## REVISION HISTORY

### Revisions per Amendment 2.0

Date: 20 Dec 2018

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Number of sites increased to 40 | Increased to help to achieve recruitment targets. | • Synopsis - Sites<br>• Section 6 |
| Two exploratory objectives of DOR and OS were changed to secondary objectives. | Following feedback from the FDA and the EMA PDCO. These objectives have moved from exploratory to secondary objectives. | • Synopsis - Objectives<br>• Section 8.2, Section 8.3 |
| Number of subjects planned was increased to 45 and hence the number of subjects in each of the histology groups was increased to approximately 15. The determination of sample size text updated accordingly. | Following feedback from the EMA PDCO, the sample size was increased to be compliant with the EMA Pediatric Investigational Plan. | • Synopsis - Study Design, Number of Subjects, Efficacy Analysis, Sample Size Rationale<br>• Section 9.3, Section 9.7.2 |
| Changed inclusion criteria #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 performance score.**" | Clarification of inclusion criteria # 5. | • Synopsis- Inclusion Criteria<br>• Section 9.3.1 |
| Changed inclusion criteria #6 "**Monoclonal** antibodies: ≥ 3 half-lives must have elapsed from infusion of last dose of antibody (including checkpoint inhibitors), and toxicity related to prior antibody therapy must be recovered to Grade ≤1."<br>"Hematopoietic growth factors: ≥14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for a short-acting growth factor. For agents that have known AEs occurring beyond 7 days after administration, this period must be extended beyond the time during which AEs | Clarification of inclusion criteria #6. | • Synopsis - Inclusion Criteria<br>• Section 9.3.1 |

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| are known to occur. **The duration of this interval must be discussed with the sponsor**." | | |
| Changed inclusion criteria #8 "Or creatinine clearance or ~~radioisotope~~ GFR ≥50 mL/min/1.73 $m^2$ based on a 12 or 24 hour urine creatinine collection." | Correction to inclusion criteria #8. | • Synopsis - Inclusion Criteria<br>• Section 9.3.1 |
| Changed exclusion criteria #1 "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, or the subject has **commenced/adjusted/**changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug administration, 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."<br>"**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. ~~For sites outside of the EU, double barrier methods of contraception must be used for subjects who have commenced/switched oral contraceptive, or adjusted dose, within 4 weeks prior to dosing~~"<br>Males who have not had a successful vasectomy (confirmed azoospermia) or if 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 ~~28 days~~ **3 months** after study drug discontinuation). No sperm donation is allowed during the study period or for ~~28 days~~ **3 months** after study drug | Clarification of exclusion criteria #1 and removal of duplicate text.<br><br>Updated duration of contraception/window before sperm donation to 3 months (after study drug discontinuation) for male subjects following site feedback to be more conservative and more in line with USPI. | • Synopsis - Exclusion Criteria<br>• Section 9.3.2 |

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| discontinuation. | | |
| Added text to exclusion criteria #2 "Concomitant medications:<br>"• **Strong CYP3A4 inducers/inhibitors (See Section 9.4.6.1.1, Drug-Drug Interactions)**". | Updated in line with eribulin study protocols. | • Synopsis - Exclusion Criteria<br>• Section 9.3.2 |
| Added $^{18}$fluordeoxyglucose (FDG)-PET/CT scans. | Included FDG/PET scans, as per standard of practice at many sites | • Synopsis - Efficacy Assessment<br>• Section 9.5.1.4, Section 9.5.1.6.7, Section 9.5.2, Table 9 |
| The exploratory endpoints of DOR and OS were changed to secondary endpoints. | Following feedback from the FDA and the EMA PDCO. These endpoints have moved from exploratory to secondary endpoints. | • Synopsis - Exploratory Endpoints<br>• Section 9.7.1.1.2, Section 9.7.1.1.3, Section 9.7.1.6.2 |
| E7389-G000-223 is a Phase 2, multicenter, open-label study to conduct a preliminary assessment of the safety and activity of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS. ~~If there is at least 1 response (PR or CR) in at least 1 of these histology types, the study will proceed to a second study, a two-arm, randomized, open-label study to assess the efficacy and safety of eribulin mesylate versus a comparator.~~ | Study design text amended in line with the change in sample size. | • Synopsis - Study Design<br>• Section 9.1, Section 9.2 |
| Changed text "In Study E7389-G000-223, ~~up to 30~~ **45** pediatric subjects, with ~~up to 10~~ **approximately 15** subjects each with RMS, NRSTS, or EWS, will be enrolled to receive eribulin mesylate **as an intravenous (IV) infusion** at a dose of 1.4 mg/m$^2$ (Recommended Phase 2 Dose [RP2D]) **on Days 1 and 8 of each 21-day cycle as** determined by the dose finding study ADVL1314 (Eisai Study E7389-A001-113)". Removed study design figure. | Study design text amended in line with the change in sample size. | • Synopsis – Study Design<br>• Section 9.1 |
| Changed text: For each histology type, ~~up to 10~~ **approximately 15** | Test amended for clarification and in line with change in sample size. | • Synopsis-Study Design, Efficacy Analyses, Interim |

| Change | Rationale | Affected Protocol Sections |
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| subjects will be treated. "**Data will be monitored on an ongoing basis; depending on evaluation by the investigators and sponsor, if sufficient responses** ~~If there is at least 1 response~~ (PRs or CRs) **are** observed, **then** this histology type will be recommended for inclusion in the ~~follow up~~ **subsequent** study." | | Analyses<br>• Section 9.1, Section 9.7.3 |
| Extended screening period from 14 to 28 days. | Following feedback from investigators, to allow more time for completion of screening procedures and to prevent unnecessary repeat scans. The screening period was extended from 14 to 28 days. | • Synopsis – Study Design<br>• Section 9.1, Section 9.5.2, Table 9 |
| Text clarified: all subjects will have an end of treatment visit within 28 days of the last dose of study medication. The follow-up period will begin immediately after the end of treatment visit until death, the subject withdraws consent unless study is terminated by sponsor. | Updated for clarification | • Synopsis – Study Design<br>• Section 9.1 |
| Added text to clarify the frequency of follow up and to increase the duration of follow up for long term survival. | Following feedback from the EMA PDCO, the duration of follow up was clarified and increased. | • Synopsis – Duration of Treatment<br>• Section 9.1<br>• Section 9.5.2, Table 9 |
| Changed text "The primary analysis is to examine the number of responders within each histology subject cohort. ~~If there is at least 1 response in a subject cohort, the corresponding histology will be recommended for inclusion in a randomized study.~~ Confirmed response (PR or CR) will be used in this analysis. ~~The analysis is planned using data from up to 24 weeks after 150 subjects in each cohort have completed response assessments.~~ **In each of the histology groups of RMS, NRSTS, and EWS, approximately 15 subjects will be enrolled and treated with eribulin mesylate. Data will be** | Following feedback from the EMA PDCO and increased sample size. | • Synopsis – Efficacy Analysis<br>• Section 9.7.1.6.1 |

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| **monitored on an ongoing basis; depending on evaluation by the investigators and sponsor, if sufficient responses (partial response [PR] or complete response [CR]) are observed, then this histology type will be recommended for inclusion in the subsequent study. At the latest, the primary analysis will be performed when approximately 15 subjects have completed 24 weeks of response assessments.** | | |
| The secondary analyses were updated to include DOR and OS. The exploratory analyses of DOR and OS were removed. | Following feedback from the FDA and the EMA PDCO, exploratory endpoints of DOR and OS were moved to secondary endpoints. | • Synopsis- Secondary Efficacy Analyses<br>• Section 9.7.1.6 |
| Schafer, et al 2016 reference updated from abstract to full publication 2018. | Reference updated with recent publication. | • Section 7.1.3.2, Section 7.2, Section 10 |
| Changed text "Additional exploratory endpoints efficacy assessments on the exposure of eribulin will be evaluated and the relationship between exposure and AEs and efficacy will also be explored.on DOR and OS (for up to 1 year after last subject in), will also be assessed." | Following feedback from the FDA and the EMA PDCO. These endpoints have moved from exploratory to secondary endpoints. | • Section 9.5.1.3.3 |
| Magnesium added to the chemistry panel for Clinical Laboratory Tests. | Updated in line with eribulin study protocols. | • Section 9.5.1.6.3, Table 8. |
| Added Appendix 2 Modified "Balis" Pediatric Scale of Peripheral Neuropathies. | Included as an appendix for easy reference. | • Appendix 2 |

## Revisions per Amendment 1.1

Date: 29 Sep 2017

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Subjects will be followed for survival approximately every 12 weeks and the follow-up period will begin immediately after the End of Treatment visit.<br><br>During the follow-up period, subjects who have gone off study without progression should have tumor assessments every 6-12 weeks, at the investigators discretion, from the date of last tumor assessment until disease progression, death, or initiation of another anticancer therapy. | The text has been updated for clarification purposes.<br>In-view of the patient population, CNS imaging will only be required for subjects with a history of protocol eligible brain metastasis and as clinically indicated. | • Synopsis ( Study Design; Follow-up section)<br>• 9.1 Overall Study Design and Plan, Follow-up section |
| Assessment grade added for NRSTS | Updated for clarification. | • Synopsis Inclusion Criteria<br>• Section 9.3.1 |
| Time of full neurological examination and assessment criteria used was modified. | Updated for clarity. | • Synopsis, Other Assessments<br>• Section 9.5.1.2.1<br>• Section 9.5.1.3.2<br>• Section 9.5.1.6<br>• Table 9, Footnote n |
| Note: CNS imaging is required to confirm eligibility for subjects with a known history of CNS disease. | In-view of the patient population, CNS imaging will only be required for subjects with a history of protocol eligible brain metastasis and as clinically indicated. | • Synopsis (Exclusion criteria)<br>• Section 9.3.2 Exclusion Criteria |
| Antibodies: 3 half-lives must have elapsed from infusion of last dose of antibody (including checkpoint inhibitors), and toxicity related to prior antibody therapy must be recovered to Grade ≤1 | Update in-line with Eribulin study protocols | • Synopsis (Inclusion Criteria)<br>• Section 9.3.1 Inclusion Criteria |
| 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, or the subject has changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug | Clarification that for sites outside the EU, double barrier method of contraception is acceptable for those subjects that are not on a stable dose of hormonal contraception. | • Synopsis (Exclusion Criteria)<br>• Section 9.3.2 Exclusion Criteria |

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| administration, 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. | | |
| If hematological toxicities do not recover following a dose reduction to dose level -1 and the use of hematopoietic growth factors, the dose should be reduced to dose level -2. If non-hematological toxicities do not recover following a dose reduction to dose level -1, a second dose reduction to dose level -2 should be made. If either hematologic or non-hematologic toxicities do not recover despite two dose reductions**,** the subject should be discontinued from treatment. However, if the subject is deemed to have clinical benefit, continuation of treatment may be discussed with the sponsor. | The text has been updated for clarification purposes. | • Synopsis (Study treatments)<br>• Section 9.4.1.1.1 Eribulin Mesylate |
| Brain scan**s** will not be performed at screening, but will be performed as clinically indicated to assess potential 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 all tumor assessment time points (eg, every 6 weeks). Brain scans will not be performed for subjects with a CR outside the brain. | In-view of the patient population, CNS imaging will only be required for subjects with a history of protocol eligible brain metastasis and as clinically indicated. | • Synopsis (Efficacy Assessments)<br>• 9.5.1.4 Tumor Assessments |
| Confirmed response (PR or CR) will be used in this analysis. | The text has been updated for clarification purposes; responses confirmed 4 weeks post initial assessment of PR/CR per RECIST 1.1 will be used in the analysis.<br>The text has been updated for clarification purposes; responses confirmed 4 weeks post initial assessment of PR/CR per RECIST 1.1 will be used in the analysis. | • Synopsis (Efficacy Analysis)<br>• Section 9.7.1.6.1 Primary Efficacy Analysis<br>• Synopsis (Interim Analysis)<br>• Section 9.7.3 Interim Analysis |

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| The mainstay of the treatment of sarcoma in all age groups is surgical excision (Table 4). | The text has been amended for clarification purposes. | • Section 7.1.1 Current Therapeutic Options |
| The prognosis for children with metastatic NRSTS at diagnosis and, recurrent NRSTS is poor. | Text updated for clarification purposes. | • Section 7.1.1.2 Treatment Strategies for Non-rhabdomyosarcoma Soft Tissue Sarcoma |
| Standard first-line treatment for patients with metastatic EWS is either a 3 drug regimen of vincristine, doxorubicin and cyclophosphamide or a 5 drug regimen VAC with ifosfamide/etoposide**.**<br><br>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). | Text updated for clarification purposes. | • 7.1.1.3 Treatment Strategies for Ewing Sarcoma |
| Laboratory assessment of cholesterol, globulin, and triglycerides was removed | Text updated due to typographical error | • Table 8 Clinical Laboratory Tests |
| Concomitant radiotherapy for local control is allowed from Week 24. | From week 24, the subject may receive radiotherapy for local control and continue to receive drug on study | • Section 9.4.6 |
| A CT/MRI scan of the brain will not be performed during the Screening Phase, but will be performed as clinically indicated to assess potential CNS disease and/or metastases and as clinically indicated and at all time points **(**including screening**)** for subjects with protocol-eligible treated brain metastases. | In-view of the patient population, CNS imaging will only be required for subjects with a history of protocol eligible brain metastasis and as clinically indicated.<br>In-view of the patient population, CNS imaging will only be required for subjects with a history of protocol eligible brain metastasis and as clinically indicated. | • 9.5.1.6.7 Other Safety Assessments, Brain Scan<br>• Table 9 Schedule of Assessments |
| Footnote k. was modified to note Pre-study phase: Screening CT or MRI of the brain should be performed between Day -14 and Day -1 for subjects with previously treated protocol-eligible brain metastases only. | In-view of the patient population, CNS imaging will only be required for subjects with a history of protocol eligible brain metastasis and as clinically indicated. | • Table 9 Schedule of Assessments |

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| For subjects with previously treated protocol-eligible brain metastases, a brain scan must be performed at all tumor assessment time points. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability. | | |
| Global change: removal of Appendix 1 Sponsor's Grading for Laboratory Values | For clarification purposes since the Sponsor's grading is aligned with CTCAE V4.0 | • Appendix 1 |

## Revisions per Amendment 1.0

## Date: 05 Jul 2017

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| Update from Ewing's sarcoma to Ewing sarcoma | Consistency of text | • Global change |
| Previous text:<br>Or creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 $m^2$ based on a 12 or 24 hour urine creatinine collection.<br>Amended text:<br>Or creatinine clearance or radioisotope **GFR ≥50** mL/min/1.73 $m^2$ based on a 12 or 24 hour urine creatinine collection. | Inclusion criteria was carried over from pediatric phase 1 study 113 and therefore has been updated in-line with the label for Halaven where impaired renal function is defined as creatinine clearance <50 mL/min. Additionally, considering that renal elimination accounts for approximately 10% total systemic clearance of eribulin, adjustment for a pediatric population is not required. | • Synopsis (Inclusion Criteria 8)<br>• Section 9.3.1 Inclusion Criteria 8 |
| Previous text:<br>2. Concomitant medications:<br>• Receiving drugs that prolong the QTc.<br>Amended text:<br>2. Concomitant medications:<br>• ~~Receiving drugs that prolong the QTc.~~ | The inclusion criteria were carried over from pediatric phase 1 study 113. The criteria have been updated in-line with the Halaven label where concomitant use of drugs that prolong the QTc is not contraindicated. | • Synopsis (Exclusion Criteria 2)<br>• Section 9.3.2 Exclusion Criteria 2 |
| Previous text:<br>Increase the frequency of ECG and electrolyte monitoring in subjects who develop Grade 2 QTc prolongation or have clinically | The text has been updated in-line with the Halaven label. | • Section 9.4.1 1.1 ERIBULIN MESYLATE, Instructions for QTc Prolongation on Electrocardiogram (ECG) |

## Revisions per Amendment 1.0

## Date: 05 Jul 2017

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| relevant electrolyte abnormalities. Permanently discontinue eribulin mesylate in subjects who develop ≥Grade 3 QTc prolongation, and monitor ECGs and electrolytes frequently until the QTc interval return to baseline.<br><br>Amended text:<br>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 eribulin mesylate in subjects who develop ≥Grade 3 QTc prolongation, and monitor ECGs and electrolytes frequently until the QTc interval return**s** to baseline. | | |
| Previous text:<br>2. Concomitant medications:<br>Corticosteroids: Subjects receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to study drug administration (except when indicated for Central Nervous System (CNS) metastases, when the exclusion is at least 28 days).<br><br>Amended text:<br>Concomitant medications:<br>Corticosteroids: Subjects receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to study drug administration (except when indicated for Central Nervous System (CNS) metastases, **then subjects must not have received corticosteroids for** ~~when the exclusion is~~ at least | Text updated to clarify that for patients with brain metastases who have discontinued corticosteroids, a 4 week washout period is required per exclusion 9, for inclusion into the study. | • Section 9.3.2 Exclusion Criteria 2 |

## Revisions per Amendment 1.0

## Date: 05 Jul 2017

| Change | Rationale | Affected Protocol Sections |
|---|---|---|
| 28 days)**.** | | |
| Previous text:<br>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 prior to randomization).<br>[f] Female subjects of childbearing potential require a negative urine or serum (depending on local practice) pregnancy test prior to starting treatment (within 7 days prior to Cycle 1 Day 1).<br><br>Amended text:<br>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~~ **72 hours** prior to ~~randomization~~ **the first dose of study drug**).<br><br>[f]Female subjects of childbearing potential require a negative urine or serum (depending on local practice) pregnancy test prior to starting treatment (within ~~7 days~~ **72 hours** prior to Cycle 1 Day 1). | Text amended to clarify that serum β-hCG or urine test is required within 72 hours of first dose of study drug and to align exclusion criteria 1, section 9.5.1.6.7 and Schedule of Procedures/ Assessments (Table 9). | • Section 9.5.1.6.7, OTHER SAFETY ASSESSMENTS, Pregnancy test, Schedule of Procedures/Assessments (Table 9), pregnancy test, f |
| Footnote k updated to j, footnote l and m updated to k, footnote n updated to l and footnote o updated to m.<br>Footnote m removed from tumor assessment at follow-up | Alignment of Schedule of Procedures/Assessments and footnotes | Schedule of Procedures/ Assessments (Table 9). |

# 1 TITLE PAGE


## Clinical Study Protocol

| | |
|---|---|
| **Study Protocol Number:** | E7389-G000-223 |
| **Study Protocol Title:** | A Phase 2, multicenter, open-label study to assess safety and preliminary activity of eribulin mesylate in pediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) and Ewing sarcoma (EWS) |
| **Sponsor:** | Eisai Inc.<br>155 Tice Boulevard<br>Woodcliff Lake,<br>New Jersey 07677<br>US<br><br>Eisai Ltd.<br>European Knowledge Centre<br>Mosquito Way<br>Hatfield, Hertfordshire<br>AL10 9SN UK |
| **Investigational Product Name:** | E7389/Halaven® (eribulin/eribulin mesylate/eribulin mesylate) |
| **Indication:** | Relapsed/refractory Rhabdomyosarcoma, Non rhabdomyosarcoma Soft Tissue Sarcoma and Ewing sarcoma in Pediatric Subjects |
| **Phase:** | 2 |
| **Approval Date(s):** | 20 Mar 2017 (Original Protocol)<br>05 Jul 2017 (Amendment 1.0)<br>29 Sep 2017 (Amendment 1.1)<br>20 Dec 2018 (Amendment 2.0) |
| **IND Number:** | 116,292 |
| **GCP Statement:** | This study is to be performed in full compliance with International Council on Harmonisation of Technical Requirements for Registration of 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. |

**Confidentiality Statement:**

This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

# 2 CLINICAL PROTOCOL SYNOPSIS

**Compound No.: E7389**

**Name of Active Ingredients:** eribulin mesylate

**Study Protocol Title**

A Phase 2, multicenter, open-label study to assess safety and preliminary activity of eribulin mesylate in pediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) and Ewing sarcoma (EWS)

**Investigator**

Douglas S Hawkins, MD.

Katie Albert, MD.

**Sites**

Approximately 40 sites in the US. The Study will be conducted by the COG network.

**Study Period and Phase of Development**

Approximately 24 to 36 months from first subject providing signed informed consent to last subject last visit (LSLV).

Phase 2

**Objectives**

**Primary Objectives**

- To conduct a preliminary assessment of activity of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS or EWS to determine whether each cohort warrants further investigation.

**Secondary Objectives**

- To evaluate the progression-free survival (PFS), using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS in all cohorts combined.
- To evaluate the safety and tolerability of eribulin in the pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS in all cohorts combined.
- To evaluate the duration of response (DOR) of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS.
- To evaluate the overall survival (OS) of pediatric subjects with relapsed/refractory RMS, NRSTS and EWS.

**Exploratory Objectives**

- To evaluate the exposure of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS.
- To explore the relationship between exposure to eribulin mesylate and adverse events (AE) and efficacy.
-

**Study Design**

E7389-G000-223 is a Phase 2, multicenter, open-label study to conduct a preliminary assessment of the safety and activity of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS.

Forty-five pediatric subjects, with approximately 15 subjects each with RMS, NRSTS, or EWS, will be enrolled to receive eribulin mesylate as an intravenous (IV) infusion at a dose of 1.4 $mg/m^2$ (Recommended Phase 2 Dose [RP2D]) on Days 1 and 8 of each 21-day cycle, as determined by the dose finding study ADVL1314 (Eisai Study E7389-A001-113).

**Outline**

- Pediatric subjects with relapsed/refractory RMS, NRSTS or EWS will be enrolled to receive therapy with eribulin mesylate.
- For each histology type, approximately 15 subjects will be treated. Data will be monitored on an ongoing basis; depending on evaluation by the investigators and sponsor, if sufficient responses (partial response [PR] or complete response [CR]) are observed, then this histology type will be recommended for inclusion in the subsequent study.
- Subjects will continue study therapy until progression of disease (per RECIST 1.1), intolerable toxicity or withdrawal of consent.

**Pre-study Phase:**

Day -28 to -1, computed 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 of Cycle 1.

**Follow-up:**

The follow-up period will begin immediately after the End of Treatment visit until death or informed consent is withdrawn, unless the study is terminated by the sponsor. Subjects will be followed for survival approximately every 12 weeks for 1 year and then annually thereafter. As well as follow-up for survival, the annual surveillance will also assess any long term effects of the study treatment.

During the follow-up period, subjects who have gone off study treatment without progression should have tumor assessments every 6-12 weeks, at the investigators discretion, from the date of last tumor assessment until disease progression, death, or initiation of another anticancer therapy, whichever occurs first, unless the study is terminated by the sponsor. Follow-up data will be required unless consent is withdrawn.

**Number of Subjects**

The target enrollment is 45 subjects.

**Inclusion Criteria**

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

1. Age: ≥12 months to <18 years old at the time of informed consent.
2. Diagnosis: Histologically confirmed RMS, NRSTS (Grade 2 or 3) or EWS which is relapsed or refractory (failed front line therapy).
3. The presence of measurable disease meeting the following criteria:
   - 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).

- 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 or therapy proven to prolong survival with an acceptable quality of life.
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 performance score.
6. Subjects must have fully recovered from the acute toxic effects of all prior anticancer therapy and must meet the following minimum duration from prior anticancer directed therapy prior to study drug administration. If, after the required time frame, the numerical eligibility criteria are met, eg, blood count criteria, the subject is considered to have recovered adequately:
   - Cytotoxic chemotherapy or other chemotherapy known to be myelosuppressive: ≥21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).
   - Anticancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or Absolute neutrophil count [ANC] counts): ≥7 days after the last dose of agent.
   - Monoclonal antibodies: ≥ 3 half-lives must have elapsed from infusion of last dose of antibody (including checkpoint inhibitors), and toxicity related to prior antibody therapy must be recovered to Grade ≤1.
   - Hematopoietic growth factors: ≥14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for a short-acting growth factor. 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.
   - Interleukins, interferons, and cytokines (other than hematopoietic growth factors): ≥21 days after the completion of interleukins, interferons or cytokines (other than hematopoietic growth factors).
   - Stem cell infusions (with or without total body irradiation [TBI]): ≥84 days.
   - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor lymphocyte infusion or boost infusion: ≥84 days after infusion and no evidence of graft versus host disease (GVHD).
   - Autologous stem cell infusion including boost infusion: ≥42 days.
   - Cellular therapy: ≥42 days after the completion of any type of cellular therapy (eg, modified T-cells, natural killer cells, dendritic cells, etc).
   - Radiation therapy (XRT)/External Beam Irradiation including Protons: ≥14 days after local XRT; ≥150 days after TBI, craniospinal XRT or if radiation to ≥50% of the pelvis; ≥42 days if other substantial BM radiation.
   - Radiopharmaceutical therapy (eg, radiolabeled antibody, $^{131}$I-Metaiodobenzylguanidine): ≥42 days after systemically administered radiopharmaceutical therapy.
7. Adequate bone marrow function, defined as:
   - ANC ≥1.0 x $10^9$/L.
   - Platelet count ≥100 x $10^9$/L (transfusion independent, defined as not receiving platelet

transfusions within a 7-day period prior to study drug administration).

- Hemoglobin at least 8.0 g/dL at Baseline (blood transfusions are allowed during the screening period to correct hemoglobin values less than 8.0 g/dL).

Note: 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 glomerular filtration rate (GFR) (see table below).

| 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 glomerular filtration rate (GFR) (Schwartz and Gauthier. J Pediatr. 1985;106:522–6) utilizing child length and stature data published by the Centers for Disease Control and Prevention (CDC).

   - Or creatinine clearance or GFR ≥50 mL/min/1.73 $m^2$ based on a 12 or 24 hour urine creatinine collection.
9. Adequate liver function, defined as:
   - Bilirubin (sum of conjugated + unconjugated) ≤1.5 x upper limit of normal (ULN) for age.
   - Alanine aminotransferase (ALT) ≤110 U/L. For the purpose of this study, the ULN for ALT is 45 U/L.
   - 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.

**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 [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, or the subject has commenced/adjusted/changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug administration, 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 if 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 or decreasing dose of corticosteroid for at least 7 days prior to study drug administration (except when indicated for Central Nervous System (CNS) metastases, then subjects must not have received corticosteroids for at least 28 days).
   - 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 (See Section 9.4.6.1.1, Drug-Drug Interactions).
3. Received prior therapy with eribulin mesylate.
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 eribulin or any of the excipients.

6. Has a 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:
   - Subjects with known congestive heart failure, symptomatic or left ventricular (LV) ejection fraction <50% or shortening fraction <27%
   - 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 4 weeks prior to study drug administration. Confirmation of radiographic stability must be done by comparing the brain scan (CT or MRI) performed during the Screening Period, using the same imaging modality, to a brain scan performed earlier (and following local therapy where applicable). Subjects must be clinically stable. It is not the intention of this protocol to treat subjects with active brain metastases.

   Note: CNS imaging is required to confirm eligibility for subjects with a known history of CNS disease.
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.
    - Laparoscopic procedure or open biopsy within 7 days prior to study drug administration.
    - 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.
    - 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. 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.
12. Subjects with known human immunodeficiency virus (HIV); due to lack of available safety data for eribulin therapy in HIV infected subjects.

**Study Treatment(s)**

Administration of eribulin mesylate by 2-5 min IV infusion at 1.4 mg/m$^2$ on Days 1 and 8 of each 21-day cycle. 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.

**Criteria for Dosing Modifications**

Dose reduction and interruption for eribulin mesylate related toxicity will be performed according to the following instructions.

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

**Table 1 Criteria for Administration of Eribulin Mesylate**

| **a): Do not administer Cycle 1 Day 1 treatment where:** |
|---|

| | |
|---|---|
| **Absolute Neutrophil Count** | <1.0 × $10^9$/L or 1,000/$mm^3$ |
| **Platelets** | <100 × $10^9$/L or 100,000/$mm^3$ |
| **Non-hematological toxicity** | Any > Grade 2 except for inadequately treated nausea and/or vomiting |
| **b): Do not administer any Day 8 treatment where:** | |
| **Absolute Neutrophil Count** | <0.75 × $10^9$/L or 750/$mm^3$ |
| **Platelets** | <75 × $10^9$/L or 75,000/$mm^3$ |
| **Non-hematological toxicity** | Any > Grade 2 except for inadequately treated nausea and/or vomiting |
| **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 |

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 the values in Table 1 or Grade ≤2 as appropriate (for Cycle 1 & 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 and Table 3).

**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). The Day 8 dosing will be **delayed for a maximum of 7 days** and as follows:

- If recovery occurs on or before Day 15, dosing will be resumed at the next lower dose level (Table 3) and this will be the new Day 8.
- If hematological or non-hematological toxicity has not resolved to the above values on Day 15, the second administration in the cycle will be omitted. Dosing will be resumed at the next lower dose level (Table 3) and as scheduled on Day 1 of the next cycle if recovery has occurred to the above values.

Please note, use of hematopoietic growth factors is not permitted in Cycle 1 and is only permitted in subsequent cycles as per institutional guidelines.

The treatment will be permanently reduced to the next lowest dose level (Table 3) after the occurrence of any of the following events:

**Table 2 Criteria for Reduction of Eribulin Mesylate to the Next Lowest Dose Level**

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

| | |
|---|---|
| **Platelets** | Grade 4 thrombocytopenia<br>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 |

### Table 3 Eribulin Mesylate Dose Modifications

Dose modifications based on adverse events (AEs) for eribulin mesylate (Starting dose determined by COG protocol ADVL1314/Eisai Study E7389-A001-113; 1.4 mg/m$^2$).

| Dose Level | Eribulin mesylate (mg/m$^2$) |
|---|---|
| 0* | 1.4 |
| -1 | 1.1 |
| -2 | 0.8 |

* Dose level 0 refers to the starting dose.

If hematological toxicities do not recover following a dose reduction to dose level -1 and the use of hematopoietic growth factors the dose should be reduced to dose level -2. If non-hematological toxicities do not recover following a dose reduction to dose level -1, a second dose reduction to dose level -2 should be made. If either hematologic or non-hematologic toxicities do not recover despite two dose reductions, the subject should be discontinued from treatment. However, if the subject is deemed to have clinical benefit, continuation of treatment may be discussed with the sponsor.

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

**Duration of Treatment**

Subjects may remain on study treatment as long as they do not meet any of the following criteria: 1) experience objective progression of disease (according to RECIST 1.1); 2) exhibit no clinical benefit (in the opinion of the investigator); 3) experience unacceptable toxicity leading to withdrawal from the study; 4) withdraw or are withdrawn from the study for any reason, or; 5) termination of the study program, 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. An end of treatment (EOT) visit within 28 days after last date of receiving investigational drug will be performed for subjects who discontinue study treatment. After discontinuation of treatment and completion of the EOT visit, subjects will be followed up for survival approximately every 12 weeks for 1 year, and then annually thereafter, unless consent is withdrawn or death.

**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 or for culture proven bacteremia or invasive fungal infection. Prophylactic granulocyte colony-stimulating factor should NOT be administered during Cycle 1.

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 the study.

**Assessments**

**Efficacy Assessments**

Tumor response and progression will be evaluated according to RECIST 1.1 criteria. Copies of all scans for tumor assessments will be sent to an imaging core laboratory designated by the sponsor for quality assessment, archiving and potential independent review. Tumor assessment scans will be performed following the guidelines provided by the imaging core laboratory. Decisions concerning treatment discontinuation due to progressive disease will be based on investigator assessment.

Tumor assessments (CT chest, and CT or MRI abdomen, pelvis, and other known or suspected sites or disease) will be performed during screening and then every 6 weeks (within the sixth week) on a fixed schedule from the date of first study drug administration. Magnetic resonance imaging scans may be used instead of CT scans for abdomen and pelvis; however, chest must be assessed using CT. Scans that were performed within the screening window, but before informed consent, may be used if they were acquired consistent with the guidelines provided by the imaging core laboratory. The same method of assessment must be used at all time-points as used at pre-study. Partial and complete responses will be confirmed at least 4 weeks after initial documentation of PR or CR typically on the next consecutive scheduled tumor assessment. After 24 weeks subjects with CR, PR or stable disease (SD) may have imaging decreased to every 9 weeks (within the ninth week).

A bone scan or $^{18}$FDG-PET/CT scan 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 cross-sectional imaging.

Brain scans will be performed as clinically indicated to assess potential 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 all tumor assessment time points (eg, every 6 weeks).

Subjects who discontinue treatment without objective evidence of disease progression will continue to have tumor assessments, per the schedule of assessments, until disease progression, death, or initiation of another anticancer therapy.

**Pharmacokinetic Assessments**

Blood samples will be collected for PK analysis of eribulin as follows:

1. Immediately post-infusion on Day 1 of each cycle for the first 3 cycles
2. Pre-infusion and immediately post-infusion on Day 8 of each cycle for the first 3 cycles

**Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments**

**Exposure-response Analyses**

Following FDA guidance, PK sampling will be conducted in subjects across the pediatric program at regular intervals in order to adequately characterize the PK of eribulin in the pediatric population in the various age cohorts to explore exposure-response relationships for activity/efficacy and safety. The relationship between exposure to eribulin mesylate and AE and efficacy will be explored graphically.

**Safety Assessments**

Safety assessments will consist of monitoring and recording all adverse events (AEs) according to Common Terminology Criteria for Adverse Events (CTCAE v4.03). This includes listing of all grades (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, the performance status, and physical examinations.

**Other Assessments**

ECG monitoring to evaluate RR, PR, QRS, and QT intervals and QTc interval (corrected for heart rate [QTc] using Fridericia's [QTcF] and Bazett's [QTcB] correction factors) at pre-study, during Cycle 1 (pre- and post-infusion Day1 and Day 8) and as clinically indicated during subsequent cycles and during follow-up (28 days after the last dose of drug).

A full neurological examination will be conducted at Screening. On subsequent cycles an assessment of neuropathy (neuropathy present/absent and CTC AE Grade) will be assessed as part of the physical examination

**Bioanalytical Methods**

Plasma concentrations of eribulin mesylate will be determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method. The lower limit of quantification (LLOQ) is 0.2 ng/mL.

**Statistical Methods**

**Study Endpoints**

**Primary Endpoints**

- Objective response: number of subjects achieving a best objective response of partial or complete response (PR or CR), by up to 24 weeks after all subjects have completed response assessment. Response assessment will be as determined by investigator.

**Secondary Endpoints**

- PFS: defined as the time from the first dose date to the date of disease progression or date of death (whichever occurs first).
- Safety and tolerability: AEs, SAEs, clinical laboratory values, ECG parameters, vital sign measurements, and performance status.
- DOR: defined as the time from the first date of documented PR or CR to the date of disease progression or date of death (whichever occurs first).
- OS: defined as the time from the first dose date to the date of death.

**Exploratory Endpoints**

- Exposure of eribulin mesylate.

**Analysis Sets**

**Full Analysis Set** (FAS) will consist of all subjects who receive at least 1 dose of study drug.

**Safety Analysis Set** (SAS) will consist of all subjects who receive at least 1 dose of study drug.

**Pharmacokinetic Analysis Set** (PAS) will include subjects who have at least 1 evaluable plasma concentration and sufficient dosing information.

**Efficacy Analyses**

The primary analysis will be based on investigator assessments of tumor response.

The primary analysis is to examine the number of responders within each histology subject cohort. Confirmed response (PR or CR) will be used in this analysis. In each of the histology groups of RMS, NRSTS, and EWS, approximately 15 subjects will be enrolled and treated with eribulin mesylate. Data will be monitored on an ongoing basis; depending on evaluation by the investigators and sponsor, if sufficient responses (partial response [PR] or complete response [CR]) are observed,

then this histology type will be recommended for inclusion in the subsequent study. At the latest, the primary analysis will be performed when approximately 15 subjects have completed 24 weeks of response assessments.

**Secondary Efficacy Analyses**

The secondary analyses will be to estimate the PFS, DOR, and OS in all cohorts combined. Median PFS, DOR, and OS will be estimated using Kaplan-Meier method.

**Pharmacokinetic Analyses**

Observed eribulin concentrations from this study will be overlaid with existing observed concentrations and model-predicted 90% prediction intervals at the same dose level from other studies to demonstrate comparability in exposure.

**Safety Analyses**

Safety analyses will be performed on all subjects who receive at least 1 dose of study drug. It will include safety data collected from screening to data cut-off. Safety data include the incidence and severity of AEs, clinical laboratory test results, performance status, 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. Treatment-emergent abnormal laboratory test results, vital signs, and ECGs will be listed.

All AEs and SAEs will be listed. Treatment-emergent AEs (TEAEs), treatment-related TEAEs, and SAEs will be summarized by cohort, system organ class, preferred term, and CTCAE v. 4.03 grade. QT intervals will be measured from Lead II and will be corrected for heart rate (QTc) using QTcF and QTcB correction factors. The primary QTc parameter will be QTcF. Secondary parameters will be QTcB, QT, QRS, and heart rate.

**Interim Analyses**

Data will be monitored on an ongoing basis; depending on evaluation by the investigators and sponsor, if sufficient responses (PR or CR) are observed, then this histology type will be recommended for inclusion in the subsequent study.

## Sample Size Rationale

A total of 45 subjects will be enrolled. In each of the histology groups of RMS, NRSTS, and EWS, approximately 15 subjects will be enrolled and treated with eribulin mesylate. The sample size is considered sufficient based on clinical judgment and is not obtained from statistical calculation.

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# 4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| ADI | adipocytic soft tissue sarcoma |
| AE | adverse event |
| ALL | acute lymphoblastic leukemia |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| BSA | body surface area |
| CI | confidence interval |
| CNS | central nervous system |
| COG | Children's Oncology Group |
| CR | complete response |
| CRA | clinical research associate |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | curriculum vitae |
| DOR | duration of response |
| ECG | Electrocardiogram |
| EFS | event-free survival |
| EMT | epithelial-mesenchymal transition |
| EWS | Ewing sarcoma |
| FDA | Food and Drug Administration |
| GCP | good clinical practice |
| GFR | glomerular filtration rate |
| GVHD | graft versus host disease |
| hCG | human chorionic gonadotropin |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |
| ICF | informed consent form |
| ICH | International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IIR | Independent imaging review |
| IRB | Institutional Review Board |

| Abbreviation | Term |
|---|---|
| IUD | intrauterine device |
| IUS | intrauterine system |
| IV | Intravenous |
| IxRS | interactive voice / web response system |
| LLN | lower limit of normal |
| LMS | Leiomyosarcoma |
| MCR | maintained complete response |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | Medicines and Healthcare Products Regulatory Agency |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| NRSTS | non-rhabdomysosarcoma soft tissue sarcoma |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PET | positron emission tomography |
| PFS | progression-free survival |
| PI | principal investigator |
| PK | Pharmacokinetic |
| PPTP | Pediatric Preclinical Testing Program |
| PR | partial response |
| PT | preferred term |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RMS | Rhabdomyosarcoma |
| RP2D | recommended Phase 2 dose |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SAS | safety analysis set |
| SD | stable disease |
| SOC | system organ class |
| STS | soft tissue sarcoma |
| TEAE | treatment-emergent adverse event |
| TBI | total body irradiation |

| Abbreviation | Term |
|---|---|
| ULN | upper limit of normal |
| VAC | vinca alkaloid, actinomycin D, and cyclophosphamide |
| WHO DD | World Health Organization Drug Dictionary |
| XRT | Radiation therapy |

# 5 ETHICS

## 5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, Informed Consent Form (ICF), and appropriate related documents will 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, ie, 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 data cut-off for the final analysis or the time of last subject/last visit, whichever occurs later.

## 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 2008.
- 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 Study 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 or guardian/legally authorized representative 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. 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 or the subject's legally authorized representative 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 or if a legally authorized 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 or the subject's legally authorized representative, and after the subject or the subject's legally authorized representative 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 or the subject's legally authorized representative 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 approximately 40 sites in the US.

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 Sarcomas

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 rhabdomyosarcoma (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 soft tissue sarcoma (STS), followed by fibrohistiocytic tumors (10%), synovial sarcoma (9%), Ewing sarcoma (EWS) and (also known as primitive neuroectodermal tumor [PNET] of soft tissue; 9.2%), fibroblastic and myofibroblastic tumors (6%), nerve sheath tumors (5%), liposarcoma (2.3%), extrarenal rhabdoid tumors (2%), leiomyosarcoma (LMS; 2%), alveolar soft parts sarcoma (1.4%), and blood vessel tumors (1.4%). An additional 9.3% of tumors are unspecified sarcoma (National Cancer Institute, 2016).

### 7.1.1 Current Therapeutic Options

The mainstay of the treatment of sarcoma in all age groups is definitive local therapy (surgical excision, radiotherapy or both (Table 4). The consensus is that all patients with RMS and EWS should receive chemotherapy as part of their primary treatment (surgery or if surgery is not feasible, radiotherapy) (Van Gaal, et al., 2012). The role of chemotherapy in the primary treatment of non-rhabdomyosarcoma (NRSTS) has not been established.

**Table 4 Principles of RMS, NRSTS and EWS Treatment**

| Treatment | RMS | EWS | NRSTS |
|---|---|---|---|
| Primary | Surgical excision (where feasible)<br>Definitive radiotherapy if wide excision not possible<br>Multi-agent neo/adjuvant chemotherapy (all patients) | Surgical excision (where feasible)<br>Definitive radiotherapy if wide excision not possible<br>Multi-agent neo/adjuvant chemotherapy (all patients) | Surgical excision (where feasible)<br>Radiotherapy (residual or high-risk disease or inoperable)<br>± 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

Treatments for relapsed/refractory disease are broadly similar across the tumor types (Table 4). Further information on treatment options for each tumor types is provided below.

#### 7.1.1.1 Treatment Strategies 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 standard approach at first relapse is active single agent or 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 or without vincristine, or 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 clinical outcomes 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 no longer curative intent. The choice of agent(s) is based upon the treatment options available at the institution including access to clinical studies, 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. This 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 at diagnosis and, recurrent 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 recurrent, unresectable or metastatic disease, but none of these regimens improved the outcome for these subjects.

The NRSTS is a broad category that includes many subtypes of sarcoma, any of which may be enrolled on this study. It is noted that in the adult sarcoma experience with eribulin mesylate, responses have been observed in leimyocsarcoma, liposarcoma, synovial sarcoma, undifferentiated sarcoma, and vascular sarcomas.

#### 7.1.1.3 Treatment Strategies for Ewing Sarcoma

Standard first-line treatment for patients with metastatic EWS is either a 3 drug regimen of vincristine, doxorubicin and cyclophosphamide or a 5 drug regimen VAC with ifosfamide/etoposide. 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.

Survival after relapse is typically less than 1 year. 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 vinca alkaloid with actinomycin-D and cyclophosphamide (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 mesylate)

#### 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 mesylate 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).

#### 7.1.3.1.1 TUMOR BIOLOGY-BASED MECHANISMS

Numerous investigations in human breast cancer models have shown that eribulin induces therapeutically meaningful changes in tumor biology and tumor-host interactions that go beyond its known classical antimitotic actions (sNDA 201532/S-013; Yoshida, et al., 2014; Funahashi, et al., 2014). Evidence for eribulin-induced changes in tumor biology and tumor-host interactions falls into 3 main areas: effects on tumor vascular function and remodeling; effects on phenotype and the epithelial-mesenchymal transition (EMT), or more specifically the reversal of EMT; and effects on tumor cell migration, invasiveness, and metastatic capacity. In summary, eribulin treatment of human breast cancer cells caused changes in morphology and gene expression as well as decreased migration and invasiveness in vitro. In human breast cancer xenograft models in immunocompromised mice, eribulin treatment was associated with increased vascular perfusion and permeability in the tumor cores, resulting in reduced tumor hypoxia, and changes in the expression of genes in tumor specimens associated with a change in phenotype (ie, reversal of EMT).

As found in human breast cancer models, recently completed nonclinical investigations of effects of eribulin on human adipocytic (ADI) sarcoma and LMS cell lines and tumor xenograft models (submitted to IND 067193, sequence 0665) have also shown that eribulin exerts effects on tumor biology and phenotype that go well beyond its classical antimitotic effects in this tumor type. Such effects include morphologic changes in SW872 ADI sarcoma and SK-UT 1 LMS cell lines consistent with transitioning to a more differentiated phenotype (Study Nos. W-20150640, W-20150639), increased perfusion in SK-LMS-1 human LMS xenografts (Study No. M15014), and upregulation of adipocyte and smooth muscle differentiation markers in SW872 ADI sarcoma and SK-UT-1 LMS cells, respectively (Study Nos. W-20150640, W-20150639). These results, analogous to the reported findings associated with reversal of the EMT in human breast cancer models (sNDA 201532/S-013; Yoshida, et al., 2014; Funahashi, et al., 2014), suggest that eribulin can cause phenotypic changes in human ADI sarcomas and LMS that result in more differentiated, less aggressive residual tumors.

### 7.1.3.2 Clinical Experience With Eribulin

A Phase 1 study (Eisai Study E7389-A001-113, Study 113) of eribulin mesylate in pediatric patients with recurrent or refractory solid tumors (excluding CNS), including lymphomas has been conducted. Eribulin mesylate was administered intravenously, once per day on Days 1

and 8 of a 21-day cycle. This study aimed to determine the MTD and/or the RP2D of this regimen in Part A1 (patients ≥12 months and <18 years). Additionally, this study aimed to describe the toxicities and the pharmacokinetics of eribulin mesylate when administered to children. In a preliminary manner, the antitumor effect of eribulin mesylate was also described. The MTD was determined to be 1.4 mg/m$^2$, which is the same dose as in the adult population. No major differences were observed in the safety profile between adults and pediatric subjects (Schafer, et al., 2018).

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 ADI (46.9%, 95% 2-sided confidence interval [CI]; 29.1, 65.3) and LMS (31.6%, 95% 2-sided CI; 17.6, 48.7) strata. The study concluded that eribulin has activity in pretreated subjects with ADI sarcoma and 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).

Pre-planned, exploratory subgroup analyses of OS and PFS by histology showed that eribulin significantly favored subjects with the ADI 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. No significant difference between the treatment arms was observed for OS or PFS in subjects with LMS histology (Halaven USPI, 2016).

This is the first time any agent has demonstrated improved OS in late line adult liposarcoma. Following the results of this study, regulatory applications were submitted globally and on 28 Jan 2016 eribulin was approved by the Food and Drug Administration (FDA) for the

treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

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, NDA 201532/Seq 0102). 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 $PFR_{12weeks}$ 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 OTH stratum, and 51.0% (95% CI: 36.6, 65.2) in total (Study E7389-J088-217 Clinical Study Report).

#### 7.1.3.3 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: <0.10 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 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 26 of 30 (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 (Rh28, Rh30, Rh30R, and Rh41 cells). CRs or MCRs were also observed in 1 of 2 Wilms' tumor, 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).

## 7.2 Study Rationale

The unique survival advantage seen in Study 309, and the activity of eribulin seen in both Studies 207 and 217, suggests that it is desirable to pursue development in pediatric sarcomas. However, the potential differences in the sensitivity of specific tumor subtypes to microtubule inhibition make it difficult to justify development of eribulin in pediatric

populations based on the clinical antitumor activity in adults alone. Strong supportive evidence from nonclinical studies is provided in Section 7.1.3.3.

In addition to the encouraging results seen in the PPTP, and the unique survival advantage observed in adult liposarcoma subtype, the aim of eribulin development in childhood sarcoma is also based upon and the unmet medical need in advanced RMS, EWS, and NRSTS. Eribulin may offer a potential new alternative to the available therapies for children who have failed standard treatments for advanced RMS, EWS, and NRSTS.

A Phase 1 study (Eisai Study E7389-A001-113, Study 113) of eribulin mesylate in pediatric patients with recurrent or refractory solid tumors (excluding CNS), including lymphomas has been conducted. The MTD was determined to be 1.4 $mg/m^2$, which is the same dose as in the adult population. No major differences were observed in the safety profile between adults and pediatric subjects (Schafer, et al., 2018).

# 8 STUDY OBJECTIVES

## 8.1 Primary Objective

The primary objectives of the study are:

- To conduct a preliminary assessment of activity of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS or EWS to determine whether each cohort warrants further investigation.

## 8.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the PFS, using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS in all cohorts combined.
- To evaluate the safety and tolerability of eribulin in the pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS in all cohorts combined.
- To evaluate the duration of response (DOR) of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS.
- To evaluate the overall survival (OS) of pediatric subjects with relapsed/refractory RMS, NRSTS and EWS.

## 8.3 Exploratory Objective(s)

- To evaluate the exposure of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS.
- To explore the relationship between exposure to eribulin mesylate and AEs and efficacy.

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan

E7389-G000-223 is a Phase 2, multicenter, open-label study to conduct a preliminary assessment of the safety and activity of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS.

Forty-five pediatric subjects, with approximately 15 subjects each with RMS, NRSTS, or EWS, will be enrolled to receive eribulin mesylate as an intravenous (IV) infusion at a dose of 1.4 mg/m$^2$ (Recommended Phase 2 Dose [RP2D]) on Days 1 and 8 of each 21-day cycle as determined by the dose finding study ADVL1314 (Eisai Study E7389-A001-113).

**Outline**

- Pediatric subjects with relapsed/refractory RMS, NRSTS or EWS will be enrolled to receive therapy with eribulin mesylate.
- For each histology type, approximately 15 subjects will be treated. Data will be monitored on an ongoing basis; depending on evaluation by the investigators and sponsor, if sufficient responses (PRs or CRs) are observed, then this histology type will be recommended for inclusion in the subsequent study.
- Subjects will continue study therapy until progression of disease (per RECIST 1.1), intolerable toxicity or withdrawal of consent.

**Pre-study Phase:**

Day -28 to -1, computed 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 of Cycle 1.

**Follow-up:**

The follow-up period will begin immediately after the End of Treatment visit until death or informed consent is withdrawn, unless the study is terminated by the sponsor. Subjects will be followed for survival approximately every 12 weeks for 1 year and then annually thereafter. As well as follow-up for survival, the annual surveillance will also assess any long term effects of the study treatment.

During the follow-up period, subjects who have gone off study treatment without progression should have tumor assessments every 6 - 12 weeks, at the investigator's discretion, from the date of last tumor assessment until disease progression is documented, death, or initiation of

another anticancer therapy, whichever occurs first, unless the study is terminated by the sponsor. Follow-up data will be required unless consent is withdrawn.

## 9.2 Discussion of Study Design

This is an open-label study to conduct a preliminary assessment of safety and activity of eribulin mesylate in pediatric subjects with relapsed/refractory RMS, NRSTS, or EWS. The secondary objective of PFS is an appropriate surrogate endpoint for studies in STS as there are significant correlations between PFS and OS ($R$=0.61) and between objective response rate (ORR) and OS ($R$=0.51) (Zer, at al., 2016).

## 9.3 Selection of Study Population

The subject population for this study comprises pediatric subjects aged ≥12 months to <18 years at the time of informed consent, with a histologically confirmed diagnosis of RMS, NRSTS, or EWS, that is considered to be relapsed or refractory (ie, subjects have failed front-line therapy).

Approximately 45 subjects will be enrolled. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

### 9.3.1 Inclusion Criteria

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

1. Age: ≥12 months to <18 years old at the time of informed consent.
2. Diagnosis: Histologically confirmed RMS, NRSTS (Grade 2 or 3) or EWS which is relapsed or refractory (failed front line therapy).
3. The presence of measurable disease meeting the following criteria:
   - 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 CT/MRI.
   - 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 or therapy proven to prolong survival with an acceptable quality of life.
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 performance score.

6. Subjects must have fully recovered from the acute toxic effects of all prior anticancer therapy and must meet the following minimum duration from prior anticancer directed

therapy prior to study drug administration. If, after the required time frame, the numerical eligibility criteria are met, eg, blood count criteria, the subject is considered to have recovered adequately:

- Cytotoxic chemotherapy or other chemotherapy known to be myelosuppressive: ≥21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).
- Anticancer agents not known to be myelosuppressive (eg, not associated with reduced platelet or absolute neutrophil count [ANC] counts): ≥7 days after the last dose of agent.
- Monoclonal antibodies: 3 half-lives must have elapsed from infusion of last dose of antibody (including checkpoint inhibitors), and toxicity related to prior antibody therapy must be recovered to Grade ≤1.
- Hematopoietic growth factors: ≥14 days after the last dose of a long-acting growth factor (eg, Neulasta) or 7 days for a short-acting growth factor. 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.
- Interleukins, interferons, and cytokines (other than hematopoietic growth factors): ≥21 days after the completion of interleukins, interferons or cytokines (other than hematopoietic growth factors).
- Stem cell infusions (with or without total body irradiation [TBI]): ≥84 days.
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including donor lymphocyte infusion or boost infusion: ≥84 days after infusion and no evidence of graft versus host disease (GVHD).
- Autologous stem cell infusion including boost infusion: ≥42 days.
- Cellular therapy: ≥42 days after the completion of any type of cellular therapy (eg, modified T-cells, natural killer cells, dendritic cells, etc).
- Radiation therapy (XRT)/External Beam Irradiation including Protons: ≥14 days after local XRT, ≥150 days after TBI, craniospinal XRT or if radiation to ≥50% of the pelvis, ≥42 days if other substantial BM radiation.
- Radiopharmaceutical therapy (eg, radiolabeled antibody, $^{131}$I-metaiodobenzylguanidine): ≥42 days after systemically administered radiopharmaceutical therapy.

7. Adequate bone marrow function, defined as:
   - 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 at least 8.0 g/dL at Baseline (blood transfusions are allowed during the screening period to correct hemoglobin values less than 8.0 g/dL)

Note: 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 as follows, derived from the Schwartz formula for estimating glomerular filtration rate (GFR) (see table below)

| 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 glomerular filtration rate (GFR) (Schwartz and Gauthier. J Pediatr. 1985;106:522–6) utilizing child length and stature data published by the Centers for Disease Control and Prevention (CDC).

   - Or creatinine clearance or GFR ≥50 mL/min/1.73 $m^2$ based on a 12 or 24 hour urine creatinine collection.

9. Adequate liver function, defined as:
   a. Bilirubin (sum of conjugated + unconjugated) ≤1.5 × upper limit of normal (ULN) for age
   b. ALT ≤110 U/L. For the purpose of this study, the ULN for ALT is 45 U/L.
   c. 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 [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, or the subject has commenced/adjusted/changed oral hormonal contraceptive product/dose within 4 weeks prior to study drug administration, 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 if 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 or decreasing dose of corticosteroid for at least 7 days prior to study drug administration (except when indicated for Central Nervous System (CNS) metastases, then subjects must not have received corticosteroids for at least 28 days)
   - Anticancer Agents: Subjects who are currently receiving other anticancer agents
   - Anti-GVHD agents posttransplant:
     - Subjects who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant

- Strong CYP3A4 inducers/inhibitors (See Section 9.4.6.1.1, Drug-Drug Interactions).

3. Received prior therapy with eribulin mesylate (when confirmed)
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 eribulin or any of the excipients.
6. Has a 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: Subjects with known congestive heart failure, symptomatic or left ventricular (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 4 weeks prior to study drug administration. Confirmation of radiographic stability must be done by comparing the brain scan (CT or MRI) performed during the Screening Period, using the same imaging modality, to a brain scan performed earlier (and following local therapy where applicable). Subjects must be clinically stable. It is not the intention of this protocol to treat subjects with active brain metastases.

   **Note:** CNS imaging is required to confirm eligibility for subjects with a known history of CNS disease
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
    - Laparoscopic procedure or open biopsy within 7 days prior to study drug administration.
    - 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.
    - Core biopsy, including bone marrow biopsy within 2 days prior study drug administration
    - Fine needle aspirate within 3 days prior to study drug administration.
11. 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
12. Subjects with known human immunodeficiency virus (HIV); due to lack of available safety data for eribulin therapy in HIV infected subjects.

### 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. If a subject discontinues study treatment, the subject will enter the Follow-Up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents. A subject removed from the study for any reason other than toxicity or progression may be replaced.

During the Follow-Up Period, subjects who have discontinued study treatment without progression should have disease assessments as per the Schedule of Assessments from the date of the last assessment until disease progression as per RECIST 1.1 is documented, death or another anticancer therapy is initiated.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to halt survival follow-up after completion of the primary study analysis.

## 9.4 Treatments

### 9.4.1 Treatments Administered

Eribulin mesylate will be administered by IV infusion over 2-5 minutes on Days 1 and 8 of each 21-day cycle. 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.

#### 9.4.1.1 Criteria for Dosing Modifications

Dose reduction and interruption will be performed according to the instructions in Section 9.4.1.1.1.

##### 9.4.1.1.1 ERIBULIN MESYLATE

Treatment will not be administered when any of the following values are recorded (Table 5).

**Table 5 Criteria for Administration of Eribulin Mesylate**

| **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 × $10^9$/L or 100,000/$mm^3$ |
| **Non-hematological toxicity** | Any > Grade 2 except for inadequately treated nausea and/or vomiting |
| **b): Do not administer any Day 8 treatment where:** | |
| **Absolute Neutrophil Count** | <0.75 × $10^9$/L or 750/$mm^3$ |
| **Platelets** | <75 × $10^9$/L or 75,000/$mm^3$ |
| **Non-hematological toxicity** | Any > Grade 2 except for inadequately treated nausea and/or vomiting |
| **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 |

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 in Table 5 or Grade ≤2 as appropriate (for Cycle 1 & 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 6 and Table 7).

**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 5). The Day 8 dosing will be **delayed for a maximum of 7 days** and as follows:

- If recovery occurs on or before Day 15, dosing will be resumed at the next lower dose level (Table 7) and this will be the new Day 8.
- If hematological or non-hematological toxicity has not resolved to the above values on Day 15, the second administration in the cycle will be omitted. Dosing will be resumed at the next lower dose level (Table 7) and as scheduled on Day 1 of the next cycle if recovery has occurred to the above values.

Please note, use of hematopoietic growth factors is not permitted in Cycle 1 and is only permitted in subsequent cycles as per institutional guidelines.

The treatment will be permanently reduced to the next lowest dose level (Table 6) after the occurrence of the following events:

**Table 6 Criteria for Reduction of Eribulin Mesylate to the Next Lowest Dose Level**

| | |
|---|---|
| **Absolute Neutrophil Count** | Grade 4 neutropenia > 7 days<br>Grade 3 or 4 febrile neutropenia and/or infection requiring treatment with antibiotics and/or growth factors |
| **Platelets** | Grade 4 thrombocytopenia<br>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 |

If hematological toxicities do not recover following a dose reduction to dose level -1 and the use of hematopoietic growth factors, the dose should be reduced to dose level -2. If non-hematological toxicities do not recover following a dose reduction to dose level -1, a second dose reduction to dose level -2 should be made. If either hematologic or non-hematologic toxicities do not recover despite two dose reductions, the subject should be discontinued from treatment. However, if the subject is deemed to have clinical benefit, continuation of treatment may be discussed with the sponsor.

Dose modifications are based on AEs for eribulin mesylate (starting dose determined by COG protocol ADVL1314/Eisai Study E7389-A001-113; 1.4 mg/m$^2$; Table 7).

**Table 7 Eribulin Mesylate Dose Modifications**

| Dose level | Eribulin mesylate (mg/m$^2$) |
|---|---|
| 0* | 1.4 |
| -1 | 1.1 |
| -2 | 0.8 |

* Dose level 0 refers to the starting dose.

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

**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 eribulin mesylate in subjects who develop ≥Grade 3 QTc prolongation, and monitor ECGs and electrolytes frequently until the QTc interval returns to baseline.

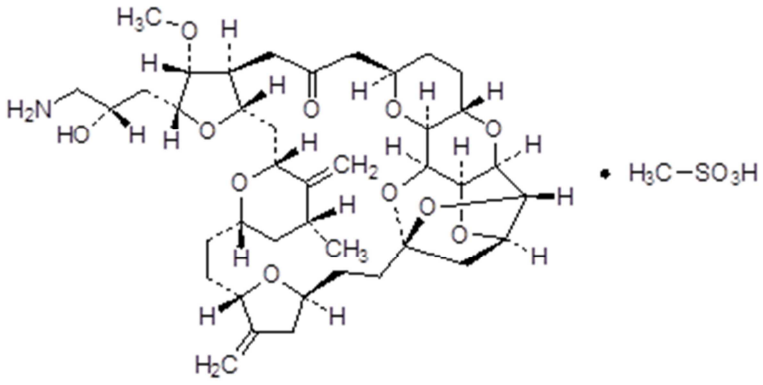
### 9.4.2 Identity of Investigational Products

Eribulin mesylate will be supplied by the sponsor in labeled containers.

#### 9.4.2.1 Chemical Name, Structural Formula of Eribulin Mesylate

- Test drug code: E7389
- Generic name: Eribulin Mesylate
- 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 Labeling for Study Drug

Eribulin mesylate will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

#### 9.4.2.3 Storage Conditions

Study drug 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.

### 9.4.3 Method of Assigning Subjects to Treatment Groups

The subjects will receive eribulin mesylate only.

### 9.4.4 Selection of Doses in the Study

Eribulin mesylate will be administered at the RP2D (1.4 mg/m$^2$; Eisai Study E7389-A001-113). Further information on dose modification is provided in Section 9.4.1.

### 9.4.5 Selection and Timing of Dose for Each Subject

Eribulin mesylate should be administered by IV infusion over 2-5 minutes on Days 1 and 8 of a 21-day cycle. 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 28 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 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 guidelines or for culture proven bacteremia or invasive fungal infection. Prophylatic granulocyte colony-stimulating factor should NOT be administered in Cycle 1.

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 the study. From week 24, the subject may receive radiotherapy for local control and continue to receive drug on study.

#### 9.4.6.1 Drug-Drug Interactions

##### 9.4.6.1.1 ERIBULIN MESYLATE

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 (Halaven USPI, 2016).

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

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

#### 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 (up to week 24), or 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 and continue to be followed for survival in the Follow-Up Period.

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 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, Medicines and Healthcare Products Regulatory Agency [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. End-of-Treatment assessments will be collected within 28 days of the last dose of study drug. Screening and Baseline characteristics and End-of-Treatment assessments are listed in the Schedule of Procedures/Assessments (Table 9).

##### 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 9). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and at baseline, a complete neurological examination. On subsequent evaluations an assessment of neuropathy (neuropathy present/absent and CTC AE Grade) will be made as part of the physical 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 PRIMARY

Efficacy will be evaluated by objective tumor responses provided as determined by the investigator according to RECIST v1.1. For analysis purposes, ORR is defined as the proportion of subjects who achieve a CR plus those who achieve a PR.

##### 9.5.1.3.2 SECONDARY

Efficacy will also be evaluated according to a secondary endpoint (PFS; defined as the time from the date of the first dose of study treatment until the date of first documentation of progressive disease (PD) or date of death [whichever occurs first]). Assessments for these endpoints are to be performed every 6 weeks by use of consistent imaging methodology (ie, CT scan/MRI or bone scan) and consistent use or nonuse of contrast media) until Week 24, then every 9 weeks. In addition, OS status (disposition) and DOR will be assessed throughout the study. For subjects receiving radiotherapy and/or surgery for local control post week 24, progression will be assessed as the date of radiotherapy/surgical procedure.

##### 9.5.1.3.3 EXPLORATORY

Additional exploratory endpoints on the exposure of eribulin will be evaluated and the relationship between exposure and AEs and efficacy will also be explored.

#### 9.5.1.4 Tumor Assessments

Tumor response and progression will be evaluated according to RECIST 1.1 criteria. Copies of all scans for tumor assessments will be sent to an imaging core laboratory designated by the sponsor. Tumor assessments will be carried out following the guidelines provided by the imaging core laboratory. Decisions concerning treatment discontinuation for PD will be based on investigator assessment.

Tumor assessments (CT chest, and CT or MRI abdomen, pelvis, and other known or suspected sites or disease) will be performed during screening and then every 6 weeks (within the sixth week) on a fixed schedule from the date of first study drug administration. Magnetic resonance imaging (MRI) scans may be used instead of CT scans for abdomen and pelvis; however, chest must be assessed using CT. The same method of assessment must be used at all time-points as used at pre-study. Partial and complete responses will be confirmed at least 4 weeks after initial documentation of PR or CR, typically on the next consecutive scheduled tumor assessment. After 24 weeks subjects with CR, PR or stable disease (SD) may have imagining decreased to every 9 weeks (within the ninth week). A bone scan using whole body bone MRI, $^{99}$m-technetium based bone scans, $^{18}$fluordeoxyglucose (FDG)-PET/CT scans or $^{18}$F-sodium fluoride positron emission tomography [NaF 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 cross-sectional imaging.

Brain scans will be performed as clinically indicated to assess potential 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 all tumor assessment time points (eg, every 6 weeks).

Subjects who discontinue treatment without objective evidence of disease progression will continue to have tumor assessments performed, per the schedule of assessments, until disease progression, death, or initiation of another anticancer therapy.

#### 9.5.1.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

##### 9.5.1.5.1 PHARMACOKINETIC ASSESSMENTS

Samples for PK analysis of eribulin will be collected immediately post-infusion on Day 1 each cycle for 3 cycles, and pre-infusion and immediately post-infusion on Day 8 each cycle for 3 cycles (Table 9). Plasma concentrations of eribulin will be tabulated and summarized by dose level and time.

##### 9.5.1.5.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Not applicable.

#### 9.5.1.6 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, according to Common Terminology Criteria for Adverse Events (CTCAE) v 4.03. This includes listing of all grades (for both increasing and decreasing severity), and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs; performance status, and physical examinations as detailed in Table 9.

**Other Assessments**

ECG monitoring to evaluate RR, PR, QRS, and QT intervals and QTc interval (corrected for heart rate [QTc] using Fridericia's [QTcF] and Bazett's [QTcB] correction factors) at pre-study, during Cycle 1 (pre- and post-infusion Day1 and Day 8) and as clinically indicated during subsequent cycles and during follow-up (28 days after the last dose of drug).

A full neurologic examination will be conducted at Screening. On subsequent cycles an assessment of neuropathy (neuropathy present/absent and CTC AE Grade) will be made as part of the physical examination.

#### 9.5.1.6.1 ADVERSE EVENTS

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 drug is eribulin mesylate.

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 and SAEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject and/or their parents or legally authorized representatives signs the study ICF through the last visit.

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 for 28 days after the subject's last dose, or until resolution, whichever comes first. SAEs will be collected for 28 days posttreatment and followed until resolution or, if resolution is unlikely, until the event or sequelae stabilize.

Progression of malignant disease 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 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 CTCAE v4 (National Institutes of Health Cancer Therapy Evaluation Program, 2010). 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.

#### 9.5.1.6.2 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.

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

#### 9.5.1.6.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 8. Subjects should be in a seated or supine position during blood

collection. The Schedule of Procedures/Assessments (Table 9) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Efforts should be made to conduct study visits on the day scheduled. If holidays or other reasons make the day impossible, then sample collection may be up to 2 days sooner or later. Clinical laboratory assessments may be conducted based on Table 9.

### Table 8 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, magnesium |
| Liver function tests | Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin |
| Renal function tests | Blood urea/blood urea nitrogen, creatinine |
| Other | * Albumin, calcium (total + ionized), glucose, lactate dehydrogenase, phosphorus, total protein, 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. Uric acid is not required at subsequent chemistry measurement time points.

Clinical laboratory tests during the Treatment Phase will be performed by designated local laboratories. All blood and urine samples will be collected and sent to the local laboratory on the day of collection unless otherwise instructed

Local laboratories will perform tests to qualify subjects for entry into the study. Laboratory certification as available will be included in the final clinical study report for this study.

All hematology, blood chemistry (including pregnancy test, as applicable), 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. Refer to Section 9.4.1.1 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 9.5.1.6.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

#### 9.5.1.6.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 9) by a validated method.

#### 9.5.1.6.5 PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 9). 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.

#### 9.5.1.6.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 9). 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 9.5.1.6.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

#### 9.5.1.6.7 OTHER SAFETY ASSESSMENTS

**Brain Scan**

A CT/MRI scan of the brain will be performed as clinically indicated and at all time points (including screening) for subjects with protocol-eligible treated brain metastases.

**Bone Scan**

Bone scans may be performed every 24 weeks during the Treatment Phase, and as clinically indicated, using $^{99}$Tc bone scans, NaF (PET) bone scans, $^{18}$FDG-PET/CT scans or whole body bone MRI. The same methodology used at screening should be performed at all subsequent bone 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 72 hours prior to the first dose of study drug).

**Karnofsky and Lansky Performance Status**

Karnofsky (for subjects >16 years of age) or Lansky (for subjects ≤16 years of age) performance status will be assessed at Screening, Days 1 and 8 during Cycle 1, Day 1 of each subsequent treatment cycle, and at the End-of-Treatment Visit.

### 9.5.2 Schedule of Procedures/Assessments

Table 9 presents the schedule of procedures/assessments for the study.

## Table 9 Schedule of Procedures/Assessments in Study E7389-G000-223

| Phase | Pretreatment | Treatment | | | | | | | | | | | | | Follow-up until 1-year | Annual Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Screening[a]** | **Cycle 1** | | | **Cycle 2[b]** | | | **Cycle 3[b]** | | | **Additional Cycles[b]** | | | **EOT** | | |
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11+** | | | **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** | | |
| **Procedures/Assessments** | | | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | |
| Inclusion/exclusion | X | | | | | | | | | | | | | | | |
| Vital signs[c] | X | X | X | | X | X | | X | X | | X | X | | X | | |
| Height[d] | X | | | | | | | X | | | X | | | X | | |
| Weight, BSA | X | X | X | | X | | | X | | | X | | | X | | |
| Physical examination | X | X | X | | X | | | X | | | X | | | X | | |
| Performance status[e] | X | X | X | | X | | | X | | | X | | | X | | |
| Pregnancy test[f] | X | | | | | | | | | | | | | X | | |
| Hematology[g] | X | Weekly | | | Weekly | | | Weekly | | | Weekly | | | X | | |
| Chemistry | X | Weekly | | | X | | | X | | | X | | | X | | |
| Eribulin mesylate administration (21-Day | | X | X | | X | X | | X | X | | X | X | | | | |

## Table 9 Schedule of Procedures/Assessments in Study E7389-G000-223

| **Phase** | **Pretreatment** | **Treatment** | | | | | | | | | | | | | **Follow-up until 1-year** | **Annual Follow-up** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period** | **Screening[a]** | **Cycle 1** | | | **Cycle 2[b]** | | | **Cycle 3[b]** | | | **Additional Cycles[b]** | | | **EOT** | | |
| **Visit** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11+** | | | **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** | | |
| **Procedures/Assessments** | | | | | | | | | | | | | | | | |
| cycle | | | | | | | | | | | | | | | | |
| Neurologic examination[n] | X | | | | X | | | X | | | X | | | | | |
| Pharmacokinetic sampling[h] | | X | X | | X | X | | X | X | | | | | | | |
| ECG[i] | X | X | X | | Clinically indicated | | | | | | | | | X | | |
| Urinalysis | X | | | | X | | | Clinically indicated | | | | | | X | | |
| Tumor assessment[j] | X | | | | | | | Every 6 weeks (counting from date of Cycle 1 Day 1) until Week 24, then every 9 weeks | | | | | | | X | |
| Brain CT/MRI[k] | X | As clinically indicated and at all time points for subjects with protocol-eligible treated brain metastases at screening | | | | | | | | | | | | | | |
| Bone scan[l] | X | Every 24 weeks and as clinically indicated | | | | | | | | | | | | | | |
| Prior/concomitant medications | | Throughout | | | | | | | | | | | | | | |

## Table 9 Schedule of Procedures/Assessments in Study E7389-G000-223

| Phase | Pretreatment | Treatment | | | | | | | | | | | | | Follow-up until 1-year | Annual Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Period | Screening[a] | Cycle 1 | | | Cycle 2[b] | | | Cycle 3[b] | | | Additional Cycles[b] | | | EOT | | |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11+ | | | 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 | | |
| Procedures/Assessments | | | | | | | | | | | | | | | | |
| Adverse events | | Throughout | | | | | | | | | | | | X | | |
| Survival status | | | | | | | | | | | | | | | X[m] | X[o] |

BSA = body surface area, CT = computed tomography, ECG = electrocardiogram, EOT = end of treatment, MRI = magnetic resonance imaging.

a. The Screening Period extends from Day -28to Day -1. Day -28 to -1, computed tomography (CT) / magnetic resonance imaging (MRI) scans must be performed within 28 days prior to study drug administration. For logistical purposes, informed consent may be obtained from Day -29. 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.
b. Assessments/procedures may be obtained within 72 hours prior to the start of the subsequent cycle.
c. Vital signs should be performed Day 1, Day 8, and at the End of Treatment (EOT) for subjects receiving eribulin mesylate.
d. Height should be measured every other cycle from Cycle 3.
e. Performance status will be measured using Karnofsky or Lansky scales.
f. Female subjects of childbearing potential require a negative urine or serum (depending on local practice) pregnancy test prior to starting treatment (within 72 hours prior to Cycle 1 Day 1).
g. Subjects will need to have hematology samples obtained weekly; an outside complete blood count can be performed when at the physician's discretion.
h. PK sample collection schedule:
    1. Immediately post- eribulin infusion on Day1 of each cycle for the first 3 cycles
    2. Pre- eribulin infusion and immediately post-infusion on Day 8 of each cycle for the first 3 cycles.
i. On Days 1 and 8 of Cycle 1, two 12-lead ECGs will be obtained: one 15-30 minutes before infusion and a second one immediately after the infusion. The post-infusion ECG should precede the collection of the post-infusion PK sample on Days 1 and 8 of Cycle 1.

j. Pre-study phase: Screening tumor assessments using CT of the chest/abdomen and pelvis and other areas of known disease or newly suspected disease should be performed between Day -28 and Day -1. Detailed image acquisition guidelines will be provided by the imaging core laboratory. Scans that were performed within this window but before informed consent may be used if they were acquired consistent with the guidelines provided by the imaging core laboratory. 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, and 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, counting from the date of first dose (or sooner if there is evidence of progressive disease) until Week 24 and then every 9 weeks (or sooner if clinically indicated) thereafter 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. A chest x-ray or skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

   Follow-Up Period: Subjects who have gone off study without progression should have tumor assessments every 6 weeks from the date of last tumor assessment until disease progression or initiation of another anti-cancer therapy. At week 24 and thereafter, these scans may be conducted every 9 weeks.

k. Pre-study phase: Screening CT or MRI of the brain should be performed between Day -28 and Day -1 for subjects with previously treated protocol-eligible brain metastases only.

   For subjects with previously treated protocol-eligible brain metastases, a brain scan must be performed at all tumor assessment time points. The same methodology and scan acquisition techniques used at screening should be used throughout the study to ensure comparability.

l. Bone scans may be performed, where indicated, using 99Tc based bone scans, NaF (PET) bone scans, $^{18}$FDG-PET/CT scans or whole body bone MRI. The same methodology used at screening should be performed at all subsequent bone assessments.

m. Subjects will be followed for survival approximately every 12 weeks from the end of treatment for 1 year, unless consent is withdrawn or death

n. A full neurological examination will be conducted at Screening. During Cycle 2 (Day 1), Cycle 3 (Day 1), and Day 1 of any additional cycle, neurological status (as a minimum, neuropathy present/absent and NCI CTC Grade) will be assessed as part of the physical examination.

o. Subjects will be followed up annually after the 1 year follow up is complete (See footnote ‘m’), for survival and assessment of any latent effects of the study treatment, unless consent is withdrawn or death

### 9.5.3 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.

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

#### 9.5.4.1 Reporting of Serious Adverse Events

**All SAEs, 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 1 business day from the date the investigator becomes aware of the event.**

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 SAEs 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 1 business day 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.

#### 9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject (or partner of a male subject) 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 9.5.4.1]).

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.

#### 9.5.4.3 Reporting of Events Associated with Special Situations

##### 9.5.4.3.1 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 9.5.4.1) 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 non-serious on the SAE form and the Adverse Event CRF.

#### 9.5.4.4 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.

#### 9.5.4.5 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.

### 9.5.5 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 9).

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. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason other than toxicity or progression may be replaced.

### 9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drugs by completing the Abuse or Diversion of Study Drug CRF.

Adverse events associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.6.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Potential Abuse-related Medication Handling Event CRF.

## 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. 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 ENDPOINT

The primary endpoint is:

- Objective response: number of subjects achieving a best objective response of partial or complete response (PR or CR), by up to 24 weeks after all subjects have completed response assessment. Response assessment will be as determined by investigator.

##### 9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints are:

- PFS: defined as the time from the first dose date to the date of disease progression or date of death (whichever occurs first).
- Safety and tolerability: AEs, SAEs, clinical laboratory values, ECG parameters, vital sign measurements, and performance status.
- DOR: defined as the time from the first date of documented PR or CR to the date of disease progression or date of death (whichever occurs first).
- OS: defined as the time from the first dose date to the date of death.

##### 9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints are:

- Exposure of eribulin mesylate.

#### 9.7.1.2 Definitions of Analysis Sets

The **Full Analysis Set** (FAS) will consist of all subjects who receive at least 1 dose of study drug.

The **Safety Analysis Set** (SAS) will consist of all subjects who receive at least 1 dose of study drug.

The **Pharmacokinetic Analysis Set** (PAS) will include subjects who have at least 1 evaluable plasma concentration and sufficient dosing information.

#### 9.7.1.3 Subject Disposition

The number and percentage of subjects who discontinue the study treatment as well as the reason for discontinuation will be summarized.

#### 9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics. Continuous demographic and baseline variables include age, weight, and vital signs; categorical variables include sex, age group, and race.

#### 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 on the Full Analysis Set by treatment, 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 (or, started at the time of or after the first dose of study drug) up to 28 days after the subject's last dose. All medications will be presented in subject data listings.

#### 9.7.1.6 Efficacy Analyses

Efficacy analyses will be performed on the FAS.

##### 9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on investigator assessments of tumor response.

The primary analysis is to examine the number of responders within each histology subject cohort. Confirmed response (PR or CR) will be used in this analysis. In each of the histology groups of RMS, NRSTS, and EWS, approximately 15 subjects will be enrolled and treated with eribulin mesylate. Data will be monitored on an ongoing basis; depending on evaluation by the investigators and sponsor, if sufficient responses (PRs or CRs) are observed, then this histology type will be recommended for inclusion in the subsequent study. At the latest, the primary analysis will be performed when approximately 15 subjects have completed 24 weeks of response assessments.

##### 9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be to estimate the PFS, DOR, and OS in all cohorts combined. Median PFS, DOR, and OS will be estimated using Kaplan-Meier method. Descriptive

statistics will be provided. Duration of response (DOR) will be calculated for subjects with an objective response of PR or CR.

#### 9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

##### 9.7.1.7.1 PHARMACOKINETIC ANALYSES

Blood samples will be collected for the PK analysis of eribulin as follows:

1. Immediately post-infusion on Day 1 of each cycle for the first 3 cycles
2. Pre-infusion and immediately post-infusion on Day 8 of each cycle for the first 3 cycles

##### 9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

**Exposure-response Analyses**

Following FDA guidance, PK sampling will be conducted in subjects across the pediatric program at regular intervals in order to adequately characterize the PK of eribulin in the pediatric population in the various age cohorts to explore exposure-response relationships for activity/efficacy and safety. The relationship between exposure to eribulin mesylate and AE and efficacy will be explored graphically.

#### 9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment arm, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include adverse events, clinical laboratory parameters, vital signs, 12-lead ECG results, and performance status.

##### 9.7.1.8.1 EXTENT OF EXPOSURE

The number of cycles administered, duration of treatment, and the number of subjects who had dose reduction and dose delay will be summarized for eribulin mesylate.

##### 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 (Baseline) 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 summarized with the number and 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 and percentage of subjects with TEAEs will also be summarized by highest CTCAE grade (CTCAE v4.03).

The number and percentage of subjects with treatment-related TEAEs will also be summarized by MedDRA SOC and PT.

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

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

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

#### 9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.6.3, the actual value and the change from baseline and to the end of treatment (defined as the last on-treatment value) will be summarized using descriptive statistics. Qualitative parameters listed in Section 9.5.1.6.3 will be summarized using frequencies (number and percentage of subjects). Shift tables will be provided presenting post-baseline against the baseline with number and percentage of subjects. Percentages will be based on the number of subjects with both baseline and the corresponding post-baseline measurements.

Laboratory test results will be assigned a classification according to CTCAE grade. Summaries of CTCAE grade and shifts from baseline will be presented.

#### 9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (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.

Shift tables will present shifts from baseline to end of treatment in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant).

In addition, the number and percentage of subjects with at least 1 post-baseline abnormal ECG result in QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Fridericia 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 increase from baseline >30 ms
- QTc interval increase from baseline >60 ms

#### 9.7.1.8.6 OTHER SAFETY ANALYSES

**Performance Status**

Karnofsky and Lansky performance status scores and their changes from baseline will be summarized using descriptive statistics.

### 9.7.2 Determination of Sample Size

A total of 45 subjects will be enrolled. In each of the histology groups of RMS, NRSTS, and EWS, approximately 15 subjects will be enrolled and treated with eribulin mesylate. The sample size is considered sufficient based on clinical judgment and is not obtained from statistical calculation.

### 9.7.3 Interim Analysis

Data will be monitored on an ongoing basis; depending on evaluation by the investigators and sponsor, if sufficient responses (PR or CR) are observed, then this histology type will be recommended for inclusion in the subsequent study.

### 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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# 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 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 2 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-G000-223

**Study Protocol Title:** A Phase 2, multicenter, open-label study to assess safety and preliminary activity of eribulin mesylate in pediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) and Ewing sarcoma (EWS)

**Investigational Product Name:** E7389 (eribulin mesylate)

**IND Number:** 116,292

## SIGNATURES

Authors:

PPD

3 Jan 2019
Date

Oncology Business Group, Eisai Ltd.

PPD

2 January 2019
Date

Oncology Business Group, Eisai Inc.

PPD

2 Jan. 2019
Date

Oncology Business Group, Eisai Inc.

PPD

Jan. 2, 2019
Date

Oncology Business Group, Eisai Inc.

# INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Study Protocol Number:** | E7389-G000-223 |
| **Study Protocol Title:** | A Phase 2, multicenter, open-label study to assess safety and preliminary activity of eribulin mesylate in pediatric subjects with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) and Ewing sarcoma (EWS) |
| **Investigational Product Name:** | E7389 (eribulin mesylate) |
| **IND Number:** | 116,292 |

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 Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

| Investigator | Signature | Date |
|---|---|---|