# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | NDA 201532/SDN 950/SE-23 |
| **Link to EDR** | \\CDSESUB1\evsprod\nda201532\0240\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\e7389-a001-113\e7389-a001-113--study-report-body.pdf |
| **Submission Date** | 3/17/2022 |
| **Submission Type** | Efficacy Supplement (fulfillment of the Pediatric Written Request (WR) with proposed labeling changes) |
| **Brand Name** | Halaven |
| **Generic Name** | Eribulin Mesylate |
| **Dosage Form and Strength** | 1 mg per 2 mL (0.5 mg per mL) eribulin mesylate in a single-dose vial |
| **Route of Administration** | For intravenous use |
| **Proposed Indication** | HALAVEN is a microtubule inhibitor indicated for the treatment of patients with:<br>• Metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.<br>• Unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen<br>*These approved indications are for the treatment of adult patients.* |
| **Applicant** | Eisai Inc. |
| **Associated IND** | IND (b) (4) |
| **OCP Review Team** | Christy John, Ph.D.; Hong Zhao, Ph.D. |
| **PM Review Team** | Youwei Bi, Ph.D. |
| **OCP Final Signatory** | Stacy Shord, PharmD, Deputy Division Director, DCPII |

## 1. EXECUTIVE SUMMARY

Eisai submitted an efficacy supplemental New Drug Application (sNDA) for HALAVEN® (eribulin mesylate) in fulfillment of the Pediatric Written Request (WR), issued on 10 November 2021, and in support of proposed revised labeling of eribulin mesylate based on the results from the three pediatric clinical studies conducted in accordance with the WR.

This current submission provides the final response to the WR, in accordance with the exclusivity provisions of Section 505A of the Federal Food, Drug and Cosmetic Act (FD&C Act). Eisai has included a request for pediatric exclusivity of 6 months for HALAVEN.

This sNDA submission contains clinical pharmacology data from three studies conducted in pediatric patients (aged 2 to <17 years) with refractory/relapsed and recurrent solid tumors – Studies E7389-A001-113 (Study 113), E7389-G000-213 (Study 213), and E7389-G000-223 (Study 223), wherein HALAVEN 1.1 to 1.8 mg/m$^2$ was administered via intravenous infusion over 2 to 5 minutes on Days 1 and 8 of each 21-day treatment cycle. Population pharmacokinetic (PK) and PK/PD (pharmacodynamics) analyses were conducted and are summarized in the submission.

Overall steady-state exposure ($AUC_{ss}$) increased proportionally with total eribulin dose indicating linear PK. Eribulin total clearance (CL) and dose-normalized AUC were comparable among different studies, and between adult and pediatric patients age sub-groups. No new safety signals were observed in patients enrolled in the three studies as established in adults.

### 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 201532 SE 23. The supplement has met the terms of the Written Request from a clinical pharmacology perspective. The supplement is approvable given that the Applicant and the FDA have reached an agreement regarding the labeling language including the results of the pediatric studies.

## 2. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

### 2.1 Overview of the Product and Regulatory Background

HALAVEN was approved on 15 November 2010 for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting. On 28 January 2016, HALAVEN was approved for the treatment of patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.

This current submission provides the final response to the WR in accordance with the exclusivity provisions of Section 505A of the FD&C Act. Eisai has included a request for pediatric exclusivity of 6 months for HALAVEN.

In accordance with the provisions of Section 505(a)(i)(1)(A)(B) of the FD&C Act, which states that an application under Section 505 proposing a labeling change as a result of any pediatric study conducted pursuant to this section shall be considered to be a priority application.

### 2.2 General Pharmacological and Pharmacokinetic Characteristics

The clinical pharmacology of eribulin has previously been described in detail in the clinical pharmacology review of the original NDA 201532 submission. Refer to the original NDA Clinical Pharmacology Review for a detailed description of the clinical pharmacology data. Briefly, the PK of eribulin is linear with a mean elimination half-life approximately 40 hours, a mean volume of distribution of 43 L/m$^2$ to 114 L/m$^2$ and mean clearance of 1.16 L/hr/m$^2$ to 2.42 L/hr/m$^2$ over the dose range of 0.25 mg/m$^2$ to 4 mg/m$^2$. The human plasma protein binding of eribulin at concentrations of 100 ng/mL to 1,000 ng/mL ranges from 49% to 65%. Eribulin exposure after multiple dosing is comparable to that following a single dose. No accumulation of eribulin is observed with weekly administration.

## 2.3 Clinical Pharmacology Questions

### *2.3.1 Do the results of the three pediatric studies fulfill the Written Request from a clinical pharmacology perspective?*

The current sNDA submission contains clinical pharmacology data from three studies conducted in pediatric patients (aged 2 to <17 years) with refractory/relapsed and recurrent solid tumors – Studies E7389-A001-113 (Study 113), E7389-G000-213 (Study 213), and E7389-G000-223 (Study 223), wherein HALAVEN 1.1 to 1.8 mg/m$^2$ was administered via intravenous infusion over 2 to 5 minutes on Days 1 and 8 of each 21-day cycle. Population PK and PK/PD analyses were conducted and are summarized.

A summary of these studies is provided in appendix **Section 3.0**.

**Written Request Clinical Pharmacology Components**

The Applicant met the following criteria of the WR:

According to the WR, the PK of eribulin in pediatric patients must be analyzed from the following minimum numbers of patients in each age group across the entire pediatric development program:

- 6 patients <6 years old
- 10 patients 6 to <12 years old
- 10 patients 12 to <18 years old

If appropriate, the PK data from these studies should be combined to develop models and explore exposure-response relationships for measures of safety and efficacy.

In response to the WR, the Applicant submitted a Population PK Report (CPMS-E7389-008R) which included a summary of the PK of eribulin in pediatric patients and its relationship to efficacy and safety endpoints from these three pediatric clinical studies. PK data from the following number of pediatric patients from each age group were analyzed to develop a PK model:

- 10 patients <6 years old
- 25 patients ≥6 to <12 years old
- 48 patients ≥12 to <18 years old

A PK/PD model was developed using the absolute neutrophil count (ANC) from these studies. Graphical exploratory PK/PD analyses were conducted for other safety and efficacy parameters in Studies 213 and 223.

Population PK

Eribulin PK was best described by a three-compartment model with linear elimination from central compartment. The population mean value for eribulin clearance was estimated to be 2.9 L/h. An allometric relationship between eribulin PK parameters and patient weight was included. Volumes of distribution of central (V1) and 2 peripheral compartments (V2, V3) were estimated to be 4.1 L, 2 L and 106 L, respectively. Overall steady-state exposure ($AUC_{ss}$) increased proportionally with total eribulin dose indicating linear PK. Both eribulin total clearance (CL) and dose-normalized AUC were comparable among different studies. The CL and dose-

normalized AUC for pediatric patients were within range of those observed in adult patients with soft tissue sarcoma (STS) (Table 1). The Population PK model is further described in appendix **Section 3.2**.

**Table 1: Summary of Predicted Model Derived Exposure Parameters**

| Population | Parameter | N | Mean | SD | Min | Median | Max | CV |
|---|---|---|---|---|---|---|---|---|
| **All Subjects** | CL (L/h) | 561 | 3.08 | 1.50 | 0.43 | 2.82 | 10.51 | 48.5 |
| | AUC (ng*h/mL) | 561 | 820 | 472 | 76.6 | 717 | 3384 | 57.5 |
| | *Dose Normalized AUC (ng*h/mL) | 561 | 852 | 457 | 265 | 756 | 4787 | 53.7 |
| **Adult STS Subjects (Studies 207, 217, 309)** | CL (L/h) | 378 | 3.22 | 1.49 | 0.60 | 2.93 | 10.51 | 46.1 |
| | AUC (ng*h/mL) | 378 | 834 | 409 | 257 | 756 | 2997 | 49.1 |
| | *Dose Normalized AUC (ng*h/mL) | 378 | 841 | 415 | 265 | 763 | 2997 | 49.4 |
| **Pediatric Subjects (Studies 113, 213, 223)** | CL (L/h) | 83 | 2.43 | 1.36 | 0.43 | 2.11 | 8.52 | 56.1 |
| | AUC (ng*h/mL) | 83 | 746 | 519 | 224 | 593 | 2877 | 69.7 |
| | *Dose Normalized AUC (ng*h/mL) | 83 | 791 | 387 | 319 | 698 | 2682 | 48.9 |

The exposure for each pediatric age group is shown in Table 2; the AUC is in range of those values observed in adults. Exposure is higher in youngest age group (2 to < 6 years old), but remains within the range of values observed in other pediatric age groups and adult patients.

**Table 2: Comparison of Exposure in Pediatrics Subgroups**

| Age group (years) | N | Median Clearance (L/h) | Mean (SD) Clearance (L/h) | Mean (SD) AUC (ng*h/mL) |
|---|---|---|---|---|
| [2, <6) | 10 | 0.97 | 1.17 (0.64) | 1320 (0.76) |
| [6, 12) | 25 | 1.92 | 1.95 (0.79) | 780 (0.49) |
| [12, 17) | 42 | 2.53 | 2.72 (1.27) | 620 (0.28) |
| 18 and older | 292 | 3.09 | 3.24 (1.47) | 800 (0.5) |

PK/PD Model for Neutrophil Count

A population PK/PD model for absolute neutrophil count was previously developed using the data from Studies 207, 217, and 309 in adult subjects with STS. The PK/PD model included the following covariates: blood transfusion, Eastern Cooperative Oncology Group (ECOG) status (adult subjects) and neutropenia co-medication (granulocyte-colony stimulating factor [G-CSF]) effect on BASE (baseline absolute neutrophil count), alkaline phosphatase, albumin and G-CSF co-medication effect on MTT (mean transit time of progenitor cells to mature neutrophils in blood), and G-CSF co-medication effect on SLOPE (estimate of eribulin effect on ANC). In the current analysis, using the absolute neutrophil count from Study 309 and including new data

from Studies 113, 213, and 223, the previous PK/PD model developed in adult subjects with STS was implemented, and only co-medication effect of irinotecan on BASE, MTT, and SLOPE was tested as additional covariate effects. The results of these analyses were consistent with previous analyses in adults with STS. The population PK/PD model is further described in appendix **Section 3.3**.

Eribulin Tumor Growth Inhibition (Studies 213 and 223)

No relationship between eribulin exposure (AUC at time of assessment) and percent change in tumor size from baseline was observed; therefore, no formal modelling of the relationship was conducted.

Exposure-Efficacy Analysis (Studies 213 and 223)

Overall, there appears to be no correlative trend in increasing exposure to eribulin with improved probability of longer PFS (progression-free survival) and OS (overall survival) in pediatric subjects with refractory/relapsed and recurrent solid tumors in Studies 213 and 223. Of the 61 subjects with both available efficacy and eribulin exposure data, 31 experienced progressive disease, 21 stable disease, 4 subjects experienced a partial response and 5 subjects' status was not estimable. No relationship between eribulin average exposure and BOR (best observed response) or ORR (overall response rate) was observed for pediatric subjects with refractory/relapsed or recurrent solid tumors in Studies 213 and 223 combined.

Exposure-Safety Analysis (Studies 213 and 223)

For the purpose of conducting graphical exposure-response analysis for adverse events (AEs), an incidence of ≥10% of subjects as part of the exposure-safety population were required to experience any particular AE at ≥Grade 3 severity. Due to this, only anemia, decreased lymphocytes and neutropenia were assessed graphically as part of the exposure-response analysis for safety. Overall, no apparent relationship in the occurrence of anemia, decreased lymphocytes, and neutropenia with increasing eribulin AUC was observed. Exposure-response analysis for dose reductions and discontinuation due to AEs was not performed due to the small number of subjects (4 from a total of 61 subjects) requiring dose reduction due to AEs.

**Overall Conclusions**

Overall steady-state exposure ($AUC_{ss}$) in different age groups increased proportionally with total eribulin dose indicating linear PK. Both eribulin total clearance (CL) and dose-normalized AUC were comparable among different studies. The CL and dose-normalized AUC for pediatric patients were within range of values observed in adult patients with STS (Table 1). Given the lack of significant activity in pediatric patients, no new indication will be granted.

## 2.4 Outstanding Issues

None.

## 2.5 Summary of Labeling Recommendations

Section 8.4 was revised as follows:

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| Proposed Language by Applicant | (b) (4) [redacted] |
| New FDA Proposed Language | The safety and effectiveness of HALAVEN in pediatric patients have not been established.<br><br>The safety and effectiveness of HALAVEN alone or in combination with irinotecan in pediatric patients were assessed but not established in three open-label studies (NCT02171260, NCT03441360, and NCT03245450) in 77 pediatric patients aged 2 to <17 years with relapsed or refractory solid tumors and lymphomas, excluding central nervous system tumors. No new safety signals were observed in these studies. The pharmacokinetics (PK) of eribulin were within range of values of adult patients with metastatic liposarcoma or other tumors given the same dose per body surface area. |
| Rationale for Changes | The Applicant proposed labeling stated that the pharmacokinetics (PK) of eribulin were comparable to that of adult patients. FDA agreed with including this information in the labeling to provide healthcare providers with additional information but modified the statement to limit implications of the comparison.<br><br>No new indication is warranted based on the results of these studies. |

# 3. APPENDIX

### 3.0 Overall Summary of the Pediatric Studies

A brief description of studies is given below:

Study 113

Study 113 was an open-label, dose escalation trial designed to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) and to characterize the toxicity and PK of

eribulin. The starting dose was 1.1 mg/m$^2$ which is approximately 80% of the MTD observed in adults. Eribulin 1.4 mg/m$^2$ administered on Day 1 and Day 8 during a 21-day cycle was determined to be the MTD in pediatric patients. Eribulin exposure increased proportionally with the dose in the pediatric population over the dose range administered in this study. There was no evidence of meaningful anti-tumor activity in the pediatric patients with refractory or recurrent solid tumors (excluding CNS) or lymphomas with histologic verification of malignancy at original diagnosis or relapse treated with eribulin. The PK data from this study is described in more details in appendix **Section 3.1**.

Study 213

Study 213 was an open-label, single-arm, multicenter trial of eribulin in combination with weekly and daily irinotecan in pediatrics with refractory or recurrent solid tumors. The primary objective for the first portion of the trial was to determine the MTD or RP2D of the combination in pediatric patients with relapsed/refractory solid tumors, excluding CNS tumors. Secondary objectives in this portion included an assessment of safety and tolerability and determination of the optimal administration schedule of irinotecan when administered with eribulin.

The second portion of the trial was designed to assess the objective response rate (ORR) and duration of response (DOR) of the combination regimen in pediatric patients with relapsed/refractory rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and Ewing sarcoma (EWS). Secondary objectives included an assessment of progression-free survival (PFS) and clinical benefit rate (CBR) at 12 weeks.

PK profile of eribulin in combination with irinotecan in pediatric patients was also assessed.

Eribulin 1.4 mg/m$^2$ administered in combination with irinotecan 40 mg/m$^2$ was determined to be the MTD. Of the 27 patients in the second portion at the RP2D, the ORR was 11% with a duration of response for each responder of 2.9 months (RMS), 1.4 months (NRSTS), and 15.4 months (EWS). The study was stopped based on a futility analysis. The PK parameters of eribulin appeared similar to the values reported from previous clinical experience at the 1.4 mg/m$^2$ dose for eribulin.

Study 223

Study 223 was an open-label, single-arm, multicenter, trial designed to assess ORR via investigator assessment in pediatric patients with relapsed/refractory RMS, NRSTS, and EWS who received eribulin. Secondary objectives included an evaluation of PFS, DOR, and safety and tolerability. There were no confirmed responses among the 21 patients. The safety data were consistent with the established safety profile of eribulin in adults.

## 3.1. Summary of Non-Compartmental Pharmacokinetics in Study 113

See a brief description of the study in appendix **Section 3.0.** PK samples were collected during Cycle 1at the following time points:

Part A1: On Days 1-4, predose, and then post-infusion at 10, 30 minutes, 1, 2, 4, 6, 24 (Day 2), 48 (Day 3), and 72 hours (Day 4); either 96 (Day 5) or 120 hours (Day 6) post-infusion; and on Day 8, pre-dose and then post-infusion at 10 minutes.

Part A2: On Day 1, predose, and then post-infusion at 10 minutes; on Day 8, predose, and then post-infusion 10 minutes.

Pharmacokinetic analysis for eribulin mesylate was conducted by Eisai using validated assays by HPLC with MS/MS detection in plasma samples.

A total of 45 pediatric patients were enrolled. Non-compartmental analysis was completed using the data from Part A1.

The dose normalized geometric mean (%CV) $AUC_{0\text{-}inf}/D$ were 475 (42), 527 (27), 501 (77), 474 (86) h*ng/mL/mg following administration of 1.1 mg/m$^2$ (n=6), 1.4 mg/m$^2$ (n=6), 1.4 mg/m$^2$ (n=5), and 1.8 mg/m$^2$ (n=5), respectively. Similarly, the dose normalized geometric mean (%CV) Cmax/D were 234 (41), 299 (28), 188 (76), and 135 (64) ng/mL/mg following administration of the same doses. These data suggest that exposure to eribulin increased proportionally with the dose in these subjects. PK results are shown in **Error! Reference source not found.**.

**Table 3: Summary of Pharmacokinetic Parameters of Eribulin Mesylate from Subjects in Part A1 (PK Analysis Set)**

| | Dose Escalation | | | PK Expansion | Combined |
|---|---|---|---|---|---|
| **Parameter** | **1.1 mg/m$^2$ (N=6)** | **1.4 mg/m$^2$ (N=6)** | **1.8 mg/m$^2$ (N=5)** | **1.4 mg/m$^2$ (N=5)** | **1.4 mg/m$^2$ (N=11)** |
| $AUC_{(0-t)}$ (h*ng/mL) | n=6 | n=6 | n=5 | n=5 | n=11 |
| Mean (SD) | 744.0 (353.03) | 758.2 (303.38) | 1363.0 (1378.53) | 1010.8 (538.94) | 873.0 (423.80) |
| Geometric Mean (%CV) | 676.1 (50.94) | 709.5 (42.14) | 1007.6 (94.29) | 894.1 (61.10) | 788.2 (50.01) |
| Median | 689.5 | 719.5 | 886.0 | 827.0 | 733.0 |
| Min, Max | 418, 1270 | 367, 1300 | 484, 3800 | 448, 1650 | 367, 1650 |
| $AUC_{(0-inf)}$ (h*ng/mL) | n=3 | n=6 | n=5 | n=4 | n=10 |
| Mean (SD) | 654.3 (342.72) | 830.5 (331.14) | 1556.6 (1619.37) | 907.8 (493.59) | 861.4 (379.11) |
| Geometric Mean (%CV) | 602.6 (51.04) | 780.9 (39.58) | 1122.6 (100.48) | 818.9 (55.05) | 795.9 (43.00) |
| Median | 463.0 | 754.5 | 936.0 | 771.5 | 754.5 |
| Min, Max | 450, 1050 | 445, 1430 | 512, 4410 | 488, 1600 | 445, 1600 |
| $AUC_{(0-inf)}$/D (h*ng/mL/mg) | n=3 | n=6 | n=5 | n=4 | n=10 |
| Mean (SD) | 498.3 (172.76) | 542.7 (151.40) | 621.8 (607.69) | 595.5 (401.86) | 563.8 (259.44) |
| Geometric Mean (%CV) | 474.7 (41.51) | 526.8 (26.60) | 474.3 (85.67) | 500.7 (77.05) | 516.2 (46.27) |
| Median | 579.0 | 487.0 | 334.0 | 499.5 | 487.0 |
| Min, Max | 300, 616 | 405, 795 | 285, 1700 | 243, 1140 | 243, 1140 |
| $C_{max}$ (ng/mL) | n=6 | n=6 | n=5 | n=5 | n=11 |
| Mean (SD) | 353.8 (59.24) | 472.3 (158.23) | 382.6 (296.97) | 382.8 (247.05) | 431.6 (197.78) |
| Geometric Mean (%CV) | 349.9 (16.41) | 443.0 (44.63) | 321.2 (66.46) | 320.5 (77.69) | 382.4 (60.09) |
| Median | 339.0 | 502.5 | 279.0 | 380.0 | 416.0 |
| Min, Max | 300, 446 | 198, 651 | 193, 909 | 125, 771 | 125, 771 |
| $C_{max}$/D (ng/mL/mg) | n=6 | n=6 | n=5 | n=5 | n=11 |
| Mean (SD) | 252.33 (122.870) | 307.00 (71.836) | 157.96 (110.176) | 230.66 (183.995) | 272.30 (133.084) |
| Geometric Mean (%CV) | 234.00 (41.379) | 298.65 (27.546) | 135.54 (63.610) | 188.44 (75.715) | 242.24 (56.339) |
| Median | 215.00 | 314.00 | 131.00 | 159.00 | 289.00 |
| Min, Max | 165.0, 495.0 | 180.0, 383.0 | 74.2, 350.0 | 89.3, 551.0 | 89.3, 551.0 |
| $T_{max}$ (h) | n=6 | n=6 | n=5 | n=5 | n=11 |

| | Dose Escalation | | | PK Expansion | Combined |
|---|---|---|---|---|---|
| **Parameter** | **1.1 mg/m$^2$ (N=6)** | **1.4 mg/m$^2$ (N=6)** | **1.8 mg/m$^2$ (N=5)** | **1.4 mg/m$^2$ (N=5)** | **1.4 mg/m$^2$ (N=11)** |
| Median | 0.170 | 0.170 | 0.370 | 0.300 | 0.200 |
| Min, Max | 0.12, 0.32 | 0.12, 0.22 | 0.08, 0.50 | 0.17, 0.32 | 0.12, 0.32 |
| $t_{1/2}$ (h) | n=3 | n=6 | n=5 | n=4 | n=10 |
| Mean (SD) | 35.17 (4.914) | 35.32 (8.600) | 42.94 (10.364) | 35.65 (7.221) | 35.45 (7.648) |
| Median | 37.00 | 38.60 | 44.00 | 33.25 | 36.45 |
| Min, Max | 29.6, 38.9 | 23.3, 44.3 | 30.6, 56.5 | 30.2, 45.9 | 23.3, 45.9 |
| $T_{last}$ (h) | n=6 | n=6 | n=5 | n=5 | n=11 |
| Median | 110.105 | 108.485 | 120.050 | 96.880 | 97.320 |
| Min, Max | 92.30, 120.67 | 96.08, 121.12 | 96.28, 120.42 | 72.82, 168.67 | 72.82, 168.67 |
| CL (mL/h) | n=3 | n=6 | n=5 | n=4 | n=10 |
| Mean (SD) | 2226.7 (957.10) | 1951.7 (469.27) | 2483.8 (1190.94) | 2348.8 (1437.56) | 2110.5 (923.71) |
| Geometric Mean (%CV) | 2105.4 (41.47) | 1899.9 (26.57) | 2108.9 (85.59) | 1996.7 (77.15) | 1938.0 (46.30) |
| Median | 1730.0 | 2055.0 | 2990.0 | 2205.0 | 2055.0 |
| Min, Max | 1620, 3330 | 1260, 2470 | 589, 3510 | 875, 4110 | 875, 4110 |
| Vd (mL) | n=3 | n=6 | n=5 | n=4 | n=10 |
| Mean (SD) | 75966.7 (34322.34) | 66766.7 (32230.40) | 89840.0 (43363.96) | 77525.0 (39176.64) | 71070.0 (33460.09) |
| Geometric Mean (%CV) | 71079.9 (46.62) | 61145.2 (47.57) | 79635.6 (64.40) | 69781.5 (58.43) | 64463.4 (49.09) |
| Median | 66600.0 | 59000.0 | 89400.0 | 74500.0 | 60750.0 |
| Min, Max | 47300, 114000 | 33700, 125000 | 32100, 138000 | 37100, 124000 | 33700, 125000 |

$AUC_{(0-t)}$ = area under the concentration-time curve from time zero to time t, $AUC_{(0-inf)}$ = area under the plasma concentration-time curve from time zero to infinity, CL = Total clearance, $C_{max}$ = maximum observed plasma concentration, CV = coefficient of variation, D = dose normalized, max = maxium, min = minimum, $T_{max}$ = observed time of maximum concentration, $T_{1/2}$ = terminal half life, $T_{last}$= area under the plasma concentration-time curve at time of last quantifiable concentration, Vd = Volume of distribution.

Source: Table 14.2.6.1

Refer to clinical review for a discussion of the efficacy and safety. In brief, only one patient experienced a partial response; no patients experienced a complete response. The DLTs were neutropenia and fatigue. The most frequently reported treatment-related AEs (>50%) were decreased WBC count (86%), decreased neutrophil count (59%), anemia (59%) and decreased lymphocyte count (54%). Grade 3 or 4 treatment related AEs were reported in 82% of subjects, the most frequently reported were decreased lymphocyte count, decreased WBC count and decreased neutrophil count.

### 3.2 Summary of Bioanalytical Method Validation and Performance

Development and validation of a sensitive, specific, and reproducible method for the determination of eribulin (free base concentration) in human plasma (sodium heparinized) using liquid chromatography-tandem mass spectrometry/mass spectrometry (LC-MS/MS) was reported in Original NDA Seq 0000. This method was used to analyze human plasma samples from Study 113.

Refer to the original NDA 201532 Clinical Pharmacology review for previous review of the analytical method validation. The analytical method validation was found acceptable in original application.

A similar LC-MS/MS method for determination of eribulin was fully validated (b) (4) (b) (4) in 2012. This method was transferred and partially validated in 2013 (b) (4) and validation results were reported in RPT03181. In 2019, (b) (4) fully validated the LC-MS/MS method for determination of eribulin (RPT04591) to analyze plasma samples from Study 213 and Study 223.

To support evaluation of a drug interaction with irinotecan in Study 213, (b) (4) developed and fully validated a LC-MS/MS method to determine irinotecan and its metabolite SN-38 in human plasma (sodium heparinized) and reported in RPT04315.

Validation of these methods showed them to be sensitive, specific, and reproducible, with all parameters within acceptable limits for the validation of LC-MS/MS, as specified by laboratory standard operating procedures and guidance documents by the FDA.

### 3.3 Summary Population PK Analysis (Study 113, 213 and 223)

The final pooled eribulin PK dataset included 5152 observations from a total of 561 subjects. For Study 113, 250 eribulin plasma concentrations from 22 subjects were available for population PK analysis. For Study 223, 106 eribulin plasma concentrations from 21 subjects were available for population PK analysis. For Study 213, 231 eribulin plasma concentrations from 40 subjects were available for population PK analysis.

Eribulin PK was best described by a three-compartment model with linear elimination from central compartment. For this analysis in pediatric subjects with refractory/relapsed and recurrent solid tumors, the previous eribulin PK model developed for the adult subjects with STS submission based on Studies 217 and 309 which included the covariate effects of albumin and bilirubin on CL was used as a starting basis upon which to assess the effect of concomitant irinotecan administration on eribulin PK.

The population mean value for eribulin clearance was estimated to be 2.9 L/h. An allometric relationship between eribulin PK parameters and subject weight was included. Volumes of distribution of central (V1) and 2 peripheral compartments (V2, V3) were estimated to be 4.08 L, 2.03 L and 106 L, respectively.

Overall steady-state exposure (AUC) increased proportionally with total eribulin dose, indicating linear PK and, overall, both eribulin total clearance (CL) and dose-normalized AUC were comparable among different studies, and between adult and pediatric studies.

Concomitant irinotecan dosing did not have a statistically significant effect on eribulin PK. Parameter estimates for the final PK model are presented in Table 4.

**Table 4: Population PK Parameter Estimates of Eribulin (Final Model) (CPMS-E7389-008R)**

| | | NONMEM Estimates | | |
|---|---|---|---|---|
| **Parameter [Units]** | **Point Estimate** | **%RSE** | **95% CI** | |
| CL [L/h] = $\Theta_{CL}$ *(WGT/67)$^{0.75}$ *(ALB/4.1)$^{\Theta ALB}$ * (BILI/0.43)$^{\Theta BILI}$ | | | | |
| $\Theta_{CL}$ [L/h] | 2.89 | 2.47 | 2.75 – 3.03 | |
| $\Theta_{ALB}$ (Albumin effect on CL) | 0.734 | 16.1 | 0.503 – 0.965 | |
| $\Theta_{BILI}$ (Bilirubin effect on CL) | -0.143 | 33.7 | -0.237 – 0.0485 | |
| V1 [L] = $\Theta_{V1}$ *(WGT/67) | | | | |
| $\Theta_{V1}$ | 4.08 | 2.60 | 3.87 – 4.29 | |
| Q2 [L/h] = $\Theta_{Q2}$ * (WGT/67)$^{0.75}$ | | | | |
| $\Theta_{Q2}$ | 2.08 | 8.89 | 1.72 – 2.44 | |
| V2 [L] = $\Theta_{V2}$ * (WGT/67) | | | | |
| $\Theta_{V2}$ | 2.03 | 6.11 | 1.79 – 2.27 | |
| Q3 [L/h] = $\Theta_{Q3}$ * (WGT/67)$^{0.75}$ | | | | |
| $\Theta_{Q3}$ | 5.31 | 2.82 | 5.02 – 5.60 | |
| V3 [L] = $\Theta_{V3}$ * (WGT/67) | | | | |
| $\Theta_{V3}$ | 106 | 2.60 | 101 – 111 | |
| **Inter-individual variability** | | | | **CV%** |
| $\omega^2_{CL}$ | 0.225 | 8.84 | | 47.4 |
| $\omega^2_{V1}$ | 0.0580 | 25.3 | | 24.1 |
| $\omega^2_{Q3}$ | 0.233 | 13.9 | | 48.3 |
| $\omega^2_{V3}$ | 0.143 | 23.4 | | 37.8 |
| **Residual variability** | | | | |
| $\sigma^2$ prop (Phase 1 studies) | 0.0347 | 13.5 | | 18.6 |
| $\sigma^2$ prop (Phase 2/3 studies/TAD ≤1.5 h) | 0.207 | 7.92 | | 45.5 |

%RSE = percent relative standard error of the estimate = SE/parameter estimate * 100; CL = Clearance, V1 = volume of central compartment, V2 = volume of first peripheral compartment, Q2 = inter-compartment clearance from V1 to V2, V3 = volume of second peripheral compartment, Q3 = inter-compartment clearance from V2 to V3, $\omega^2_{CL}$, $\omega^2_{V1}$, $\omega^2_{Q3}$, $\omega^2_{V3}$ = covariance of random effect of CL, V1, Q3, and V3, respectively, $\sigma^2$prop = proportional component of the residual error model, ALB = albumin, BILI = bilirubin, PK = pharmacokinetic, TAD = time after dose.

## 3.4 Population PK/PD Analysis for Neutrophil/ANC (Studies 113, 213, 223, and 309)

PK/PD analysis was performed for subjects receiving eribulin from Studies 113, 213, 223 and 309 that provided both PK for eribulin and baseline and post-dose blood samples for absolute neutrophil count (ANC). A total of 4590 ANC observations from 308 subjects were available. The PK/PD population for exposure-response analysis for tumor size consisted of 61 subjects from Studies 213 and 223.

The effect of eribulin administration on ANC was modeled using a PK/PD model for hematological toxicity, where model-predicted eribulin concentrations were assumed to reduce the neutrophil proliferation rate or to induce cell loss. The structural model for characterizing ANC profile consisted of 4 parameters: baseline absolute neutrophil count (BASE), mean transit time of progenitor cells to mature neutrophils in blood (MTT), feedback factor (GAMMA [□]), and estimate of eribulin effect on ANC (SLOPE). The effect of eribulin was tested using SLOPE. The base model included estimation of inter-individual variability (IIV) on all parameters and a proportional error model for estimation of residual variability. A population PK/PD model for neutrophil count was previously developed using the data from Studies 207, 217, and 309 in adult subjects with STS. The PK/PD model included the following covariates: blood transfusion,

Eastern Cooperative Oncology Group (ECOG) status (adult subjects) and neutropenia co-medication (granulocyte-colony stimulating factor [G-CSF]) effect on BASE, alkaline phosphatase, albumin and G-CSF co-medication effect on MTT, and G-CSF co-medication effect on SLOPE. In the current analysis, using the neutrophil count data from Study 309 and including new data from Studies 113, 213, and 223 the previous PK/PD model developed in adult subjects with STS was implemented, and only co-medication effect of irinotecan on BASE, MTT, and SLOPE was tested as additional covariate effects.

The final model for neutropenia included the covariates blood transfusion, ECOG status ≥1, G-CSF co-administration and age <18 years on baseline neutrophil count, G-CSF and irinotecan co-administration, and albumin effects on MTT and G-CSF co-administration effect on the SLOPE for drug effect remaining significant in the neutropenia PK/PD model. This model was therefore selected as the final PK/PD neutropenia model.

The parameter estimates for the final neutropenia PK/PD model are presented in Table 5.

**Table 5:Population PK/PD Parameter Estimates of Eribulin Neutropenia (Final Model) (CPMS-E7389-008R)**

| | | NONMEM Estimates | | |
|---|---|---|---|---|
| **Parameter [Units]** | **Point Estimate** | **%RSE** | **95% CI** | |
| BASE = $\Theta_{BASE}$ * $\Theta_{ECOG}^{ECOG}$ * $\Theta_{BT}^{BT}$* $\Theta_{GCSF}^{GCSF}$.$\Theta_{AGE<18}^{AGE<18}$ | | | | |
| Basal Neutrophil Count [x $10^9$/L] | 4.41 | 4.38 | 4.03 – 4.79 | |
| Effect of ECOG ≥1 on basal | 1.08 | 1.91 | 1.04 – 1.12 | |
| Effect of BT on basal | 1.23 | 7.59 | 1.05 – 1.41 | |
| Effect of G-CSF on basal | 0.730 | 5.74 | 0.648 – 0.812 | |
| Effect of Age <18 on basal | 0.714 | 5.67 | 0.635-0.793 | |
| MTT = $\Theta_{MTT}$ * $\Theta_{GCSF}^{GCSF}$*(ALB/4.1)$^{\Theta ALB}$ $\Theta_{IRNT}^{IRNT}$ | | | | |
| Mean transit time [MTT; h] | 53.4 | 11.6 | 41.3 – 65.5 | |
| Effect of G-CSF on MTT | 0.810 | 2.10 | 0.777 – 0.843 | |
| Effect of albumin on MTT | 0.390 | 13.7 | 0.285 – 0.495 | |
| Effect of irinotecan on MTT | 0.914 | 2.58 | 0.868-0.960 | |
| GAMMA = $\Theta_{GAMMA}$ | | | | |
| Feedback Parameter ($\gamma$) | 0.217 | 2.01 | 0.208 – 0.226 | |
| SLOPE = $\Theta_{SLOPE}$ * $\Theta_{GCSF}^{GCSF}$ | | | | |
| Effect of eribulin on ANC | 0.210 | 4.63 | 0.191 – 0.229 | |
| Effect of GCSF on drug effect | 1.19 | 6.14 | 1.05 – 1.33 | |
| Inter-individual variability ($\omega^2$) | | | | CV% |
| $\omega^2$BASE | 0.127 | 11.2 | | 35.6 |
| $\omega^2$MTT | 0.0205 | 20.6 | | 14.3 |
| $\omega^2$SLOPE | 0.172 | 34.7 | | 40.7 |
| Residual variability ($\sigma^2$) | | | | CV% |
| $\sigma^2$ prop | 0.214 | 6.50 | | 54.2 |

%RSE = percent relative standard error of the estimate = SE/parameter estimate * 100; ΘBASE = baseline absolute neutrophils, ΘMTT = neutrophil maturation time, ΘGAMMA = feedback parameter, ΘSLOPE = SLOPE relating eribulin concentrations to decreased neutrophil proliferation, $\omega^2_{BASE}$, $\omega^2_{MTT}$, $\omega^2_{GAMMA}$, $\omega^2_{SLOPE}$ = covariance of random effect of BASE, MTT, GAMMA and SLOPE, respectively, $\sigma^2$prop = proportional component of the residual error model, $\Theta ECOG^{ECOG}$ = ECOG≥1 effect on BASE, $\Theta GCSF^{GCSF}$ = G-CSF effect on MTT, ΘALB = ALB effect on MTT, $\Theta_{AGE<18}^{AGE<18}$ = AGE <18 years effect on BASE and $\Theta_{IRTC}^{IRTC}$ = Irinotecan effect on MTT; ALB = albumin, ANC = absolute neutrophil count, BASE = baseline absolute neutrophil count, ECOG = Eastern Cooperative Oncology Group, G-CSF = granulocyte-colony stimulating factor, MTT = mean transit time, PD = pharmacodynamic, PK = pharmacokinetic.

The typical population parameter estimates for BASE, MTT, GAMMA and SLOPE were 4.41 x 109/L, 53.4 h, 0.217, and 0.210 mL/ng, respectively. Baseline neutrophils were 23% and 8% higher in subjects receiving blood transfusion and ECOG score ≥1, respectively.Baseline neutrophils were 27% lower in subjects receiving G-CSF treatment and 29% lower in subjects <18 years of age. Mean transit time was 19% lower in subjects receiving G-CSF and a small increase in MTT was observed with increasing albumin levels (exponent = 0.390). Also, MTT was 9% slower in subjects receiving irinotecan. In addition, eribulin effect on inhibition of neutrophil proliferation was 19% higher in subjects receiving G-CSF treatment. Structural model parameters were estimated with excellent precision, with %RSE ≤11.6%. IIV was medium to moderate ranging between 14.3% for MTT and 40.7% for Baseline. Residual variability in neutrophil levels was moderate at 54.2%.

The results of the neutropenia PK/PD analyses for eribulin were consistent with previous analyses in adult subjects with STS.

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