STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7389-G000-213
Study Protocol Title:	A Phase 1/2 single-arm study evaluating the safety and efficacy of eribulin mesilate in combination with irinotecan in children with refractory or recurrent solid tumors.
Date:	25 Jun 2021
Version:	Final, Version 1.0

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic class
AUC	area under the concentration-time curve
BOR	best overall response
BP	blood pressure
BSA	body surface area
CBR	clinical benefit rate
CI	confidence interval
Cmax	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DES	dose evaluable set
DLT	dose limiting toxicity
DOR	duration of response
EWS	Ewing sarcoma
FAS	full analysis set
HR	heart rate
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NRSTS	non-rhabdomyosarcoma soft tissue sarcoma

ORR	objective response rate
PAS	pharmacokinetic analysis set
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
Q1	25th percentile
Q3	75th percentile
QT	QT interval is the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	response evaluation criteria in solid tumors
RMS	rhabdomyosarcoma
RP2D	recommend phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
Tmax	time of maximum observed plasma concentration
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E7389-G000-213 titled "A Phase 1/2 single-arm study evaluating the safety and efficacy of eribulin mesilate in combination with irinotecan in children with refractory or recurrent solid tumors".

3.1 Study Objectives

3.1.1 Primary Objective(s)

The primary objectives are:

Phase 1: To determine the maximum tolerated dose (MTD) and Recommended Phase 2 Dose (RP2D) of eribulin mesilate in combination with weekly and daily irinotecan hydrochloride in pediatric subjects with relapsed/refractory solid tumors, excluding CNS.

Phase 2: To assess the objective response rate (ORR) and duration of response (DOR) of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) and Ewing sarcoma (EWS).

3.1.2 Secondary Objective(s)

Phase 1:

- To assess the safety and tolerability of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects
- To determine the optimal schedule of irinotecan hydrochloride when administered with standard schedule (Days 1 and 8) of eribulin mesilate in pediatric subjects

Phase 2:

- To assess Progression Free Survival (PFS) of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects
- To assess the Clinical Benefit Rate (CBR) of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects

Phase 1 & 2:

To evaluate the pharmacokinetic (PK) profile of eribulin, irinotecan and its active metabolite and compare to appropriate historical data.

3.1.3 Exploratory Objective(s)

The exploratory objective of Phase 1 & 2 is:

- To explore the relationship between model-derived exposure to eribulin and the active metabolite for irinotecan (SN 38) in terms of area under the curve and AEs and efficacy endpoints using a model-based approach

3.2 Overall Study Design and Plan

This study is divided into 2 phases.

3.2.1 Phase 1

Phase 1 will determine the MTD/RP2D and optimal schedule of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects with relapsed/refractory solid tumors, excluding CNS.

Eribulin mesilate will be administered as an intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle, at the RP2D determined in the single-agent dose finding study E7389-A001-113 (1.4 mg/m^2)

Irinotecan hydrochloride will be administered as an IV infusion using *2 different dose schedules*:

- Schedule A: Days 1-5 of a 21-day cycle at the following doses: 20 mg/m^2 and 40 mg/m^2

And

- Schedule B: Days 1 and 8 of a 21-day cycle at the following doses: 100 mg/m^2 and 125 mg/m^2.

Table1 Study Medication Dose Levels by Schedule

Dose Level	Eribulin mesilate (mg/m^2)	Irinotecan hydrochloride (mg/m^2)
Schedule A		
−2[#]	0.8	20
-1	1.1	20
0*	1.4	20
1	1.4	40
Schedule B		

Table1 Study Medication Dose Levels by Schedule

Dose Level	Eribulin mesilate (mg/m^2)	Irinotecan hydrochloride (mg/m^2)
-1	1.1	100
0*	1.4	100
1	1.4	125

*Dose level 0 refers to the starting dose.

#Dose level -2 is a further dose reduction in Schedule A for subjects <12 months only.

Dose Escalation

The traditional 3+3 design will be used for the conduct of Phase 1 part of this study.

The MTD is defined as the highest dose level at which less than 1/3 of subjects experience a DLT during Cycle 1 of therapy. The MTD will be determined based on the incidence of DLTs in Cycle 1 of each dose level. Subjects who do not complete Cycle 1 for any reason other than toxicity, ie, DLT, will be replaced in that cohort in order to complete the number necessary (up to 6) to assess the safety of the dose level cohort.

Toxicities subsequent to Cycle 1 will also be reviewed, but will not count towards determination of dose escalation and MTD/RP2D. If protocol-defined DLTs are observed in a subject after the first cycle at any dose level, the dose will be reduced to the next lower dose level for subsequent cycles.

Definition of DLT

DLTs are defined as any of the following using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE Version 5.0) during Cycle 1:

Hematological:

1. Neutropenia Grade 4 that lasts > 7 days

2. Thrombocytopenia Grade 4 on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7-day period

3. Thrombocytopenia Grade 3 complicated by bleeding or requiring platelet or blood transfusion

4. Neutropenia Grade 3 or 4 complicated by fever and/or infection (ANC $<1.0 \times 10^9$/L, fever $\geq$38.0°C).

5. Myelosuppression that causes a delay of >14 days between treatment cycles

6. Grade 4 neutropenia or platelets < 75,000/mm3 on Day 8 that does not resolve to ANC ≥750/mm3 and platelets ≥ 75,000/mm3 (transfusion independent) by Day 11 will be considered dose-limiting.

Non-hematological:

1. Grade 3 or 4 non-hematological toxicities related to study drug **except for**:
   - inadequately treated nausea and/or vomiting,
   - Grade 3 liver enzyme elevation (including ALT/AST),
   - Grade 3 fever or Grade 3infection,
   - Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
2. Grade 3 or above diarrhea despite adequate treatment
3. Non-hematological toxicity that causes a delay of ≥14 days between treatment cycles
4. Day 8 dose omission or interruption for more than 2 weeks due to non-recovery of any toxicity related to the study drug
5. For subjects <12 months (at the time of DLT), any ≥Grade 2 drug-related non-hematological toxicity
6. **DLT exception**: Allergic reactions that lead to discontinuation of study drug during Cycle 1.

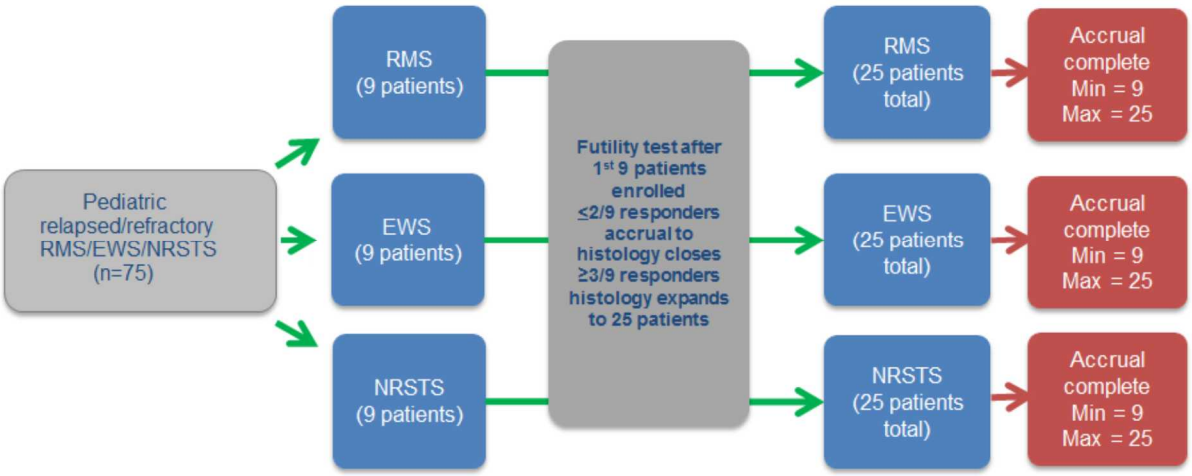
MTDs will be obtained for both Schedule A and Schedule B and the most appropriate schedule will be taken forward to Phase 2 and will represent the RP2D (See Section 9.4.1 in the protocol for details on schedule selection).

3.2.2 Phase 2

Phase 2 will evaluate the safety and efficacy of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects with relapsed/refractory RMS, NRSTS, and EWS, using the combination dose and schedule determined in Phase 1 (RP2D). The RP2D as determined from the phase 1 portion of the study was Schedule A Dose Level 1, ie, eribulin (1.4 mg/m^2) Day 1 and Day 8 and irinotecan (40 mg/m^2) Days 1-5.

Up to approximately 75 pediatric subjects (approximately 25 subjects per histology type of RMS, NRSTS, and EWS) who meet all the inclusion criteria and none of the exclusion criteria, will be enrolled on to Phase 2, using a Simon's two-stage design (Simon, 1989).

Trial schema of Phase 2



Outline

- Subjects will be enrolled on to the RMS, NRSTS, or EWS histology type; the proportion of the responders (ORR) will be estimated.
- Subjects will continue with their treatment until progression of disease, intolerable toxicity or withdrawal of consent.
- Each tumor histology type will have a futility analysis after 9 subjects are treated. Recruitment will be suspended for up to 24 weeks after 9 subjects have been enrolled to complete ORR assessment. If more than 2 responses (partial responses [PR] or complete responses [CR]) are observed and documented in that histology type, then recruitment will continue, and that histology type will expand to approximately 25 subjects in total. If 2 or fewer responses (PR or CR) are observed, recruitment to that histology type will close.
- The study will enroll a minimum of 27 (ie, 9 for each negative histology type) and a maximum of approximately 75 (ie, approximately 25 for each positive histology type) subjects.

Pretreatment Phase:

The Pretreatment Phase will last for up to 28 days and will include a Screening Period and a Baseline Period. Day -28 to -1, computerized tomography (CT) / magnetic resonance imaging (MRI) scans must be performed within 28 days prior to study drug administration. All clinical and laboratory test results to determine eligibility must be performed within 7 days prior to study drug administration, unless otherwise indicated.

Treatment Phase:

The Treatment Phase will start on Day 1 (D1) of Cycle 1 (C1). Subjects will receive eribulin mesilate by IV infusion on Days 1 and 8 of a 21-day cycle together with IV irinotecan hydrochloride administered on either:

- Day 1-5

or

- Days 1 and 8 of a 21-day cycle (See Study Design of Phase 1)

The most appropriate schedule will be taken forward to Phase 2 and will represent the RP2D (See Study Design of Phase 2).

Follow-up

All subjects will have an off-treatment visit within 28 days after the last dose of study medication. After discontinuation from study treatment and completing the off-treatment visit, subjects will be followed up at least 4 weeks later (ie, greater than or equal to 28 days after last dose but no more than 1 year) unless they withdraw consent. Subjects who discontinue without objective evidence of disease progression will continue to have tumor assessments performed as per the Schedule of Assessments until disease progression, death, or another anticancer therapy is initiated, whichever occurs first, unless study is terminated. Follow-up data will be required unless consent is withdrawn.

4 DETERMINATION OF SAMPLE SIZE

Phase 1: Up to 6 subjects can be enrolled in up to 3 dose levels, there are 2 schedules being evaluated (Schedule A and Schedule B). Therefore, a maximum of 36 subjects are anticipated to be enrolled on this phase (not including subjects <12 months). Note: Subjects <12 months will not contribute to the determination of MTD/RP2D and data is for descriptive purposes only.

Phase 2: Up to approximately 75 subjects (approximately 25 in each histology group) will be enrolled. Simon's two-stage design will be used for each histology group. The following hypothesis will be tested at a one-sided 5% significance level:

H_o: $p \leq 30\%$ Vs H_a: $p \geq 55\%$.

In the first stage, 9 subjects will be accrued. If there are 2 or fewer responses in these 9 subjects, the enrollment to this histology type (RMS, NRSTS, and EWS) will be stopped. Otherwise, 16 additional subjects will be enrolled in the second stage for a total of 25 subjects. The null hypothesis will be rejected if 12 or more responses are observed in 25 subjects. This design yields a type I error rate of 0.05 (one-sided) and the power of 80% when the true response rate is 55%.

5 STATISTICAL METHODS

Unless otherwise stated, tables, listings, and figures will be presented by dose level for Phase 1, and by histology type for Phase 2.

Descriptive statistics for continuous variables include: n, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. Categorical variables will be summarized as number and percentage of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoint(s)

The primary endpoints are:

- Phase 1: The MTD/RP2D of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects with relapsed/refractory solid tumors, excluding CNS tumors. Note: Subjects <12 months will not contribute to the determination of MTD/RP2D and data is for descriptive purposes only.

- Phase 2: Objective response rate (ORR): defined as the proportion of subjects achieving a best overall response of confirmed partial or complete response, as determined by investigator assessment. Duration of response (DOR): defined as the time from the first date of documented PR or CR to the date of disease progression or date of death (whichever occurs first).

5.1.2 Secondary Endpoint(s)

Phase 1 & 2:

- Safety and tolerability: adverse events (AEs), serious adverse events, clinical laboratory values, ECG parameters, vital sign measurements and physical examinations.

- The pharmacokinetic profile of eribulin, irinotecan, and its active metabolite

Phase 2:

- Progression-free survival (PFS): defined as the time from the first dose date to the date of disease progression as determined by investigator assessment or death.

- The Clinical Benefit Rate (CBR): defined as the proportion of subjects with best overall response (BOR) of CR, PR, or durable SD based on RECIST 1.1 (durable SD is defined as SD with duration of >11 weeks).

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

The following analysis sets will be defined:

- **Full Analysis Set (FAS)** will consist of subjects who receive at least 1 dose of either study drug.
- **Safety Analysis Set** will consist of subjects who receive at least 1 dose of either study drug.
- **Pharmacokinetic Analysis Set (PAS)** will include subjects who have documented dosing history and at least one post-dosing quantifiable drug concentration.
- **Dose Evaluable Set (DES)** for Phase 1 will consist of all subjects who completed Cycle 1 treatment and were evaluated for DLT, and those who discontinued during Cycle 1 due to DLT. DES will be used for evaluation of each dose level for dose-escalation and for determination of MTD.

5.2.2 Subject Disposition

The number and percentage of subjects who discontinue the study treatment will be tabulated, along with the primary reason for discontinuation.

5.2.3 Protocol Deviations

Protocol deviations will be determined prior to database lock. The protocol deviations data as collected in the clinical database will be presented in tables and/or listings as appropriate.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized for the FAS using descriptive statistics. They will include age (year), age group, race [White, Black or African American, Asian (Japanese, Chinese, Other Asian), American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other], ethnicity (Hispanic or Latino, not Hispanic or Latino), height (cm), weight (kg), and BSA (body surface area), as well as Karnofsky performance score (for subjects >16 years of age) or Lansky play-performance score (for subjects ≤16 years of age). Cancer history and prior anticancer therapies will be summarized.

For continuous variables, the number of non-missing observations, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum will be presented. For categorical variables the number and percentage of patients will be presented.

MEDICAL HISTORY

The number and percentage of subjects reporting a history of any medical condition will be summarized for the FAS. Listing of medical history will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) 2017 or current (WHODDMAR18_HD_B2). The number (percentage) of subjects who have taken prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class (ie, anatomical class, therapeutic class) and WHO drug preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 28 days after the subject's last dose. All medications will be presented in subject data listings.

A medication that cannot be determined as prior/concomitant/post-treatment due to missing/incomplete dates will be regarded as a concomitant medication. The summary of prior and concomitant medications will be summarized respectively. All medications will be presented in subject data listings.

5.2.6 Treatment Compliance

Subjects with treatment related protocol deviations/violations will be summarized by treatment group.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

This study is a multicenter study. Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

Not applicable.

5.3.3 Multiple Comparisons/Multiplicity

Not applicable.

5.3.4 Examination of Subgroups

No subgroup analyses are planned for this study.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

In general, missing data including dates will be treated as missing and no data imputation will be applied, unless otherwise specified.

5.3.6 Other Considerations

Not applicable.

5.4 Efficacy Analyses

The primary efficacy analyses (ORR) for Phase 2 will be performed at the time of data cutoff, ie, when all subjects have discontinued the treatment or completed at least 6 months of treatment.

ORR, DOR, PFS, and CBR will be summarized descriptively on the FAS for Phase 2. Endpoints related to tumor assessments will be based on investigator assessments.

5.4.1 Primary Efficacy Analyses

Objective response rate (ORR) is defined as the proportion of subjects achieving the best overall response (BOR) of CR or PR as per RECIST 1.1 (Eisenhauer, et al., 2009). Confirmed response will be used. Subjects who do not have a clinical response assessment for any reason will be considered non-responders and will be included in the denominator when calculating the response rate.

ORR and the corresponding 90% confidence interval (CI) will be estimated and summarized for each histology type. Simon's two stage design will be used within each histology type. The following hypothesis will be tested at a one-sided 5% significance level:

$$H_o: p \leq 30\% \qquad \text{Vs} \qquad H_a: p \geq 55\%.$$

The first stage will enroll 9 subjects. A futility analysis will be performed when the data for the 9 subjects is available. If there are 2 or less responders (CR or PR) among the 9 subjects, the enrollment in this histology type will be stopped. If there are 3 or more responders (CR or PR), the enrollment will continue to be up to approximately 25 subjects in the second stage. If there are 12 or more responders out of 25 subjects, the null hypothesis will be rejected.

Efficacy endpoints of tumor assessment and tumor response will be presented in subject data listings.

Duration of response (DOR) will be calculated for responders and summarized descriptively using Kaplan-Meier method.

5.4.2 Secondary Efficacy Analyses

Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the first study dose date to the date of disease progression (PD) as determined by investigator review or death (whichever occurs first). If a subject has not experienced PD or death, then the subject's data will be censored at the date of the last adequate radiologic assessment.

The PFS censoring rules in this SAP and definition of progression date follow the Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)".

Table 2 Censoring Rules for Progression-free Survival Endpoint

Situation	End Date	Censored
Investigator documented PD	Date of the first assessment of the series of radiologic tests that determined PD	No
Death during the study before first PD	Date of death	No
No baseline or post baseline tumor assessments	Date of first dose	Yes
No progression and no death at the time of data cutoff	Date of last adequate tumor assessment* prior to data cutoff	Yes
Nonstudy anticancer treatment initiated before progression or death	Date of last adequate tumor assessment* prior to or on date of nonstudy anticancer treatment	Yes
Death or progression after more than one missed tumor assessments	Date of last adequate tumor assessment* prior to missed tumor assessments	Yes

PD = progressive disease.

* Adequate tumor assessment is radiologic assessment at regular interval as defined in the protocol.
Data cutoff generally refers to the data scope at each analysis (e.g., dry run or final analysis), from an executed cutoff or as of the final study data.

The distribution of PFS and time curve will be estimated using Kaplan–Meier method (Kaplan and Meier, 1958). Median survival time and the corresponding 90% CI will be estimated using Kaplan–Meier method for each histology type. PFS will also be graphically summarized by Kaplan-Meier curves for each histology type.

Clinical Benefit Rate

Clinical benefit rate (CBR) defined as the number of subjects with best overall response (BOR) of CR, PR, or durable SD based on RECIST 1.1, divided by the number of subjects in FAS, and corresponding confidence interval will be calculated. Durable SD is defined as SD with duration of more than 11 weeks.

The count and percentage of subjects with clinical benefit as well as exact 90% CI for the CBR will be summarized for each histology type.

5.4.3 Other Efficacy Analyses

No other efficacy analyses are planned for this study.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

PK analysis will be based on PK Analysis Set.

Phase 1:

Blood samples will be collected for PK analysis of both irinotecan (and its metabolite, SN-38) and eribulin as follows:

For subjects ≥12 months of age and >10 kg:

- Cycle 1, Day 1: At the end of the irinotecan infusion (irinotecan is administered first), and at the end of the eribulin infusion, then at 1, 2, 4, 6, and 24 hours post-eribulin infusion. Both irinotecan (and its metabolite, SN-38) and eribulin will be assayed.

- At 72 and 120 hours post-eribulin infusion, eribulin only will be assayed.

Please note that eribulin will be administered immediately after the end of irinotecan infusion and PK blood sample draw.

Subjects <12 months of age as well as those ≥12 months of age and ≤10 kg (subjects under 6 kg will not have PK samples taken):

- Cycle 1, Day 1: At the end of the irinotecan infusion (irinotecan is administered first) and then immediately after the end of the eribulin infusion (ie, 10 ± 5 minutes from the start of the eribulin infusion).

- Cycle 1, Day 4 or 5: During the collection of the first twice weekly CBC sample.

- Cycle 1, Day 8: Before the eribulin infusion and then immediately after the end of the eribulin infusion (ie, 10 ± 5 minutes from the start of the eribulin infusion).

Please note that eribulin will be administered immediately after the end of irinotecan infusion and PK blood sample draw.

Plasma concentrations of eribulin, irinotecan and its active metabolite SN-38 will be tabulated and summarized by dose level, day and time. PK parameters for eribulin, irinotecan, and SN-38 will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: maximum observed plasma concentration (C_{max}), time of maximum observed concentration following drug administration (t_{max}), area under the concentration-time curve (AUC).

Phase 2:

Eribulin will be assessed on Cycle 1 Day 1 (at the end of infusion, 0.5 to 6 hours and 24 to 120 hours after eribulin infusion) and on Cycle 1 Day 8 (pre-dose of eribulin and at the end of the infusion).

The Phase 2 PK data will be assessed using a PopPK approach. A population PK model for eribulin will be developed using non-linear mixed effect modelling. The model will be parameterized in terms of clearance and volume of distribution.

5.5.2 Pharmacokinetic Analyses and Pharmacodynamic Analyses

Exploratory/graphical analysis will be conducted for PK/pharmacocodynamic evaluations, ie, dose and/or exposure effect relationships will be explored for the effects of eribulin mesilate on tumor responses as determined by RECIST 1.1 (CR, PR and SD), PFS and ORR, as well as AEs/dose reductions, and may be followed by model-based analysis. Further details will be documented separately.

5.5.3 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

5.6 Safety Analyses

The primary endpoint for Phase 1, the incidence of DLTs, will be summarized by dose level for the DES using frequency and percentage. All other evaluation of safety will be performed on the Safety Analysis Set. Safety data that will be evaluated include adverse events, clinical laboratory results, ECG, vital signs, and Karnofsky/Lansky performance status score.

Descriptive summary statistics (e.g., n, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum for continuous variables; n [%] for categorical variables) of clinical laboratory test results, vital signs measurements, ECG parameters, and changes from baseline will be presented.

5.6.1 Extent of Exposure

Descriptive summary statistics will be presented for the number of cycles/weeks on treatment, total dose (mg/m^2) per subject, actual dose intensity (mg/m^2/week) per subject, and relative dose intensity per subject.

Duration of treatment (weeks), dose intensity (mg/m^2/week), and relative dose intensity (%) will be calculated as the following:

Duration of treatment (weeks) = (date of first dose of last cycle + 21 – date of first dose of study drug) / 7.

Actual Dose intensity (mg/m^2/week) = Total dose (mg/m^2) / Duration of treatment (weeks)

Relative dose intensity (%) = Actual Dose intensity / Planned dose intensity × 100.

The number of subjects with study drug dose reduction, treatment interruption, and discontinuation due to adverse events will be summarized.

5.6.2 Dose Limiting Toxicities

The primary objective for phase 1 is to determine MTD and RP2D. The MTD is defined as the highest dose level at which less than 1/3 of subjects experience a DLT during Cycle 1 of therapy. The MTD will be determined based on the incidence of DLTs in Cycle 1 of each dose level.

MTDs will be obtained for both Schedule A and Schedule B and the most appropriate schedule will be taken forward to Phase 2 and will represent the RP2D (See Section 9.4.1 in the protocol for details on schedule selection).

The primary endpoint for Phase 1, ie, the incidence of DLTs will be summarized by dose level for the Dose Evaluable Set (DES) using frequency and percentage.

5.6.3 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 22.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment, or

- Reemerges during treatment, having been present at pre-treatment (Baseline) but stopped before treatment, or

- Worsens in severity during treatment relative to the pretreatment state, when the AE was continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade (CTCAE v5.0).

The number (percentage) of subjects with treatment-related TEAEs will also be summarized.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs of fatal outcome will be summarized by MedDRA SOC and PT. A subject data listing of all AEs with fatal outcome will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

5.6.4 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all hematology and chemistry parameters listed in the protocol Section 9.5.1.4.3, the actual value and the change from baseline to each post-baseline visit will be summarized using descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum).

Laboratory test results will be assigned a classification according to CTCAE grade (Appendix 1 in the protocol). Shifts of CTCAE grade from baseline to worst post-baseline will be presented. Percentages will be based on the number of subjects with both non-missing baseline and at least one post-baseline result for relevant parameters.

Urinalysis data will be listed.

5.6.5 Vital Signs

Descriptive statistics for vital signs parameters (ie, systolic and diastolic blood pressure (BP), heart rate, temperature, weight/BSA, and height) and changes from baseline will be presented by visit.

A listing of all vital sign measurements will be provided.

5.6.6 Electrocardiograms

Resting 12-lead electrocardiogram (ECG) assessments will be performed at screening, during Cycle 1 (pre- and post-infusion Day 1 and Day 8) and as clinically indicated during subsequent cycles and during off-treatment Visit (within 28 days after the last dose of drug).

QT intervals will be measured from Lead II and will be corrected for heart rate (QTc) using Fridericia's (QTcF) and Bazett's (QTcB) correction factors. The primary QTc parameter will be QTcF. Secondary parameters will be QTcB, QT, QRS, and heart rate (HR). Descriptive statistics for electrocardiogram parameters and changes from baseline will be presented by visit.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to worst post-baseline categories.

In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval > 450 ms
- QTc interval > 480 ms
- QTc interval > 500 ms

Change from baseline in QTc interval:

- QTc interval increases from baseline > 30 ms
- QTc interval increases from baseline > 60 ms

5.6.7 Other Safety Analyses

The changes of Karnofsky and Lansky performance status scores from baseline to worst post-baseline will be presented in shift tables.

5.7 Other Analyses

Not applicable.

5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

6 INTERIM ANALYSES

There will be an interim analysis to define MTD and RP2D prior to initiating Phase 2 of the study. It is anticipated that selection of the RP2D will be based on an integrated evaluation of safety, efficacy, and PK data. In Phase 2, for each histology (RMS, NRSTS and EWS), there will be 1 futility analysis of efficacy: this is planned after data from the first 9 subjects is available. At the futility analysis, if there are 2 or fewer responses, then enrollment to that histology will be discontinued. Enrollment to that histology will be suspended for up to 24 weeks after 9 subjects have been enrolled to complete ORR assessment. An assessment of tolerability will also be conducted at this time.

7 CHANGES IN THE PLANNED ANALYSES

If the SAP needs to be revised after its finalization prior to the database lock, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The Baseline value will be defined as the last non-missing measurement prior to the first dose of the study drug.

Descriptive statistics for continuous variables include number of non-missing measurements (n), mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum.

Descriptive statistics for categorical variables will be summarized as number (percentage) of subjects.

Confidence intervals for proportions will be reported as two-sided and calculated using Clopper-Pearson method (Clopper and Pearson, 1934). Time-to-event variables will be estimated using Kaplan-Meier product-limit method.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS v9.4 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

1. *Clopper, CJ and Pearson, ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika. 1934; 26: 404–413.*

2. *Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer 2009; 45(2): 228-47.*

3. *Kaplan, E. L.; Meier, P. (1958). Nonparametric estimation from incomplete observations, J. Amer. Statist. Assn. 53 (282): 457–481.*

4. *Simon R., Optimal two-stage designs for phase II clinical trials, Controlled Clinical Trials 1989; 10: 1 – 10.*

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 1.

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Anaemia (Hemoglobin)	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion	life-threatening consequences; urgent intervention indicated
White blood cell (Leukocytes) decreased	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocyte count decreased	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophil count decreased	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelet count decreased	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 – 20.0×ULN ifbaseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0×ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
ALT	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
AST	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin (hyperbilirubinemia)	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal

Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high(hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyltranspeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Magnesium, serum-high (hypermagnesemia)	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	N/A	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Magnesium, serum-low (hypomagnesemia)	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
Phosphate, serum-low (hypophosphatemia)	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L; intervention initiated	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/Lsymptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L intervention initiated	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of	<120 mmol/L life-threatening consequences

Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN without physiologic consequences	N/A	>ULN with physiologic consequences	life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetictransaminase), GGT = γ-glutamyltranspeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 5.0. Published: Nov 27, 2017.

13.2 Measurements of Performance Status

The following table of Karnofsky Performance Status and Lansky Play-Performance Scale for Pediatric Patients is copied from the protocol, Appendix 2.

Karnofsky Performance Status and Lansky Play-Performance Scale for Pediatric Patients

Rating/ Score	Description	
	Lansky	**Karnofsky**
100	Fully active, normal	Normal, no complaints
90	Minor restrictions with strenuous physical activity	Able to carry on normal activities. Minor signs or symptoms of disease
80	Active, but gets tired more quickly	Normal activity with effort
70	Both greater restriction of, and less time spent in, active play	Care for self. Unable to carry on normal activity or do active work
60	Up and around, but minimal active play; keeps busy with quieter activities	Requiring occasional assistance, but able to care for most needs
50	Lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities	Requires considerable assistance and frequent medical care
40	Mostly in bed; participates in quiet activities	Disabled, requires special care and assistance
30	Stuck in bed; needs help even for quiet play	Severely disabled, Hospitalization indicated though death nonimminent
20	Often sleeping; play is entirely limited to very passive activities	Very sick. Hospitalization necessary. Active supportive treatment necessary
10	Does not play nor get out of bed	Moribund
0	Unresponsive	Dead

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