) < 0.8;
- AUC_t: area under the plasma concentration-time curve from time zero to the last quantifiable time point, calculated by the linear trapezoidal rule;
- AUC_{24}: area under the plasma concentration-time curve from time zero to 24 hours, calculated by the linear trapezoidal rule;
- AUC_∞: area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated as $[AUC_t + C_t/\lambda_z]$, where C_t is the last quantifiable concentration;
- C_{max}: maximum observed plasma concentration, obtained directly from the observed concentration versus time data;
- t_{max}: time to C_{max}, obtained directly from the observed concentration versus time data;
- $t_{½}$: terminal phase half-life, calculated as $[0.693/\lambda_z]$;
- CL: total clearance, calculated as $[Dose/AUC_\infty]$;

- V_{ss}: volume of distribution at the steady state, calculated as [MRT_{∞}*CL], where MRT_{∞} is the mean residence time extrapolated to infinity;
- V_z: volume of distribution based on the terminal phase, calculated as [CL/λ_z].

The following PK parameters will be calculated for diagnostic purposes and listed, but they will not be summarized:

- λ_z lower: Lower limit of time (h) included in the calculation of λ_z;
- λ_z N: Number of data points used in the calculation of λ_z;
- λ_z upper: Upper limit of time (h) included in the calculation of λ_z;
- Rsq: Regression coefficient for calculation of λ_z;
- AUC %Extrap: Percentage of AUC_{∞} due to extrapolation from the last quantifiable time point to infinity.

Additional PK parameters may be determined when appropriate.

13.4. Population Pharmacokinetic Analysis

Population PK analysis will be performed using nonlinear mixed effect modeling. Concentration data obtained from both dense and sparse PK sampling will be combined to develop the population PK model. Effect of age and body size on *nab*-paclitaxel PK will be assessed. Other relevant covariates for the main PK parameters will also be identified. The between-subject variability for PK parameters will be estimated, as appropriate. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored.

13.5. Statistical Analysis

Plasma concentrations from *nab*-paclitaxel will be listed and summarized by nominal time and cohort using descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, min, and max).

Noncompartmental PK parameters from *nab*-paclitaxel will be listed and summarized by cohort using descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, min, and max).

If data allow, select PK parameters (CL and V_{ss}) will be summarized by age group as appropriate (eg, < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to ≤ 24 years).

Mean and individual plots of plasma concentrations will be presented in both original and semi-logarithmic scales.

14. QUALITY OF LIFE ANALYSIS

Not applicable for this study.

15. INTERIM ANALYSIS

In Phase 2, Simon's Minimax Two-stage design will be employed per disease indication with each incorporating the following parameters: 5% significance level, 80% power and an upper and lower boundary of interest of 10% and 28%, respectively, for the ORR. Each of the disease indications will therefore enroll up to 23 efficacy evaluable subjects across Phase 2 (14 subjects in stage one and an additional 9 subjects in stage two) meaning a maximum total of 69 subjects evaluable for the primary endpoint.

For purposes of the primary endpoint analysis, the ORR is defined using the maximum likelihood estimator.

For each of the 3 groups in stage one, if < 2 of the 14 evaluable subjects have a response, then enrollment into that disease indication group will be stopped; otherwise enrollment shall continue as planned in stage two.

No formal production of tables or listings is required for the interim analysis go/no-go decision regarding continuation into stage two for any of the 3 disease indications.

16. TOP-LINE AND CLOSE OF STUDY FINAL ANALYSIS

The top-line analysis will only be conducted once the last subject to discontinue treatment, regardless of disease indication, has completed their 28-day follow-up visit. The date the last subject's 28-day follow-up visit occurs will become the earliest cut-off date upon which all TLGs will be produced and based, and used for production of the clinical study report (CSR).

The close of study analysis will be conducted once the last subject to discontinue from the study /complete the study has done so. At the maximum, the final analysis will take place approximately 1 year after the last subject to discontinue study treatment has done so, i.e. 1 year after the last subjects last dose date. All TLGs associated with data collected during the follow-up period will be rerun at this time.

17. CHANGES TO THE STATISTICAL ANALYSES SECTION OF THE PROTOCOL

In the protocol, the EE Population is defined, partly, as "all treated subjects who meet eligibility criteria". This has been modified to "all treated subjects who meet eligibility criteria relevant to efficacy". Subjects found to have failed to meet eligibility likely to affect efficacy will be identified and logged in the protocol deviation/violation tracker.

REFERENCES

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Karnofsky D, Abelman W, Craver L, Burchenal J. The use of nitrogen mustards in the palliative treatment of carcinoma. Cancer 1948;1:634-56.

Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. Cancer 1987;60(7):1651-6.

APPENDIX A1 – CONVENTIONS RELATED TO DATES

1. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (ie, the Date9. date format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- **Procedure Dates** are the dates on which given protocol-specified procedures are performed. They include the dates of laboratory testing, physical examinations, tumor scans, etc. They should be present whenever data for a protocol-specified procedure are present and should only be missing when a procedure is marked as NOT DONE in the database. Procedure dates will not be imputed.
- **Log Dates** are dates recorded in CRF data logs. Specifically, they are the start and end dates for adverse events and concomitant medications/procedures. They should not be missing unless an event or medication is marked as *ongoing* in the database. Otherwise, incomplete log dates will be imputed according to the rules in Appendix A1, Section 3 (eg, for duration or cycle assignment, etc.). However, in listings, log dates will be shown as recorded without imputation.
- **Milestone Dates** are dates of protocol milestones such as randomization, study drug start date, study drug termination date, study closure date, etc.. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- **Outcome Dates** are dates corresponding to study endpoints such as survival, progression, etc. In most cases, they are derived either from a milestone (eg, the survival date is derived from the death date), or a procedure date (eg, the progression date is derived from the date of the tumor scan that was used to determine progression). They may be subject to endpoint-specific censoring rules if the outcome did not occur, but are not otherwise subject to imputation.
- **Special Dates** cannot be classified in any of the above categories and they include the date of birth. They may be subject to variable-specific censoring and imputation rules.
- **Last Contact Dates** for the survival analysis is the maximum date collected in the database, if the imputed date used for response date or AE date, the last contact dates should be the latest date of those imputed date and maximum date in the database.

Dates recorded in comment fields will not be imputed or reported in any specific format.

2. Calculation Using Dates

Calculations using dates (eg, subject's age or relative day after the first dose of study drug) will adhere to the following conventions:

- Study days after the start day of study drug will be calculated as the difference between the date of interest and the first date of dosing of study drug plus 1 day. For subjects who are not treated, the Cycle 1 Day 1 will be defined as Day 1. The generalized calculation algorithm for relative day is the following:
    - If TARGET DATE >= DSTART then STUDY DAY = (TARGET DATE – DSTART) + 1;
    - Else use STUDY DAY = TARGET DATE – DSTART.

  Note that Study Day 1 is the first day of treatment of study drug or Cycle 1 Day 1 for subjects who are not treated. Negative study days are reflective of observations obtained during the baseline/screening period. Note: Partial dates for the first study drug are not imputed in general. All effort should be made to avoid incomplete study drug start dates.
- Age (expressed in days) is calculated: AGE = CONSENT/ASSENT DATE – DATE of BIRTH + 1. In practice, age will be transformed to years by dividing the difference by 365.25 days, then truncating.
    - Preference is for using calculated age from clinical database. When not available, calculated age from CRF or interactive voice recognition system (IVRS) may be used
    - Partial birth date: impute missing day as 15th of the month; impute missing month as July; set missing age for missing year
- Intervals that are presented in weeks will be transformed from days to weeks by using (without truncation) the following conversion formula:

  WEEKS = DAYS /7
- Intervals that are presented in months will be transformed from days to months by using (without truncation) the following conversion formula:

  MONTHS = DAYS /30.4375

3. Guideline of Missing Date Imputation

3.1 Impute Missing Adverse Events/ Prior or Concomitant Medications

A. Incomplete Start Date:

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date, i.e. set to the stop date.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as TEAE provided the end date of the AE is after the first dose date or the end date is also missing.

B. Incomplete End Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date or prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is **not equal to** the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is **not equal to** the month of the last dosing date, then the last day of the month will be assigned to the missing day.

3.2 Prior/Concomitant Procedures

Prior/concomitant procedures are defined as surgeries and transplants such as stem-cell transplants.

Partially missing start/stop dates for prior/concomitant procedures will be imputed in the analysis dataset for prior/concomitant procedures. If the stop date is complete with no missing year, month, or day, and the partially missing start date imputed by the rule below is after the stop date, then the start date will be imputed by the stop date.

Partially missing prior/concomitant procedure start dates will be imputed by the earliest possible date given the non-missing field(s) of the date.

Partially missing prior/concomitant procedure stop dates will be imputed by the latest possible date given the non-missing field(s) of the date.

3.3 Medical History

Partially missing medical history start dates will be imputed in the derived dataset for medical history. The 16th of the month will be used to impute a partially missing start date that has only the day missing, and July 1st will be used to impute a partially missing start date that has both the month and day missing. Should the imputed date equal or exceed the informed consent/assent date, the imputed medical history date will be set to 1 day prior to the informed consent/assent date.

3.4 Imputing Missing Disease Progression Date

If the day of the disease progression is missing, then the first day of the non-missing month will be assigned to the missing day; if the month or year of the missing date is missing, then the date will not be imputed and treated as missing.

3.5 Imputing Missing Dates for Prior Therapies

Prior therapies are defined as prior radiation therapies, prior systemic anticancer therapies, and other prior anticancer therapies. Should the imputed date equal or exceed the informed consent/assent date, the imputed start date will be set to 2 days prior to the informed consent/assent date, while the imputed end date will be set to 1 day prior to the informed consent/assent date.

A. Incomplete Start Date:

If the start day of any prior therapy date is missing, then the first day of the non-missing month will be assigned to the missing day; if month or year of the missing date is missing, then the date will not be imputed and treated as missing.

B. Incomplete End Date:

Incomplete date of end of last therapy will be imputed using the following rule: If missing day, impute 15th day of the month; if missing month, impute missing month as middle month (or the earlier month of two month if two months tie) between therapy start month and month of cycle 1 day 1. Should the imputed date be within 21 days of cycle 1 day 1, then the imputed date will be re-set to the 22nd day before cycle 1 day 1.

APPENDIX A2 – SCHEDULE OF ASSESSMENTS

The Table of Events is applicable to both Phase 1 and Phase 2 of the study.

Events	**Screening Period**	**Treatment Period**										**Follow-up Period**	
	Screening	**Cycle 1**						**Subsequent Cycles**					
Day[a]	**-14 to -1**	**1**	**2**	**3**	**4**	**8**	**15**	**1**	**8**	**15**	**EOT**	**28-day Safety Visit**[b]	**Disease Progression/ Survival**
STUDY ENTRY													
Informed consent and if applicable assent	X												
Prior cancer history	X												
Prior cancer therapies[c]	X												
Complete medical history	X												
Demographics	X												
Prior/ concomitant medication evaluation	X (-28 from screening)	Continuous, until 28 days after treatment discontinuation											
Prior/ concomitant procedures evaluation	X (-28 from screening)	Continuous, until 28 days after treatment discontinuation											
Inclusion/exclusion criteria	X												
IRT registration	X												
Archival tumor tissue collection (optional)	X, after eligibility confirmation												
SAFETY ASSESSMENTS													
Adverse event evaluation	Continuous starting after informed consent/assent signature, until 28 days after treatment discontinuation (and as noted in protocol Section 6.2.1.1)												

Events	Screening Period	Treatment Period										Follow-up Period	
	Screening	Cycle 1						Subsequent Cycles					
Day[a]	-14 to -1	1	2	3	4	8	15	1	8	15	EOT	28-day Safety Visit[g]	Disease Progression/ Survival
Physical examination (source documented only)	X	X				X	X	X	X	X	X	X	
Weight	X	X				X	X	X	X	X	X	X	
Height	X	X				X	X	X	X	X	X	X	
Body surface area calculation		X				X	X	X	X	X			
Vital signs[d]	X	X				X	X	X	X	X	X	X	
Hematology laboratory	X	X				X	X	X	X	X	X	X	
Chemistry laboratory[e]	X	X						X			X	X	
Urine homovanillic acid and vanillylmandelic acid (for neuroblastoma only)	X							Every other cycle, starting in Cycle 2			X	X	
LVSF assessment by echocardiogram/ MUGA/ other medically appropriate method	X							Every other cycle starting in Cycle 3			X		
12-lead electrocardiogram	X							Every other cycle starting in Cycle 3			X		
Serum β-hCG (if indicated)[f]	X	As clinically indicated											
Urine β-hCG (if indicated)[f]	X	As clinically indicated									X		

Events	Screening Period	Treatment Period										Follow-up Period	
	Screening	Cycle 1						Subsequent Cycles					
Day[a]	-14 to -1	1	2	3	4	8	15	1	8	15	EOT	28-day Safety Visit[b]	Disease Progression/ Survival
Pharmacokinetic samples[g]		X	X	X	X								
EFFICACY ASSESSMENTS													
Tumor evaluation (CT/MRI, see protocol Section 6.3)	X (-28 to -1)	Every 8 weeks (± 5 days) from Cycle 1 Day 1, until progression or new anticancer treatment											
MIBG scan (in subjects with neuroblastoma)	X (-28 to -1)	If assessable by MIBG scan at screening, every 8 weeks (± 5 days) from Cycle 1 Day 1, until disease progression or new anticancer treatment. If not assessable by MIBG scan, at screening and suspected progression only.											
Bone marrow biopsy (in subjects with neuroblastoma)		Only at confirmation of complete response											
Lansky performance status (in subjects < 12 years old)	X	X						X			X	X	
Karnofsky performance status (in subjects ≥ 12 years old)	X	X						X			X	X	
INVESTIGATIONAL PRODUCT (IP)													
Administer *nab*-paclitaxel		X				X	X	X	X	X			
FOLLOW-UP													
Survival follow-up													Every 1 month for 1 year
Anticancer therapy since *nab*-paclitaxel discontinuation												X	At every survival follow-up visit for 1 year

β-hCG = β human chorionic gonadotropin, C#D# = Cycle number Day number, CR= complete response, CT = computed tomography scan, EOT = end of treatment visit, IRT = Integrated Response Technology, LVSF = left ventricular shortening fraction, MIBG = ^{123}I-metaiodobenzylguanidine scan, MRI = magnetic resonance imaging, MUGA = multi-gated acquisition scan.

[a] An administrative window of ± 2 days is permitted for all visits except C1D1.

[b] If the EOT visit occurs within 7 days of the 28-day safety visit, laboratory evaluations only need to be repeated for abnormal parameters at the EOT visit.

[c] Prior cancer therapies includes surgery, radiation, stem cell transplant, systemic or any other therapy for the subject's cancer.

[d] Vital sign measurements must be recorded in the database at screening and EOT only, and kept in the source documents at all other visits. However, if an abnormal (out of range) value is reported at a given visit, that parameter should be collected in the case report form (CRF) at every subsequent scheduled visit until it returns to normal.

[e] In subjects with neuroblastoma ferritin will be analyzed.

[f] For all female subjects of childbearing potential (see protocol Inclusion 8), a serum pregnancy test will be done at screening. A urine pregnancy test will be repeated within 72 hours before first treatment if the serum pregnancy test occurred > 72 hours before dosing, and at EOT. Pregnancy tests conducted after screening will be recorded in the source documentation only.

[g] All subjects will have pharmacokinetic samples taken on C1D1. A subset of subjects will have samples taken on C1D2, C1D3, and C1D4 as described in protocol Section 6.4.