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Clinical Study Protocol

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	
Sponsor	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA	Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	E7389/HALAVEN (eribulin mesilate)	
Indication:	Refractory or recurrent solid tumors in children	
Phase:	1/2	
Approval Date(s):	28 Sep 2016	(Original Protocol)
	10 May 2018	(Protocol Amendment 01)
	02 Aug 2018	(Protocol Amendment 02)
	12 Oct 2018	(Protocol Amendment 03)
	10 Jul 2019	(Protocol Amendment 04)
	14 Jul 2020	(Protocol Amendment 05)
	29 Mar 2021	(Protocol Amendment 06)
IND Number:	116292	
EudraCT Number:	2016-003352-67	
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.	

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REVISION HISTORY

Amendment 06

Date: 29 Mar 2021

Change	Rationale	Affected Protocol Sections
To clarify subjects aged >6 months and <12 months will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 Day 1 and Day 8) with the irinotecan dose maintained Dose Level 1 (40 mg/m^2 Day 1 – Day 5) of a 21-day cycle.	Subjects >6 months and <12 months of age are included per request from European Medicines Agency's Paediatric Committee (EMA PDCO). For eribulin, the dose selected (0.8 mg/m^2) is aligned with guidance on pediatric dosing Children's Cancer and Leukaemia Group (CCLG)-Chemotherapy Standardization Group 2008) which recommends that the dose in patients aged <12 months should be approximately 75% of calculated dose by body surface area. As eribulin has not been tested previously in this infant age group and is being used in combination with irinotecan in this study, the dose selected is the same as the lowest dose level in this study (Dose Level -2). This approach also takes into account that while eribulin is predominantly excreted unchanged in urine (5-7%) and feces (82%), it is partially (< 15%) metabolized by the cytochrome P450 (CYP) 3A4 liver enzyme and liver maturation of CYP3A4 has not occurred fully in these younger subjects. For irinotecan, the starting dose remains the same as the ≥12 months age group (40 mg/m^2), which is consistent with standard practice with irinotecan in this population and with previous studies with irinotecan used in combination, where the identified full dose of irinotecan is maintained for the infant age group (Hawkins, et al., 2018).	Synopsis (Study Design [Phase 2], Inclusion criteria), 9.1 (Phase 2), 9.2, 9.3.1b 9.4.1, Table 11, 9.4.4 (Phase 2).
Amended Inclusion Criterion 1b to include subjects >6 months and <12 months of age in Phase 2.	As requested by the EMA PDCO.	Synopsis, 9.3.1, 9.4.1
For subjects >6 months and <12 months of age in Phase 2, further dose reductions have been included	Additional dose reductions for eribulin in infants have been included in case of toxicities requiring a dose reduction.	Synopsis, Table 5, 9.4.1, Table 11, 9.4.4

Change	Rationale	Affected Protocol Sections
for this age group for eribulin in case of toxicities requiring a dose reduction. Specified if toxicities do not recover after 2 dose reductions, treatment with that agent must be discontinued.		
Pharmacokinetic (PK): Specified that subjects who weigh under 6 kg will not have samples for PK analysis taken.	To align with the Spanish Agency of Medicines and Medical Devices (AEMPS) requirements from Amendment 02.	Synopsis, 9.5.1.3.2 (Phase 2 (Cycle 1)
Vital signs, physical examination, and chemistry assessments during Phase 2 for the >6 months and <12 months age group will be weekly.	Additional assessments for safety monitoring in the infant subjects.	9.5.1.5, Table 14
Urinalysis assessments during Phase 2 for the >6 months and <12 months age group will be as clinically indicated after Cycle 1.	Additional assessments for safety monitoring in the infant subjects.	9.5.1.5, Table 14
Hematology assessments during Phase 2 will be twice weekly for the >6 months and <12 months age group (every 3 to 4 days).	Additional assessments for safety monitoring in the infant subjects.	9.5.1.5, Table 14
Subjects in the age groups > 6 months to < 12 months and ≥18 to ≤25 years old are included for descriptive purposes only and will not contribute to the full sample size analyses. Subjects in the age group > 6 months to <12 months will receive approximately 75% of the RP2D of eribulin (rationale for lower dose is provided in Section 9.4.4) and therefore should not been included in the full sample size analyses. The EMA PDCO requested that subjects in the age group ≥18 to ≤25 years old should not be included in the full sample size analyses.	To clarify how data from these age groups will be reported.	Synopsis, 9.7.2
References were added to the reference list.		10
Minor editorial, grammatical, and formatting changes	For consistency/clarification.	Throughout

Amendment 05

Date: 14 Jul 2020

Change	Rationale	Affected Protocol Sections
Extended study duration from 36 to 42 months.	Due to slower than anticipated enrollment in Phase 1.	Synopsis, 5.1
As per protocol amendment #5, the recommended Phase 2 dose (RP2D) was selected to be Schedule A Dose Level 1 – eribulin (1.4 mg/m^2) Day 1 and Day 8 and irinotecan (40 mg/m^2) Days 1-5.	Included the RP2D following completion of the Phase 1 portion of the study, as per requests from health authorities for additional countries participating in the Phase 2 portion of the study.	Synopsis, 9.1, 9.1.2, 9.2, 9.4.1, 9.4.4, 9.5.1.5 (Table 14 [footnote l])
Updated Inclusion Criterion 1a • ≥12 months to ≤25 years at the time of consent (no more than 25% of subjects between the ages of 18 and 25 years will be enrolled in this study).	Increasing the upper age limit to enroll a low number (≤25%) of patients 18 to 25 given the similarity in the pathophysiology and treatment paradigms of sarcoma for children and young adults.	Synopsis, 9.3.1
Updated Exclusion Criterion 10. Have had or are planning to have the following invasive procedures: • Central line placement or subcutaneous port placement is not considered major surgery. ~~but must be placed at least 2 days prior to study drug administration.~~	Removed "but must be placed at least 2 days prior to study drug administration," as this 2-day window was not deemed necessary for non-major procedures and moved as a sub-bullet.	Synopsis, 9.3.2
Criteria for administration of study drug; Day 8 Bowel function deteriorated since pre-treatment/baseline and requires antidiarrheal medications for within 24 hours before the next administration of irinotecan hydrochloride.	Clarified that this criteria is specific for irinotecan hydrochloride administration rather than for eribulin administration.	Synopsis (Table 1), 9.4.1 (Table 7)
Included dose levels specifically for the Phase 2 portion of the study	Included to allow more flexibility on dose reductions for either study drug depending upon which agent is causing the toxicity.	Synopsis, 9.4.1
Included, "If, in the opinion of the Investigator, a dose reduction as per the criteria noted in Table 2 is not necessary, due to adequate supportive care and use of prophylaxis (eg, growth factor support) to prevent recurrences, each individual case should be	Included following feedback from Investigators to allow some flexibility on dosing and dose reductions where the subject is receiving clinical benefit and where this is considered to be safe.	Synopsis, 9.4.1

Change	Rationale	Affected Protocol Sections
discussed with and agreed by the Sponsor." For Schedule A, irinotecan doses Days 2-5 can be delayed up to cycle Day 10 (of a 21 day cycle), at the discretion of the investigator and as long as the subject meets the criteria for administration of study medication for Day 8.		
Added that CT scans will be with oral and intravenous (IV) contrast unless clinically contraindicated.	Clarified, following feedback from investigators, that in some instances use of oral/IV contrast is not possible in a pediatric population.	Synopsis, 9.5.1.3.1
Clarified that if only chest CT is performed then oral CT contrast is not required.	This exception for not using oral contrast is clarified.	Synopsis, 9.5.1.3.1
Included 'irrespective of dose delays'	Clarified that the schedule of tumor assessments should be maintained as per protocol and not changed due to dose delays.	Synopsis, 9.5.1.3.1
For bone scans, added: approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Bone lesions must be followed with anatomic imaging.	To be consistent with section 9.5.1.3.1 of the protocol.	Synopsis, 9.5.1.3.1, 9.5.1.5 (Table 13 [footnote r] and Table 14 [footnote r])
Specified that eribulin, irinotecan and its active metabolite, SN-38 will be analyzed using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods.	Added test methods details for clarity.	Synopsis, 9.5.1.3.4
Removed: "In Phase 1 (Dose-Escalation), pharmacokinetics of irinotecan and SN-38 will be assessed with (Cycle 1, Day 1) and without eribulin coadministration (Cycle 1, Day 12) for Schedule A. Pharmacokinetics of eribulin will be assessed in Cycle 1."	There is no PK blood sampling on Cycle 1 Day 12 to evaluate PK.	Synopsis, 9.7.1.7.1
Updated reference for consortium study ADVL1314 (Schafer, et al., 2018).	Full paper now published and therefore included as a reference.	7.1.3.3.2, 10

Change	Rationale	Affected Protocol Sections
In instances where a subject becomes pregnant, the following language has been included "The Investigator should confirm whether they agree to follow-up assessments (including survival follow-up) or whether the subject wishes to withdraw consent. If a subject withdraws consent, the date should be documented in the source documents"	To clarify if subjects become pregnant that the investigator should confirm whether, despite stopping study treatment they would agree to follow-up or if consent will be withdrawn.	9.5.3.2
Minor editorial, grammatical, and formatting changes	For consistency/clarification.	Throughout

The table below describes revisions in Amendment 04 per the protocol template (Nov 2016).

Revisions per Amendment 04

Date: 10 Jul 2019

Change	Rationale	Affected Protocol Sections
Updated description of sample size for Phase 2 to 'approximately 75' or 'approximately 25 per histology' and updated trial schema.	To allow for more flexibility.	Synopsis, 9.1, 9.2, 9.3, 9.7.1.6.1, 9.7.2
Updated inclusion criterion #8 to remove the use of radioisotope for the measurement of the glomerular filtration rate (GFR).	Correction to inclusion criterion #8.	Synopsis, 9.3.1
Amended exclusion criterion #3 to allow subjects who received prior therapy with irinotecan hydrochloride in Phase 2 if there was no tumor progression during prior irinotecan therapy.	Following feedback from investigators subjects who received prior irinotecan hydrochloride should be eligible as long there was no tumor progression during irinotecan therapy.	Synopsis, 9.3.2
Clarification of exclusion criterion #4.	To clarify that the exclusion is for any other malignancy than that being studied, other than stated exceptions.	Synopsis, 9.3.2
Updated exclusion criterion #9.	To clarify that patients that do not have a history of CNS metastasis are not required to undergo a brain scan.	Synopsis, 9.3.2
Included language 'subjects known to have reduced UGT1A1	Added language regarding hematological safety monitoring	Synopsis, 9.4.1

Change	Rationale	Affected Protocol Sections
activity will be monitored carefully for hematological toxicity'.	for subjects with reduced UGT1A1 activity in line with the irinotecan SmPC.	
Added FDG-PET scans.	Scan included as standard practice in many sites.	Synopsis, 9.5.1.3.1, 9.5.1.5 (Table 11 [footnote r], Table 12 [footnote r])
Updated details of MIBG scans for neuroblastoma patients.	To provided clarification that MIBG scans are optional for neuroblastoma patients.	Synopsis, 9.5.1.3.1, 9.5.1.5 (Table 11 [footnote u])
Updated description of secondary efficacy analyses. Progression-free survival (PFS) will be analyzed by Kaplan-Meier methodology and median PFS with corresponding confidence interval will be presented. Clinical benefit rate (CBR) definition updated in places to remove 'at week 12' in the heading as the duration is defined within the definition.	Updated description of PFS and CBR (no change to analyses).	Synopsis, 9.7.1.1.2, 9.7.1.6.2
Updated the description of safety data analysis in statistical methods section.	To appropriately reflect Eisai oncology standard safety analysis.	Synopsis, 9.7.1.8, 9.7.1.8.3, 9.7.1.8.5, 9.7.1.8.6
Updated List of Abbreviations and Definitions of Terms.	To add to or correct the current list to agree with Protocol.	4
Updated estimated study LSLV date (to Mar 2021).	Correction of study end date.	5.1
Updated formal name of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).	The ICH updated its formal title in 2018.	5.2
Updated description of laboratory analysis values, ECG and other safety analyses.	For clarification.	9.7.1.8.3, 9.7.1.8.5, 9.7.1.8.6
Minor administrative changes.	For consistency/clarification.	Throughout

The table below describes revisions in Amendment 03 per the new protocol template (Nov 2016).

Revisions per Amendment 03

Date: 12 Oct 2018

Change	Rationale	Affected Protocol Sections
Updated the exploratory objective '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'.	Updated for clarification.	Synopsis, 8.3
Clarification that the duration of treatment up to 1 year is from the 'start of study treatment'.	Added for clarification.	Synopsis, 9.1.2, 9.3.3, 9.4.1
Updated exclusion criterion #12 to include that subjects with active or severe chronic inflammatory bowel disease or bowel obstruction are excluded from the study.	Updated per ANSM and Greece EOF request.	Synopsis, 9.3.2
ECG and electrolyte monitoring will occur 'more frequently in consultation with cardiologist advice and in line with local practice'.	Updated per ANSM request.	Synopsis, 9.4.1
For neuroblastoma subjects (Phase 1 only), included MIBG assessments and when to perform them.	Added following request from Investigator.	Synopsis, 9.5.1.3.1, 9.5.1.5 (Table 11 [footnote u])
Clarification that toxicity during Phase 2 will be monitored on an ongoing basis using the same rule as Phase 1. 'If the number of AEs that would have qualified as DLTs on the Phase 1 portion exceeds 1/3, a meeting with the investigators will be convened to determine if the dose should be lowered. Likewise if ongoing moderate toxicities develop into "intolerable Grade 2" events, the recommended Phase 2 dose may also be re-evaluated in	Added following responses to ANSM.	Synopsis, 9.7.1.8

Change	Rationale	Affected Protocol Sections
consultation with the protocol investigators'. All other evaluation of safety other than the Phase 1 primary objective in DLT evaluation will be performed on the Safety Analysis Set.		
Updated interim analyses to include an assessment of tolerability. Removed 'safety summaries may be provided periodically' due to this update.	More detail provided following ANSM request.	Synopsis, 9.7.3
Added 'No attenuated live vaccines must be administered for the duration of the study and 6 months following discontinuation of irinotecan'.	Added per ANSM request.	9.4.6.2
Included monthly pregnancy tests are required for all sexually active subjects.	Added per ANSM request.	9.5.1.4.3, 9.5.1.4.7, 9.5.1.5 (Table 11 [footnote i], Table 12 [footnote i])
Added magnesium as part of the clinical laboratory testing panel.	Added per ANSM request.	9.5.1.4.3 (Table 10), 9.5.1.5 (Table 11 [footnote k], Table 12 [footnote k]), Appendix 1
Removed assessment for globulin.	Assessment not required.	9.5.1.4.3 (Table 10), 9.5.1.5 (Table 11 [footnote k], Table 12 [footnote k])
Updated sponsor's grading for CTCAE laboratory values.	New laboratory values for CTCAE v5.0.	Appendix 1

The table below describes revisions in Amendment 02 per the new protocol template (Nov 2016).

Revisions per Amendment 02

Date: 02 Aug 2018

Change	Rationale	Affected Protocol Sections
Added restriction to concomitant use with St. John's Wort in exclusion criterion #2.	Added to be compliant with irinotecan SmPC.	Synopsis, 9.3.2, 9.4.6.1

Change	Rationale	Affected Protocol Sections
Added criteria for study drug discontinuation. Added new Tables (Tables 3 and 8) which list the criteria for study drug discontinuation.	Added for additional subject safety following request from MHRA.	Synopsis, 9.4.1
Amended PK sampling schedule to reduce the frequency of PK blood draws in relation to the subjects weight/blood volume. Subjects under 6 kg will not have samples for PK analysis taken.	Added following request from AEMPS.	Synopsis, 9.5.1.3.2, 9.5.1.5 (Table 11 [footnote m])
Updated Tables 11 and 12 (previously Tables 9 and 10) to indicate that Screening is from -28 to -1 days (rather than -14 to -1).	Reflects the change made in the previous amendment.	9.5.1.5 (Table 11, Table 12)

The table below describes revisions in Amendment 01 per the new protocol template (Nov 2016).

Revisions per Amendment 01

Date: 10 May 2018

Change	Rationale	Affected Protocol Sections
Up to approximately 50 study sites.	Plan to increase the number of investigational sites as more sites are necessary to complete the study.	Synopsis, 6
Added Ewing sarcoma (EWS) as a treatment group.	Ewing sarcoma (EWS) patients were included in this study following review from the FDA, preclinical (PPTP) data (eribulin/irinotecan) and noting a partial response in Ewing patients in Study E7389-A001-113.	Synopsis, 7.1.1 (Table 4), 7.2, 8.1, 9.1 , 9.2, 9.3, 9.3.1, 9.4.3, 9.7.2, 9.7.3, 10
Included duration of response (DOR) as part of the primary objective for Phase 2.	Included duration of response as part of the primary objective for Phase 2 following review by the FDA.	Synopsis, 8.1, 9.2, 9.7.1.6.1, 9.7.1.6.2
Replaced ‘extra-cranial solid tumors’ with ‘solid tumors (excluding CNS)’.	Amend for clarity that Phase 1 of this protocol is not intended to treat patients with CNS tumors.	Synopsis, 8.1, 9.1, 9.2, 9.3.1, 9.7.1.1.1
Expanded maximum number of subjects for Phase 2 of study from	Each histology group has a maximum of 25 subjects for Phase 2. RMS, NRSTS and the newly added EWS groups, bring	Synopsis, 9.1, 9.2, 9.3, 9.7.2

Change	Rationale	Affected Protocol Sections
50 to 75, consistent with addition of an EWS treatment group.	the maximum number of subjects to 75.	
Subjects <12 months are included for descriptive purposes only and will not contribute to the determination of the MTD/RP2D for this study, or to the sample size.	Included to clarify how data from <12 month age group will be managed.	Synopsis, 9.1, 9.2, 9.3, 9.3.1, 9.4.1, 9.7.1.1.1, 9.7.2
Amended inclusion criterion #1 to include subjects aged >6 months to <12 months for Phase 1 and Schedule A only.	The infant subject group was included as per request from BFARM and EMA Pediatric Investigational Plan (PIP). For added safety, infant subjects are to be enrolled 1 dose level below the ≥12 months to <18 years group.	Synopsis, 9.1, 9.3.1, 9.4.1
Extended the window in which computerized tomography (CT) / magnetic resonance imaging (MRI) scans can be performed from previous 14 days to up to 28 days before study drug administration.	Following feedback from the investigators. An extended screening window (28 days before first dose) for pre-screening scans was included.	Synopsis, 9.1.1, 9.1.1.1, 9.5.1.5 (Table 9 [footnotes b, p, q], Table 10 [footnotes b, p, q])
Included clarification on duration of treatment. 'As long as the subject is still receiving clinical benefit and has not experienced intolerable toxicity, he or she can continue to receive study treatment for up to 1 year, after which any continued treatment would need to be discussed with the Sponsor'.	In order to be compliant with the EMA PIP, the duration of treatment may be for up to 1 year.	Synopsis, 9.1.2, 9.3.3, 9.4.1
Included clarification on Follow-Up '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) unless they withdraw consent'.	In order to be compliant with the PIP, the follow-up period must be at least 28 days after last dose of study drug.	Synopsis, 9.1.3, 9.3.3, 9.5.1.5 (Table 9 [footnote t], Table 10 [footnote t])
Included clarification on performance level Karnofsky or Lansky score: Patients who are unable to walk because of paralysis and/or previous surgeries, but who are in	Clarification of inclusion criterion #5.	Synopsis, 9.3.1

Change	Rationale	Affected Protocol Sections
a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.		
Increased the required time for males to be on highly effective contraception from 28 days to 3 months (exclusion criterion #1). Increased the restriction on sperm donation from 28 days to 3 months after study drug discontinuation.	EU SmPC for irinotecan recommends that "men have to use effective contraception during and up to 3 months after treatment".	Synopsis, 9.3.2
Removed 'irinotecan hydrochloride' from Phase 1 exclusion criterion #3. Fixed numbering: exclusion criteria #3 and #4 were intended to be 2 bullet points within exclusion criterion #3.	Following feedback from the Investigators, amendment to allow prior treatment with irinotecan hydrochloride in Phase 1 as this is commonly used as first-line treatment in this setting.	Synopsis, 9.3.2
Added new exclusion #13 "Has received a live-virus vaccination within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted."	Included in line with the Irinotecan SmPC.	Synopsis, 9.3.2
Change in protocol on drug-drug interactions to include the following: Avoid co-administration of irinotecan with strong CYP3A4 inhibitors and inducers, and UGT1A1 inhibitors. For subjects requiring anti-epileptic therapy, switch to a non-enzyme inducing anti-epileptic agent.	Included in line with the Irinotecan SmPC.	9.3.2 (exclusion criterion #2 and Synopsis, CYP3A4 only), 9.4.6.1.2
Inclusion of an option to remain on treatment in the event of an adverse event which leads to treatment interruption or delay of either study drug. The subject may continue treatment with the other study drug as long as there is a clinical benefit for up to 1 year, after which any continued treatment would need to be discussed with the Sponsor.	To allow subjects to continue on either study drug in the event of an AE which leads to discontinuation of the other study drug.	Synopsis, 9.3.3, 9.4.1

Change	Rationale	Affected Protocol Sections
Hematological toxicity: Subjects who have Grade 4 neutropenia or platelets <75,000/mm^3 on Day 8 will have their dose withheld. If the toxicity resolves to ANC ≥750/mm^3 and platelets ≥75,000/mm^3 (transfusion independent) by Day 11, the dose may be given. If the toxicity does not resolve to ANC ≥750/mm^3 and platelets ≥75,000/mm^3 by Day 11, the dose will be omitted and this will be considered a DLT. Subjects should receive subsequent cycles of drug but at the next lower dose level. Subjects who require that their Day 8 dose be omitted for Grade 4 neutropenia or platelets <75,000 mm^3 after two dose reductions must be removed from protocol therapy. Subjects who meet hematological DLT criteria on Day 8 will have their Day 8 dose omitted. Subjects should receive subsequent cycles of drug but at the next lower dose level. Subjects who require that their Day 8 dose be omitted for hematologic DLT after two dose reductions must be removed from protocol therapy. **Non-hematological toxicity:** Subjects who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug prior to the Day 8 dose (with the exception of the DLT exclusions) will be considered to have had a DLT. If the toxicity resolves to meet eligibility or ≤Grade 2 (if not part of eligibility criteria) by Day 8, the dose may be given but at the next lower dose level. Subjects who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug on Day 8 prior to dosing	Updated dose-modification criteria in line with protocol E7389-G000-213.	Synopsis, 9.4.1

Change	Rationale	Affected Protocol Sections
(with the exception of the DLT exclusions) will have their dose withheld and this will be considered a DLT. If the toxicity resolves to meet eligibility or ≤Grade 2 (if not part of eligibility criteria) by Day 11, the dose may be given but at the next lower dose level. If the toxicity does not resolve by Day 11, the dose will be omitted. Subjects should receive subsequent cycles of drug but with dose modifications. For subjects <12 months any ≥Grade 2 non-hematological toxicity attributable to study drug prior to the Day 8 dose will have their dose omitted. Subjects should receive subsequent cycles of drug at the next lower dose level. Subjects who have a dose-limiting hematological or non-hematological toxicity that does not resolve to meet eligibility or baseline parameters within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.		
Any drug-related non-hematological toxicity ≥Grade 2 in infant subject population (<12 months) will be considered a DLT.	Additional DLT criteria included for the infant subjects.	Synopsis, 9.4.1
For subjects <12 months, if following de-escalation from dose level -1 (to dose level -2 in Schedule A), 2 DLTs are observed, that dose and schedule will be declared too toxic for further evaluation.	Additional dose modification criteria included for the infant subjects.	Synopsis, 9.4.1
Eribulin dose defined for dose level -2 for subjects <12 months in Schedule A.	Added safety for infant subjects.	Synopsis, 9.4.1
Myelosuppression that causes a delay of >14 days between treatment cycles is added as a hematological DLT.	Included as a DLT following team review and review of the previous pediatric eribulin protocol.	Synopsis, 9.4.1

Change	Rationale	Affected Protocol Sections
Updated CTCAE from v4.03 to v5.0.	v5.0 CTCAE is the current version.	Synopsis, 9.4.1, 9.5.1.4, 9.5.1.4.1, 9.7.1.8.2, 10 , 12 (Appendix 1)
After data cutoff for the primary analysis, tumor assessments may be performed as clinically indicated using the investigator's discretion, following the prevailing local standard of care.	Clarification on tumor assessments after data cutoff.	Synopsis, 9.5.1.3.1
Removed: "To confirm responses, tumor assessments should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. If the institutional investigator determines that the subject has progressed based on clinical evidence, he/she may opt not to confirm this finding radiographically."	A statement that all responses must be confirmed no less than 28 days following the initial assessment of response, was included so this was contradictory and required removal. A subject can always discontinue for clinical progression but it is censored for progression-free survival.	Synopsis, 9.5.1.3.1
Changed schedule for tumor assessments: rather than performing tumor assessments every 6 weeks on a fixed schedule, they will instead be performed every 6 weeks until Week 12 and every 9 weeks thereafter on a fixed schedule Therefore the assessments would be; Week 6, 12, 21, 30 etc.	Following feedback from the investigators, the schedule of tumor assessments was felt to be too burdensome therefore the frequency after 12 Weeks was reduced. Schedule of assessments needed to be updated to reflect the change in the fixed schedule of tumor assessments.	Synopsis, 9.5.1.3.1, 9.5.1.5
Lesions identified on bone scans should be followed with anatomic imaging, rather than cross-sectional imaging.	Clarification.	Synopsis, 9.5.1.3.1
Following feedback from the Principal Investigator, included: "An exception to the requirement for following chest disease by CT will be allowed where subjects have either non-parenchymal tumors, mediastinal and/or chest wall lesions. These may be assessed (at Screening and post-baseline) using contrast-enhanced MRI. However, a chest CT is required at Screening for all subjects, and lung parenchymal	This is more in line with clinical practice and will improve compliance with the tumor assessment schedule.	Synopsis, 9.5.1.3.1

Change	Rationale	Affected Protocol Sections
lesions should be followed using CT (as per standard practice). If there is either an equivocal new lung lesion based on MRI or symptoms suggesting a new lesion, these should also be confirmed with chest x-ray or CT". Confirmation by chest x-ray may be used in lieu of CT.		
A brain scan CT or MRI will be performed as clinically indicated to assess potential for CNS disease and/or metastases. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at Screening and at all tumor assessment time points.	In view of the patient population, CNS imaging will only be required as clinically indicated for subjects with a history of protocol-eligible treated brain metastasis.	Synopsis, 9.5.1.3.1, 9.5.1.5 (Table 9 [footnote q]), Table 10 [footnote q])
Include PK sampling schedule for subjects <12 months. <u>Subjects <12 months of age:</u> • Cycle 1, Day 1: Before the irinotecan and eribulin infusion 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).	Included PK sampling schedule suitable for subjects <12 months.	Synopsis, 9.5.1.3.2, 9.5.1.5 (Table 9 [footnote m])
Updated Principles of the World Medical Association Declaration of Helsinki from 2008 to 2013.	2013 is the current version.	5.2
Added background on EWS.	Introduction was changed to include background on EWS because EWS was added as a treatment group.	7.1.1.3, 7.1.2

Change	Rationale	Affected Protocol Sections
Updated section with MTD/RP2D data from a recently published Eisai clinical study.	Including results from the completed Phase 1 Study E7389-A001-113.	7.1.3.3.2
Removed 'non-hematological toxicities' from right column of Tables.	Wording was redundant.	9.4.1 (Table 5, Table 6)
Included storage and labeling information for irinotecan hydrochloride as an Investigational Product.	Labeling and storage specifications provided.	9.4.2, 9.4.2.3, 9.4.2.4.1, 9.4.2.4.3
Added clarification regarding the pregnancy test: 'A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug'.	Clarification of information contained in exclusion criterion #1.	9.5.1.4.7, 9.5.1.5 (Table 9 [footnote i], Table 10 [footnote i])
Removed tumor assessment from schedule of assessments on Cycle 2 Day 15.	This box was checked in error in the original protocol. Tumor assessments start at 6 weeks from C1D1 on a fixed schedule.	9.5.1.5 (Table 9, Table 10)
For 12-lead ECG, added '(after irinotecan administration and prior to eribulin infusion on the days when administered together)'.	Clarification on when to perform the pre-eribulin infusion ECG assessments.	9.5.1.5 (Table 9 [footnote n], Table 10 [footnote n])
Vital signs, Physical exam and Chemistry assessments during Phase 1 for <12 months subject group will be weekly.	Additional assessments for the infant subjects.	9.5.1.5 (Table 9)
Urinalysis assessments during Phase 1 for <12 months subject group will be as clinically indicated after Cycle 1.	Additional assessments for the infant subjects.	9.5.1.5 (Table 9)
Hematology assessments during Phase 1 will be twice weekly for subjects <12 months (every 3 to 4 days).	Additional assessments for the infant subjects.	9.5.1.5 (Table 9)
Added the Balis peripheral neuropathy scale as Appendix 3.	Original protocol referred to the Balis peripheral neuropathy scale in exclusion criterion #7, but did not provide the scale.	12 (Appendix 3)

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7389

Name of Active Ingredient: eribulin mesilate and irinotecan hydrochloride

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

Investigator

PPD

Sites

Up to approximately 50 sites

Study Period and Phase of Development

Approximately 42 months from first subject signed informed consent to last subject last visit (LSLV).

Phase 1/2, open-label, non-randomized.

Objectives

Primary Objectives

- 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)

Secondary Objectives

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) at 12 weeks of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects

Phase 1 and 2:

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

Exploratory Objectives

Phase 1 and 2:

- 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

Study Design

E7389-G000-213 is a Phase 1/2, multicenter, open-label study to assess the safety and efficacy of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects.

This study is divided into 2 phases:

Phase 1: Will determine the MTD/RP2D 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), starting dose.

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

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

And

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

These doses of irinotecan are derived from studies looking at MTD of single agent irinotecan or irinotecan combinations administered at the various corresponding schedules (Blaney, et al, 2001; Vassal, et al, 2003; Casey, et al, 2009).

Dosing schedules to be evaluated are described below:

Schedule A

Eribulin mesilate on Day 1 and Day 8 of a 21 day cycle (Starting dose determined by COG protocol ADVL1314/Eisai Study E7389-A001-113).

Irinotecan hydrochloride on Days 1-5 of a 21 day cycle.

Dose Level	Eribulin mesilate (mg/m^2)	Irinotecan hydrochloride (mg/m^2)
-2	0.8	20
-1	1.1	20
0*	1.4	20
1	1.4	40

*Dose level 0 refers to the starting dose.

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

Schedule B

Eribulin mesilate and irinotecan hydrochloride on Day 1 and Day 8 of a 21-day cycle.

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.

Subjects will be enrolled alternately on Schedule A or Schedule B (ie, every other subject will be enrolled on to Schedule A), as allocated by the Sponsor. If enrollment is halted or discontinued for any schedule, subjects will be enrolled on to the other schedule provided it is open for accrual.

Subjects <12 months will be enrolled on to Schedule A only and at one dose level behind ≥12 months subjects in order to maximize safety for infant subjects.

Dose Escalation

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

For both schedules A and B, 3 subjects will be entered into each dose level. The first subject at each dose level, within a schedule, must complete the Day 8 assessments before further subjects can be entered at the same dose level. All 3 subjects in the cohort will be followed for a full cycle before the next dose level opens. If 1 subject experiences a DLT, the cohort will need to be expanded to 6 subjects on the same dose level.

If no DLT is observed in a dose cohort, then the dose can be escalated and 3 subjects can be enrolled onto the next dose level. The MTD is defined as the highest dose level at which fewer than 1/3 of subjects experience a DLT during Cycle 1 of therapy.

If, at dose level 0, there are 2 or more subjects with a DLT out of 3 subjects (or 2 DLTs out of 6 subjects after expansion) in Cycle 1, the MTD will have been exceeded and the dose will be de-escalated to dose level -1, and the next 3 subjects will be enrolled onto this lower dose level.

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. 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 ≥38.0°C)
5. Myelosuppression that causes a delay of >14 days between treatment cycles
6. Grade 4 neutropenia or platelets < 75,000/mm^3 on Day 8 that does not resolve to ANC ≥ 750/mm^3 and platelets ≥ 75,000/mm^3 (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 3 infection,
- 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

Accrual will be suspended when a cohort of 3 or 6 has enrolled with pending toxicity data or when the MTD/RP2D for the combination has been met. If, following de-escalation from dose level 0 (to dose level-1), 2 DLTs are observed, that dose and schedule will be declared too toxic for further evaluation. For subjects <12 months, if following de-escalation from dose level -1 (to dose level -2 in Schedule A), 2 DLTs are observed, that dose and schedule will be declared too toxic for further evaluation. Up to 36 pediatric subjects (18 subjects per schedule) who meet all the inclusion criteria and none of the exclusion criteria, will be enrolled in Phase 1. The sample size does not include subjects <12 months.

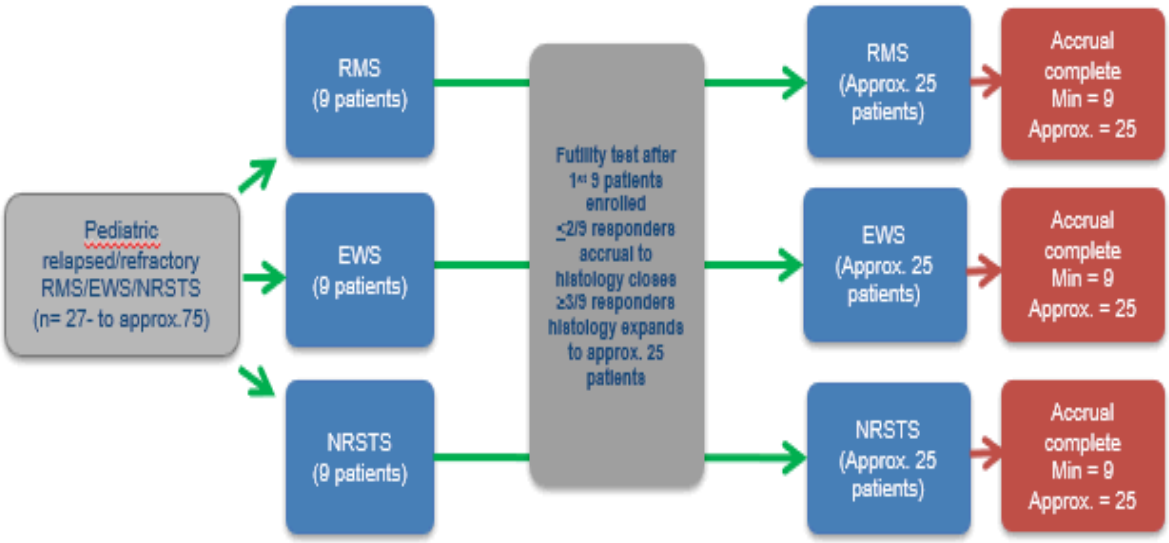
MTDs will be obtained for both Schedule A and Schedule B and the most appropriate schedule will be taken forward to Phase 2 and will represent the RP2D (See Section 9.4.1 for details on schedule selection).

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. As per protocol amendment #5, following review of the data from the Phase 1 portion of the study, Schedule A Dose Level 1 - eribulin (dose 1.4 mg/m^2) Day 1 and Day 8 and irinotecan (dose 40 mg/m^2) Days 1-5, was selected as the dose and schedule to take forward into Phase 2 (RP2D). As per Amendment 6, subjects aged >6 months and

<12 months will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 Day 1 and Day 8) with the irinotecan dose maintained Dose Level 1 (40 mg/m^2 Day 1 – Day 5) of a 21-day cycle in order to maximize safety for infant subjects.

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

Trial schema Phase 2



Outline

- Subjects will be enrolled on to either 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. If 2 or fewer responses (PR or CR) are observed, recruitment to that histology type will close. An assessment of tolerability will be also be conducted at this time.
- The study will enroll a minimum of 27 (ie, 9 for each negative histology type), and approximately 75 (ie, approximately 25 for each positive histology type) subjects.

Pre-study Phase:

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:

- Days 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).

Subjects in both Phase 1 and Phase 2 can remain on treatment for up to 1 year if they are receiving clinical benefit, as outlined in the Duration of Treatment.

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.

Number of Subjects

The maximum number of subjects is approximately 111 (not including subjects of age <12 months).

Up to 36 subjects in Phase 1 and a total of approximately 75 subjects in Phase 2.

For Phase 2, Simon's two-stage design will be used. Nine subjects will be enrolled on to each histology type (RMS, NRSTS and EWS) in the first stage, at which point a futility analysis will be performed. Enrollment will be terminated if 2 or fewer responses are observed in these 9 subjects. If more than 2 responses are observed, then enrollment will continue to approximately 25 subjects in each histology type.

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Age:

a. ≥12 months to ≤25 years at the time of consent (no more than 25% of subjects between the ages of 18 and 25 years will be enrolled in this study).

b. In Phase 1, >6 months and <12 months at the time of consent (Schedule A only) subjects will be enrolled one dose level behind the ≥12 months subjects in order to maximize safety for infant subjects. In Phase 2, subjects aged >6 months and <12 months at the time of consent will be enrolled to Schedule A with a modified dose of eribulin, Dose Level -2 (0.8 mg/m^2 Day 1 and Day 8) with the irinotecan dose maintained (40 mg/m^2 Day 1 – Day 5) of a 21-day cycle in order to maximize safety for infant subjects.

2. Diagnosis:

   Phase 1: Histologically confirmed solid tumor, excluding CNS tumors, which is relapsed or refractory, and for which there are no currently available therapies.

   Phase 2: Histologically confirmed RMS, NRSTS and EWS which is relapsed or refractory having received at least 1 prior systemic therapy, including primary treatment.

3. Disease status:

   Phase 1: Subjects must have either measurable or evaluable disease as per RECIST 1.1.

   Phase 2: Subjects must have measurable disease as per RECIST 1.1.

Measurable disease is defined as meeting the following criteria:

a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is serially measurable according to RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI).

b. Lesions that have had radiotherapy must show subsequent radiographic evidence of increase in size by at least 20% to be deemed a target lesion.

4. Therapeutic options: Subject's current disease state must be one for which there is no known curative therapy.

5. Performance level: Performance score ≥50% Karnofsky (for subjects >16 years of age) or Lansky (for subjects ≤16 years of age). Subjects who are unable to walk because of paralysis and/or previous surgeries, but who are in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

6. Subjects must have fully recovered from the acute toxic effects of all prior anticancer treatments prior to study drug administration:

   - Myelosuppressive chemotherapy: Must not have received within 21 days prior to study drug administration (42 days if prior nitrosourea).
   - Hematopoietic growth factors: Must not have received a long-acting growth factor (eg, Neulasta) within 14 days, or a short-acting growth factor within 7 days. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the sponsor.
   - Targeted therapy (antineoplastic agent, eg, tyrosine kinase inhibitor): Must not have received an antineoplastic targeted therapy within 14 days. For agents that have known AEs occurring beyond 14 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the sponsor.
   - Immunotherapy: Must not have received immunotherapy, eg, tumor vaccines, within 42 days.
   - Monoclonal antibodies: Must not have received within at least 3 half-lives of the antibody after the last dose of a monoclonal antibody.

- Radiotherapy (XRT): Must not have received within 14 days prior to study drug administration (small field) or 42 days for craniospinal XRT, or if ≥50% radiation of pelvis.
- Autologous Stem cell infusion: At least 84 days must have elapsed after stem cell infusion prior to study drug administration
- Allogeneic bone marrow transplant, including mini-transplant: No evidence of active Graft vs. Host disease and at least 100 days must have elapsed after transplant or stem cell infusion prior to study drug administration

7. Adequate bone marrow function, defined as:
   - Peripheral absolute neutrophil count (ANC) $\geq 1.0 \times 10^9$/L.
   - Platelet count $\geq 100 \times 10^9$/L (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to study drug administration).
   - Hemoglobin (Hb) at least 8.0 g/dL at baseline (blood transfusions are allowed during the screening period to correct Hb values less than 8.0 g/dL).

   As blood transfusions are permitted to meet the hemoglobin criteria, subjects requiring transfusion must not be known to be refractory to red blood cell or platelet transfusions.

8. Adequate renal function, defined as:
   - A serum creatinine based on age/gender, derived from the Schwartz formula for estimating GFR (Schwartz and Gauthier, 1985), See table below.
   - Or serum creatinine clearance or GFR ≥50ml/min/1.73m^2, based on a 12 or 24h urine creatinine collection.

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

9. Adequate liver function, defined as:
   - Bilirubin (sum of conjugated + unconjugated) ≤1.5 times the ULN for age.
   - Alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN), unless there are bone metastases, in which case liver-specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of the total alkaline phosphatase.
   - Serum albumin ≥2 g/dL.

10. Informed consent: All subjects and/or their parents or guardians must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines. Subjects must be willing to comply with all aspects of the protocol.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic [β-hCG] *or* human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of β-hCG [*or* hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

- Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 6 months after study drug discontinuation, ie:
        - Total abstinence (if it is their preferred and usual lifestyle)
        - An intrauterine device (IUD) or intrauterine system (IUS)
        - A contraceptive implant
        - an oral contraceptive**

    OR

    - Do not have a vasectomized partner with confirmed azoospermia.

    For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double barrier methods of contraception such as condoms plus diaphragm or cervical/vault cap with spermicide.

*All post pubertal females will be considered to be of childbearing potential unless they have early menopause [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing].

Must be on a stable dose of the **same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug and for the duration of the study and for 6 months after study drug discontinuation.

Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 3 months after study drug discontinuation). No sperm donation is allowed during the study period or for 3 months after study drug discontinuation.

2. Concomitant Medications:
    - Corticosteroids: Subjects receiving corticosteroids who have not been on a stable dose for at least 7 days prior to study drug administration.
    - Anticancer agents: Subjects who are currently receiving other anticancer agents.
    - Anti-GVHD agents post-transplant: Subjects who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant.
    - Strong CYP3A4 inducers/inhibitors including traditional herbal medicinal products (eg, St. John's Wort). See Section 9.4.6.1, Drug-Drug Interactions.
3. Prior Therapies:

- Phase 1: Received prior therapy with eribulin mesilate within 6 months prior to study drug administration.
- Phase 2: Received prior therapies with eribulin mesilate or irinotecan hydrochloride (for prior irinotecan hydrochloride, subjects can be included if there was no tumor progression during irinotecan therapy).

4. Any other malignancy that required treatment (except non-melanoma skin cancer, or histologically confirmed complete excision of carcinoma in situ), within 2 years prior to study drug administration.
5. Has hypersensitivity to either study drug or any of the excipients.
6. Has a known prior history* of viral hepatitis (B or C) as demonstrated by positive serology (presence of antigens) or have an uncontrolled infection requiring treatment (* Subjects with a known prior history of hepatitis B or C may be eligible pending agreement with the sponsor).
7. Has >Grade 1 peripheral sensory neuropathy or >Grade 1 peripheral motor neuropathy graded according to the Modified ("Balis") Pediatric Scale of Peripheral Neuropathies.
8. Has cardiac pathology, defined as:
   - Subjects with known congestive heart failure, symptomatic or LV ejection fraction <50% or shortening fraction <27% and subjects with congenital long QT syndrome, bradyarrhythmias, or QTc >480 msec on at least 2 separate ECGs.
9. Has CNS disease: Subjects with brain or subdural metastases are not eligible unless the metastases are asymptomatic and do not require treatment or have been adequately treated by local therapy (eg, surgery or radiotherapy) and have discontinued the use of corticosteroids for this indication for at least 28 days prior to study drug administration. Subjects must be clinically stable. It is not the intention of this protocol to treat subjects with active brain metastases.

   Note: Screening CNS imaging for subjects with a known history of CNS disease is required.
10. Have had or are planning to have the following invasive procedures:
    - Major surgical procedure or significant traumatic injury within 28 days prior to study drug administration.
      - Central line placement or subcutaneous port placement is not considered major surgery.
    - Laparoscopic procedure or open biopsy within 7 days prior to study drug administration.
    - Core biopsy, including bone marrow biopsy within 2 days prior to study drug administration.
    - Fine needle aspirate within 3 days prior to study drug administration.
11. Subjects with known human immunodeficiency virus (HIV); due to lack of available safety data for eribulin therapy in HIV infected patients.
12. Has any serious concomitant illness that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (including active or severe chronic inflammatory bowel disease or bowel obstruction).
13. Has received a live-virus vaccination within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted.

Study Treatments

Administration of eribulin mesilate by IV infusion on Days 1 and 8 of a 21-day cycle in combination with irinotecan hydrochloride administered by IV infusion on either Days 1-5 of a 21-day cycle (Schedule A), or Days 1 and 8 of a 21-day cycle (Schedule B).

Irinotecan will be administered first (on days where both treatments are due to be administered), as a 30 minute infusion, followed by eribulin as a 2-5 minute bolus infusion. Eribulin may be diluted in up to 100 mL 0.9% sodium chloride and administered as an IV infusion over 15 minutes (maximum infusion duration), where clinically appropriate.

In the event of an adverse event which leads to treatment interruption or delay of either study drug, the subject may continue treatment with the other study drug, as long as there is a clinical benefit, for up to 1 year, from start of study treatment, after which any continued treatment would need to be discussed with the Sponsor.

Phase 1

The dosing schedules being evaluated for Phase 1 are summarized in the Study Design section of the synopsis.

Subjects will be allocated in an alternate fashion to either Schedule A or Schedule B, ie, every other subject will be allocated to Schedule A, until an MTD is reached. Subjects are allocated to respective treatment schedules by the Sponsor. If enrollment is halted or discontinued for any schedule, subjects will be enrolled on the other schedule provided it is open for accrual.

Subjects <12 months will be allocated to Schedule A only and will be enrolled at one dose-level behind ≥12 months subjects. These subjects are included for descriptive purposes only and will not contribute to the determination of the MTD/RP2D for this study.

Phase 2

The dose and schedule that is deemed the most appropriate from Phase 1 will be used in Phase 2, following sponsor review together with the investigators. If there is no difference in the safety and efficacy between Schedules A and B, following review with the investigators, Schedule B will be taken forward to Phase 2 on the basis of convenience.

If a large number of dose modifications are observed after completion of Cycle 1 (eg, intolerable Grade 2 toxicities), the sponsor will discuss with investigators whether a lower dose level than the MTD should be carried forward as the RP2D for this study.

As per protocol amendment #5, the data from the Phase 1 portion of this study showed that there was a tolerable safety profile in both schedules, with similar PK profiles; however, 2 PRs were noted in Schedule A, one of which was confirmed. Following discussions with the investigators and independent experts, based upon the similar toxicity and PK profiles and taking into account the 2 PRs noted in Schedule A, Schedule A Dose Level 1 (eribulin 1.4 mg/m^2 D1 and D8 with irinotecan 40 mg/m^2 D1 – D5 of a 21- day cycle) was selected as the RP2D for the Phase 2 portion of this study.

As per Amendment 6, subjects aged >6 months and <12 months will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 D1 and D8) with the irinotecan dose maintained Dose Level 1 (40 mg/m^2 D1 – D5) of a 21- day cycle.

Criteria for Dosing Modifications

Dose reduction and interruption for eribulin mesilate and irinotecan hydrochloride-related toxicity will be performed according to the following instructions:

Treatment will not be administered if any of the following values are recorded (Table 1).

Table 1 Criteria for Administration of Study Medication

a): Do not administer Cycle 1 Day 1 treatment where:	
Absolute Neutrophil Count	$<1.0\times 10^9$/L or 1,000/mm^3
Platelets	$<100 \times 10^9$/L or 100,000/mm^3
Non-hematological toxicity	Any > Grade 2 except for inadequately treated nausea and/or vomiting.
Gastrointestinal toxicity	Bowel function deteriorated since pre-treatment/baseline and requires antidiarrheal medications for within 24 hours before the next chemotherapy administration.
b): Do not administer any Day 8 treatment where:	
Absolute Neutrophil Count	$<0.75 \times 10^9$/L or 750/mm^3
Platelets	$<75 \times 10^9$/L or 75,000/mm^3
Non-hematological toxicity	Any > Grade 2 except for inadequately treated nausea and/or vomiting.
Gastrointestinal toxicity	Bowel function deteriorated since pre-treatment/baseline and requires antidiarrheal medications for within 24 hours before the next administration of irinotecan hydrochloride.
c): Do not administer any subsequent Day 1 treatment where:	
Absolute Neutrophil Count	$<1.0 \times 10^9$/L or 1,000/mm^3
Platelets	$<75 \times 10^9$/L or 75,000/mm^3
Non-hematological toxicity	Any > Grade 2 except for inadequately treated nausea and/or vomiting.
Gastrointestinal toxicity	Bowel function deteriorated since pre-treatment/baseline and requires antidiarrheal medications for within 24 hours before the next chemotherapy administration.

If the dose cannot be administered as planned due to treatment-related toxicity, the dose should be delayed according to the following instructions.

Day 1 of each cycle: If treatment cannot be administered on Day 1, the dosing should be delayed until recovery to above these values (Tables 1a Cycle 1 & 1c subsequent cycles). The Day 1 dose will be

rescheduled for when the criteria for treatment administration are met. The dose level may have to be reduced following a dose delay in accordance to the instructions for dose reduction. (Table 2).

Day 8 of each cycle: If treatment cannot be administered on Day 8, the dosing should be delayed until recovery to above these values (Table 1) as follows:

Hematological toxicity:

- Subjects who have Grade 4 neutropenia or platelets <75,000/mm^3 on Day 8 will have their dose withheld. If the toxicity resolves to ANC ≥750/mm^3 and platelets ≥75,000/mm^3 (transfusion independent) by Day 11, the dose may be given. If the toxicity does not resolve to ANC ≥750/mm^3 and platelets ≥75,000/mm^3 by Day 11, the dose will be omitted and this will be considered a DLT. Subjects should receive subsequent cycles of drug but at the next lower dose level (Table 4). Subjects who require that their Day 8 dose be omitted for Grade 4 neutropenia or platelets <75,000 mm^3 after two dose reductions must be removed from protocol therapy.

- Subjects who meet hematological DLT criteria on Day 8 will have their Day 8 dose omitted. Subjects should receive subsequent cycles of drug but at the next lower dose level. Subjects who require that their Day 8 dose be omitted for hematologic DLT after two dose reductions must be removed from protocol therapy.

Non-hematological toxicity:

- Subjects who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug prior to the Day 8 dose (with the exception of the DLT exclusions) will be considered to have had a DLT. If the toxicity resolves to meet eligibility or ≤Grade 2 (if not part of eligibility criteria) by Day 8, the dose may be given but at the next lower dose level.

- Subjects who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug on Day 8 prior to dosing (with the exception of the DLT exclusions) will have their dose withheld and this will be considered a DLT. If the toxicity resolves to meet eligibility or ≤Grade 2 (if not part of eligibility criteria) by Day 11, the dose may be given but at the next lower dose level. If the toxicity does not resolve by Day 11, the dose will be omitted. Subjects should receive subsequent cycles of drug but with dose modifications (Table 4).

- For subjects <12 months any ≥Grade 2 non-hematological toxicity attributable to study drug prior to the Day 8 dose will have their dose omitted. Subjects should receive subsequent cycles of drug at the next lower dose level (Table 4).

- Subjects who have a dose-limiting hematological or non-hematological toxicity that does not resolve to meet eligibility or baseline parameters within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

For Schedule A, irinotecan doses Days 2-5 can be delayed up to cycle Day 10 (of a 21 day cycle), at the discretion of the investigator and as long as the subject meets the criteria for administration of study medication for Day 8 as detailed in Table 1. If the subject does not meet the Day 8 criteria for administration by cycle Day 10 then dosing should not occur until the next cycle and as long as the subject meets the subsequent Day 1 dosing criteria for administration (Table 1).

Please note, use of hematopoietic growth factor support is not permitted in Cycle 1 and is only permitted in subsequent cycles as per institutional guidelines. Subjects known to have reduced UGT1A1 activity will be monitored carefully for hematological toxicity.

The treatment will be permanently reduced to the next lowest dose level (Table 4) after the occurrence of the following events.

Table 2 Criteria for Reduction of Study Medication to the Next Lowest Dose Level

Absolute Neutrophil Count	Grade 4 neutropenia >7 days. Grade 3 or 4 febrile neutropenia and/or infection requiring treatment with antibiotics and/or growth factors.
Platelets	Grade 4 thrombocytopenia. Grade 3 thrombocytopenia requiring platelet or blood transfusion or both.
Non-hematological toxicity	Grade 3 or 4 non-hematological toxicities (attributable to study drug); except Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia that respond to supplementation. For subjects <12 months (at the time of DLT), any ≥Grade 2 non-hematological toxicity attributable to study drug prior to the Day 8 dose will have their dose omitted and this will be considered a DLT. Subjects should receive subsequent cycles of drug but with dose modifications as per Table 10.
Gastrointestinal toxicity	≥Grade 3 or intolerable Grade 2 diarrhea. For subjects on dose levels 0 and -1 dose reductions of 20% of the current irinotecan dose should be made. If there are 2 or more diarrhea DLTs on these dose levels, the irinotecan dose levels will be re-evaluated by the Sponsor, and an appropriate lower dose level will be agreed with the investigator. If the diarrhea toxicity does not recover following a dose reduction of 20% (of dose level 0 or -1), treatment should be discontinued.

If hematological or non-hematological toxicities do not recover following a dose reduction to dose level -1 (dose-level -2 for subjects <12 months) and the use of hematopoietic growth factors, for hematological toxicities, the subject will discontinue treatment (except for cases of irinotecan related diarrhea, see Table 2).

However, if the subject is deemed to have clinical benefit, continuation of treatment may be discussed with the sponsor.

If, in the opinion of the investigator, a dose reduction as per the criteria noted in Table 2 is not necessary, due to adequate supportive care and use of prophylaxis (eg, growth factor support) to prevent recurrences, each individual case should be discussed with and agreed by the Sponsor.

To ensure safety for subjects, the study drug must be discontinued in the cases outlined in the table below:

Table 3 Criteria for Discontinuation of Study Medication

ALT >3 × ULN and total bilirubin >2 × ULN
ALT >8 × ULN at any time, regardless of total bilirubin or accompanying symptoms
ALT >5 × ULN for 2 or more weeks, regardless of total bilirubin or accompanying symptoms
ALT >3 × ULN, accompanied by symptoms consistent with hepatic injury (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash). Clinical judgement should be used based on the combination of the laboratory LFT results and clinical symptoms. Additionally, in subjects with liver metastases with pre-existing ALT>3 x ULN at study baseline, any additional increase in ALT values from baseline and clinical symptoms consistent with a syndrome of hepatic injury as described above should be considered for further assessment and drug discontinuation. Clinical symptoms alone consistent with deterioration of liver function should lead to additional laboratory assessments and evaluation of potential study drug related liver toxicity.

Instructions for QTc prolongation on electrocardiogram (ECG):

Increase the frequency of ECG and electrolyte monitoring in subjects who: develop Grade 2 QTc prolongation, are receiving agents that are known to prolong QTc interval or have clinically relevant electrolyte abnormalities.

Permanently discontinue study treatment in subjects who develop ≥ Grade 3 QTc prolongation, and monitor ECGs and electrolytes more frequently in consultation with cardiologist advice and in line with local practice until the QTc interval returns to baseline.

Table 4 Study Medication Dose Levels by Schedule for Phase 1

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		
-1	1.1	100
0	1.4	100
1	1.4	125

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

Do not re-escalate dose level after the dose level has been reduced.

Phase 2

Following protocol amendment #5, Schedule A Dose Level 1 (eribulin 1.4 mg/m^2 D1 and D8 with irinotecan 40 mg/m^2 D1 – D5 of a 21- day cycle) was selected as the RP2D for the Phase 2 portion of this study for subjects ≥ 12 months of age.

As per Amendment 6, subjects > 6 months and < 12 months of age should receive Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 D1 and D8) with the irinotecan dose maintained (Dose Level 1, 40 mg/m^2 D1 – D5) of a 21-day cycle.

The dose levels as per Table 5 should be used in the Phase 2 portion of the study when following the criteria for dose reductions (Table 2), the agent most likely to be the cause of toxicity (eg, irinotecan for diarrhea, eribulin for neuropathy or neutropenia) should be reduced by one dose level if these criteria are met. If in the investigator's opinion both agents should be reduced this may be permitted after discussion with the Sponsor.

Table 5 Schedule A Dose Levels for Phase 2

Dose Level	Eribulin mesilate (mg/m^2)
Eribulin – Days 1 & 8	
-4	0.4
-3	0.6
-2**	**0.8**
-1	1.1
1*	**1.4**
Irinotecan hydrochloride (mg/m^2) – Days 1-5	
-2	20
-1	30
1*	**40**

For subjects ≥12 months to < 25 years of age:

*Dose level 1 eribulin (1.4 mg/m^2 Days 1 and 8) and irinotecan (40 mg/m^2 Days 1 – 5).

For subjects >6 to <12 months of age:

**Dose level -2 for eribulin (0.8 mg/m^2 Days 1 and 8) and Dose level 1(40 mg/m^2 Days 1 – 5) for irinotecan is maintained.

Do not re-escalate dose level after the dose level has been reduced. If toxicities do not recover after two dose reductions, treatment with that agent must be discontinued.

Duration of Treatment

Subjects benefiting from study treatment in the opinion of the investigator will continue to receive treatment, until disease progression (according to RECIST 1.1), intolerable toxicity, subject

noncompliance with safety or efficacy assessments, initiation of another anticancer therapy, voluntary discontinuation by the subject at any time, or study termination by the sponsor, whichever occurs first.

As long as the subject is still receiving clinical benefit and has not experienced intolerable toxicity, he or she can continue to receive study treatment for up to 1 year, from start of study treatment after which any continued treatment would need to be discussed with the Sponsor.

An Off-Treatment Visit will be performed within 28 days from last date of receiving study drug for subjects who discontinue study treatment. 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.

Concomitant Drug/Therapy

Supportive care will be allowed as per institutional guidelines. Growth factors that support platelet or white blood cell number or function can only be administered in accordance with dose modification guidelines (prophylactic granulocyte colony-stimulating factor should NOT be administered during Cycle 1) or for culture proven bacteremia or invasive fungal infection.

Use of prophylactic antidiarrheal medication prior to dosing to ameliorate irinotecan hydrochloride-associated diarrhea is allowed as per institutional guidelines (Benson, et al., 2004).

Subjects should not receive any other anticancer therapy (including chemotherapy, radiation therapy, cancer immunotherapy or targeted therapy) or investigational agents while receiving study drug. If these therapies are administered, the subject will be discontinued from the study.

Assessments

Efficacy Assessments

Tumor response and progression will be evaluated according to RECIST 1.1 criteria. Tumor assessments will be performed every 6 weeks until Week 12 and every 9 weeks thereafter on a fixed schedule. For Phase 2, copies of scans for tumor assessments will be sent to an imaging core laboratory designated by the sponsor for quality assessment and archival and potential independent review. Computed tomography (CT) scans (with oral and intravenous contrast, unless clinically contraindicated) of chest, abdomen, and pelvis and other known sites of disease will be obtained at pre-study (within 28 days prior to Cycle 1 Day 1), and every 6 weeks thereafter (counting from C1D1), irrespective of dose delays. Magnetic resonance imaging (MRI) scans may be used instead of CT scans for abdomen and pelvis; however, chest must be assessed using CT. If only chest CT is performed, then oral CT contrast is not required. The same method of assessment must be used at all time-points as used at pre-study. However, a chest x-ray may be used to identify new lesions in lieu of chest CT where appropriate (and after initial chest CT at screening).

An exception to the requirement for following chest disease by CT will be allowed where subjects have either non-parenchymal tumors, mediastinal and/or chest wall lesions. These may be assessed (at Screening and post-baseline) using contrast-enhanced MRI. However, a chest CT is required at Screening for all subjects, and lung parenchymal lesions should be followed using CT (as per standard practice). If there is either an equivocal new lung lesion based on MRI or symptoms suggesting a new lesion, these should also be confirmed with chest x-ray or CT.

After 12 weeks, subjects with CR, PR or stable disease (SD) may have imaging frequency decreased to every 9 weeks.

A bone scan (technetium-^{99}m [Tc]-based scintigraphy, whole body bone MRI. ^{18}F-sodium fluoride positron emission tomography [NaF PET]), or ^{18}FDG-PET will be performed at screening, approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Bone lesions must be followed with anatomic imaging.

Subjects with neuroblastoma (which can be included in phase 1 only) may have meta-iodobenzulguanidine (MIBG) scintigraphy and bilateral bone marrow biopsies assessments performed at sites where this is standard practice, at the discretion of the treating physician. This is an optional assessment for neuroblastoma subjects. Subjects that have positive lesions by MIBG scan at screening (within 28 days prior to administration of study drug) are not required to undergo PET or technetium-^{99}m bone scans. After identifying positive lesions at screening, repeat measurements may be performed within 4 weeks after confirmation of a PR or CR or as clinically indicated. Subjects with positive urinary catecholamines at baseline, should be assessed in cases of CR (catecholamines should be negative to confirm CR). Subjects with MIBG positive lesions at screening will be evaluable for MIBG response using the revised version of the International Neuroblastoma Response Criteria (INRC) scoring (Brodeur GM, et al., 1993).

A brain scan (CT with contrast or MRI [pre- and post-gadolinium]) will be performed as clinically indicated to assess potential for CNS disease and/or metastases. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at Screening and at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm CR within 1 week following response confirmation, or if clinically indicated.

All responses must be confirmed no less than 28 days following the initial assessment of response. In order for stable disease (SD) to be considered the best overall response, it must occur ≥5 weeks following the first dose of study drug.

All subjects will have an Off-Treatment Visit within 28 days after the last dose of study medication. Subjects that discontinue treatment 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 the study is terminated. Follow-up data will be required unless consent is withdrawn.

After data cut-off for the primary analysis, tumor assessments may be performed as clinically indicated using the investigator's discretion, following the prevailing local standard of care.

Pharmacokinetic Assessments

Blood samples (2 mL per sample) will be collected for PK analysis of both irinotecan and its metabolite (SN-38), and eribulin as follows:

Phase 1 (Cycle 1):

<u>Subjects ≥12 months of age and >10 kg:</u>

- 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 the 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 the irinotecan infusion and PK blood sample draw.

Phase 2 (Cycle 1):

Eribulin assay only: Cycle 1, Day 1 (at the end of the 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). Subjects who weigh under 6 kg will not have PK samples taken.

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs (as per CTCAE v5.0 for both increasing and decreasing severity) and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; periodic measurement of vital signs and the performance of physical examinations.

Other Assessments

ECG monitoring to evaluate RR, PR, QRS, and QT intervals (QTc B or F) and QTc interval at pre study, during Cycle 1 (pre- and post-infusion Day 1 and Day 8) and as clinically indicated during subsequent cycles and during Off Treatment Visit (28 days after the last dose of drug).

Pharmacodynamic, Pharmacogenomic, and other Biomarker Assessments

Not applicable.

Bioanalytical Methods

Eribulin, irinotecan and its active metabolite, SN-38 will be analyzed using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods.

Statistical Methods

Primary Endpoints

- Phase 1: The MTD/RP2D of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects with relapsed/refractory solid tumors, excluding CNS tumors
- 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 review.

Secondary Endpoints

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 review, 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 >11 weeks)

Subjects aged >6 to <12 months and subjects ≥18 to ≤25 years will be included for descriptive purposes only and will not contribute to the full sample size analyses for this study. As subjects in the age group > 6 months to <12 months will receive approximately 75% of the RP2D of eribulin (rationale for lower dose is provided in Section 9.4.4 of the protocol) and the EMA PDCO requested that subjects in the age group ≥18 to ≤25 years old should not be included in the full sample size analyses.

Analysis Sets

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 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. The DES will be used for evaluation of each dose level for dose-escalation.

Dose escalation (Phase 1)

The number of subjects with DLTs will be summarized for each dose level in each schedule being evaluated. The incidence of adverse events will also be summarized for each dose level, by preferred term and body system. Laboratory data and other safety assessments, such as vital signs, ECG, will be summarized for each dose level.

Primary Efficacy Analysis (Phase 2)

Efficacy analyses will be performed on the FAS. Antitumor activity of eribulin mesilate in combination with irinotecan hydrochloride will be assessed by ORR, defined as the proportion of subjects with best response designation of CR or PR as per RECIST 1.1, during treatment, divided by the number of subjects in the FAS.

ORR will be estimated and summarized for each histology type. A Simon 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: $p \leq 30\%$ Vs 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 (investigator assessed responses). If there are 2 or less responders 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 the second stage up to approximately 25 subjects. If there are 12 or more responders out of 25 subjects, the null hypothesis will be rejected. Collect and hold of tumor scans will enable a possibility to confirm responses in case independent review is required.

In addition, ORR along with respective confidence interval will also be provided by histology. Duration of response (DOR) will be calculated for responders and summarized descriptively. DOR is 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).

Secondary Efficacy Analyses

PFS will be analyzed by Kaplan-Meier methodology and median PFS with 90% confidence interval will be presented.

Clinical benefit rate, defined as the proportion of subjects with best overall response (BOR) of CR, PR or durable SD based on RECIST 1.1, will be summarized descriptively. Durable SD is defined as SD with duration of more than 11 weeks.

Pharmacokinetic Analyses

Plasma concentrations of eribulin, irinotecan and its active metabolite SN-38 will be tabulated and summarized by dose level, day and time. In Phase 1, 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). The Phase 2 PK data will be assessed using a PopPK approach, with the addition of Phase 1 data.

In Phase 1 the PK of both drugs (eribulin and irinotecan) will be assessed on C1D1 and in Phase 2 eribulin will be assessed on C1D1 and C1D8.

Pharmacokinetic and Pharmacodynamic Analyses

Exploratory/graphical analysis will be conducted for PK/ pharmacodynamic (PD) 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. In addition the effects of eribulin mesylate administration on absolute neutrophil count (ANC) may be evaluated using a semi-physiological model for hematological toxicity. Further details will be documented separately in a population analysis plan (PAP).

Safety Analyses

The primary endpoint for Phase 1, ie, the incidence of DLTs during Cycle 1 will be summarized by dose cohort for the DES using frequency and percentage.

Additionally, toxicity in Phase 2 for the Safety Analysis Set will be monitored on an ongoing basis. If the number of AEs that would have qualified as DLTs on the Phase 1 portion exceeds 1/3, a meeting

with the investigators will be convened to determine if the dose should be lowered. The rule of one-third (1/3) will be applied to the number of subjects in an increment of 3 subjects at the same dose level (eg, 3, 6, 9 subjects). Likewise, if ongoing moderate toxicities develop into "intolerable Grade 2" events, the recommended Phase 2 dose may also be re-evaluated in consultation with the protocol investigators.

All evaluation of safety other than the Phase 1 primary objective in DLT evaluation will be performed on the Safety Analysis Set. Safety data that will be evaluated include adverse events, clinical laboratory results, physical examination results, ECG, and vital signs.

Safety analyses will be performed on all subjects who received at least 1 dose of study drug. It will include safety data collected from screening to data cutoff and the incidence and severity of AEs, clinical laboratory test results, physical examination findings, ECG readings, and vital signs measurements.

Vital signs, resting 12-lead ECGs, hematology, clinical chemistry and urinalysis data will be listed. Descriptive summary statistics (mean, standard deviation, median, minimum and maximum) of clinical laboratory test results, vital signs measurements, ECG parameters, and changes from Baseline will be presented by cohort and overall.

All AEs and SAEs will be listed. Treatment-emergent AEs, treatment-related TEAEs, and SAEs will be summarized by cohort, system organ class, and preferred term and CTCAE v5.0 grade. QT intervals will be measured from Lead II and will be corrected for heart rate (QTc) using Fridericia's (QTcF) correction factor. The primary QTc parameter will be QTcF. Secondary parameters will be QTcB, QT, QRS, and heart rate.

Interim Analyses

There will be an interim analysis to define MTD and RP2D prior to initiating Phase 2 of the study. 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 during the futility analysis (eg, from when the 9th subject is enrolled up until 24 weeks, or until 3 responses have been achieved). An assessment of tolerability will also be conducted at this time.

Sample Size Rationale

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).

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

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

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, approximately 16 additional subjects will be enrolled in the second stage for a total of approximately 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 power of 80% when the true response rate is 55%. Note:

Subjects aged >6 to <12 months and subjects ≥18 to ≤25 years will be included for descriptive purposes only and will not contribute to the full sample size analyses for this study.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BOR	best overall response
CBR	clinical benefit rate
CNS	central nervous system
COG	Children's Oncology Group
CR	complete response
CRA	clinical research associate
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
DES	Dose Evaluable Set
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
EWS	Ewing sarcoma
FAS	Full Analysis Set
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GVHD	graft versus host disease
Hb	hemoglobin
HR	hazard ratio
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
LC-MS/MS	liquid chromatography with tandem mass spectrometry

Abbreviation	Term
LSLV	last subject last visit
MIBG	meta-iodobenzulguanidine
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NRSTS	non-rhabdomyosarcoma soft tissue sarcoma
ORR	objective response rate
PAS	Pharmacokinetic Analysis Set
PD	pharmacodynamic
PET	positron emission tomography
PFR	progression-free rate
PFS	progression-free survival
PK	pharmacokinetic
PPTP	Pediatric Preclinical Testing Program
PR	partial response
RMS	rhabdomyosarcoma
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	Summary of Product Characteristics
STS	soft tissue sarcoma
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAC	vinca alkaloid with actinomycin-D and cyclophosphamide
XRT	radiotherapy

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations (eg, Federal Regulations, Title 21 CFR Part 56). Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in CRA[s], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

The definition for end of the study, as required by certain regulatory agencies, is the time of last subject/last visit. It is estimated that the study duration will be 42 months and will end in Sept 2021.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products,

International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject and/or the subject's parents or guardian the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Assent, when appropriate, will be obtained according to institutional guidelines. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject and/or the subject's parents or guardian should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read and/or the subject's parents or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject and/or the subject's parents or guardian, and after the subject and/or the subject's parents or guardian has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (eg, Federal Regulations, Title 21 CFR Part 50). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject and/or the subject's parents or guardian should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to 50 investigational sites.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 Childhood Soft Tissue Sarcoma

Sarcomas represent about 6% of all malignancies in children and adolescents, and 1% in adults, with an annual incidence of 10 in 1 million children under the age of 15 years and 2 to 3 per 100,000 in adults (German Childhood Cancer Registry, 2010; Storm, 1998). The incidence of sarcomas increased by almost 2% per year in children during 1988 to 1997, mainly due to an increase in urogenital rhabodomyosarcoma (RMS) (Pastore, et al., 2006). Although the incidence of sarcoma increases with age, sarcoma makes up a larger proportion of all cancers in children (Gurney, et al., 1999). The most common histological type in childhood is rhabdomyosarcoma (RMS), which accounts for approximately 39% of all cases of STS.

Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) is a heterogeneous group of tumors derived from mesenchymal tissue. NRSTS is discussed as a unique group due to the rarity of each histopathological subtype, and accounts for about 3% to 5% of all childhood malignancies. Although NRSTS can occur at any age group, the disease more commonly occurs in children above the age of 5 years. Certain subtypes, such as synovial sarcoma and alveolar soft part sarcoma, straddle both age groups (Ferrari, et al., 2011). Fibrosarcoma, malignant peripheral nerve sheath tumor, and other fibromatous neoplasms account for 10% to 20% of childhood STS.

"Other specified" STS is a heterogeneous subgroup accounting for approximately 25% of cases with the most frequently reported histological types including synovial sarcoma and leiomyosarcoma (LMS), whereas the 'unspecified' STSs account for approximately 10% of the total number of STS cases (Stiller, et al., 2001).

7.1.1 Current Therapeutic Options

The aim of treatment of sarcoma in all age groups is broadly similar, with the goal of primary treatment being complete surgical excision (Table 6). If surgery is not feasible, then radiotherapy should be considered. In RMS, multi-agent chemotherapy should be administered as part of primary treatment, either in the adjuvant or neoadjuvant setting (Van Gaal, et al., 2012). However, the role of adjuvant or neoadjuvant chemotherapy in the primary treatment of NRSTS has not been established by randomized trials.

Treatments for relapsed/refractory disease are broadly similar across the tumor types (Table 6). Further information on treatment options for each tumor types is provided below.

Table 6 Principles of RMS, NRSTS and EWS Treatment

Treatment	RMS	EWS	NRSTS
Primary	Surgical excision (where feasible) Definitive radiotherapy if wide excision not possible Multi-agent neo/adjuvant chemotherapy (all patients)	Surgical excision (where feasible) Definitive radiotherapy if wide excision not possible Multi-agent neo/adjuvant chemotherapy (all patients)	Surgical excision (where feasible) Radiotherapy (residual or high-risk disease or inoperable) ± Adjuvant chemotherapy (role not established)
First Relapse	Multi-agent chemotherapy	Multi-agent chemotherapy	Single-agent or combination chemotherapy
≥Second Relapse	Investigational treatments	Investigational treatments	Investigational treatments

EWS = Ewing sarcoma, NRSTS = non-rhabdomyosarcoma soft tissue sarcoma, RMS = rhabdomyosarcoma.

Source: National Cancer Institute, 2016. Childhood Soft Tissue Sarcoma Treatment-for Health Professionals PDQ®. Retrieved Feb 2016, from http://www.cancer.gov/publications/pdq/information-summaries

7.1.1.1 Treatment for Rhabdomyosarcoma

Patients with RMS who relapse after initial treatment, or who experience progressive disease while on treatment, have a poor prognosis. The 5-year survival rate for these patients varies between 17% and 24%, and is only 5% in patients with alveolar RMS (Pappo, et al., 1999; Dantonello, et al., 2009). Standard treatment for patients following relapse is suboptimal and no standard regimen has been identified. Local therapy (surgery and/or radiotherapy) should be considered where feasible.

Treatment selection for patients with relapsed or progressive RMS depends on the site(s) of recurrence, prior chemotherapy, and individual patient factors. Treatment for local or regional recurrence may include wide local excision, surgical removal of tumor, metastatectomy for isolated pulmonary metastasis, or radiotherapy. The gold standard first-line chemotherapy treatment for RMS is a vinca alkaloid with actinomycin-D and cyclophosphamide (VAC). The standard approach at first relapse is combination chemotherapy, not previously used in the treatment of the patient's sarcoma. The following are treatment options for relapsed, progressive, or recurrent RMS (Saylors, et al., 2001; Mascarenhas, et al., 2010):

- Etoposide-containing regimens: ifosfamide and etoposide, or ifosfamide, carboplatin, and etoposide.
- Cyclophosphamide-containing regimens: cyclophosphamide and topotecan, or vinorelbine and cyclophosphamide.
- Topoisomerase inhibitor-containing regimens: irinotecan with vincristine, or temozolomide, topotecan, vincristine, and doxorubicin.

Several factors can adversely influence the possibility of cure with further treatment after the first relapse: presence of metastatic disease, prior use of radiotherapy and chemotherapy containing alkylating agents, large size and unfavorable site of the tumor, nodal involvement at initial diagnosis, alveolar histology, and short time to relapse (Chisholm, et al., 2011). The presence of metastatic disease is the strongest predictor of adverse clinical outcome in patients with RMS. Despite aggressive multimodality treatments, these children fare poorly; only 25% are expected to be free of disease 3 years after diagnosis (Maurer, et al., 1993; Crist, et al., 2001).

Following the second relapse, there is no evidence-based standard therapy in this setting and the goal of treatment is usually no longer of curative intent. The choice of agent(s) is based upon the treatment options available at the institution including access to clinical trials, individual patient/tumor factors (eg, extent of disease, comorbidities, intensity of prior treatment, age) and patient/parent choice.

The evaluation of new agents in development is therefore particularly relevant in this setting. The approach of studying single agent investigational agents in the relapsed setting has been followed for targeted agents (eg, bortezomib and pazopanib) and new chemotherapeutic agents (eg, ixabepilone, irinotecan, vinorelbine, and temozolomide).

7.1.1.2 Treatment Strategies for Non-Rhabdomyosarcoma Soft Tissue Sarcoma

The prognosis for children with metastatic NRSTS is poor. Decisions about treatment options are based on site of recurrence, tumor biologic characteristics, prior therapies and individual patient considerations.

Standard treatment options for metastatic childhood STS include multimodality therapy with chemotherapy, radiotherapy, and surgical resection of pulmonary metastases. Only 3 prospective multi-institutional clinical trials for NRSTS have been conducted, with fewer than 200 subjects enrolled. Thus, the approach to the treatment of NRSTS in children depends largely on the experience in adults with STS (Meyer and Spunt, 2004). The treatment paradigms in adults tend to include an anthracycline in first-line with or without ifosfamide, followed by gemcitabine and docetaxel or trabectedin as second-line therapy. Several combination regimens have undergone clinical evaluation in subjects with unresectable or metastatic disease, but none of these regimens improved the outcome for these subjects.

7.1.1.3 Treatment Strategies for Ewing Sarcoma

Standard first-line treatment for patients with metastatic EWS is induction VIDE (Vincristine, ifosfamide, Doxorubicin, Etoposide) followed either by maintenance VAC or VAI. In patients who relapse after initial therapy the disease is almost universally fatal. Salvage therapies include ifosfamide and etoposide, cyclophosphamide and topotecan, and temozolomide and irinotecan, or investigational therapies. Although the sarcoma can respond to these combinations, all responses are partial and tend to be of short duration.

The addition of ifosfamide and etoposide or dose intensification has failed to improve outcomes in patients with metastatic disease. Patients with lung only metastases seem to have a better prognosis than patients with bone metastases. Up to 20% of patients will have long term remissions with chemotherapy and local treatment, but those results have not improved in the past 20 years.

There is no standard therapy for third line treatment of EWS, and investigational therapies are recommended. There is no targeted therapy approved for EWS. Several years ago there was enthusiasm for Insulin-like growth factor (IGFR) inhibitors after several anecdotal responses were observed in early phase trials. Confirmatory Phase 2 trials demonstrated a response rate of only 8% (Balamuth and Womer, 2010). The development of the IGF1R monoclonal antibody, Ganitumab, is ongoing (COG study AEWS1221).

7.1.2 Fulfillment of a Therapeutic Need

The backbone of the established gold standard treatment for RMS is a VAC. The activity of VAC in RMS has not been improved by regimens that alter this backbone. For NRSTS the standard treatment of doxorubicin with or without ifosfamide has not been improved upon for 20 years. For EWS the established standard of 5 drug regimen including vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide has marginally improved the outcomes for patients with localized disease but not for those with relapsed or metastatic disease. As a consequence, new alternatives to the available therapies for children who have failed standard treatments for advanced RMS, EWS, and NRSTS, are urgently needed.

7.1.3 E7389 (eribulin mesilate)

7.1.3.1 Mechanism of Action

Eribulin is a synthetic analogue of halichondrin B, a product isolated from the marine sponge *Halichondria okadai*. Eribulin is an inhibitor of microtubule dynamics with a unique microtubule binding site and different effects on microtubule dynamics compared with other marketed tubulin-targeting agents. Eribulin binds with high affinity to the plus ends of microtubules, where it suppresses the growth phase of microtubule dynamics without affecting the corresponding shortening phase (Jordan, et al., 2005; Smith, et al., 2010). Vinca alkaloids (eg, vinblastine) also bind to the plus ends of the microtubule and, with lower affinity, along the sides of the microtubule, whereas taxanes (eg, paclitaxel and docetaxel) and epothilones (eg, ixabepilone) bind to β-tubulin subunits inside the microtubule (Jordan and Wilson, 2004). In addition to directly suppressing microtubule growth, eribulin mesilate induces formation of nonproductive tubulin aggregates, lowering concentrations of free tubulin available for polymerization and thus further inhibiting microtubule growth. It is not known whether these differences will offer a potential advantage in terms of safety or efficacy in comparison to existing microtubule inhibitors used for treating pediatric cancers. The tubulin-targeting agents paclitaxel and docetaxel have shown minimal activity in pediatric clinical trials, whereas the vinca alkaloids have an established role in the treatment of childhood RMS and EWS (Ferrari and Casanova, 2005). Due to some similarity with vinca alkaloid microtubule binding sites, eribulin may have a

broader spectrum of antitumor activity in childhood cancers than the taxanes, even in the presence of multidrug resistance (Cortes, et al., 2011).

7.1.3.2 Regulatory Status

Eribulin mesilate (E7389); HALAVEN is indicated in the EU for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease and for adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (Halaven Summary of Product Characteristics, 2016).

Eribulin has recently been approved by the FDA (28 Jan 2016) and the EMA (02 May 2016) for the treatment of unresectable/metastatic liposarcoma following the results of 'A randomized trial of eribulin versus dacarbazine in advanced leiomyosarcoma and liposarcoma'. Eribulin demonstrated an overall survival (OS) benefit over dacarbazine, hazard ratio (HR) 0.77 *P*=0.0169, with an OS of 13.5 months for subjects on the eribulin arm compared with 11.5 months for subjects on the dacarbazine arm (Schöffski, et al., 2016; Eisai Study, E7389-G000-309). In liposarcoma subjects specifically, eribulin demonstrated an OS benefit over dacarbazine, HR 0.51, with an OS of 15.6 months for subjects on the eribulin arm compared with 8.4 months for subjects on the dacarbazine arm.

7.1.3.3 Clinical Experience with Eribulin

7.1.3.3.1 ADULT POPULATION

A Phase 2 proof of concept study (Eisai Study E7389-E044-207, Study 207), a non-randomized, multicenter Phase 2 study in adults with intermediate or high grade advanced STS (Schöffski, et al., 2011), was conducted with a primary endpoint of progression-free rate at Week 12 ($PFR_{12weeks}$). This study reached statistical significance in the adipocytic (ADI) (46.9%, 95% two-sided confidence interval [CI]; 29.1, 65.3) and LMS (31.6%, 95% two-sided CI; 17.6, 48.7) strata. The study concluded that eribulin has activity in pretreated subjects with ADI sarcoma and leiomyosarcoma (LMS); however, outcomes in pretreated subjects with synovial sarcoma and other types of STS did not meet the pre-specified primary efficacy criteria for activity. The study yielded objective responses in 2 subjects with ADI sarcoma (n=32), with 1 subject experiencing a complete response (CR) and the other a partial response (PR).

Following the result of this proof of concept study (Study 207), a pivotal Phase 3 study (Eisai Study E7389-G000-309, Study 309) in adult ADI and LMS subtypes 'A randomized trial of eribulin versus dacarbazine in advanced leiomyosarcoma and liposarcoma' was conducted.

The primary endpoint was to evaluate the efficacy of eribulin compared with dacarbazine in terms of overall survival (OS). This study demonstrated that eribulin had an OS benefit over dacarbazine, Hazard Ratio (HR) 0.768, *P*=0.02 with an OS of 13.5 months for subjects on the eribulin arm compared with 11.5 months for subjects on the dacarbazine arm. There was no significant difference in progression-free survival (PFS) between the treatment arms in the overall population (Schöffski, et al., 2016).

Exploratory subgroup analyses of OS and PFS by histology showed that eribulin significantly favored subjects with the ADI (adipocytic, also known as liposarcoma) subtype. For OS, this yielded a HR of 0.51 (95% CI 0.35, 0.75), *P*=0.0006, with a median OS of 15.6 months for subjects on the eribulin arm compared with 8.4 months for subjects on the dacarbazine arm. The difference in PFS was also highly significant in subjects with the ADI subtype in favor of eribulin, with a HR of 0.52 (95% CI 0.35, 0.78), *P*=0.0015 and a median PFS of 2.9 months for subjects on the eribulin arm compared with 1.7 months for subjects on the dacarbazine arm. The OS (HR 0.90, 95% CI 0.69, 1.18) and PFS (1.05, 95% CI 0.81, 1.35) differences between the treatment arms in subjects with LMS histology did not reach statistical significance (HALAVEN USPI, 2015). This is the first time any agent has demonstrated improved OS in late line adult liposarcoma.

In addition to the pivotal study (Study 309) and following the results of Study 207, a Phase 2 study was also conducted in Japan (Eisai Study E7389-J081-217). This study evaluated the safety and efficacy of eribulin in previously treated Japanese subjects with advanced STS. The primary efficacy endpoint was $PFR_{12weeks}$. The results of this study demonstrated significant activity in the ADI and LMS subtypes. The PFR_{12wks} was 60.0% (95% CI: 42.1, 76.1) in the ADI or LMS stratum, 31.3% (95% CI: 11.0, 58.7) in the other (OTH) stratum, and 51.0% (95% CI: 36.6, 65.2) in total (Study E7389-J088-217 Clinical Study Report).

7.1.3.3.2 PEDIATRIC POPULATION

A Phase 1 study (Study E7389-A001-113) has been conducted by Eisai. This was an open label, multi-center, dose escalation study of eribulin mesilate in pediatric subjects with recurrent or refractory solid tumors (excluding CNS), including lymphomas. This study found that eribulin mesilate was well tolerated in this pediatric population and that the MTD/RP2D of eribulin mesilate in pediatric subjects was 1.4 mg/m^2 on Day 1 and Day 8 of a 21-Day cycle(same as the adult dose). The primary DLT was neutropenia. (Schafer, et al., 2018).

7.1.3.4 Non-Clinical Evidence for Activity of Eribulin in Pediatric Sarcomas

The potential antitumor activity of eribulin in human pediatric tumor models was evaluated in the NCI's Pediatric Preclinical Testing Program (PPTP; Study Nos. PPC-2-12-02N submitted to IND 067193, sequence 0636 and PPC-2013-01N submitted to IND 067193, sequence 0652). In the 24 cell line in vitro screening panel, eribulin demonstrated potent cytotoxic activity with a median relative half maximal inhibitory concentration value of 0.27 nM (range: < 0.1 to 14.8 nM). The panel included 4 RMS (RD, Rh18, Rh30, and Rh41) and 4 EWS cell lines. The in vitro pattern of activity for eribulin was somewhat similar to that previously described by the PPTP for vincristine (Kolb, et al., 2013).

In the PPTP's in vivo panel of 43 human pediatric tumor xenografts, eribulin induced significant differences in event-free survival (EFS) distribution compared with control in 29 of 35 (83%) of the evaluable solid tumor xenografts and in 8 of 8 (100%) of the evaluable acute lymphoblastic leukemia (ALL) xenografts. An objective response was observed in 18 of 35 (51%) solid tumor xenografts. Complete responses (CRs) or maintained CRs

(MCRs) were observed in 6 of 7 RMS xenograft models, 1 of 2 Wilms' tumors, 4 of 5 EWS, 2 of 4 glioblastoma, and 3 of 6 osteosarcoma xenografts. For the ALL panel, all 8 xenografts achieved CR or MCR (Kolb, et al., 2013).

The PPTP concluded that the high level of activity observed for eribulin against the PPTP preclinical models made eribulin an interesting agent to consider for pediatric evaluation. The activity pattern observed for eribulin in the solid tumor panels is comparable or superior to that observed previously for vincristine. Eribulin showed high activity against RMS, EWS, osteosarcoma, and ALL xenografts (Kolb, et al., 2013).

7.1.4 Irinotecan Hydrochloride

The activity of irinotecan in pediatric solid tumors has been investigated since shortly after its approval for colon cancer in 1996. Responses have been noted in RMS and Ewing's sarcoma. Although early trials showed single agent response rates as high as 38% (Bisogno, et al., 2006), larger trials have shown lower response rates, under 10% (Bomgaars, et al., 2007). Preclinical as well as clinical studies have demonstrated substantial improvement in activity when irinotecan is combined with other agents, such as the microtubule inhibitor vincristine, with one study (Pappo, et al., 2007) reporting a 70% response rate in RMS for the combination. This led to a Phase 3 trial comparing the outcomes of untreated RMS patients with vincristine, Actinomycin D and cyclophosphamide (VAC, the current standard of care) with VAC alternating with vincristine and irinotecan (VAC/VI). Results from this study showed that VAC/VI did not significantly improve OS or EFS compared with VAC (2-year EFS 64% in each group; 2-year OS 86% and 84% in VAC/VI and VAC groups, respectively; Hawkins, et al., 2014).

Various schedules of irinotecan have been investigated in pediatric patients, with every 3 week dosing and daily times 5 every 3 weeks, or daily times 5 for 2 weeks in a row, with a one week break. Anti-tumor activity is similar with different schedules, but toxicity profiles can be markedly different (Mascarenhas, et al., 2010); Less frequent dosing results in more hematologic toxicity and alopecia, whereas more frequent dosing results in more gastrointestinal toxicity, including diarrhea and less neutropenia. After up to a year of induction cytotoxic chemotherapy, pediatric patients tend to tolerate the daily dosing regimens better, and they have become standard salvage regimens for several pediatric tumors (Wagner, 2015).

7.2 Study Rationale

Anti-microtubule agents have shown moderate single agent activity against RMS both in the clinic and in the laboratory. This activity is significantly enhanced in combination regimens with alkylating agents (cyclophosphamide, ifosfamide) or camptothecins (irinotecan, topotecan). The hypothesis behind this trial is that substituting the antimicrotubule agent, eribulin, which is more potent in preclinical models, for vincristine as a combination partner with irinotecan will result in substantial efficacy against RMS, NRSTS and EWS. It should be possible to use a regimen of eribulin and irinotecan (ie, replace vincristine) considering that the primary toxicity profiles of each individual agent do not overlap the synergy

observed when irinotecan is combined with a microtubule inhibitor, and the activity observed for eribulin in the solid tumor panels of the PPTP (described above) is comparable or superior to that observed previously for vincristine.

8 STUDY OBJECTIVES

8.1 Primary Objectives

- 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 RMS, NRSTS, and EWS

8.2 Secondary Objectives

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 (Day 1 and 8) of eribulin mesilate in pediatric subjects

Phase 2:

- To assess the Progression Free Survival (PFS) of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects
- To assess the Clinical Benefit Rate (CBR) at 12 weeks of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects

Phases 1 & 2:

- To evaluate the pharmacokinetic profile of eribulin, irinotecan and its active metabolite and compare to appropriate historical data

8.3 Exploratory Objectives

Phases 1 & 2:

- 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

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E7389-G000-213 is a Phase 1/2, multicenter, open-label study to assess the safety and efficacy of eribulin mesilate in combination with irinotecan hydrochloride in pediatric subjects.

The study is divided into 2 Phases:

- **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.
- **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.

Phase 1

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) in pediatric subjects with relapsed/refractory solid tumors, excluding CNS.

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

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

And

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

Subjects will be allocated in an alternate fashion to either Schedule A or Schedule B by the Sponsor, ie every other subject will be allocated to Schedule A until an MTD is reached.

Subjects <12 months will be allocated to Schedule A only and at one dose-level behind subjects ≥12 months. These subjects are included for descriptive purposes only and will not contribute to the determination of the MTD/RP2D for this study.

Phase 2

Pediatric subjects with relapsed/refractory RMS, NRSTS or EWS will be enrolled on to either the RMS, NRSTS or EWS histology cohort, and the proportion of the responders ORR will be estimated at the RP2D determined in the Phase 1 portion of the study. As per protocol amendment #5, this is Schedule A Dose Level 1 eribulin (1.4 mg/m^2) Day 1 and Day 8 and irinotecan (40 mg/m^2) Days 1-5. Subjects will continue with their treatment until

progression of disease, intolerable toxicity or withdrawal of consent. As per Amendment 6, subjects aged >6 months and <12 months will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 Day 1 and Day 8) with the irinotecan dose maintained Dose Level 1 (40 mg/m^2 Day 1 – Day 5) of a 21-day cycle.

Each tumor histology type will have a futility analysis after 9 subjects are treated. Enrollment 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 responses are observed, enrollment to that histology type will close.

The study will enroll a minimum of 27 (ie, 9 for each negative histology type), and a total of approximately 75 (ie, approximately 25 for each positive histology type) subjects.

The end of the study will be the time of the last subject/last visit. However, subjects will continue to receive study treatment as long as they demonstrate clinical benefit.

An overview of the study design (Phase 2) is presented in Figure 1.

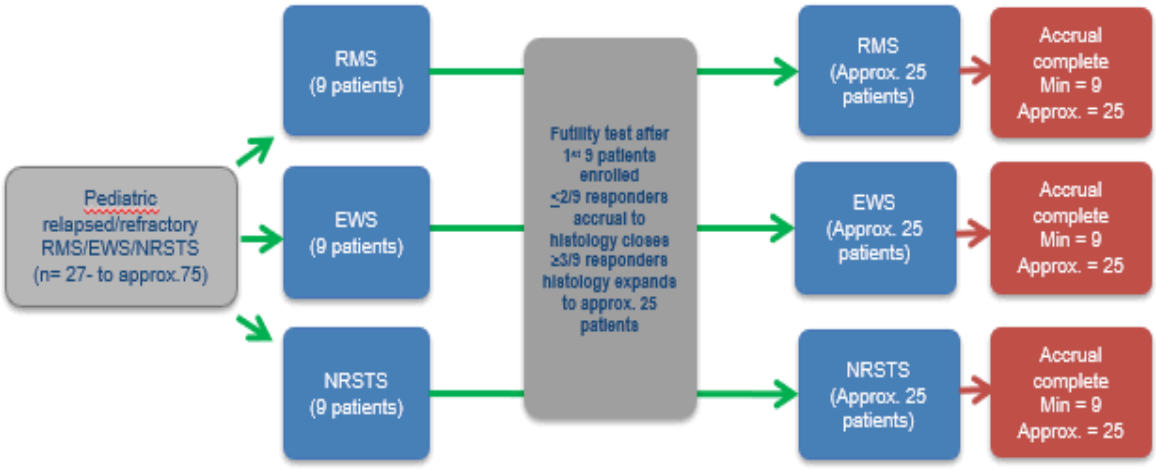


Figure 1 Study E7389-G000-213 Design: Phase 2

EWS = Ewing sarcoma, NRSTS = non-rhabdomyosarcoma soft tissue sarcoma, RMS = rhabdomyosarcoma

9.1.1 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, computed tomography (CT) / magnetic resonance imaging

(MRI) scans must be performed within 28 days prior to administration of study drug. All clinical and laboratory test results to determine eligibility must be performed within 7 days prior to administration of study drug, unless otherwise indicated.

9.1.1.1 Screening Period

Screening will occur between Day -28 and Day -1. The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent can be obtained from Day -29 after the study has been fully explained to each subject and/or the subject's parents or guardian, and before the conduct of any screening procedures or assessments. Assent, when appropriate, will be obtained according to institutional guidelines. Subjects must be willing to comply with all aspects of the protocol. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

The Screening Disposition case report form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.2 Treatment Phase

The Treatment Phase will commence from Day 1 (D1) of Cycle 1 (C1). In Phase 1 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:

- Days 1-5

or

- Days 1 and 8 of a 21 day cycle.

In Phase 2, the RP2D determined from Phase 1 (eribulin 1.4 mg/m^2 D1 and D8 with irinotecan 40 mg/m^2 D1 – D5 of a 21- day cycle) should be used.

The Schedule of Assessments should be followed for the subjects' visits and efforts should be made to conduct study visits on the scheduled day (+/- 3 days).

As long as the subject is still receiving clinical benefit and has not experienced intolerable toxicity, he or she can continue to receive study treatment for up to 1 year, from start of study treatment, after which any continued treatment would need to be discussed with the Sponsor.

9.1.3 Follow-Up Period

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 that discontinue treatment 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 the study is terminated. This follow-up data will be required unless consent is withdrawn.

9.2 Discussion of Study Design

Study E7389-G000-213 is to be conducted as a multicenter, single arm study evaluating the safety and efficacy of eribulin mesilate in combination with irinotecan in children with refractory or recurrent solid tumors.

This study will follow on from Study E7389-A001-113, which has the primary aim of establishing the Maximum Tolerated Dose (MTD)/Recommended Phase 2 dose (RP2D) of eribulin mesilate in pediatric subjects with relapsed/refractory solid tumors, excluding CNS.

The aim of study E7389-G000-213 is two-fold:

Phase 1: To determine the MTD/Recommended Phase 2 Dose (RP2D) and optimal schedule of eribulin mesilate in combination with weekly or 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 RMS, NRSTS and EWS.

The maximum number of subjects is approximately111: Up to 36 subjects in Phase 1 and approximately 75 subjects in Phase 2. The sample size does not include subjects <12 months.

In Phase 1, eribulin mesilate will be administered as an intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle at the dose determined by COG study ADVL1314 (Eisai Study E7389-A001-113), 1.4 mg/m^2, together with IV irinotecan hydrochloride administered in two different dose schedules:

Schedule A

- Irinotecan hydrochloride 20 mg/m^2 Days 1-5 of a 21-day cycle
- Irinotecan hydrochloride 40 mg/m^2 Days 1-5 of a 21-day cycle

Schedule B

- Irinotecan hydrochloride 100 mg/m^2 Day 1 and Day 8 of a 21-day cycle
- Irinotecan hydrochloride 125 mg/m^2 Day 1 and Day 8 of a 21-day cycle

These doses of irinotecan are derived from studies looking at the MTD of single agent irinotecan or irinotecan combinations administered at the various corresponding schedules (Blaney, et al., 2001; Vassal, et al., 2003; Casey, et al., 2009).

The rationale for the two different dose schedules of irinotecan is that the dose-limiting toxicity (DLT) of irinotecan is schedule–dependent. When given on a weekly or every 2 week or 3 week schedule, the DLT is typically neutropenia. When given on a more frequent schedule i.e. daily, the DLT tends to be gastrointestinal toxicity such as diarrhea. After induction therapy, which can last for up to 1 year, pediatric patients may have more sensitivity to agents with a hematologic toxicity, and alternate schedules of irinotecan have been developed in children with relapsed or refractory sarcoma. When combined with temozolomide, daily irinotecan (either 10 days every 3 weeks or 5 days every 3 weeks) has equivalent activity to single agent irinotecan but superior hematologic tolerance (Wagner, et al., 2004; Casey, et al., 2009).

The Phase 1 portion of this study will evaluate two schedules of irinotecan; weekly dosing (Schedule B), or daily dosing (Schedule A), in parallel to assess if there are major toxicity or efficacy differences between the two schedules of irinotecan when combined with standard weekly dosing of eribulin. Following Sponsor review of the safety and efficacy data from Phase 1 in conjunction with the study investigators, the dose and schedule that is the most appropriate will be used in Phase 2, to evaluate the efficacy of eribulin in combination with irinotecan in subjects with RMS, NRSTS and EWS.

As per protocol amendment #5, the data from the Phase 1 portion of this study showed that there was a tolerable safety profile in both schedules, with similar PK profiles; however, 2 PRs were noted in Schedule A, one of which was confirmed. Following discussions with the investigators and independent experts, based upon the similar toxicity and PK profiles and taking into account the 2 PRs noted in Schedule A, Schedule A Dose Level 1 (eribulin 1.4 mg/m^2 D1 and D8 with irinotecan 40 mg/m^2 D1 – D5 of a 21- day cycle) was selected as the RP2D for the Phase 2 portion of this study.

As per Amendment 6, subjects aged >6 months and <12 months will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 Day 1 and Day 8) with the irinotecan dose maintained Dose Level 1 (40 mg/m^2 Day 1 – Day 5) of a 21-day cycle.

9.3 Selection of Study Population

Up to 111 pediatric subjects (36 subjects in Phase 1 [the sample size does not include subjects of age <12 months] and approximately 75 subjects in Phase 2) will be enrolled into the study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to participate in the study.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Age:
   a. ≥12 months to ≤25 years old at the time of consent (no more than 25% of subjects between the ages of 18 and 25 years will be enrolled in this study).
   b. In Phase 1, >6 months and <12 months at the time of consent (Schedule A only) subjects will be enrolled one dose level behind the ≥12 months subjects in order to

maximize safety for infant subjects. In Phase 2, subjects aged >6 months and <12 months at the time of consent will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 D1 and D8) with the irinotecan dose maintained (Dose Level 1, 40 mg/m^2 D1 – D5) of a 21-day cycle in order to maximize safety for infant subjects.

2. Diagnosis:

   Phase 1: Histologically confirmed solid tumors, excluding CNS tumor, which is relapsed or refractory, and for which there are no currently available therapies.

   Phase 2: Histologically confirmed RMS, NRSTS or EWS which is relapsed or refractory having received at least 1 prior therapy, including primary treatment.

3. Disease status:

   Phase 1: Subjects must have either measurable or evaluable disease as per RECIST 1.1.

   Phase 2: Subjects must have measurable disease as per RECIST 1.1.

Measurable disease is defined as meeting the following criteria:

   a. At least 1 lesion of ≥1.0 cm in the longest diameter for a non-lymph node or ≥1.5 cm in the short-axis diameter for a lymph node that is serially measurable according to RECIST 1.1 using computed tomography/magnetic resonance imaging (CT/MRI).
   b. Lesions that have had radiotherapy must show subsequent radiographic evidence of increase in size by at least 20% to be deemed a target lesion.

4. Therapeutic options: Subject's current disease state must be one for which there is no known curative therapy.
5. Performance level: Performance score ≥50% Karnofsky (for subjects >16 years of age) or Lansky (for subjects ≤16 years of age). Subjects who are unable to walk because of paralysis and/or previous surgeries, but who are in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.
6. Subjects must have fully recovered from the acute toxic effects of all prior anticancer treatments prior to study drug administration:
   - Myelosuppressive chemotherapy: Must not have received within 21 days prior to study drug administration (42 days if prior nitrosourea).
   - Hematopoietic growth factors: Must not have received a long-acting growth factor (eg, Neulasta) within 14 days or a short-acting growth factor within 7 days. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the sponsor.
   - Targeted therapy (antineoplastic agent, eg, tyrosine kinase inhibitor): Must not have received an antineoplastic targeted therapy within 14 days. For agents that have known AEs occurring beyond 14 days after administration, this period must be extended beyond the time during which AEs are known to occur. The duration of this interval must be discussed with the sponsor.
   - Immunotherapy: Must not have received immunotherapy, eg, tumor vaccines, within 42 days.

- Monoclonal antibodies: Must not have received within at least 3 half-lives of the antibody after the last dose of a monoclonal antibody.
- Radiotherapy (XRT): Must not have received within 14 days prior to study drug administration (small field) or 42 days for craniospinal XRT, or if ≥50% radiation of pelvis.
- Autologous Stem cell infusion: At least 84 days must have elapsed after stem cell infusion prior to study drug administration.
- Allogeneic bone marrow transplant, including mini-transplant: No evidence of active Graft vs. Host disease and at least 100 days must have elapsed after transplant or stem cell infusion prior to study drug administration.

7. Adequate bone marrow function, defined as:
   - Peripheral absolute neutrophil count (ANC) $\geq 1 \times 10^9$/L.
   - Platelet count $\geq 100 \times 10^9$/L (transfusion independent, defined as not receiving platelet transfusions within a 7-day period prior to study drug administration).
   - Hemoglobin (Hb) at least 8.0 g/dL at baseline (blood transfusions are allowed during the screening period to correct Hb values less than 8.0 g/dL).

As blood transfusions are permitted to meet the hemoglobin criteria, subjects requiring transfusion must not be known to be refractory to red blood cell or platelet transfusions.

8. Adequate renal function, defined as:
   - A serum creatinine based on age/gender, derived from the Schwartz formula for estimating GFR (Schwartz and Gauthier, 1985), See table below.
   - Or serum creatinine clearance or GFR ≥50ml/min/1.73m^2, based on a 12 or 24h urine creatinine collection.

Age	Maximum Serum Creatinine (mg/dL)	
	Male	**Female**
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR (Schwartz, et al. J. Peds, 106:522,1985) utilizing child length and stature data published by the CDC.

9. Adequate liver function, defined as:
   - Bilirubin (sum of conjugated + unconjugated) ≤1.5 times the ULN for age.

- Alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN (in the case of liver metastases ≤5 × ULN), unless there are bone metastases, in which case liver-specific alkaline phosphatase must be separated from the total and used to assess the liver function instead of the total alkaline phosphatase.
- Serum albumin ≥2 g/dL.

10. Informed consent: All subjects and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines. Subjects must be willing to comply with all aspects of the protocol.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Pregnancy, breastfeeding, contraception: Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic [ß-hCG] (or human chorionic gonadotropin [hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß -hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

- Females of childbearing potential* who:
    - Do not agree to use a highly effective method of contraception for the entire study period and for 6 months after study drug discontinuation, ie:
        - Total abstinence (if it is their preferred and usual lifestyle)
        - An intrauterine device (IUD) or intrauterine system (IUS)
        - A contraceptive implant
        - an oral contraceptive**

    OR

    - Do not have a vasectomized partner with confirmed azoospermia.

    For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double barrier methods of contraception such as condoms plus diaphragm or cervical/vault cap with spermicide.

    *All post pubertal females will be considered to be of childbearing potential unless they have early menopause (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

    **Must be on a stable dose of the same oral hormonal contraceptive product for at least 4 weeks before dosing with study drug and for the duration of the study and for 6 months after study drug discontinuation.

Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 3 months after study drug discontinuation). No sperm donation is allowed during the study period or for 3 months after study drug discontinuation.

2. Concomitant Medications:
   - Corticosteroids: Subjects receiving corticosteroids who have not been on a stable dose for at least 7 days prior to study drug administration.
   - Anticancer agents: Subjects who are currently receiving other anticancer agents.
   - Anti-GVHD agents post-transplant: Subjects who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant.
   - Strong CYP3A4 inducers/inhibitors including traditional herbal medicinal products (eg, St. John's Wort). See Section 9.4.6.1, Drug-Drug Interactions.

3. Prior Therapies:
   - Phase 1: Received prior therapy with eribulin mesilate within 6 months prior to study drug administration.
   - Phase 2: Received prior therapies with eribulin mesilate or irinotecan hydrochloride (for prior irinotecan hydrochloride, subjects can be included if there was no tumor progression during irinotecan therapy).
4. Any other malignancy that required treatment (except for non-melanoma skin cancer, or histologically confirmed complete excision of carcinoma in situ), within 2 years prior to study drug administration.
5. Has hypersensitivity to either study drug or any of the excipients.
6. Has a known prior history* of viral hepatitis (B or C) as demonstrated by positive serology (presence of antigens) or have an uncontrolled infection requiring treatment (* Subjects with a known prior history of hepatitis B or C may be eligible pending agreement with the sponsor).
7. Has > Grade 1 peripheral sensory neuropathy or > Grade 1 peripheral motor neuropathy graded according to the Modified ("Balis") Pediatric Scale of Peripheral Neuropathies.
8. Has cardiac pathology, defined as:
   - Subjects with known congestive heart failure, symptomatic or LV ejection fraction <50% or shortening fraction <27% and subjects with congenital long QT syndrome, bradyarrhythmias, or QTc >480 msec on at least 2 separate ECGs.
9. Has CNS disease: Subjects with brain or subdural metastases are not eligible unless the metastases are asymptomatic and do not require treatment or have been adequately treated by local therapy (eg, surgery or radiotherapy) and have discontinued the use of corticosteroids for this indication for at least 28 days prior to study drug administration. Subjects must be clinically stable. It is not the intention of this protocol to treat subjects with active brain metastases.

Note: Screening CNS imaging for subjects with a known history of CNS disease is required.

10. Have had or are planning to have the following invasive procedures:
    - Major surgical procedure or significant traumatic injury within 28 days prior to study drug administration.
      - Central line placement or subcutaneous port placement is not considered major surgery
    - Laparoscopic procedure or open biopsy within 7 days prior to study drug administration.
    - Core biopsy, including bone marrow biopsy within 2 days prior to study drug administration.
    - Fine needle aspirate within 3 days prior to study drug administration.
11. Subjects with known human immunodeficiency virus (HIV); due to lack of available safety data for eribulin therapy in HIV infected patients.
12. Has any serious concomitant illness that in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (including active or severe chronic inflammatory bowel disease or bowel obstruction).
13. Has received a live-virus vaccination within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. After discontinuation from study treatment and completing 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. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. The Discontinuation From Treatment CRF page will be completed indicating the primary reason(s) for discontinuation. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing CRF page. Before a subject is withdrawn from study medication due to AE, the possibility of continuing on a single agent should be considered. In the event of an adverse event which leads to treatment interruption or delay of either study drug. The subject may continue treatment with the other study drug as long as there is a clinical benefit for up to 1 year, from start of study treatment, after which any continued treatment would need to be discussed with the Sponsor.

During the Follow-Up Period, subjects who have discontinued study treatment without objective disease progression should have tumor assessments performed according to the

Schedule of Assessments from the date of the last assessment until disease progression is documented or another anticancer therapy is initiated, whichever occurs first, unless the study is terminated or the subject withdraws consent for follow-up.

9.4 Treatments

9.4.1 Treatments Administered

Administration of eribulin mesilate by IV infusion on Days 1 and 8 of a 21-day cycle in combination with irinotecan hydrochloride administered by IV infusion on either Days 1-5 of a 21-day cycle (Schedule A), or Days 1 and 8 of a 21-day cycle (Schedule B).

Irinotecan will be administered first (on days where both treatments are due to be administered), as a 30-minute infusion, followed by eribulin as a 2-5 minute bolus infusion. Eribulin may be diluted in up to 100 mL 0.9% sodium chloride and administered as an IV infusion over 15 minutes (maximum infusion duration), where clinically appropriate.

As long as the subject is still receiving clinical benefit and has not experienced intolerable toxicity, he or she can continue to receive study treatment for up to 1 year, from start of study treatment, after which any continued treatment would need to be discussed with the Sponsor.

In the event of an adverse event which leads to treatment interruption or delay of either study drug, the subject may continue treatment with the other study drug, as long as there is a clinical benefit for up to 1 year, from start of study treatment after which any continued treatment would need to be discussed with the Sponsor.

Phase 1

The dosing schedules being evaluated for Phase 1 will be as follows:

Schedule A

Eribulin mesilate on Day 1 and Day 8 of a 21 day cycle (Starting dose determined by COG protocol ADVL1314/Eisai Study E7389-A001-113).

Irinotecan hydrochloride on Days 1-5 of a 21-Day cycle.

Dose Level	Eribulin mesilate (mg/m^2)	Irinotecan hydrochloride (mg/m^2)
-2	0.8	20
-1	1.1	20
0*	1.4	20
1	1.4	40

*Dose level 0 refers to the starting dose.

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

Schedule B

Eribulin mesilate and irinotecan hydrochloride on Day 1 and Day 8 of a 21-day cycle.

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.

Subjects will be allocated in an alternate fashion to either Schedule A or Schedule B, ie, every other subject will be allocated to Schedule A, by the Sponsor until an MTD is reached. If 1 schedule halts or pauses enrollment subjects will be enrolled on the other schedule provided it is open for accrual.

Subjects <12 months will be enrolled on to Schedule A only and at 1 dose level behind ≥12 months subjects in order to maximize safety for infant subjects. These subjects are included for descriptive purposes only and will not contribute to the determination of the MTD/RP2D for this study, or to the sample size.

Dose Escalation

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

For both schedules A and B, 3 subjects will be entered into each dose level. The first subject at each dose level must complete the Day 8 assessments before further subjects can be entered at the same dose level. All 3 subjects in the cohort will be followed for a full cycle before the next dose level opens. If 1 subject experiences a DLT, the cohort will need to be expanded to 6 subjects on the same dose level.

If no DLT is observed in a dose cohort, then the dose can be escalated and 3 subjects can be enrolled onto the next dose level. The MTD is defined as the highest dose level at which fewer than 1/3 of subjects experience a DLT during Cycle 1 of therapy.

If, at dose level 0, there are 2 or more subjects with a DLT out of 3 subjects (or 2 DLTs out of 6 subjects after expansion) in Cycle 1, the MTD will have been exceeded and the dose will be deescalated to dose level -1, and the next 3 subjects will be enrolled onto this lower dose level.

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.

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 ≥38.0°C)
5. Myelosuppression that causes a delay of >14 days between treatment cycles

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 3 infection,
- 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

Accrual will be suspended when a cohort of 3 has enrolled with pending toxicity data or when the MTD/RP2D for the combination has been met. If, following de-escalation from

dose level 0 (to dose level-1), 2 DLTs are observed, that dose and schedule will be declared too toxic for further evaluation. For subjects <12 months, if following de-escalation from dose level -1 (to dose level -2 on Schedule A), 2 DLTs are observed, that dose and schedule will be declared too toxic for further evaluation. Subjects <12 months are included for descriptive purposes only and will not contribute to the determination of the MTD/RP2D for this study. Up to 36 pediatric subjects (18 subjects per schedule) who meet all the inclusion criteria and none of the exclusion criteria, will be enrolled in Phase 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 9.4.4 for details on schedule selection).

If a large number of dose modifications are observed after completion of cycle 1 (eg, intolerable Grade 2 toxicities), the sponsor will discuss with investigators whether a lower dose level than the MTD should be carried forward as the RP2D for this study.

Criteria for Dosing Modifications

Dose reduction and interruption for eribulin mesilate and irinotecan hydrochloride-related toxicity will be performed according to the following instructions:

Treatment will not be administered if any of the following values are recorded (Table 7).

Table 7 Criteria for Administration of Study Medication

a): Do not administer Cycle 1 Day 1 treatment where:	
Absolute Neutrophil Count	$<1.0 \times 10^9$/L or 1,000/mm^3
Platelets	$<100 \times 10^9$/L or 100,000/mm^3
Non-hematological toxicity	Any >Grade 2 except for inadequately treated nausea and/or vomiting.
Gastrointestinal toxicity	Bowel function deteriorated since pre-treatment/baseline and requires antidiarrheal medications for within 24 hours before the next chemotherapy administration.
b): Do not administer any Day 8 treatment where:	
Absolute Neutrophil Count	$<0.75 \times 10^9$/L or 750/mm^3
Platelets	$<75 \times 10^9$/L or 75,000/mm^3
Non-hematological toxicity	Any >Grade 2 except for inadequately treated nausea and/or vomiting.
Gastrointestinal toxicity	Bowel function deteriorated since pre-treatment/baseline and requires antidiarrheal

	medications for within 24 hours before the next administration of irinotecan hydrochloride.
c): Do not administer any subsequent Day 1 treatment where:	
Absolute Neutrophil Count	<1.0 × 10^9/L or 1,000/mm^3
Platelets	<75 × 10^9/L or 75,000/mm^3
Non-hematological toxicity	Any >Grade 2 except for inadequately treated nausea and/or vomiting.
Gastrointestinal toxicity	Bowel function deteriorated since pre-treatment/baseline and requires antidiarrheal medications for within 24 hours before the next chemotherapy administration.

If the dose cannot be administered as planned due to treatment-related toxicity, the dose should be delayed according to the following instructions.

Day 1 of each cycle: If treatment cannot be administered on Day 1, the dosing should be delayed until recovery to above these values (Table 7a Cycle 1 & c subsequent cycles). The Day 1 dose will be rescheduled for when the criteria for treatment administration are met. The dose level may have to be reduced following a dose delay in accordance to the instructions for dose reduction (Table 8).

Day 8 of each cycle: If treatment cannot be administered on Day 8, the dosing should be delayed until recovery to above these values (Table 7b) as follows:

Hematological toxicity:

- Subjects who have Grade 4 neutropenia or platelets <75,000/mm^3 on Day 8 will have their dose withheld. If the toxicity resolves to ANC ≥750/mm^3 and platelets ≥75,000/mm^3 (transfusion independent) by Day 11, the dose may be given. If the toxicity does not resolve to ANC ≥750/mm^3 and platelets ≥75,000/mm^3 by Day 11, the dose will be omitted and this will be considered a DLT. Subjects should receive subsequent cycles of drug but at the next lower dose level (Table 10). Subjects who require that their Day 8 dose be omitted for Grade 4 neutropenia or platelets <75,000 mm^3 after two dose reductions must be removed from protocol therapy.

- Subjects who meet hematological DLT criteria on Day 8 will have their Day 8 dose omitted. Subjects should receive subsequent cycles of drug but at the next lower dose level. Subjects who require that their Day 8 dose be omitted for hematologic DLT after two dose reductions must be removed from protocol therapy.

Non-hematological toxicity:

- Subjects who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug prior to the Day 8 dose (with the exception of the DLT exclusions) will be

considered to have had a DLT. If the toxicity resolves to meet eligibility or ≤Grade 2 (if not part of eligibility criteria) by Day 8, the dose may be given but at the next lower dose level.

- Subjects who have Grade 3 or Grade 4 non-hematological toxicity attributable to the study drug on Day 8 prior to dosing (with the exception of the DLT exclusions) will have their dose withheld and this will be considered a DLT. If the toxicity resolves to meet eligibility or ≤Grade 2 (if not part of eligibility criteria) by Day 11, the dose may be given but at the next lower dose level. If the toxicity does not resolve by Day 11, the dose will be omitted. Subjects should receive subsequent cycles of drug but with dose modifications (Table 10).

- For subjects <12 months any ≥Grade 2 non-hematological toxicity attributable to study drug prior to the Day 8 dose will have their dose omitted. Subjects should receive subsequent cycles of drug at the next lower dose level (Table 10).

- Subjects who have a dose-limiting hematological or non-hematological toxicity that does not resolve to meet eligibility or baseline parameters within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

For Schedule A, irinotecan doses days 2-5 can be delayed up to cycle Day 10 (of a 21 day cycle), at the discretion of the Investigator and as long as the subject meets the criteria for administration of study medication for Day 8 as detailed in Table 7. If the subject does not meet the Day 8 criteria for administration by cycle Day 10 then dosing should not occur until the next cycle and as long as the subject meets the subsequent Day 1 dosing criteria for administration (Table 8).

Please note, use of hematopoietic growth factor support is not permitted in Cycle 1 and is only permitted in subsequent cycles as per institutional guidelines. Subjects known to have reduced UGT1A1 activity will be monitored carefully for hematological toxicity.

The treatment will be permanently reduced to the next lowest dose level (Table 10) after the occurrence of the following events

Table 8 Criteria for Reduction of Study Medication to the Next Lowest Dose Level

Absolute Neutrophil Count	Grade 4 neutropenia >7 days Grade 3 or 4 febrile neutropenia and/or infection requiring treatment with antibiotics and/or growth factors

Platelets	Grade 4 thrombocytopenia Grade 3 thrombocytopenia requiring platelet or blood transfusion or both
Non-hematological toxicity	Grade 3 or 4 toxicities (attributable to study drug); except Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia that respond to supplementation For subjects <12 months any ≥ Grade 2 non-hematological toxicity attributable to study drug prior to the Day 8 dose will have their dose omitted and this will be considered a DLT. Subjects should receive subsequent cycles of drug but with dose modifications as per Table 10
Gastrointestinal toxicity	≥ Grade 3 or intolerable Grade 2 diarrhea For subjects on dose levels 0 and -1 dose reductions of 20% of the current irinotecan dose should be made. If there are 2 or more diarrhea DLTs on these dose levels, the irinotecan dose levels will be re-evaluated by the Sponsor, and an appropriate lower dose level will be agreed with the investigator. If the diarrhea toxicity does not recover following a dose reduction of 20% (of dose level 0 or -1), treatment should be discontinued

If hematological or non-hematological toxicities do not recover following a dose reduction to dose level -1 (dose-level -2 for subjects <12 months) and the use of hematopoietic growth factors, for hematological toxicities, the subject will discontinue treatment (except for cases of irinotecan related diarrhea, see below). However, if the subject is deemed to have clinical benefit, continuation of treatment may be discussed with the sponsor.

To ensure safety for subjects, the study drug must be discontinued in the cases outlined in Table 9.

If, in the opinion of the Investigator, a dose reduction as per the criteria noted in Table 8 is not necessary, due to adequate supportive care and use of prophylaxis (eg, growth factor support) to prevent recurrences, each individual case should be discussed with and agreed by the Sponsor.

Table 9 Criteria for Discontinuation of Study Medication

ALT >3 × ULN and total bilirubin >2 × ULN

ALT >8 × ULN at any time, regardless of total bilirubin or accompanying symptoms
ALT >5 × ULN for 2 or more weeks, regardless of total bilirubin or accompanying symptoms
ALT >3 × ULN, accompanied by symptoms consistent with hepatic injury (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash). Clinical judgement should be used based on the combination of the laboratory LFT results and clinical symptoms. Additionally, in subjects with liver metastases with pre-existing ALT >3 x ULN at study baseline, any additional increase in ALT values from baseline and clinical symptoms consistent with a syndrome of hepatic injury as described above should be considered for further assessment and drug discontinuation. Clinical symptoms alone consistent with deterioration of liver function should lead to additional laboratory assessments and evaluation of potential study drug related liver toxicity.

Instructions for QTc prolongation on electrocardiogram (ECG):

Increase the frequency of ECG and electrolyte monitoring in subjects who: develop Grade 2 QTc prolongation, are receiving agents that are known to prolong QTc interval, or have clinically relevant electrolyte abnormalities. Permanently discontinue study treatment in subjects who develop ≥ Grade 3 QTc prolongation, and monitor ECGs and electrolytes more frequently in consultation with cardiologist advice and in line with local practice until the QTc interval returns to baseline.

Table 10 Study Medication Dose Levels by Schedule for Phase 1

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		
-1	1.1	100
0	1.4	100
1	1.4	125

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

Do not re-escalate dose level after the dose level has been reduced.

Phase 2

As per protocol amendment #5, the data from the Phase 1 portion of this study showed that there was a tolerable safety profile in both schedules, with similar PK profiles; however, 2 PRs were noted in Schedule A, one of which was confirmed. Following discussions with the investigators and independent experts, based upon the similar toxicity and PK profiles and taking into account the 2 PRs noted in Schedule A, Schedule A Dose Level 1 (eribulin 1.4

mg/m^2 D1 and D8 with irinotecan 40 mg/m^2 D1 – D5 of a 21- day cycle) from Phase 1 was selected as the RP2D for the Phase 2 portion of this study for subjects ≥ 12 months of age.

As per Amendment 6, subjects aged >6 months and <12 months will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 D1 and D8) with the irinotecan dose maintained Dose Level 1 (40 mg/m^2 D1 – D5) of a 21-day cycle.

A modified dose of eribulin with the irinotecan dose maintained is being used for subjects <12 months in order to maximize safety for infant subjects. The modified dose of eribulin is aligned with the Children's Cancer and Leukaemia Group (CCLG) (Chemotherapy Standardization Group 2008) guidance on pediatric dosing where a dose has not been established.

The dose levels as per Table 11 should be used in the Phase 2 portion of the study when following the criteria for dose reductions (Table 8), the agent most likely to be the cause of toxicity (eg, irinotecan for diarrhea, eribulin for neuropathy or neutropenia) should be reduced by one dose level if these criteria are met. If in the investigator's opinion both agents should be reduced this may be permitted after discussion with the Sponsor.

Table 11 Schedule A Dose Levels for Phase 2

Dose Level	Eribulin mesilate (mg/m^2)
Eribulin – Days 1 & 8	
-4	0.4
-3	0.6
-2**	**0.8**
-1	1.1
1*	**1.4**
Irinotecan hydrochloride (mg/m^2) – Days 1-5	
-2	20
-1	30
1*	**40**

For subjects ≥12 month to ≤ 25 years of age:

* Dose level 1 eribulin (1.4 mg/m^2 Days 1 and 8) and irinotecan (40 mg/m^2 Days 1 – 5).

For subjects >6 months and <12 months of age:

**Dose level -2 for eribulin (0.8 mg/m^2 Days 1 and 8) and Dose level 1 for irinotecan (40 mg/m^2 Days 1 – 5) is maintained.

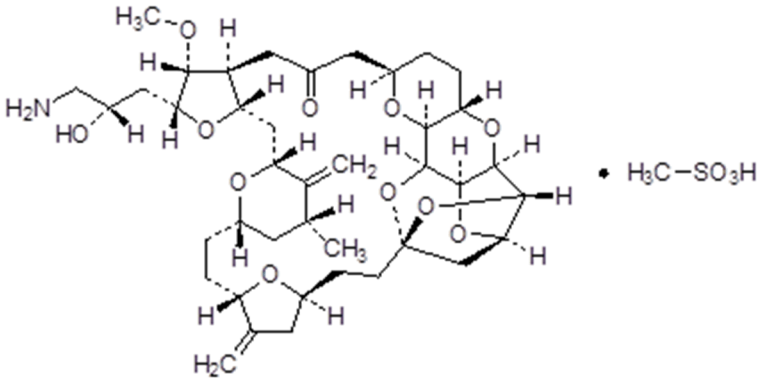
Do not re-escalate dose level after the dose level has been reduced. If toxicities do not recover after 2 dose reductions, treatment with that agent must be discontinued.

9.4.2 Identity of Investigational Products

Eribulin mesilate will be supplied by the sponsor in labeled vials. Irinotecan hydrochloride will either be supplied by sponsor or sourced locally by the investigator site, depending on local requirements.

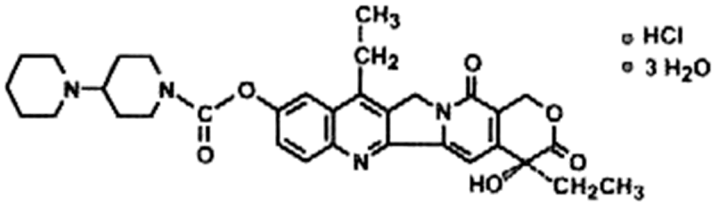
9.4.2.1 Chemical Name, Structural Formula of Eribulin Mesilate

- Test drug code: E7389
- Generic name: Eribulin Mesilate
- Chemical name (IUPAC): 11,15:18,21:24,28-Triepoxy-7,9-ethano-12,15-methano-9*H*,15*H*-furo[3,2-*i*] furo[2',3':5,6]pyrano[4,3-b][1,4]dioxacyclopentacosin-5(4*H*)-one, 2-[(2*S*)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-,(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-, methanesulfonate (salt)
- Molecular formula: $C_{41}H_{63}NO_{14}S$ ($C_{40}H_{59}NO_{11}$ · CH_4O_3S)
- Molecular weight: 826.0
- Structural formula:



9.4.2.2 Irinotecan Hydrochloride

- Generic name: irinotecan hydrochloride
- Chemical name (IUPAC): *(S)*-4,11-diethyl-39 3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-4-yl-[1,4'-bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate
- Molecular formula: $C_{33}H_{38}N_4O_6$•HCl•$3H_2O$
- Molecular weight: 677.19
- Structural formula:



Irinotecan Hydrochloride

9.4.2.3 Labeling for Investigational Products

Both Eribulin mesilate and irinotecan hydrochloride will be labeled in accordance with each country specific labeling requirements, and will be translated into the required language(s) for each applicable country.

9.4.2.4 Storage Conditions

9.4.2.4.1 GENERAL

Investigational Products will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.2.4.2 ERIBULIN MESILATE

Eribulin mesilate is provided as a single use vial, the contents of which can either be administered undiluted or diluted in up to 100 mL of 0.9% sodium chloride injection, PhEur. Undiluted or diluted solutions of eribulin mesilate can be stored for up to 4h at room temperature or up to 24h under refrigeration (2 -8°C). Further information on storage and handling is provided in the Summary of Product Characteristics (SmPC) provided by the manufacturer.

9.4.2.4.3 IRINOTECAN HYDROCHLORIDE

Irinotecan hydrochloride will be sourced, labeled for investigational use and stored in accordance with the storage conditions detailed in Irinotecan hydrochloride SmPC.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive eribulin mesilate in combination with irinotecan hydrochloride.

There is no randomization in this study. In Phase 1 subjects will be enrolled in alternate fashion to Schedule A or Schedule B (ie, every other subject will be enrolled onto Schedule A). If enrollment is halted or discontinued for any schedule, subjects will be enrolled on to the other schedule provided it is open for accrual.

In Phase 2 subjects will be enrolled according to histology type (RMS, NRSTS or EWS).

9.4.4 Selection of Doses in the Study

Eribulin mesilate will be administered at RP2D and irinotecan hydrochloride will be administered at the different dosing schedules (Schedules A & B) for Phase 1.

Phase 1

The doses of irinotecan to be used in the Phase 1 dosing schedules are derived from studies looking at MTD of single agent irinotecan or irinotecan combinations administered at the various corresponding schedules (Blaney, et al., 2001; Vassal, et al., 2003; Casey, et al., 2009).

Schedule A: Eribulin mesilate will be administered on Day 1 and Day 8 of a 21 day cycle (Starting dose determined by COG protocol ADVL1314/Eisai Study E7389-A001-113). Irinotecan hydrochloride will be administered on Days 1-5 of a 21-Day cycle.

Schedule B: Eribulin mesilate and irinotecan hydrochloride will be administered on Day 1 and Day 8 of a 21-Day cycle.

Phase 2

The dose and schedule that is deemed the most appropriate from Phase 1 will be used in Phase 2, following sponsor review together with the investigators. If there is no difference in the safety and efficacy between schedules A and B, following review with the investigators, Schedule B will be taken forward to Phase 2 on the basis of convenience. As per protocol amendment #5, the data from the Phase 1 portion of this study showed that there was a tolerable safety profile in both schedules, with similar PK profiles; however, 2 PRs were noted in Schedule A, one of which was confirmed. Following discussions with the investigators and independent experts, based upon the similar toxicity and PK profiles and taking into account the 2 PRs noted in Schedule A, Schedule A Dose Level 1 (eribulin 1.4 mg/m^2 D1 and D8 with irinotecan 40 mg/m^2 D1 – D5 of a 21- day cycle) was selected as the RP2D for the Phase 2 portion of this study. Further information on dose modification for each agent is provided in Section 9.4.1.

As per Amendment 6, subjects aged >6 months and <12 months will be enrolled to Schedule A with a modified dose of eribulin Dose Level -2 (0.8 mg/m^2 Day 1 and Day 8) with the irinotecan dose maintained Dose Level 1 (40 mg/m^2 Day 1 – Day 5) of a 21- day cycle.

For eribulin, the dose selected (0.8 mg/m^2) is aligned with guidance on pediatric dosing (CCLG-Chemotherapy Standardization Group 2008) which recommends the dose for patients aged <12 months should be approximately 75% of calculated dose for by body surface area. As eribulin has not been tested previously in this infant age group and is being used in combination with irinotecan in this study, the dose selected is the same as the lowest dose level provided in this study (Dose-Level -2). This approach also takes into account that while eribulin is predominantly excreted unchanged in urine (5-7%) and feces (82%), it is partially (< 15%) metabolized by the cytochrome P450 CYP3A4 liver enzyme and liver maturation of CYP3A4 has not occurred fully in these younger subjects (Salem, et al., 2014).

For irinotecan, the dose remains the same as the ≥12 months age group (40 mg/m^2 Day 1 – Day 5), which is consistent with standard practice with irinotecan in this population and with previous studies with irinotecan used in combination, where the identified full dose of irinotecan is maintained for the infant age group (Hawkins, et al., 2018).

9.4.5 Selection and Timing of Dose for Each Subject

Administration of eribulin mesilate by IV infusion on Days 1 and 8 of a 21-day cycle in combination with irinotecan hydrochloride administered by IV infusion on either Days 1-5 of a 21-day cycle (Schedule A), or Days 1 and 8 of a 21-day cycle (Schedule B).

Irinotecan will be administered first (on days where both treatments are due to be administered), as a 30 minute infusion, followed by eribulin as a 2-5 minute bolus infusion. Eribulin may be diluted in up to 100 mL 0.9% sodium chloride, and administered as an IV infusion over 15 minutes (maximum infusion duration), where clinically appropriate.

9.4.6 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 30 days after the final dose of study drug will be recorded. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with eribulin mesilate or irinotecan hydrochloride may be continued during the study.

Supportive care will be allowed as per institutional guidelines. Growth factors that support platelet or white blood cell number or function can only be administered in accordance with dose modification criteria (prophylactic granulocyte colony-stimulating factor should NOT be administered during Cycle 1) or for culture proven bacteremia or invasive fungal infection.

Subjects should not receive any other anticancer therapy (including chemotherapy, radiation therapy, immunotherapy or biologic therapy) or investigational agents while receiving study drug. If these therapies are administered, the subject will be removed from study treatment.

9.4.6.1 Drug-Drug Interactions

9.4.6.1.1 ERIBULIN MESILATE

In adults, no drug-drug interactions are expected with CYP3A4 inhibitors, CYP3A4 inducers or P-glycoprotein (P-gp) inhibitors. Clinically meaningful differences in exposure (AUC) were not observed in patients with advanced solid tumors when HALAVEN was administered with or without ketoconazole (a strong inhibitor of CYP3A4 and a P-gp inhibitor) and when HALAVEN was administered with or without rifampin (a CYP3A4 inducer). Eribulin does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4 enzymes or induce CYP1A2, CYP2C9, CYP2C19 or CYP3A4 enzymes at relevant clinical concentrations. Eribulin is not expected to alter the plasma concentrations of drugs that are substrates of these enzymes.

Currently, drug-drug interactions of eribulin mesilate have not been studied in children, therefore pediatric subjects taking medications that are strong CYP3A4 inducers (eg, St. John's Wort, phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital,) or inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or taking nutritional supplements known to inhibit/induce CYP3A4, will be excluded from the study. Check prescribing information of all concomitant medications for all subjects.

Please refer to http://medicine.iupui.edu/flockhart/table.htm for the most current information.

9.4.6.1.2 IRINOTECAN HYDROCHLORIDE

There is no information on drug-drug interactions of irinotecan hydrochloride in the pediatric population. In adult patients with colorectal cancer, the administration of 5-fluorouracil (5-FU) and leucovorin (LV) did not substantially alter the disposition of irinotecan hydrochloride when the drugs were coadministered, however formal in vivo or in vitro drug interaction studies to evaluate the influence of irinotecan hydrochloride on the disposition of 5-FU and LV have not been conducted. The possible pharmacokinetic interactions of irinotecan hydrochloride with other concomitantly administered medications have not been formally investigated.

Avoid co-administration of irinotecan with strong CYP3A4 inhibitors and inducers (listed above in Section 9.4.6.1.1), and UGT1A1 inhibitors (eg, ketoconazole, atazanavir, gemfibrozil, indinavir). For subjects requiring anti-epileptic therapy, switch to a non-enzyme inducing anti-epileptic agent. Check prescribing information of all concomitant medications for all subjects.

9.4.6.2 Prohibited Concomitant Therapies and Drugs

Subjects should not receive other antitumor therapies while on study. If subjects receive additional antitumor therapies, such as chemotherapy, hormone therapy, palliative radiotherapy, or cancer immunotherapy, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These subjects should complete all off-treatment assessments. In addition, no attenuated live vaccines must be administered for the duration of the study and 6 months following discontinuation of irinotecan.

Details of other prohibited concomitant therapies and drugs are provided in Section 9.3.2 (exclusion criterion #2).

9.4.7 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. Clinical Research Associates (CRAs) will review treatment compliance during site visits and at the completion of the study.

9.4.8 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, MHRA). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity.

9.5.1.2 Baseline Assessments

Baseline characteristics and assessments will be collected at the Screening Visit.

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history relating to anticancer treatment must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations (comprehensive or symptom directed) will be performed as designated in the Schedule of Procedures/Assessments (Table 13 and Table 14). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 TUMOR RESPONSE ASSESSMENTS

Tumor assessment will be performed based on RECIST 1.1. Investigator-determined response assessments at each assessment time point will be entered onto the appropriate CRF. Tumor assessments will be performed every 6 weeks until Week 12 and every 9 weeks thereafter on a fixed schedule. For Phase 1, neuroblastoma subjects can also be evaluated by meta-iodobenzulguanidine (MIBG) scintigraphy. For Phase 2, copies of scans for tumor assessments will be sent to an imaging core laboratory designated by the sponsor for quality assessment, archival, and potential independent review.

Computed tomography (CT) scans (with oral and intravenous contrast, unless clinically contraindicated) of chest, abdomen, and pelvis and other known sites of disease will be obtained at pre-study (within 28 days prior to Cycle 1 Day 1), and every 6 weeks thereafter (counting from C1D1), irrespective of dose delays. Magnetic resonance imaging (MRI) scans may be used instead of CT scans for abdomen and pelvis; however, chest must be assessed using CT. If only chest CT is performed then oral CT contrast is not required. The same method of assessment must be used at all time-points as used at pre-study. However, a chest x-ray may be used to identify new lesions in lieu of chest CT where appropriate (and after initial chest CT at screening). Post-screening scans may be performed without contrast if a medical contraindication develops while on study treatment. If iodinated IV contrast is contraindicated, chest CT should be done without IV contrast. MRI should be performed for all other body regions (with gadolinium unless contraindicated (eg, severe renal dysfunction). An exception to the requirement for following chest disease by CT will be allowed where subjects have either non-parenchymal tumors, mediastinal and/or chest wall lesions. These

may be assessed (at Screening and post-baseline) using contrast-enhanced MRI. However, a chest CT is required at Screening for all subjects, and lung parenchymal lesions should be followed using CT (as per standard practice). If there is either an equivocal new lung lesion based on MRI or symptoms suggesting a new lesion, these should also be confirmed with chest x-ray or CT.

After 12 weeks, subjects with CR, PR or stable disease (SD) may have imaging frequency decreased to every 9 weeks. A bone scan using whole body bone MRI, technetium-^{99}m based bone scans, ^{18}F-sodium fluoride positron emission tomography [NaF PET], or ^{18}FDG-PET will be performed during screening to establish a baseline (a historical bone scan performed within 6 weeks before study drug administration is acceptable), approximately every 24 weeks (in conjunction with a scheduled tumor assessment visit), and as clinically indicated. Lesions identified on bone scans should be followed with anatomic imaging.

A brain scan (CT with contrast or MRI [pre- and post-gadolinium]) will be performed as clinically indicated to assess potential for CNS disease and/or metastases. For subjects with a history of protocol-eligible treated brain metastases, a brain scan will be required at Screening and at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm CR within 1 week following response confirmation, or if clinically indicated.

Low-dose non-contrast CT transmission scans from a positron emission tomography-CT (PET-CT) combination scanner are not acceptable, however, they may be used if they are of diagnostic quality and are obtained with contrast as indicated above. Ultrasound should not be used for radiographic tumor assessment.

If subcutaneous masses or nodes are palpable (eg, bulky) and are assessable by both clinical and radiographic techniques, the radiographic (CT/MRI) technique should be used for the assessment of target and non-target lesions.

Subjects with neuroblastoma (which can be included in phase 1 only) may have meta-iodobenzulguanidine (MIBG) scintigraphy and bilateral bone marrow biopsies assessments performed at sites where this is standard practice, at the discretion of the treating physician. This is an optional assessment for neuroblastoma subjects. Subjects that have positive lesions by MIBG scan at screening (within 28 days prior to administration of study drug) are not required to undergo PET or technetium-^{99}m bone scans. After identifying positive lesions at screening, repeat measurements may be performed within 4 weeks after confirmation of a PR or CR or as clinically indicated. Subjects with positive urinary catecholamines at baseline, should be assessed in cases of CR (catecholamines should be negative to confirm CR). Subjects with MIBG positive lesions at screening will be evaluable for MIBG response using the revised version of the International Neuroblastoma Response Criteria (INRC) scoring (Brodeur GM, et al., 1993).

All responses must be confirmed no less than 28 days following the initial assessment of response. In order for stable disease (SD) to be considered the best overall response, it must occur ≥5 weeks following the first dose of study drug.

All subjects will have an Off-Treatment Visit within 28 days after the last dose of study medication. Subjects that discontinue treatment 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 the study is terminated. This follow-up data will be required unless consent is withdrawn.

After data cutoff for the primary analysis, tumor assessments may be performed as clinically indicated using the investigator's discretion, following the prevailing local standard of care.

9.5.1.3.2 PHARMACOKINETIC ASSESSMENTS

Blood samples (2 mL) will be collected for PK analysis of both irinotecan and its metabolite (SN-38), and eribulin as follows:

Phase 1 (Cycle 1):

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.

Phase 2 (Cycle 1):

Eribulin assay only:

Cycle 1, Day 1 (at the end of the infusion, 0.5 to 6 hours and 24 to 120 hours after eribulin infusion) and on Cycle 1, Day 8 (predose of eribulin and at the end of the infusion). Subjects who weigh under 6 kg will not have PK samples taken.

9.5.1.3.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Not applicable.

9.5.1.3.4 BIOANALYTICAL METHODS

Eribulin, irinotecan and its active metabolite, SN-38, will be analyzed using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods.

9.5.1.4 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grades (for both increasing and decreasing severity), and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and ECGs; performance status, and performance of physical examinations as detailed in Table 13 and Table 14.

9.5.1.4.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drugs are eribulin mesilate and irinotecan hydrochloride.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject and/or their parents or legally authorized representatives signs the study ICF through the last visit. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. SAEs will be collected for 28 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed until resolution or for 28 days after the subject's last dose of study medication, whichever comes first. Serious AEs will be collected for 28 days post treatment and followed until resolution or, if resolution is unlikely, until the event or sequelae stabilize.

Progression of malignant disease (PD) should not be recorded as an adverse event in studies where it is included as an endpoint for underlying disease. However, the symptoms experienced as a part of progression of disease should be recorded as the adverse event. If the progression leads to an untoward medical occurrence (increased pain, pleural effusion, etc), then this medical occurrence should also be recorded as the adverse event.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to Common Terminology Criteria for Adverse Event (CTCAE v5.0 [National Institutes of Health Cancer Therapy Evaluation Program, 2017]). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable

- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

Every effort must be made to identify the cause of death if it occurs within 28 days of last dose. The cause of death must be recorded on the adverse event page.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of

the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 12. The Schedule of Procedures/Assessments (Table 13 and Table 14) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 12 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium, glucose, magnesium, calcium, phosphorus
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	*Albumin, cholesterol, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

RBC = red blood cell, WBC = white blood cell.

* All to be assessed at baseline. Cholesterol, triglycerides and uric acid not required for assessment at subsequent chemistry measurement time points.

Clinical laboratory tests during the Treatment Phase will be performed by local laboratories. Laboratory certification as available will be included in the final clinical study report for this study.

All hematology, blood chemistry and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle. Please note, following screening, monthly pregnancy tests are required for all sexually active subjects. Refer to Table 8 and Table 9 for the management of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], heart rate [beats per minute], body temperature [in centigrade]), and height, and weight/BSA will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 13 and Table 14) by a validated method, such as the Mosteller formula for children:

$$BSA\ (m^2) = \frac{\sqrt{body\ weight\ (kg) \times body\ height\ (cm)}}{\sqrt{3600}}$$

9.5.1.4.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 13 and Table 14). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

9.5.1.4.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 13 and Table 14). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

9.5.1.4.7 OTHER SAFETY ASSESSMENTS

Pregnancy Test

A serum β-hCG or urine test (depending on local practice) will be performed for females of childbearing potential prior to starting treatment (within 7 days of administration of study drug) (Table 13). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Thereafter, monthly pregnancy tests are required for all sexually active subjects.

9.5.1.5 Schedule of Procedures/Assessments

Table 13 and Table 14 present the schedule of procedures/assessments for the study.

Table 13 Schedule of Procedures/Assessments in Study E7389-G000-213: Phase 1

Phase	Pre-study	Treatment[a]												Off Treatment Visit	Follow-Up[t]
Period	Screening[b]	Cycle 1			Cycle 2[c]			Cycle 3[c]			Additional Cycles[c]				
Visit	1	2	3	4	5	6	7	8	9	10	11+				
Day	-28 to -1	1	8	15	1	8	15	1	8	15	1	8	15	Within 28 days after last dose of drug	≥28 days after last dose of drug
Procedures/Assessments															
Informed consent[d]	X														
Medical history	X														
Inclusion/exclusion	X														
Vital signs[e]	X	X	X		X	X		X	X		X	X		X	
		Weekly for subjects <12 months			Weekly for subjects <12 months			Weekly for subjects <12 months			Weekly for subjects <12 months				
Height[f]	X							X			X			X	
Weight, BSA[g]	X	Weekly			X			X			X			X	
Physical exam	X	Weekly			X			X			X			X	
					Weekly for subjects <12 months			Weekly for subjects <12 months			Weekly for subjects <12 months				
Neurologic exam	X				X			X			X			X	
Performance status[h]	X	Weekly			X			X			X			X	
Pregnancy test[i]	X													X	

Table 13 Schedule of Procedures/Assessments in Study E7389-G000-213: Phase 1

Phase	**Pre-study**	**Treatment[a]**												**Off Treatment Visit**	**Follow-Up[t]**
Period	**Screening[b]**	**Cycle 1**			**Cycle 2[c]**			**Cycle 3[c]**			**Additional Cycles[c]**				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11+**				
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**Within 28 days after last dose of drug**	**≥28 days after last dose of drug**
Procedures/Assessments															
Hematology[j]	X	Weekly			Weekly			Weekly			Weekly			X	
		Twice weekly for subjects <12 months (every 3 to 4 days)			Twice weekly for subjects <12 months (every 3 to 4 days)			Twice weekly for subjects <12 months (every 3 to 4 days)			Twice weekly for subjects <12 months (every 3 to 4 days)				
Chemistry[k]	X	Weekly			X			X			X			X	
					Weekly for subjects <12 months			Weekly for subjects <12 months			Weekly for subjects <12 months				
Eribulin mesilate administration		X	X		X	X		X	X		X	X			
Irinotecan hydrochloride administration (Schedule A)		X (D1-5)			X (D1-5)			X (D1-5)			X (D1-5)				
Irinotecan hydrochloride administration (Schedule B)		X	X		X	X		X	X		X	X			
Pharmacokinetic sampling[m]		X	X												

Table 13 Schedule of Procedures/Assessments in Study E7389-G000-213: Phase 1

Phase	**Pre-study**	**Treatment[a]**												**Off Treatment Visit**	**Follow-Up[t]**
Period	**Screening[b]**	**Cycle 1**			**Cycle 2[c]**			**Cycle 3[c]**			**Additional Cycles[c]**				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11+**				
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**Within 28 days after last dose of drug**	**≥28 days after last dose of drug**
Procedures/Assessments															
12-lead ECG[n]	X	X	X		As clinically indicated									X	
Urinalysis[o]	X				X			As clinically indicated						X	
					As clinically indicated for subjects <12 months										
Tumor assessment[p]	X							Every 6 weeks (counting from date of first dose) until Wk 12, then every 9 weeks[e]						X	
Brain CT/MRI[q]	X	Clinically indicated and all timepoints for subjects with protocol-eligible treated brain mets at screening													
Bone Scan[r]	X	Approximately every 24 weeks (in conjunction with scheduled tumor assessment) and as clinically indicated													
MIBG Scintigraphy (neuroblastoma only)[u]	X	Clinically indicated													
Prior / concomitant medications[s]		Throughout													
Adverse events/SAEs		Throughout													
Subsequent anti-cancer treatments and survival															X

a. Efforts should be made to conduct study visits on the scheduled day (+/- 3 days).

b. The Screening Period extends from Day -28 to Day -1. Computed tomography (CT) / magnetic resonance imaging (MRI) scans must be performed within 28 days prior to administration of study drug. All clinical and laboratory studies to determine eligibility must be performed **within 7 days prior to study drug administration,** unless otherwise indicated. Laboratory values used to assess eligibility must be no older than 7 days at the start of therapy.
c. Assessments/procedures may be obtained within 72 hours prior to the start of the subsequent cycle.
d. For logistical purposes, informed consent may be obtained from Day -29.
e. Vital signs will be performed on Day 1 and Day 8 of each cycle for ≥12 months subjects and weekly for subjects <12 months.
f. Height will be measured at Screening and on Day 1 of every other cycle starting from cycle 3.
g. BSA is based on a calculation at recruitment that is accepted and customarily used by the site, such as the Mosteller formula for children, adjustments to dosing to be made if 10% change in body weight.
h. Performance status will be measured using Karnofsky or Lansky scales (Appendix 2).
i. Women of childbearing potential require a negative urine or serum (depending on local practice) pregnancy test prior to starting treatment (within 7 days prior to recruitment). Sexually active subjects must use an acceptable method of birth control. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Thereafter, monthly pregnancy tests are required for sexually active subjects.
j. Hematology lab tests will be performed weekly for ≥12 month subjects and twice weekly for subjects <12 months; a complete blood count can be performed at an external laboratory when the subject is not attending the investigator site for dosing or other study visits.
k. Albumin, calcium, magnesium, cholesterol, lactate dehydrogenase, phosphorus, total protein, triglycerides, and uric acid are all to be assessed at baseline. Cholesterol, triglycerides and uric acid are not required for assessment at subsequent chemistry measurement time points.
l. Eribulin will be administered on Day 1 and Day 8 of a 21-day cycle together with irinotecan either on Schedule A (Days 1-5) or Schedule B (Day 1 and Day 8) of a 21-day cycle.
m. PK sample collection schedule:
For subjects ≥12 months of age and >10 kg:
Phase 1 (Cycle 1):
- 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 h post-eribulin infusion, eribulin only will be assayed.

Subjects <12 months of age as well as those ≥12 months of age and ≤10 kg (subjects <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).

n. 12-lead ECG will be obtained pre-infusion (after irinotecan administration and prior to eribulin infusion on the days when administered together) and post-infusion on Day 1 and Day 8 of Cycle 1 and as clinically indicated during subsequent cycles and during follow-up (28 days after the last dose of drug).
o. If urine protein is ≥2+ on urinalysis, a 24 hour urine test should be performed.
p. **Pre-study phase**: Screening tumor assessments using CT of the chest/abdomen/pelvis and other areas of known disease or newly suspected disease should be performed between Day -28 and Day -1. Scans of the abdomen, pelvis, and other areas of the body may be done with MRI instead of CT, but evaluation of the chest must be done with CT. **Treatment phase**: Tumor assessments of the chest/abdomen/pelvis and other areas of known disease that were scanned at screening, or newly suspected disease, must be performed every 6 weeks (within Week 6) during Treatment Cycles (or sooner if there is evidence of progressive disease) until Week 12 and then the frequency may decrease to every 9 weeks (or sooner if clinically indicated) thereafter for subjects that have CR, PR or SD and should utilize the same methodology (CT/MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments (see section 9.5.1.3.1 for exception on chest CT and more details).

During the Follow-Up Period, subjects who discontinued study treatment without progression should have tumor assessments as per schedule of assessments until death, disease progression is documented, or another anticancer therapy is initiated. After Week 12, these scans may be conducted every 9 weeks.

q. **Brain:**
Pre-study phase: Screening CT or MRI of the brain should be performed to assess potential for CNS disease and/or metastases between Day -28 and Day -1 for subjects with previously treated protocol-eligible brain metastases only.
Treatment phase: For subjects with previously treated protocol-eligible brain metastases, a brain scan must be performed at all tumor assessment time points. For all subjects, CT/MRI of the brain should be performed if clinically indicated. In subjects with body scans indicating a confirmed CR (according to RECIST 1.1), a CT/MRI of the brain will also be required within 1 week after the confirmation assessment to confirm the absence of brain metastases. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.

r. A bone scan whole body bone MRI, ^{18}F-NaF PET or ^{18}FDG-PET to assess bone metastases will be performed at screening (within 6 weeks prior to first dose (historical scans acceptable) to establish a baseline, and then approximately every 24 weeks (in conjunction with scheduled tumor assessment) and as clinically indicated thereafter. The same methodology used at screening should be performed at all subsequent bone assessments.

s. Information on anticancer treatment will be collected while subjects are in follow-up for disease progression.

t. During the Follow-Up stage, data will be collected on all subjects for subsequent anti-cancer treatments and survival (at least 4 weeks after last dose and up to 1 year). This Follow-Up may be conducted as a phone call if the subject is unable to attend the hospital.

u. Subjects with neuroblastoma may have MIBG scintigraphy and bilateral bone marrow biopsies at sites where this is standard practice (this is an optional assessment). Subjects with MIBG positive lesions at screening (within 28 days of the administration of study drug) are not required to undergo PET or technetium99 bone scans. After identifying positive lesions at screening, repeat measurements may be performed within 4 weeks after confirmation of PR or CR, or as clinically indicated; urinary catecholamines may be assessed at Baseline and in case of CR for subjects with elevated catecholamines at Baseline. Subjects with positive lesions at screening will be evaluable for MIBG response using the revised version of the International Neuroblastoma Response Criteria (INRC) scoring (Brodeur GM, et al., 1993).

Table 14 Schedule of Procedures/Assessments in Study E7389-G000-213: Phase 2

Phase	**Pre-study**	**Treatment[a]**												**Off Treatment Visit**	**Follow-Up[t]**
Period	**Screening[b]**	**Cycle 1**			**Cycle 2[c]**			**Cycle 3[c]**			**Additional Cycles[c]**				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11+**				
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**Within 28 days after last dose of drug**	**≥28 days after last dose of drug**
Procedures/Assessments															
Informed consent[d]	X														
Medical history	X														
Inclusion/exclusion	X														
Vital signs[e]	X	X	X		X	X		X	X		X	X		X	
		Weekly for subjects <12 months			Weekly for subjects <12 months			Weekly for subjects <12 months			Weekly for subjects <12 months				
Height[f]	X							X			X			X	
Weight, BSA[g]	X	Weekly			X			X			X			X	
Physical exam	X	Weekly			X			X			X			X	
					Weekly for subjects <12 months			Weekly for subjects <12 months			Weekly for subjects <12 months				
Neurologic exam	X				X			X			X			X	
Performance status[h]	X	Weekly			X			X			X			X	
Pregnancy test[i]	X													X	

Table 14 Schedule of Procedures/Assessments in Study E7389-G000-213: Phase 2

Phase	**Pre-study**	**Treatment[a]**												**Off Treatment Visit**	**Follow-Up[t]**
Period	**Screening[b]**	**Cycle 1**			**Cycle 2[c]**			**Cycle 3[c]**			**Additional Cycles[c]**				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11+**				
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**Within 28 days after last dose of drug**	**≥28 days after last dose of drug**
Procedures/Assessments															
Hematology[j]	X	Weekly			Weekly			Weekly			Weekly			X	
		Twice weekly for subjects <12 months (every3 to 4 days)			Twice weekly for subjects <12 months (every 3 to 4 days)			Twice weekly for subjects <12 months (every 3 to 4 days)			Twice weekly for subjects <12 months (every 3 to 4 days)				
Chemistry[k]	X	Weekly			X			X			X			X	
					Weekly for subjects <12 months			Weekly for subjects <12 months			Weekly for subjects <12 months				
Eribulin mesilate administration[l]		X	X		X	X		X	X		X	X			
Irinotecan hydrochloride administration (Schedule A)		X (D1-5)			X (D1-5)			X (D1-5)			X (D1-5)				
Irinotecan hydrochloride administration (Schedule B)		X	X		X	X		X	X		X	X			
Pharmacokinetic sampling[m]		X	X												

Table 14 Schedule of Procedures/Assessments in Study E7389-G000-213: Phase 2

Phase	**Pre-study**	**Treatment[a]**												**Off Treatment Visit**	**Follow-Up[t]**
Period	**Screening[b]**	**Cycle 1**			**Cycle 2[c]**			**Cycle 3[c]**			**Additional Cycles[c]**				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11+**				
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**Within 28 days after last dose of drug**	**≥28 days after last dose of drug**
Procedures/Assessments															
12-lead ECG[n]	X	X	X		As clinically indicated									X	
Urinalysis[o]	X				X			As clinically indicated						X	
					As clinically indicated for <12 months										
Tumor assessment[p]	X							Every 6 weeks (counting from date of first dose) until Wk 12, then every 9 weeks[e]						X	
Brain CT/MRI[q]	X	Clinically indicated and all timepoints for subjects with protocol-eligible treated brain mets at screening													
Bone Scan[r]	X	Approximately every 24 weeks (in conjunction with scheduled tumor assessment) and as clinically indicated													
Prior / concomitant medications[s]		Throughout													
Adverse events/SAEs		Throughout													
Subsequent anti-cancer treatments and survival															X

a. Efforts should be made to conduct study visits on the scheduled day (+/- 3 days)
b. The Screening Period extends from Day -28 to Day -1. Computed tomography (CT) / magnetic resonance imaging (MRI) scans must be performed within 28 days prior to study drug administration. All clinical and laboratory studies to determine eligibility must be performed **within 7 days prior to study drug administration** unless otherwise indicated. Laboratory values used to assess eligibility must be no older than 7 days at the start of therapy.

c. Assessments/procedures may be obtained within 72 hours prior to the start of the subsequent cycle.
d. For logistical purposes, informed consent may be obtained from Day -29.
e. Vital signs will be performed on Day 1 and Day 8 of each cycle for subjects aged ≥12 months and weekly for < 12 months.
f. Height will be measured at Screening and on Day 1 of every other cycle starting from cycle 3.
g. BSA based on a calculation at enrollment that is accepted and customarily used by the site, such as the Mosteller formula for children, adjustments to dosing to be made if 10% change in body weight.
h. Performance status will be measured using Karnofsky or Lansky scales (Appendix 2).
i. Women of childbearing potential require a negative urine or serum (depending on local practice) pregnancy test prior to starting treatment (within 7 days prior to study drug administration). Sexually active subjects must use an acceptable method of birth control. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Thereafter, monthly pregnancy tests are required for sexually active subjects.
j. Hematology lab tests will be performed weekly for subjects aged ≥12 months and twice weekly for subjects <12 months; a complete blood count can be performed at a local laboratory when the subject is not attending the investigator site for dosing or other study visits.
k. Albumin, calcium, magnesium, cholesterol, lactate dehydrogenase, phosphorus, total protein, triglycerides, and uric acid are all to be assessed at baseline. Cholesterol, triglycerides and uric acid are not required for assessment at subsequent chemistry measurement time points.
l. Eribulin will be administered on Day 1 and Day 8 of a 21-day cycle together with irinotecan either on Schedule A (Days 1-5) or Schedule B (Day 1 and Day 8) of a 21-day cycle, depending on which schedule is found to be most appropriate for Phase 2. As per protocol amendment #5, Schedule A Dose Level 1 was selected as the RP2D for the Phase 2 portion of this study.
m. PK sample collection schedule:
Phase 2 (Cycle 1): Eribulin assay only:
Cycle 1, Day 1 (at the end of the 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), Subjects who weigh < 6 kg will not have PK samples taken.
n. 12-lead ECG will be obtained pre-infusion (after irinotecan administration and prior to eribulin infusion on the days when administered together) and post-infusion on Day 1 and Day 8 of Cycle 1 and as clinically indicated during subsequent cycles and during follow-up (28 days after the last dose of drug).
o. If urine protein is ≥2+ on urinalysis, a 24 hour urine test should be performed.
p. **Pre-study phase:** Screening tumor assessments using CT of the chest/abdomen/pelvis and other areas of known disease or newly suspected disease should be performed between Day -28 and Day -1.
Treatment phase: Tumor assessments of the chest/abdomen/pelvis and other areas of known disease that were scanned at screening, or newly suspected disease, must be performed every 6 weeks (within Week 6) during Treatment Cycles (or sooner if there is evidence of progressive disease) until Week 12 and then the frequency may decrease to every 9 weeks (or sooner if clinically indicated) thereafter for subjects that have CR, PR or SD and should utilize the same methodology (CT/MRI) and scan acquisition techniques (including use or nonuse of IV contrast) as were used for the screening assessments (see section 9.5.1.3.1 for exception on chest CT and more details). During the Follow-Up Period, subjects who discontinued study treatment without progression should have tumor assessments as per schedule of assessments until death, disease progression is documented or another anticancer therapy is initiated. After Week 12, these scans may be conducted every 9 weeks.
q. **Brain:**
Pre-study phase: Screening CT or MRI of the brain should be performed to assess potential for CNS disease and/or metastases between Day -28 and Day -1 for subjects with previously treated protocol-eligible brain metastases only.
Treatment phase: For subjects with previously treated protocol-eligible brain metastases, a brain scan must be performed at all tumor assessment time points. For all subjects, CT/MRI of the brain should be performed if clinically indicated. In subjects with body scans indicating a confirmed CR (according to RECIST 1.1), a CT/MRI of the brain will also be required within 1 week after the confirmation assessment to confirm the absence of brain metastases. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.
r. A bone scan (whole body bone MRI, ^{18}F-NaF PET, or ^{18}FDG-PET to assess bone metastases will be performed at screening (within 6 weeks prior to first dose (historical scans acceptable) to establish a baseline, and then approximately every 24 weeks (in conjunction with scheduled tumor assessment) and as clinically indicated thereafter. The same methodology used at screening should be performed at all subsequent bone assessments.

s. Information on anticancer treatment will be collected while subjects are in follow-up for disease progression.
t. During the Follow-Up stage, data will be collected on all subjects for subsequent anti-cancer treatments and survival (at least 4 weeks after last dose and up to 1 year). This Follow-Up may be conducted as a phone call if the subject is unable to attend the hospital.

9.5.2 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of soft tissue sarcomas.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, radiologic studies, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.3 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.3.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event. Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 24 hours by emailing or faxing the completed SAE form.

Serious adverse events, regardless of causality assessment, must be collected through the last visit in the Treatment Phase, and for 28 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.3.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.3.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study. The investigator should confirm whether they agree to follow-up assessments (including survival follow-up) or whether the subject wishes to withdraw consent. If a subject withdraws consent, the date should be documented in the source documents.

9.5.3.3 Reporting of Events Associated with Special Situations

9.5.3.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose.
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol.

Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.3.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.3.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.3.5 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the competent authorities of all involved European member states.

9.5.4 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 13 and Table 14).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or other. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason may be replaced.

9.5.5 Abuse or Diversion of Study Drug

Not applicable.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines (CCGs). The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

The primary endpoints of the study 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.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

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).

9.7.1.2 Definitions of Analysis Sets

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.

9.7.1.3 Subject Disposition

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

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics data will be summarized descriptively. Data to be tabulated will include data such as sex, age, and race as well as weight and disease-specific status and medical history.

9.7.1.5 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. The number (percentage) of subjects who took prior and concomitant medications will be summarized by dose level, Anatomical Therapeutic Chemical (ATC) class (ie, anatomical class, therapeutic 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 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 30 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

The primary efficacy analyses 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, PFS, and CBR will be summarized descriptively on the FAS. Endpoints related to tumor assessments will be based on investigator assessments. Collect and hold of tumor scans will enable a possibility to confirm responses in case independent review is required.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

ORR will be estimated and summarized for each histology type. A Simon 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, the enrollment will continue to the second stage to approximately 25 subjects. If there are 12 or more responders out of 25 subjects, the null hypothesis will be rejected. For final review, collect and hold of tumor scans will enable the final report to confirm responses by potential independent radiologic review.

In addition, ORR along with respective confidence interval will be provided by histology. Duration of response (DOR) will be calculated for responders and summarized descriptively. DOR is 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).

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

PFS will be analyzed by Kaplan-Meier methodology and median PFS with 90% confidence interval will be presented. 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, will be summarized by descriptive statistics for the FAS. Durable SD is defined as SD with duration of more than 11 weeks.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Plasma concentrations of eribulin, irinotecan and its active metabolite SN-38 will be tabulated and summarized by dose level, day and time. For Phase 1, 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).

In Phase 1 the PK of both drugs (eribulin and irinotecan) will be assessed on C1D1 and in Phase 2 eribulin will be assessed on C1D1 and C1D8. The Phase 2 PK data will be assessed using a PopPK approach, pooled with Phase 1 data. 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 parameters.

9.7.1.7.2 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Exploratory/graphical analysis will be conducted for PK/PD 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. In addition, the effects of eribulin

mesylate administration on absolute neutrophil count (ANC) may be evaluated using a semi-physiological model for hematological toxicity.

Further details will be documented separately in a population analysis plan (PAP).

9.7.1.8 Safety Analyses

The primary endpoint for Phase 1, i.e., the incidence of DLTs will be summarized by dose level for the DES using frequency and percentage.

Additionally, toxicity in Phase 2 for the Safety Analysis Set will be monitored on an ongoing basis. If the number of AEs that would have qualified as DLTs on the Phase 1 portion exceeds 1/3, a meeting with the investigators will be convened to determine if the dose should be lowered. The rule of one-third (1/3) will be applied to the number of subjects in an increment of 3 subjects at the same dose level (eg, 3, 6, 9 subjects). Likewise, if ongoing moderate toxicities develop into "intolerable Grade 2" events, the recommended Phase 2 dose may also be re-evaluated in consultation with the protocol investigators.

All evaluation of safety other than the Phase 1 primary objective in DLT evaluation will be performed on the Safety Analysis Set. Safety data that will be evaluated include adverse events, clinical laboratory results, ECG, and vital signs.

Descriptive summary statistics (mean, standard deviation, median, minimum, maximum) of clinical laboratory test results, vital signs measurements, ECG parameters, and changes from baseline will be presented.

9.7.1.8.1 EXTENT OF EXPOSURE

The number of cycles administered, duration of treatment, and the number of subjects requiring dose reductions, treatment interruption, treatment delay, and treatment discontinuation due to adverse events will be summarized.

9.7.1.8.2 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 20.0 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 pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is 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 TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

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 leading to death will be summarized by

MedDRA SOC and PT. A subject data listing of all AEs leading to death 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.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. Hematology and chemistry values and their changes from baseline will be summarized using descriptive statistics (mean, standard deviation, median, minimum, maximum). Shift from baseline to post-baseline CTCAE grade for hematology and chemistry tests will be presented.

Laboratory test results will be assigned a classification according to CTCAE grade (Appendix 1). Urinalysis data will be listed.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, temperature, weight, and height) and changes from baseline will be presented by visit.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments will be performed. 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.

A shift table will be provided for baseline to post-baseline shift in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant).

In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in QTcF 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

9.7.1.8.6 OTHER SAFETY ANALYSES

Karnofsky and Lansky performance status scores will be summarized descriptively.

9.7.2 Determination of Sample Size

For the first line therapy in pediatric patients with NRSTS, RMS, or EWS, the literature indicated that the ORR (complete or partial response) ranged from 33.3% to 63% (Pappo, et al., 1997; Sandler, et al., 2001). In children or patients with refractory solid tumor or rhabdomyosarcoma, the ORR of a treatment ranged from 0 to 50% (Jacobs, et al., 2010; Mascarenhas, et al., 2010). At the time of the design of this study, there was limited data available for eribulin and irinotecan as a treatment in the target populations.

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

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

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

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, approximately 16 additional subjects will be enrolled in the second stage for a total of approximately 25 subjects per histology. 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 power of 80% when the true response rate is 55%.

Note: Subjects aged >6 to <12 months and subjects ≥18 to ≤25 years will be included for descriptive purposes only and will not contribute to the full sample size analyses for this study. As subjects in the age group >6 months to <12 months will receive approximately 75% of the RP2D of eribulin (rationale for lower dose is provided in Section 9.4.4 of the protocol) and the EMA PDCO requested that subjects in the age group ≥18 to ≤25 years old should not be included in the full sample size analyses.

9.7.3 Interim Analysis

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.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after its initial finalization, 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.

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C-SSRS Reference

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

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 indicated	life-threatening consequences; urgent intervention indicated
White blood cell (Leukocytes) decreased	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/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 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophil count decreased	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/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 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/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 if baseline 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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>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 symptoms	<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

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, 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.

Appendix 2 Measurements of Performance Status

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

Appendix 3 Modified "Balis" Pediatric Scale of Peripheral Neuropathies

Peripheral Motor Neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.
- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.
- Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

PROTOCOL SIGNATURE PAGE

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.

Investigational Product Name: E7389 (eribulin mesilate)

IND Number: 116,292

SIGNATURES

Authors:

PPD

4/5/2021

Date

Oncology Business Group, Eisai Co., Ltd.

PPD

4/2/2021

Date

Oncology Business Group, Eisai Inc.

PPD

4/5/2021

Date

PPD , Oncology Business Group, Eisai Co., Ltd.

PPD

4/2/2021

Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

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.
Investigational Product Name:	E7389 (eribulin mesilate)
IND Number:	116292

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date