STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7389-M000-219
Study Protocol Title:	A Randomized, Open-label, Multicenter, Phase 1b/2 Study of Eribulin Mesylate in Combination with PEGylated Recombinant Human Hyaluronidase (PEGPH20) versus Eribulin Mesylate Alone in Subjects with Human Epidermal Growth Factor Receptor 2 (HER2)-Negative, High-Hyaluronan (HA) Metastatic Breast Cancer (MBC)
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
BOR	best overall response
CBR	clinical benefit rate
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
E	Eribulin Mesylate alone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EP	Eribulin Mesylate in combination with PEGylated Recombinant Human Hyaluronidase (PEGPH20)
HA	hyaluronan
HER2	human epidermal growth factor receptor 2
IV	intravenous
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MSE	musculoskeletal events
NE	not evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PE	pulmonary embolism
PEGPH20	PEGylated recombinant human hyaluronidase
PFS	progression-free survival

Abbreviation	Term
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PR	partial response
PT	preferred term
RECIST 1.1	Response Evaluation Criteria in Solid Tumors (version 1.1)
RP2D	recommended Phase 2 dose
RR	response rate, respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TE	thromboembolic
TEAE	treatment-emergent adverse event
TNBC	triple negative breast cancer
US	United States
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-M000-219 (Amendment 01, dated as 27Oct2016). This was an originally planned, Randomized, Open-label, Multicenter, Phase 1b/2 Study of Eribulin Mesylate in Combination with PEGylated Recombinant Human Hyaluronidase (PEGPH20) versus Eribulin Mesylate Alone in Subjects with Human Epidermal Growth Factor Receptor 2 (HER2)-Negative, High-Hyaluronan (HA) Metastatic Breast Cancer (MBC). This study was carried out only for Phase 1b as planned during the study process due to its early termination. Therefore, this SAP is only focused on statisical methods and analyses that will be performed in the final for the data of Phase 1b, but the information on the original study design (overall for both Phase 1b and Phase 2) is explained first in Section 3.1 for Study Objectives, in Section 3.2 for Overall Design and Plan, in Section 4 for Sample Size Determination, and in Section 5.1 for Study Endpoints.

This SAP will be finalized and approved before the database lock of the study.

3.1 Study Objectives

3.1.1 Primary Objectives

- For the Phase 1b part – to determine safety tolerability and recommended Phase 2 dose (RP2D) of eribulin mesylate in combination with PEGPH20 in subjects with HER2-negative MBC previously treated with up to two lines of systemic anticancer therapy in the metastatic setting.
- For the Phase 2 part – to evaluate objective response rate (ORR) of eribulin mesylate in combination with PEGPH20 in subjects with HER2-negative, HA-high, MBC previously treated with up to two lines of systemic anticancer therapy in the metastatic setting.

3.1.2 Secondary Objectives

- To evaluate progression-free survival (PFS)
- To evaluate overall survival (OS)
- To evaluate the safety and tolerability

3.1.3 Exploratory Objective(s)

- To explore clinical benefit rate (CBR)
- To explore disease control rate (DCR)
- To explore duration of response (DOR)
- To explore efficacy for subjects enrolled in Phase 1b

- To evaluate exposure-response relationship
- To explore pharmacokinetics of PEGPH20 and eribulin mesylate when co-administered
- To identify and explore tumor and blood markers (e.g. Plasma HA levels) that correlate with clinical outcomes, including efficacy

3.2 Overall Study Design and Plan

This was a randomized, open-label, multicenter, Phase 1b/2 study of eribulin mesylate in combination with PEGPH20 versus eribulin mesylate alone in subjects with HER2-negative, HA-high, MBC previously treated with up to two lines of systemic anti-cancer therapy (cytotoxic drugs or targeted anti-cancer agents) in the metastatic setting. CDK4/6 inhibitors and mTOR inhibitors would not be considered as prior lines of therapy. Any single agents or combination of scheduled pre-planned treatments (given concomitantly, sequentially, or both) would be considered as one regimen. Hormonal therapy and bone metastases treatment (eg, bisphosphonates, denosumab, etc) would not be considered forms of systemic anti-cancer therapy.

3.2.1 Phase 1b and Phase 2

Study Phase 1b would occur in two parts (Part 1 and Part 2 ("Expansion Part")):

Part 1: would conduct run-in safety cohorts (dose levels 1, 0, and -1, as necessary) of 6 subjects each, until RP2D to be determined as followed:

- The part 1 would have dose-limiting toxicity (DLT) assessed in the first cycle, and would include at least 1 initial safety run-in cohort in which the first 6 enrolled subjects (with any hyaluronan [HA] level) would receive PEGPH20 at a dose of 3 µg/kg intravenously (IV) on Days -1 and 7 of a 21-day cycle, each dose followed approximately 24 (±4) hours later with eribulin mesylate 1.4 mg/m2 IV on Days 1 and 8 (dose level 1).
- Dose level 1 could be selected as the RP2D if no more than 1 subject had a DLT; otherwise, a second cohort of 6 subjects would receive a lower dose of PEGPH20 at 1.6 µg/kg on Days -1 and 7, each dose followed approximately 24 (±4) hours later with eribulin mesylate 1.4 mg/m2 IV on Days 1 and 8 (dose level 0).
- Dose level 0 could be selected as the RP2D if no more than 1 subject of this second cohort had a DLT; otherwise, a third cohort of 6 subjects would receive PEGPH20 1.6 µg/kg on Days -1 and 7, each dose followed approximately 24 (±4) hours later with eribulin mesylate at a lowered dose of 1.1 mg/m2 IV on Days 1 and 8 (dose level - 1).
- If no more than 1 of 6 subjects in this third cohort had a DLT, the Phase 2 part would proceed with dose level -1 as the RP2D. Otherwise, alternative doses would be explored prior to the start of Phase 2.

Part 2 ("Expansion Part"): Upon determination of the RP2D, would begin Phase 1b "Expansion Part" by enrolling 12 additional subjects (using Phase 1b criteria, ie subjects previously treated with up to 2 lines of systemic anticancer therapy) at the RP2D. This would result in a total of 18 subjects at RP2D for further safety analysis.

Following completion of one treatment cycle by the Phase 1b "Expansion Part" subjects, a safety evaluation of all Phase 1b subjects, focusing on incidence of TE events, would be conducted prior to proceeding with the Phase 2 part of the study. If ≤ 1 out of 18 subjects experienced a TE event, the upper limit of the 1-sided 80% exact CI for the true TE rate would not be greater than 15.7%. If ≤ 2 out of 18 subjects experienced a TE event, the upper limit of the 1-sided 80% exact CI for the true TE rate would not be greater than 22.3%. If more than 2 TE events occurred in 18 subjects in Phase 1b, then the sponsor in collaboration with Halozyme would decide on further required changes to the study conduct**.**

In the Phase 2 part, approximately 84 subjects (with HA-high levels only) would be stratified by triple negative breast cancer (TNBC) status and randomized 1:1 to receive eribulin mesylate and PEGPH20 (Arm A) at the established RP2D level (defined below) or eribulin mesylate alone (Arm B) at 1.4 mg/m2:

- RP2D level 1: PEGPH20 (3 µg/kg) plus eribulin mesylate (1.4 mg/m2) or
- RP2D level 0: PEGPH20 (1.6 µg/kg) plus eribulin mesylate (1.4 mg/m2) or
- RP2D level -1: PEGPH20 (1.6 µg/kg) plus eribulin mesylate (1.1 mg/m2)

3.2.2 Study Drugs Administration

On Days -1 and 7 of each 21-day cycle, Phase 1b subjects and Phase 2 (Arm A, only) subjects would receive PEGPH20 via IV injection over 10 minutes, approximately 1 mL/minute (a window of +2 minutes would be allowed, ie, infusion could be 10 to 12 minutes). On the following day, approximately 24 (±4) hours after Day -1 and Day 7 doses of PEGPH20, eribulin mesylate via IV injection over 2 to 5 minutes would be administered. Phase 2 subjects in Arm B would receive eribulin mesylate alone on Day 1 and Day 8 of each 21-day cycle.

For the subjects of Phase 1b and Phase 2 Arm A, dexamethasone 8 mg twice daily would be administered orally in each treatment cycle to alleviate musculoskeletal toxicities. Subjects would take dexamethasone orally within 2 hours prior to the beginning of each PEGPH20 and 8 to 12 hours after the completion of the infusions. The investigator might adjust the dose of dexamethasone based on the clinical presentation of each subject.

3.2.3 Subject Study Phases

For subjects in the study there would be the following three study phases:

- The Pre-treatment phase: consisted of the 21-day Screening Period and Baseline Period. The Baseline Period would include the Baseline Visit (all subjects),

performed on or before designated Study Day -2 or C1D-1, prior to administration of their first dose of PEGPH20 (see Schedule of Procedures/Assessments, Table 7 in Protocol).

- Treatment phase: would begin with the first dose of study drug administration in Cycle 1 and would continue in 21-day cycles until completion of the End of Treatment visit (within 30 days of the last study drug administration) or subject discontinuation of study, whichever occurred first. In the presence of clinical benefit, subjects would remain on study treatment until unacceptable toxicity (excluding Thromboembolic (TE) events which required discontinuation of PEGPH20 yet subjects might continue on eribulin mesylate alone), or disease progression occurred, or the subject withdrew consent.
- Follow-up phase: would start at the End of Treatment visit and would continue as long as the subject was alive or until the subject withdrew consent or lost to follow-up. Subjects who discontinued study treatment before disease progression would continue to undergo disease assessment every 6 weeks ±1 week until documentation of disease progression or start of another anticancer therapy. Follow-up assessment for survival would be performed every 12 weeks ±1 week.

3.2.4 Tumor, Safety and PK Assessments

Tumor assessments would be performed every 6±1 weeks from the date of first dose of study drugs or sooner if clinically indicated, until documentation of disease progression. In subjects who discontinued study therapy without documented disease progression, every effort would be made to continue monitoring their disease status by radiologic imaging every 6 weeks, until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, or withdrawal of consent, whichever occurred first.

Pharmacokinetic (PK) assessments of eribulin mesylate and PEGPH20 would be performed for all 12 subjects in the Phase 1b Expansion Part. Only subjects receiving combination treatment with PEGPH20 and eribulin mesylate (Arm A) in the Phase 2 part would undergo sparse PK sampling for population pharmacokinetic/pharmacodynamic (PK/PD) analysis, where feasible.

Safety assessments would be by monitoring and recording of all adverse events (AEs), including all CTCAE v4.03 grades (both increasing and decreasing severity) and serious AEs (SAEs), regular monitoring of hematology, and clinical chemistry, urinalysis, regular measurement of vital signs, 12-lead ECGs, and ECOG and detail schedules would be found in protocol Table 7 (Schedule of Procedures/Assessments).

4 DETERMINATION OF SAMPLE SIZE

The sample size calculation was based on the comparisons of the primary endpoint ORR. Assuming ORR_{EP} =0.35 and ORR_{E} =0.15, forty evaluable subjects per arm would provide a power of 0.800 in testing of ORR_{EP} vs ORR_{E} when using normal approximation to binomial

test with a one-sided significance of 0.10. Up to 114 subjects would be enrolled in the trial, comprising of up to 30 in the Phase 1b part (6 to 18 in the safety run-in cohort plus 12 in the Expansion part) and 84 in the Phase 2 part (to obtain 80 evaluable subjects).

5 STATISTICAL METHODS

5.1 Study Endpoints

In this study, all the primary, secondary, and exploratory endpoints on tumor related measurement/definition would be from the investigator assessment per RECIST 1.1.

5.1.1 Primary Endpoints

- The primary endpoint of Phase 1b was the RP2D of the eribulin mesylate and PEGPH20 combination.
- The primary efficacy endpoint of Phase 2 was ORR defined as the proportion of subjects who had a best overall response (BOR) of complete response (CR) or partial response (PR).

5.1.2 Secondary Endpoints (Phase 2)

- Progression-Free Survival (PFS) – defined as the time from date of randomization to date of first documentation of disease progression or death, whichever occurred first
- Overall Survival (OS) – defined as the time from the date of randomization until date of death from any cause

5.1.3 Exploratory Endpoints (Phase 2)

- Clinical Benefit Rate (CBR) was the proportion of subjects who had a BOR of CR or PR or durable stable disease (SD). Stable disease must be maintained at ≥ 23 weeks after randomization to be considered durable SD, and any stable disease required at least 1 post-treatment assessment that met the SD criteria ≥5 weeks after the start of treatment (Phase 1b) or randomization (Phase 2).
- Disease Control Rate (DCR) was the proportion of subjects who had a BOR of CR, PR, or SD.
- Duration of Response (DOR) was defined as the time from the date that the criteria were met for CR or PR (whichever was recorded first) to the date that progressive disease (PD) was objectively documented or death, whichever occurred first.

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

- DLT Evaluable Set will include subjects enrolled in Phase 1b who completed the first treatment cycle (ie, took at least 2 doses of eribulin mesylate and PEGPH20 with no more than 1 dose reduction) and had sufficient safety evaluation. This will be the analysis set for DLT evaluation in the Phase 1b Part 1 of the study.
- Safety Analysis Set will include subjects who received at least 1 dose of the study drug. This will be the analysis set for both safety and efficacy evaluations.
- Pharmacokinetic (PK) Analysis Set will include all eribulin mesylate and PEGPH20-treated subjects with at least 1 quantifiable eribulin concentration with a documented related dosing history. This will be the analysis set for PK data.

Enrolled subjects will also be considered in the final, and they are the subjects who signed the informed consent form.

5.2.2 Subject Disposition

The number (percentage) of subjects enrolled (ie, signed informed consent form), treated, discontinued from study/treatment (with reasons according to the categories in the CRF) will be summarized. The study status at the end of study or data cutoff will be summarized using the data from the survival follow-ups. The data will be listed as well.

5.2.3 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and reviewed before the database lock. Major protocol deviations by each category will be summarized. The data will be listed as well.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized. Continuous demographic and baseline variables will include age, weight, height, BMI (BMI (kg/m2) = Weight in Kilograms / (Height in Meters)^2), and BSA; categorical variables will include sex, age group (<65, ≥65 years), race, race group (White and Non-White), ethnicity, geographic region, enrollment strata (Triple Negative Breast Cancer, Other HER2 negative Metastatic Breast Cancer), estrogen status, progesterone status, Eastern Cooperative Oncology Group (ECOG) Performance Status, New York Heart Association (NYHA) classification, and pregnancy test. The data will be listed as well.

Medical History

The number (percentage) of subjects reporting a history of any medical condition and current medical condition, as recorded on the CRF, will be summarized. Medical History will be

coded using MedDRA (version 19.1 or newer), and summarized by System Organ Class (SOC) and Preferred term (PT). The data will be listed as well.

Disease History

Disease history and characteristics data at study entry will be summarized as recorded on eCRF. The data will be listed as well.

5.2.5 Prior and Concomitant Therapy

All investigator terms (verbatim terms) for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class and WHO DD 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 any study drugs and were continuing at the time of the first dose of any study drugs, or (2) started on or after the date of the first dose of any study drugs up to 28 days after the subject's last dose. Medications that cannot be determined to be prior/concomitant/post-treatment due to missing or incomplete dates will be regarded as concomitant.

Previous anti-cancer medications and previous anti-cancer procedures will be summarized similarly. Previous radiotherapies will also be summarized per the CRF data category.

The data summarized will be listed as well.

5.2.6 Treatment Compliance

Dose modifications (i.e., reduction and missing) will be summarized (see Section 5.6.1).

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Data from all centers will be pooled in 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 will be performed.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

Rules of handling full/partial missing dates and the censoring rules for PFS are explained in Section 8. Handling missing data in analyses of ORR, CBR and DCR is explained in Section 5.4. Any potential outlier values will be investigated and they will be analyzed as originally reported in the locked database.

5.3.6 Other Considerations

No other consideration.

5.4 Efficacy Analyses

All the efficacy endpoints defined in the protocol for Phase 2 (in Section 5.1), except OS and the duration of response, will be summarized for Phase 1b data. Their definitions will use the first date of any study drugs instead of the date of randomization, and the BOR will be determined from the confirmed CR or PR (after 28 days starting at the initial CR or PR observed) per RECIST 1.1.

In the efficacy analyses,

- Number (percentage) of subjects involved in objective response rate (CR or PR), disease control rate (CR, PR or SD), clinical benefit rate (CR, PR or durable SD), and durable SD rate will be reported together with their 95% confidence intervals (using the exact method of binomial distribution). Each BOR category will also be summarized in number (percentage) of subjects. In the analyses of ORR, CBR and DCR, subjects with missing data will be considered as non-responders and will be included in the denominator when calculating ORR, CBR and DCR. The figure of percent change of sum of target lesions' diameters from baseline and the figure of subjects' timepoint overall responses will be presented as well. The data and the tumor timepoint assessments (on target lesions, non-target lesions, new lesions) from the CRF will be listed as well.
- The Kaplan-Meier (KM) estimated PFS (month) at median, Q1 and Q3, and the KM estimated rates of PFS at the timepoints of 3, 6 and 12 months will be reported together with their 95% confidence intervals (the methods of generalized Brookmeyer and Crowley for survivals and Greenwood Formula for rates). The KM estimated PFS will also be plotted. The censoring rules for PFS calculation are explained in Section 8. The data will be listed as well.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Available PK data will be summarized, plotted and listed.

No pharmacodynamic, pharmacogenomic, and other biomarker data will be available.

5.6 Safety Analyses

5.6.1 Extent of Exposure

First and last dosing dates will be derived, separately, for each of study drugs (i.e. PEGHPH20 and Eribulin) and overall:

Study Drug	First Dosing date	Last Dosing date
Eribulin	first non-missing eribulin dosing date	last non-missing eribulin dosing date
PEGPH20	first non-missing PEGPH20	last non-missing PEGPH20 dosing date
Overall	Minimum of 2 study drugs' first dosing dates	Maximum of 2 study drugs' last dosing dates

In the analyses, the number of cycles/weeks/doses on treatment, cycle length, cumulative dose received, average dose intensity, relative dose intensity, and the number of subjects with dose reduction/missing, will be summarized by study drug. The data will be listed as well.

Per protocol, one cycle would be 21 days of treatment. The following calculations will be carried out in the analyses:

- The duration of treatment (weeks) for each study drug will be calculated as:
  - (First dosing date of the study drug in the final cycle - first dosing date of the study drug in the first cycle + 21)/7.
- The duration of overall treatment (weeks) will be calculated as:
  - (First dosing date of any study drugs in the final cycle - First dosing date of any study drugs in the first cycle + 21)/7 (note: '+21' if the first PEGPH20 dose in final cycle was not missing, and '+20' if the first PEGPH20 dose in final cycle was missing and first eribulin dose in the final cycle was not missing).
- The average cycle length of each study drug: will be calculated as the duration of each drug treatment divided by its corresponding number of cycles received in the study.

- Cumulative dose per subject (mg for eribulin, µg for PEGPH20), average dose intensity per subject (mg/m^2/week for eribulin and µg/kg/week for PEGPH20), and relative dose intensity per subject (percentage of cumulative dose relative to planned dose):
    - Average dose intensity (mg/m^2/week) for eribulin = total dose (mg)/ baseline BSA(m^2)/duration of eribulin treatment (weeks)
    - Average dose intensity (µg/ kg/week) for PEGPH20= total dose (µg)/baseline weight(kg)/duration of PEGPH20 treatment (weeks)
    - Relative dose intensity (%)=average dose intensity (mg/m2/week for eribulin, µg/kg/week for PEGPH20)/planned dose intensity, where the planned eribulin dose intensity is 0.933 mg/m2/week and the planned PEGPH20 dose intensity is 2 ug/kg/week for dosing level 1 (3 ug/kg) and 1.067 ug/kg/week for dosing level 0 (1.6 ug/kg)

5.6.2 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 19.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database. The CTCAE grading (Version 4.03 or higher) will be considered in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerged during treatment (i.e., AE onset or worsening is on or after first dose date of any study drugs, or up to 28 days following last dose of any study drugs), having been absent at pretreatment (Baseline) or

- Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

Only those AEs that are treatment emergent will be summarized in tables. A subject will be counted only once within each category (ie, SOC, PT, grade, or other specific category to be summarized in table) even if the subject experienced more than 1 TEAE within the category. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The following TEAE summary analyses will be performed:

- An overview summary table will include number (percentage) of subjects with any TEAE, with any treatment-related TEAE, with any TEAE of grade 3 or above, with any TEAE of grade 3 or grade 4, with any serious TEAE, with any TEAE leading to study drug withdrawal, with any TEAE leading to study drug dose reduction, with any TEAE

leading to study drug interruption, and with any TEAE of special interest. This overall summary will be repeated similarly for treatment-related TEAEs.

- TEAEs will be summarized by SOC, PT and grade in number (percentage) of subjects. Repeat this analysis for the TEAEs that are treatment-related, serious, serious and treatment-related, leading to death/dose modification/dose discontinuation, separately.
- TEAEs will be summarized by PT and grade in number (percentage) of subjects.
- Fatal TEAEs will be summarized by SOC and PT in number (percentage) of subjects. Repeat this analysis for non-fatal TEAEs, for TEAEs leading to study dose withdrawn, and for TEAEs leading to study dose reduction/interruption, separately.
- TEAEs of special interest will also be summarized in number (percentage) of subjects for each type of special interest by PT and grade. Repeat this analysis for treatment-related TEAEs, for serious TEAEs, and for treatment-related and serious TEAEs, separately.

5.6.2.1 Death

All deaths, deaths within 28 days of last dose, and deaths >28 days of last dose will be summarized. Deaths will be listed as well.

5.6.3 Laboratory Values

Clinical laboratory test parameters, per category, are listed in Table 1. The test results will be standardized using System International (SI) units and categorized according to CTCAE grade (v4.03 or higher) (see protocol Appendix 6).

Each laboratory test parameter will be summarized by visit, on the actual value observed, and on its change from baseline (except the parameters from Urinalysis). Grade shifting table from baseline to the worst during treatment period will also be summarized per parameter. The data will be listed as well.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), ANC, Coagulation[a] (PT, PTT, INR)
Clinical Chemistry	
Electrolytes	Sodium, potassium, chloride, calcium, magnesium
Liver Function Tests	ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin
Renal Function	BUN, serum creatinine
Pregnancy	Serum or urine β-hCG
Other	Albumin, glucose[b], LDH, total protein, uric acid
Urinalysis (urine dipstick)	Glucose, ketones, pH, protein, blood RBCs, leukocytes, specific gravity. Urine microscopy (if clinically indicated), culture, and sensitivity in case of UTI

ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, BUN = blood urea nitrogen, LDH = lactate dehydrogenase, PT=prothrombin time, PTT=partial thromboplastin time, INR=international normalized ratio, RBC = red blood cells, UTI=urinary tract infection, WBC = white blood cells.

a: Coagulation tests at screening visit and when clinically indicated

b: Fasting glucose at screening only

5.6.4 Vital Signs

Each parameter of vital signs assessments (diastolic and systolic BP, pulse rate, respiratory rate, temperature, weight, body surface area) will be summarized by visit on actual value observed and on its change from baseline. The data will be listed as well.

5.6.5 Electrocardiograms

Each parameter of electrocardiogram (ECG) assessments (heart rate, QT interval, QTcB interval, QTcF interval, RR interval) will be summarized by visit on actual value observed and on its change from baseline (or from the first assessment observed during study if no baseline available). The data will be listed as well.

ECG findings (normal, abnormal-not clinically significant, abnormal-clinically significant) will also be summarized on shifting from baseline to the worst during treatment period. The data will be listed as well.

5.6.6 Other Safety Analyses

5.6.6.1 Dose-limiting Toxicity in Phase1b Study

Per protocol, Part 1 Phase 1b subjects would get dose-limiting toxicity (DLT) assessed in the first treatment cycle to determine the RP2D during the study. The DLTs will be summarized and the data will be listed as well.

Per the protocol, the definition of DLT would be one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to either of the study drugs:

- Hematologic Toxicities:
  - Any Grade 4 thrombocytopenia or neutropenia lasting >7 days
  - Neutropenia Grade 3 or 4 complicated by fever and/or infection (ANC < 1.0 x 109/L, fever ≥ 38.5°C).
  - Thrombocytopenia Grade 3 complicated by bleeding and/or requiring platelet or blood
  - transfusion
- Nonhematologic Toxicities:
  - Any Grade DVT, PE or stroke.
  - Any Grade 4 toxicity.
  - Any clinically significant Grade 3 toxicity EXCLUDING:
  - Nausea, vomiting, or diarrhea controlled by medical intervention within 72 hours.
  - Hypersensitivity reactions Grade 3 or 4 including allergy reactions or anaphylaxis symptomatic bronchospasm requiring parenteral medication(s) with or without urticaria; allergy-related edema/angioedema.
  - Discontinuation or delay of more than 2 weeks of either study drug due to treatment-related AE will be considered as a DLT.

5.6.6.2 ECOG Performance Status

ECOG performance status will be summarized on shifting from baseline to the worst during treatment period. The data will be listed as well.

5.7 Other Analyses

No other analysis will be performed.

5.8 Exploratory Analyses

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriately titled/labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

6 INTERIM ANALYSES

Not applicable.

7 CHANGES IN THE PLANNED ANALYSES

Final analyses will be focused on the analyses planned in this document based on Phase 1b data due to the early termination of this study.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Data Report

Data reporting for both safety and efficacy analyses will use Safety Analysis Set, data reporting for PK analyses will use PK Analysis Set, and the DLT reporting will use DLT Evaluable Set. All the data reporting (tables, listings, figures) will be performed by dosing level. All descriptive statistics for continuous variables will be reported in mean, standard deviation (SD), median, Q1, Q3, minimum and maximum. Unless otherwise specified, all categorical variables will be summarized and reported in number (percentage) of subjects. The data summarized will be listed as well. Some data will only be listed if listing is enough for data reporting.

8.2 Baseline

Baseline is defined as the non-missing value most recently collected prior to the first dose of any study drugs.

8.3 Study Day

Study Day is defined as days from the first dosing date of any study drugs (i.e., PEGPH20 and Eribulin), in detail as

- For a date on or after the first dosing date, Study Day= event date – first dosing date of any study drugs+1,
- For a date prior to the first dosing date, Study Day= event date – first dosing date of any study drugs.

8.4 Day to Month to Year

1 month = 30.4375 days; 1 year = 365.25 days.

8.5 Censoring Rule

Table 2 shows the primary censoring rules for the derivation of PFS based upon investigator's tumor assessment and 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 Analysis of Progression-Free Survival

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Date of the first dose	Censored
2	Progression documented between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
4	New anti-cancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anti-cancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after two or more missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored
2	No post-baseline tumor assessments but known to be alive	Date of the first dose	Censored

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease,

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than two missed visits is defined if the duration between the last tumor assessment and death or PD is longer than 84 days (12 weeks) for subjects on the every 6 week scanning schedule during treatment /follow up phase in this study:

The priority of the censoring rules is as follows:

1. If the subject had PD or death, the following sequence will be applied:
    - If a subject did not have baseline tumor assessment (No. 1), the subject will be censored on date of the first dose. However, if the subject died or had clinical progression within 84 days (12 weeks) after the first dose and did not receive new anti-cancer treatment, the date of death or clinical progression will be the PFS event date (not censored).
    - If a subject had new anti-cancer treatment before PD or death (No. 4), the subject will be censored on the date of the last tumor assessment prior to or on the date of new anti-cancer treatment.
    - If a subject missed two assessments before PD or death (No. 7), the subject will be censored on the date of the last tumor assessment before PD or death. Note that if a subject is censored by both this criterion and the anti-cancer treatment criteria, the earliest censoring date will be used.
    - Otherwise, if a subject had an event (No. 2, No. 5 or No. 6), the earliest event date will be used.
2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4, or No. 7).

8.6 Missing Date Handling

- Adverse Event with missing or partial missing date :

  Adverse Event with incomplete start date will be considered as treatment emergent if:

a. Day and month are missing and the year is equal to or after the year of the first dosing date;
b. Day is missing, and the year is after the year of the first dose;
c. Day is missing and the year is equal to the year of the first dosing date and the month is equal to or after the month of the first dosing date;
d. Year is missing; or
e. Complete date is missing.

- Therapy (medication, procedure, radiotherapy) date missing or partial missing:
  See Section 5.2.5 for the missing date handling in determination of prior and concomitant medications. For the case of missing efficacy data, see Section 5.4. For other cases, detail of handling will be provided in a separate document (analysis datasets specification).

8.7 Unscheduled Visit

Data from unscheduled visits (eg, vital signs or laboratory tests) will be excluded from the by-visit summary but will contribute to the worst value in required summary tables. Listings will include all, the scheduled and unscheduled.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications will be provided in separate document (analysis datasets specification).

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS version 9 or higher.

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

Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Washington, DC, USA, May 28, 2009.

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). Eur J Cancer. 2009; 45:228-47.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

See Protocol Appendix 6.

SIGNATURE PAGE

Remove table rows that are not applicable. For example, if there is only 1 author delete the table rows for the second author.

Author(s): *If there is 1 author, remove "(s)" in the heading; if there is more than 1 author, remove the parentheses around the "s."*	
Study Statistician signs here	
<Name, degree(s)> <title>	Date
(Note: There may be more than 1 SAP author, eg, a CRO statistician may also be an author of the SAP.) *If applicable, the second author signs here*	
<Name, degree(s)> <title> <legal name of non-Eisai company>*(if applicable)*	Date
Approval:	
The biostatistics head signs here	
Biostatistics Head of <insert therapeutic area> <Name, degree(s)> <title, department>	Date
The study director signs here	
Study Director <Name, degree(s)> <title, department>	Date
Additional approver(s) as per local SOP or as otherwise required.	
<Function title> <Name, degree(s)> <title, department>	Date