1 April 2016
EMA/CHMP/147213/2017 – Corr*
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Halaven

International non-proprietary name: eribulin

Procedure No. EMEA/H/C/002084/II/0028

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

*Text correction in the section "Efficacy data and additional analyses" on page 52 and Table 52 on page 90.

Table of contents

List of abbreviations

ADI: adipocytic soft tissue sarcoma

AE: adverse event

AESI: adverse event of special interest

AJCC: American Joint Committee on Cancer

ALP: alkaline phosphatase

BOR: best overall response

CBR: clinical benefit rate

CI: confidence interval

CR: complete response

CSR: clinical study report

CTCAE: Common Terminology Criteria for Adverse Events

CV: coefficient of variation

ECOG: Eastern Cooperative Oncology Group

FDA: Food and Drug Administration

HR: hazard ratio

LMS: leiomyosarcoma

MedDRA: Medical Dictionary for Regulatory Activities

ORR: overall response rate

OS: overall survival

PD: pharmacodynamics

PFR: progression free rate

PFS: progression free survival

PK: pharmacokinetic

PN: peripheral neuropathy

PP: per protocol

PR: partial response

PT: preferred term

QoL: quality of life

QTcF: QT interval using Fredericia's formula

SAE: serious adverse event

SAP: statistical analysis plan

SD: standard deviation or stable disease

SDQ: sponsor derived query

SOC: system organ class

STS: soft tissue sarcoma

TEAE: treatment-emergent adverse event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eisai Europe Ltd. submitted to the European Medicines Agency on 29 July 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of soft tissue sarcoma following the outcome of the Phase 309; as a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated in order to update the efficacy and safety information. The Package Leaflet and RMP are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the PI in line with the latest QRD template version 9.1.

The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision PIP/0136/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant obtained Scientific Advice (EMEA/H/SA/641/3/2010/II) from the CHMP on 16 December 2010 in the area of clinical development.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Filip Josephson Co-Rapporteur: Sinan B. Sarac

Timetable	Actual dates
Submission date	29 July 2015
Start of procedure:	22 August 2015
CHMP Co-Rapporteur Assessment Report	15 October 2015
CHMP Rapporteur Assessment Report	19 October 2015
PRAC Rapporteur Assessment Report	19 October 2015
PRAC members comments	28 October 2015
PRAC Outcome	6 November 2015
CHMP members comments	9 November 2015
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 November 2015
Request for supplementary information (RSI)	19 November 2015
CHMP Rapporteur Assessment Report	2 March 2016
PRAC Rapporteur Assessment Report	2 March 2016
PRAC members comments	9 March 2016
PRAC Outcome	17 March 2016
CHMP members comments	21 March 2016
Updated CHMP Rapporteur Assessment Report	23 March 2016
Opinion	1 April 2016

2. Scientific discussion

2.1. Introduction

Soft tissue sarcomas (STS) are a rare group of heterogeneous mesenchymal tumours. There are more than 50 histologic subtypes of STS, many of which are associated with distinct clinical profiles, response to individual therapies and prognosis. Many of the individual subtypes are very rare. In the past, all subtypes of STS were grouped together for the purposes of treatment, however consensus is now emerging that treatment selection should be governed by histology, particularly in the setting of advanced disease. Soft tissue sarcomas account for less than 1% of all adult solid tumours (Burningham, et al., 2012) and the international annual incidence of STS is reported to range from 1.8 to 5/100 000 per year (Wibmer, et al., 2010). It was estimated that 12 020 new cases of STS would be reported in the US in 2014 and 4 740 deaths would occur as a result of the disease (Siegel, et al., 2014). In the EU, the total crude incidence of sarcomas was 5.6 per 100,000 per year with an estimated 27,908 new cases per year, of which 84% were soft tissue sarcomas and 14% were bone sarcomas (Stiller et al, 2013). The 5-year survival in Europe for adult STS (excluding visceral STS) averages 60%, with substantial geographic

variations (Storm, 1998). The median survival time in patients with metastatic STS is 11 to 15 months, and only a small subgroup of these patients achieve long term survival. With the median survival of ≤ 1 year for patients with metastatic STS, there is a need for more effective treatments in this setting (Billingsley, et al., 1999; Van Glabbeke, et al., 1999).

For localised disease, surgical resection with or without adjuvant radiotherapy is usually the preferred first-line approach. Adjuvant chemotherapy is also sometimes considered although its role remains controversial because of conflicting results (ESMO guideline 2014). However even when radical surgery is performed, in about 50% of the time, cases of high-grade sarcoma develop metastases which lead to death (Delaney et al., 1991).

For advanced STS, the majority of patients receive 1st line chemotherapy with doxorubicin alone or in combination with ifosfamide. Of those patients receiving adjuvant or first-line chemotherapy, approximately half will receive a second-line regimen (Minchom, 2010). At the time of the study, options for second line therapy included the use of standard-dose ifosfamide (or high-dose ifosfamide in patients who have already received standard dose (Minchom, 2010), trabectedin, and gemcitabine (either alone or in combination with docetaxel), dacarbazine, or best supportive care (ESMO clinical practice guideline, 2014). Since the start of the study, pazopanib has been approved in EU on 3 August 2012 for the treatment of patients with advanced STS of selected tumour types, who have received prior chemotherapy. However none of these agents has as yet demonstrated a statistically significant improvement in overall survival. Recently a study comparing trabectedin (Yondelis) to dacarbazine in pretreated locally advanced/metastatic liposarcoma or leiomyosarcoma patients failed to demonstrate an OS benefit (Demetri et al, 2015).

About the product

Eribulin mesylate (Halaven) is a synthetic analog of halichondrin B (HalB), a large polyether macrolide isolated from the marine sponge Halichondria okadai (Hirata and Uemura, 1986). Results of in vitro studies demonstrate that eribulin inhibits cell growth in a wide range of established human cancer cell lines including breast, colon, prostate, ovarian, small cell and non-small cell lung cancer and uterine sarcoma. Eribulin exerts its anti-cancer effects via a tubulin-based antimitotic mechanism, leading to G2/M (GAP 2/mitosis stages of cell cycle) cell cycle blocks, disruption of mitotic spindles and ultimately apoptotic cell death.

In the European Union, Halaven is approved for the following indication:

"HALAVEN is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease (see section 5.1). Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless patients were not suitable for these treatments."

The MAH has now applied for an extension of the indication to include:

"HALAVEN is also indicated for the treatment of patients with inoperable soft tissue sarcoma (STS) who have received prior chemotherapy for advanced or metastatic disease (see section 5.1). Efficacy and safety have been established primarily in patients with leiomyosarcoma and liposarcoma."

To substantiate this claim, the MAH has submitted one pivotal Phase III study (study 309) and two supportive Phase II studies (studies 207 and 217).

The final approved indication further to the CHMP review is:

"HALAVEN is indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease (see section 5.1)."

2.2. Non-clinical aspects

2.2.1. Pharmacology

Primary pharmacodynamic studies

To evaluate the primary pharmacodynamic effects of eribulin mesilate in nonclinical models of human soft tissue sarcoma (STS), the following in vitro and in vivo studies were conducted.

• Antiproliferative activity against human adult and paediatric sarcoma cells (in vitro)

• Antitumor activity in human adult and paediatric sarcoma xenograft models (in vivo)

In vitro studies

As a part of the Paediatric Preclinical Testing Program (PPTP) supported by the US National Cancer Institute (NCI), antiproliferative effects of eribulin mesilate against 10 childhood STS cell lines including 4 rhabdomyosarcomas (RMS), 2 rhabdoid, and 4 Ewing's sarcomas were evaluated. The median half maximal inhibitory concentration (IC50) values of eribulin mesilate in these 3 types of STS cell lines were 0.14, 0.27, and 0.14 nmol/L, respectively. Another panel of 20 human childhood Ewing's sarcoma cell lines demonstrated a median IC50 value of 0.38 nmol/L. Eribulin mesilate inhibited the proliferation of the MES-SA human uterine sarcoma cell line with an IC50 value of 1.99 nmol/L.

In vivo studies

Antitumor activity of eribulin mesilate against nonclinical models of human STS was evaluated in SK-LMS-1 (human leiomyosarcoma), A673 (human Ewing's sarcoma), and HT-1080 (human fibrosarcoma) xenograft models grown subcutaneously in athymic mice. In the SK-LMS-1 model, eribulin mesilate (0.19 – 1.5 mg/kg) dose-dependently inhibited tumor growth at 0.75 and 1.5 mg/kg. In the A673 and HT-1080 models, eribulin mesilate (0.875 – 3.5 mg/kg for A673, 1.27 and 1.69 mg/kg for HT-1080) almost completely inhibited tumour growth, with complete responses (CRs) observed in some mice.

In the PPTP evaluation, eribulin mesilate (1 mg/kg) administration resulted in a CR or maintained complete response (MCR) against 8 of the 11 human STS xenograft models; the CRs/MCRs were found in 4 of the 5 Ewing's sarcoma and 4 of the 4 RMS xenograft models. In dose-response studies in 4 selected xenograft models of Ewing's sarcoma and RMS, eribulin mesilate (0.25, 0.5, and 1 mg/kg) was active against 3 of the 4 models, with MCRs and CRs observed at doses ≥0.25 or ≥0.5 mg/kg. The treatments were well tolerated in all mice in all of the xenograft studies.

2.2.2. Ecotoxicity / environmental risk assessment

Using a worst-case combined refined Fpen value of 0.000088 for breast cancer and STS (based on EU epidemiological data for all breast cancer and STS patients, maximum dose of 2.2 mg and maximum possible number of treatment cycles, 17 per year for all patients), the overall PECSURFACEWATER value for eribulin has been calculated to be 0.000097 µg/L. This value is >100 times lower than the action limit of 0.01 µg/L.

The log Kow of eribulin mesilate is 2.25, such that it does not present a hazard with respect to bioaccumulation and persistence. Therefore, the drug substance, eribulin mesilate, is not classifiable as a Persistent, Bioaccumulative and Toxic (PBT) substance.

A Phase II environmental fate and effects assessment is not necessary for HALAVEN 0.44 mg/mL Solution for Injection.

Despite there being no environmental trigger for further environmental testing, 3 studies have been performed using eribulin mesilate:

- Acute toxicity study using *Daphnia magna* (OECD 202) NOEC=0.46 mg/l
- Activated sewage sludge respiration inhibition test (OECD 209) NOEC = 56 mg/l
- Ready biodegradability test (OECD 301B) Not readily biodegradable (7-8%)

2.2.3. Discussion on non-clinical aspects

The MAH has presented in vitro data showing antiproliferative activity against the human uterine sarcoma cell line MES-SA with an IC50 of 1.99 nmol/l. In a xenograft model in athymic mice, eribulin mesilate showed antitumor activity against the human leiomyosarcoma cell line SK-LMS-1.

These in vitro and in vivo data support the clinical development of eribulin mesilate in the treatment of soft tissue sarcoma.

With regard to the ERA, it is agreed that no further Phase II testing is required, as a consequence of introducing a new indication. Although eribulin mesilate was shown not to be readily biodegradable, due to the very low anticipated exposure it is unlikely to result in a significant risk to the environment.

2.2.4. Conclusion on the non-clinical aspects

The non-clinical data submitted support this application for an extension of indication.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of eribulin mesilate. Considering the above data, eribulin mesilate is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of clinical studies contributing to PK / PD of Eribulin

Study Type	Study Identifier	Section Number	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration
BA	RE7389-G000-309	5.3.1.4	E7389 Bioanalytical Report: A Randomized, Open-Label, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Eribulin with Dacarbazine in Subjects with Soft Tissue Sarcoma	LC/MS/MS	E7389; 1.4 mg/m^2 administered as a 2-5 minute bolus IV infusion on Day 1 and Day 8 of a 21-Day treatment cycle
BA	PBC038-052	5.3.1.4	To evaluate the reliability of an analytical method for the determination of E7389 concentrations in human plasma by a high performance liquid chromatography with tandem mass spectrometry	LC/MS/MS	E7389; 0.2, 0.4, 4, and 100 ng/mL
BA	PBC038-062	5.3.1.4	To determine E7389 concentrations as free base in human plasma obtained in the clinical study "An Open Label, Multicenter, Phase 2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Previously Treated Subjects With Advanced Soft Tissue Sarcoma (Study E7389-J081-217)"	LC/MS/MS	E7389; 1.1 or 1.4 mg/m^2 administered as a 2-5 minute bolus IV infusion on Day 1 and Day 8 of a 21-Day treatment cycle
BA	DSD2004-36 (Study DSDB2004-004)	5.3.1.4	Validation of LC/MS/MS methods for the determination of E7389 in human plasma and urine	Methods validation study (LC/MS/MS)	E7389; 0.2 to 100 ng/mL
PK/Plasma protein binding	DMPKAB2012-002	5.3.2.1	To characterize the in vitro protein binding of E7389 in human plasma using equilibrium dialysis	LC/MS/MS	E7389; 5, 50, and 500 ng/mL
PK/Hepatic Metabolism	301054911	5.3.2.2	To assess the potential of E7389 to induce CYP enzymes 1A2, 2B6, 2C9 and 3A4 in cultures of human hepatocytes	Metabolite formation of specific probe substrate for each enzyme using LC/MS	E7389; 1, 5, and 10 µmol/L
PK/Hepatic Metabolism	DMPKAM2010-003	5.3.2.2	To determine the inhibition potential of E7389 in vitro against several forms of CYPs	LC/MS/MS	E7389; Up to 200 µmol/L
PK	XS-0084	5.3.2.3	To assess the inhibitory effects of E7389 using BCRP expressing vesicles, and OCT1, OAT1, OAT3 or OATP1B1 expressing cells	Liquid scintillation counter	E7389; 0.1, 0.3, 1.0, 3.0, and 10 µmol/L
PK	XS-0085	5.3.2.3	To evaluate E7389 as a potential substrate of BCRP, OAT1, OAT3, OATP1B1, and OCT1	Transcellular transport or cellular uptake of E7389 LC/MS/MS	E7389; 5 and 10 µmol/L
PK	DMPKA2013-139	5.3.2.3	To evaluate E7389 at lower concentrations as a potential substrate of BCRP, MRP2, MRP4, and BSEP	LC/MS/MS	E7389; 0.3 and 1 µmol/L
PK	DMPKA2013-121	5.3.2.3	To evaluate if E7389 was a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1, and inhibitor of MATE1	E7389 concentrations in cell lysates an	E7389; 3 and 10 µmol/L
PK	EISAI-01-13Dec2010	5.3.2.3	To provide data on the interaction of E7389 with the ABC transporters: human MRP2 (ABCC2), human MRP4 (ABCC4), human BSEP (ABCB11/sP-gp), and the uptake transporters: human OATP1B3 (OATP8), human OCT1, and human OCT2	Vascular transport inhibition and substrate assays; uptake transporter inhibition and substrate assays	E7389; 3 and 10 µmol/L

Table 2: Overview of clinical studies contributing to efficacy and safety

Phase/Study Number	Population	Design	Endpoints	Number of Subjects Enrolled	Status
Phase 2					
E7389-E044-207 Phase II Study of E7389 Administered as an IV Infusion Day 1 and 8 Every Three Weeks in Pretreated Patients With Advanced and/or Metastatic Soft Tissue Sarcoma	Subjects with advanced and/or metastatic soft tissue sarcoma, including leiomyosarcoma, adipocytic, synovial sarcoma, other types of sarcoma who have failed standard chemotherapy	Non-randomized, open-label, multicenter	**Primary:** PFR_{12WKS} **Secondary** PFS, ORR, clinical response benefit, time to onset of response[a], OS, and safety parameters	128	Completed
E7389-J081-217 An Open-label, Multi-center, Phase 2 Study to Evaluate the Efficacy and Safety of Eribulin in Previously Treated Subjects with Advanced Soft Tissue Sarcoma	Subjects with advanced or metastatic STS 1 of 2 types (ADI or LMS), or other types of sarcoma (Japan), who have disease progression following at least 1 standard chemotherapy for advanced or metastatic STS	Non-randomized, open-label, multi-center	**Primary:** PFR_{12WKS} **Secondary:** OS, PFS, ORR, DCR, dSDR, CBR	52	Completed
Phase 3					
E7389-G000-309 A Randomized, Open-label, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Eribulin with Dacarbazine in Subjects with Soft Tissue Sarcoma	Subjects with advanced (locally recurrent, locally advanced, and/or metastatic) STS (subtypes ADI or LMS) not amenable to surgery and/or radiotherapy, who have disease following at least 2 standard regimens for advanced STS, 1 of which must have included an anthracycline (unless contraindicated)	Randomized, open-label, multicenter study	**Primary:** OS **Secondary:** PFS, PFR_{12WKS},CBR, DCR, dSDR PK, PD, PK/PD, and safety parameters **Exploratory:** ORR, QoL,	452	Ongoing

ADI=adipocytic, CBR=clinical benefit rate, DCR=disease control rate, dSDR=durable stable disease rate, IV=intravenous, LMS=leiomyosarcoma, PFS=progression free survival, PFR_{12WKS}=progression free rate at 12 weeks, PD=pharmacodynamics, PK=pharmacokinetics, ORR=objective response rate, OS=overall survival, QoL=quality of life, STS=soft tissue sarcoma.
a: For subjects with objective response.

2.3.2. Pharmacokinetics

New plasma concentration data are available from the two phase II studies (207 and 217) and from the phase III study (309) of eribulin in the treatment of advanced STS. In study 207, PK sampling was performed on Day 1 in cycle 1 only. In studies 217 and 309, PK sampling was performed on Day 1 and 8 in cycles 1 and 3. The pharmacokinetic data was used to perform two new Population PK and PK/PD analyses. The first analysis (Report No CPMS-E7389-003R) included data from Study 207 pooled with data from 7 previous Phase 1 studies (Studies 101, 102, 103, 105, 108, 109, and 110) and one previous Phase 2 Study (Study 211). The second analysis (Report No CPMS-E7389-005R) included also data from the STS studies 217 and 309.

The results of the first analysis (Report No CPMS-E7389-003R), including STS data from study 207 only, were in line with previous population PK analyses of eribulin and are not further discussed. The results from the analysis including data from all STS studies (207, 217 and 309) are described below.

In addition, the MAH submitted a number of new *in vitro* studies on protein binding, interaction potential, and transporter substrate specificity.

2.3.2.1. Population Pharmacokinetic Analyses

The final population analyses included 478 subjects who contributed a total of 4566 eribulin plasma concentrations (1753 observations from 253 subjects from Studies 101, 102, 105, 108, 109, 110, and 207 and 1753 observations from 253 subjects from Studies 217 and 309).

Model-based analyses consisted of a population PK model for eribulin and population PK/PD models for longitudinal tumour size measurements (depending on any apparent eribulin exposure PK/PD

relationship), neutropenia and change from baseline in QTcF. All models were developed using NONMEM 7.2. Model building and covariate assessments were conducted using standard methods.

The final population PK model was used to derive individual PK parameters and eribulin exposures, which were then incorporated into the PK/PD datasets to be used in the subsequent population PK/PD analyses.

The results from this population PK analysis were consistent with those from previous analyses. The PK of eribulin were best described by a three compartment model with linear elimination from the central compartment and parameterized for CL, V1, Q2, V2, Q3 and V3. The use of an allometric model with body weight, used in a previous eribulin PK analysis, was also used in this case. The IIV was estimated for CL, V1, Q2 and V3, but not for volume of distribution for V2 and inter-compartmental clearance for the 2nd and 3rd compartments (Q2). Residual variability was described by a proportional error model and estimated separately for data rich Phase 1 studies and for sparse data in the Phase 2/3 studies and for the maximum duration of infusion period (≤1.5 h).

Eribulin CL was found to increase with increasing albumin levels (power = 0.693) and decline with increasing bilirubin (power = -0.129). No significant effect of gender, age, race, ECOG status, renal function (creatinine clearance) or tumour type (STS vs. others) on eribulin exposure was identified. Model parameters are presented in the table below.

Table 3: Final model Population pharmacokinetic parameter estimates of eribulin (CPMS-E7389-005R)

		NONMEM Estimates		
Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**	
$CL [L/h] = \Theta_{CL} * (WGT/70)^{0.75} * (ALB/4)^{\Theta ALB} * (BILI/0.5)^{\Theta BILI}$				
Basal clearance - Θ_{CL} [L/h]	2.83	2.72	2.68-2.98	
Albumin effect on CL (Θ_{ALB})	0.693	27.8	0.315-1.07	
Bilirubin effect on CL (Θ_{BILI})	-0.129	37.1	-0.223- - 0.0353	
$V_1 [L] = \Theta_{V1} * (WGT/70)$				
Θ_{V1}	4.06	2.73	3.84 – 4.28	
$Q_2 [L/h] = \Theta_{Q2} * (WGT/70)^{0.75}$				
Θ_{Q2}	2.15	9.35	1.76 – 2.54	
$V_2 [L] = \Theta_{V2} * (WGT/70)$				
Θ_{V2}	1.97	6.60	1.72 – 2.22	
$Q3 [L/h] = \Theta_{Q3} * (WGT/70)^{0.75}$				
Θ_{Q3}	5.26	3.12	4.94 – 5.58	
$V_3 [L] = \Theta_{V3} * (WGT/70)$				
Θ_{V3}	101	2.64	95.8 - 106	
Inter-individual variability CV%				
ω^2_{CL}	0.230	9.78		48.0
ω^2_{V1}	0.0480	34.8		21.9
ω^2_{Q3}	0.245	13.1		49.5
ω^2_{V3}	0.125	25.6		35.4
Residual variability				**CV %**
σ^2 prop (Phase 1 studies)	0.0369	13.8		19.2
σ^2 prop (Phase 2/3 studies/TAD <= 1.5 h)	0.205	8.78		45.3

Abbreviations: %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, ω^2_{CL}, ω^2_{V1}, ω^2_{Q2}, ω^2_{Q3}, ω^2_{V3} = covariance of random effect of CL, V1, Q2, Q3 and V3, respectively, σ^2prop = proportional component of the residual error model, TAD = Time after dose

2.3.2.2. New in vitro studies using human biomaterial

Study B2012-002: *In vitro* protein binding of eribulin in human plasma

Blank plasma aliquots from volunteers were spiked with eribulin (E7389) to achieve final concentrations of 5, 50, and 500 ng/mL. Plasma samples were spiked into the membrane side of Rapid Equilibrium Devices (RED). Phosphate buffer solution was spiked into the outer well of the RED. After an overnight incubation, an aliquot was removed from each side of the membrane. The resulting samples were extracted and concentrations of eribulin were determined by LC/MS/MS. The percentage of protein binding in plasma was determined by comparing the concentrations calculated from each side of the membrane.

The protein binding of eribulin (5, 50 and 500 ng/mL) in human plasma was 61.6%, 67.4% and 63.8%, respectively. There was no concentration dependency.

Study 301054911: Eribulin induction potential on CYP1A2, 2B6 and 3A4

Eribulin was incubated in three separate preparations of human hepatocyte cultures at concentrations of 1, 5 and 10 µM for three days. Hepatocytes were also incubated with positive controls, β-naphthoflavone (20 µM) for CYP1A1/2, phenobarbital (2 mM) for CYP2B6 and rifampicin (20 µM) for CYP2C9 and 3A4. The enzyme induction was determined using probe substrates selective for these drug-metabolizing enzymes and quantitative RT-PCR for mRNA expression. The cytotoxicity potential of eribulin towards hepatocyte cultures was tested using a MTT assay at the end of the 3-day exposure period.

The positive control inducers produced at least 12-fold increase in the enzyme activities for CYP1A2, CYP2B6 and CYP3A4 in all three donors. As expected, the induction in CYP2C9 activity by rifampicin was relatively low (2.8-9.1-fold).

Eribulin caused no induction for all enzymes tested. Instead, a decrease in enzyme activities was found for all three donors, with a maximal decrease at 10 µM of 32-77%. The RT-PCR data generally supported the activity results. The cytotoxicity assessment using the MTT assay showed no obvious decrease in hepatocyte viability in cultures of hepatocytes for all donors at any of concentrations examined (1, 5 and 10 µM).

Study 2010-003: Eribulin inhibition of select CYPs in microsomes

Co-incubation of probe substrates at their respective Km values and multiple eribulin concentrations (up to 200 µM) in human liver microsomes (HLM) was utilized to create IC50 curves. The P450s explored were CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A. Positive controls utilising probe inhibitors was also assessed to verify the validity of the incubations.

For all P450s except CYP3A, the IC50 values for inhibition by eribulin were greater than 200 µM. For CYP3A, the IC50 values for inhibition by eribulin against the probe substrates of midazolam, nifedipine, and testosterone were 2.21, 1.17, and 10.6 µM, respectively.

Table 4: Results of eribulin CYP inhibition assay

P450 Tested	Probe Reaction	Probe Substrate Concentration	Probe Inhibitor	Probe Inhibitor IC_{50}	E7389 IC_{50}
CYP1A	phenacetin O-deethylation	40 µM	α-naphthoflavone	6.67 nM	> 200 µM
CYP2B6	bupropion hydroxylation	140 µM	ticlopidine	134 nM	> 200 µM
CYP2C8	amodiaquine N-deethylation	10 µM	montelukast	109 nM	> 200 µM
CYP2C9	tolbutamide hydroxylation	100 µM	sulfaphenazole	353 nM	> 200 µM
CYP2C19	(S)-mephenytoin 4′-hydroxylation	30 µM	ticlopidine	561 nM	> 200 µM
CYP2D6	(±)-bufuralol 1′-hydroxylation	20 µM	quinidine	93.2 nM	> 200 µM
CYP2E1	chlorzoxazone 6-hydroxylation	250 µM	diethyldithiocarbamate	81.4 µM	> 200 µM
CYP3A	midazolam 1′-hydroxylation	3 µM	ketoconazole	15.2 nM	2.21 µM
	nifedipine oxidation	2 µM		13.2 nM	1.17 µM
	testosterone 6β-hydroxylation	50 µM		23.5 nM	10.6 µM

Study 2013-121: Eribulin as a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3 and MATE, and as inhibitor of MATE

The purpose of the present study was to evaluate if eribulin was a substrate of OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1, and inhibitor of MATE1. For the substrate assays, eribulin (0.3, 1, or 3 µmol/L) was co–incubated in transfected Chinese Hamster Ovary (CHO), Human Embryonic Kidney (HEK) or MDCKII cells overexpressing OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, and MATE1 with or without a selective transporter inhibitor. The parental cells were used as the control. Following the incubation, eribulin concentrations in cell lysates were analysed using LC/MS/MS. For the evaluation of inhibition, eribulin was co–incubated in transfected and parental cells overexpressing MATE1 with probe substrate [14C]–metformin. The amount of the probe substrate in cell lysates was analyzed using a liquid scintillation counter. Transporter mediated uptake was represented by the difference in fold uptake in the transporter expressing cells and the parental cells.

At concentrations ranging from 0.3–1 µmol/L of eribulin, generally less than two-fold uptake of eribulin was observed in transfected cells compared to those in the parental cells. In addition, the fold increase in each transfected cell was not significantly reduced in the presence of selective inhibitor. Active transport was demonstrated by uptake of the model substrates, which was inhibited by the control inhibitors.

Table 5: Overview of eribulin substrate assay

Cell Line	Fold Uptake							
	0.3 µmol/L		1 µmol/L		3 µmol/L		Control	
	E7389 only	E7389 + inhibitor	E7389 only	E7389 + inhibitor	E7389 only	E7389 + inhibitor	Control	Control + inhibitor
OATP1B1[a]	NA	NA	2.2	2.4	NA	NA	9.7	2.8
OATP1B3[b]	NA	1.4	1.6	0.9	NA	NA	2.5	1.2
OAT1[c]	NA	NA	0.6	0.6	NA	NA	3.3	1.5
OAT3[d]	1.0	0.9	1.0	1.4	NA	NA	34.9	2.9
OCT1[e,f]	0.8	0.8	0.9	0.8	NA	NA	15.2	1.5
OCT2[g]	NA	0.8	0.8	0.8	NA	NA	5.0	0.7
MATE1[f,h]	0.9	1.1	1.0	1.1	1.0	1.3	17.2	2.8

a: Control is [^{3}H]–estrone 3–sulfate, inhibitor is rifampcin.
b: Control is [^{3}H]–estradiol 17β–glucuronide, inhibitor is rifampcin.
c: Control is [^{3}H]–para-aminohippuric acid, inhibitor is probenecid.
d: Control is [^{3}H]–estrone 3–sulfate, inhibitor is probenecid.
e: Control is [^{14}C]–metformin, inhibitor is verapamil.
f: Studies were performed at Solvo Biotechnology, detection of E7389 conducted at Eisai Inc, values are mean of 2 and 20 minute timepoints for overview only.
g: Control is [^{14}C]–metformin, inhibitor is quinidine.
h: Control is [^{14}C]–metformin, inhibitor is pyrimethamine.
BLQ = Below limit of quantitation.
NA = Not applicable.

The results from the inhibition study suggest that up to 10 µmol/L of eribulin did not inhibit the MATE1–mediated transport of the probe substrate.

Study 2013-139: Eribulin as a substrate of BCRP, MRP2, MRP4 and BSEP

The purpose of the study was to evaluate eribulin at lower concentrations as a potential substrate of BCRP, MRP2, MRP4, and BSEP.

For the BCRP substrate assays, the transcellular transport of eribulin at 0.3 and 1 µmol/L in the absence or presence of a BCRP inhibitor (KO 143) was measured in transwell inserts using BCRP-transfected (MDCKII-BCRP) cells and parental cells. Flux ratio (FR) was defined as the ratio of the apparent permeability coefficient (Papp) in basolateral-to-apical (BA) direction to that of apical-to-basolateral (A-B) direction. The FR was normalized by the parental cells, expressed as the corrected flux ratio (CFR). KO 143 was co-incubated with eribulin to determine if CFR values decreased.

Eribulin was assessed as a substrate of MRP2, MRP4, and BSEP using vesicle membrane assays. Eribulin at 0.3 and 1 µmol/L was incubated in the transporter-enriched vesicle membranes and the control vesicle membranes. The ATP/AMP ratios were calculated to assess the ATP dependent transport. Transporter inhibitors (benzbromarone, MK 571, and cyclosporin A for MRP2, MRP4, and BSEP, respectively) was co-treated with eribulin to determine if ATP/AMP ratios decreased.

In the BCRP substrate assay, the corrected flux ratio (CFR) values for 0.3 and 1 µmol/L of eribulin were 0.8 and 0.9, respectively. The respective CFR values for eribulin were 0.8 and 0.3 in the presence of KO 143, i.e. there was no substantial reduction of eribulin transport in presence of inhibitor (Table). The CFR for [3H]prazosin, a known BCRP substrate, was 4.1 and 1.0 in the absence and presence of KO 143, a known BCRP inhibitor, respectively, indicating that the BCRP activity in MDCKII-BCRP was substantially greater than that in MDCKII-mock cells and the activity was blocked by cotreating with a BCRP inhibitor.

In the MRP2, MRP4, and BSEP substrate assays, almost all the ATP/AMP ratios of eribulin treatments in the transporter enriched vesicle membranes were less than 2 fold and the co-treatment of transporter inhibitors did not decrease the ATP/AMP ratios of eribulin (Table 7). Results with model substrates ([3H]E17βG for MRP2, [3H]DHEAS for MRP4, and [3H]taurocholate for BSEP) indicated transporter activity in the transfected vesicles but not in control vesicles.

Table 6: Results for eribulin as BCRP substrate

Transporter	Cell lines	0.3 µmol/L E7389		1 µmol/L E7389	
		E7389	E7389 + KO 143	E7389	E7389 + KO 143
BCRP	FR (MDCKII-mock)	2.6	1.4	2.2	2.1
	FR (MDCKII-BCRP)	1.9	1.1	1.9	0.6
	CFR	0.7	0.8	0.9	0.3

Table 7: Results for eribulin as substrate of MRP2, MRP4 and BSEP

Transporters	Vesicle Membranes	Time (min)	ATP/AMP Ratios			
			0.3 µmol/L E7389		1 µmol/L E7389	
			E7389 only	E7389 + inhibitor [a]	E7389 only	E7389 + inhibitor [a]
MRP2	MRP2	5	1.9	ND	1.2	ND
		10	1.0	1.1	1.7	0.8
	Control	5	0.9	ND	1.1	ND
		10	0.8	ND	0.9	ND
MRP4	MRP4	2	2.1	ND	1.1	ND
		4	1.5	1.3	1.5	0.9
	Control	2	1.6	ND	0.9	ND
		4	1.3	ND	2.2	ND
BSEP	BSEP	5	0.8	ND	0.8	ND
		10	0.7	0.8	0.8	0.9
	Control	5	0.8	ND	0.7	ND
		10	0.8	ND	0.7	ND

a: benzbromarone, MK 571, and cyclosporin A for MRP2, MRP4, and BSEP assays, respectively.
ND: not determined.

The results of this study suggest that eribulin, at 0.3 and 1 µmol/L, is not a substrate of BCRP, MRP2, MRP4, or BSEP.

Study EISAI-01-13DEC2010: Eribulin as an inhibitor and/or substrate of MRP2, MRP4, BSEP, OATP1B3, OCT1 and OCT2.

This study investigated if eribulin was an inhibitor and/or substrate of MRP2, MRP4, BSEP, OATP1B3, OCT1 and OCT2 by measuring its inhibition of model substrates and transport, respectively, in membrane vesicles or transfected cells. MRP2, MRP4 and BSEP were investigated in membrane vesicles and OATP1B3, OCT1 and OCT2 in transfected CHO cells. Control vesicles and parental cells were used as negative controls. The substances used, its concentration and intended use is given in the table below.

Table 8: Substances used in this study

Substrate	Incubation concentration	Use
Eribulin	0.01, 0.03, 0.1, 0.3, 1, 3, and 10 µM	Test drug
E-17-βG	50 µM	MRP2 substrate
DHEAS	0.02 µM	MRP4 substrate
Taurocholate	2 µM	BSEP substrate
Benzbromarone	100 µM	MRP2 inhibitor
MK571	150 µM	MRP4 inhibitor
Cyclosporin A	20 µM	BSEP inhibitor
Fluo-3	10 µM	OATP1B3 substrate
TEA	3.6 µM	OCT1/2 substrate
Fluvastatin	30 µM	OATP1B3 inhibitor
Cimetidine	1000 µM	OCT1 and OCT2 inhibitor
Verapamil	100 µM	OCT1 and OCT2 inhibitor

The results of the studies are summarised in the table below.

Table 9: Inhibition and substrate potential of eribulin on MRP2, MRP4, BSEP, OATP1B3, OCT1 and OCT2

Summary of Results				
	E7389 (Eribulin mesylate)			
	Inhibition Assays		Substrate Assays	
Uptake	OATP1B3	26.09 % Inhibition (at 10 µM)	OATP1B3	0.99- to 2.16-fold activation
	OCT1	NI	OCT1	NI
	OCT2	NI	OCT2	NI
Efflux	MRP2	NI	MRP2	NI
	MRP4	NI	MRP4	NI
	BSEP	NI	BSEP	NI

NI: No significant interaction was detected

Table 10: Accumulation of eribulin in OATP1B3 Expressing and Control Cells Measured in the Uptake Transporter Substrate Feasibility Assay

Compound	Concentration (µM) / Incubation time (min)	Accumulation in transporter expressing cells (ng/mg protein)	Accumulation in control cells (ng/mg protein)	Transporter specific accumulation (fold)
E7389	3 / 2	33.65 ± 8.78	23.99 ± 4.33	1.4
	3 / 20	102.36 ± 10.61	47.4 ± 10.87	2.16
	10 / 2	143.76 ± 29.34	81.07 ± 13.99	1.77
	10 / 20	396.55 ± 59.48	183.29 ± 24.5	2.16
E7389	10 / 20	801.13 ± 114.85	915.64 ± 202.37	0.87
E7389 + 30µM fluvastatin	10 / 20	1447.82 ± 739.46	384.24 ± 127	3.77

Based on the data presented above, eribulin is not a clinically relevant inhibitor of any of the investigated transporters (based on the 50*$C_{max(u)}$ cut-off of 8.5 µM). Eribulin seems to be a weak substrate of OATP1B3. However, the known OATP1B3 inhibitor fluvastatin did not inhibit the uptake of eribulin. Taken together, the modest OATP1B3 accumulation (1.4-2.16 fold) and the lack of fluvastatin inhibition of eribulin OATP1B3 uptake clearly indicates that eribulin is actually not a substrate of OATP1B3 in vitro.

In conclusion, eribulin is neither an inhibitor nor a substrate of MRP2, MRP4, BSEP, OATP1B3, OCT1 and OCT2 in vitro at clinically relevant concentrations.

Study XS-0084: Eribulin as an inhibitor of BCRP, OCT1, OAT1, OAT3 and OATP1B1

This study investigated if eribulin was an inhibitor of BCRP, OCT1, OAT1, OAT3 and OATP1B1 by measuring its inhibition of model substrates in membrane vesicles (BCRP) or transfected S_2 and HEK293 cells (OCT1, OAT1, OAT3 and OATP1B1). Control vesicles and parental cells were used as negative controls. The substances used, its concentration and intended use is given in the table below.

Table 11: Substances used in this study

Substance	Incubation concentration	Use
Eribulin	0.1, 0.3, 1, 3, and 10 µM	Test drug
Methotrexate	100 µM	BCRP substrate
Benzbromarone	50 µM	BCRP inhibitor
Estradiol glucuronide	0.05 µM	OATP1B1 substrate
Rifampicin	10 µM	OATP1B1 inhibitor
TEA	5 µM	OCT1 substrate
Quinidine	30 µM	OCT1 inhibitor
p-aminohippuric acid	5 µM	OAT1 substrate
estrone sulfate	0.05 µM	OAT3 substrate
Probenecid	100 µM	OAT1/3 inhibitor

The results of the studies are summarised below.

Table 12. Inhibition potential of eribulin on BCRP, OCT1, OAT1, OAT3 and OATP1B1

	BCRP mediated uptake of [^{3}H]-Methotrexate	OCT1 mediated uptake of [^{14}C]-Tetraethylammonium	OAT1 mediated uptake of [^{3}H]-p-Aminohippuric acid	OAT3 mediated uptake of [^{3}H]-Estrone sulfate	OATP1B1-mediated uptake of [^{3}H]-Estradiol glucuronide
E7389 (µmol/L)	% of control	% of control	% of control	% of control	% of control
0	100.0	100.0	100.0	100.0	100.0
0.1	100.7	97.0	104.5	90.5	123.0
0.3	103.1	109.0	103.8	74.1	107.9
1	94.7	95.5	108.8	81.7	110.8
3	76.5	99.2	101.6	80.0	101.4
10	99.1	85.0	102.4	84.1	71.8
Benzbromarone [a]	2.6	NA	NA	NA	NA
Quinidine [b]	NA	33.9	NA	NA	NA
Probenecid [c]	NA	NA	8.6	7.6	NA
Rifampicin [d]	NA	NA	NA	NA	9.3

NA: not applicable
a: Benzbromarone at 50 µmol/L; b: Quinidine at 30 µmol/L; c: Probenecid at 100 µmol/L; d: Rifampicin at 10 µmol/L

Study XS-0085: Eribulin as a substrate of BCRP, OCT1, OAT1, OAT3 and OATP1B1

The transcellular transport or cellular uptake of eribulin at 5 and 10 µmol/L was measured in BCRP, OAT1, OAT3, OATP1B1, and OCT1 expressing cells and respective control cells. The concentrations of eribulin in the samples were determined by LC/MS/MS. The Papp ratio, a parameter for assessing the efflux of BCRP, and R value, a Papp ratio normalized by control cells, were calculated to assess the BCRP susceptibility of eribulin. The cleared volume, a parameter for assessing cellular uptake, was used to evaluate the susceptibility of OAT1, OAT3, OATP1B1, and OCT1. The cellular uptake of eribulin was assessed by measuring the concentrations of eribulin in cell lysate.

Efficient uptake of model substrates was observed, indicating functional transport in the cell systems.

No uptake of eribulin by BCRP was observed. Although the cleared volumes of eribulin at 10 µmol/L in OAT1 expressing cells were significantly higher than the ones in the control cells, the difference was suggested mainly due to lower cleared volume of eribulin at 10 µmol/L observed in the control cells. The cleared volumes of eribulin at 10 µmol/L were similar to those at 5 µmol/L in the OAT1 expressing cells.

Overall, the data indicate that eribulin is not a substrate of BCRP, OAT1, OAT3, or OATP1B1. However, eribulin at 5 and 10 µmol/L exhibited higher cleared volumes in OCT1 expressing cells compared to those in the control cells, suggesting that eribulin may be an OCT1 substrate.

Table 13: BCRP trancellular transport assay

Compounds	Incubation time (min)	P_{app} ratio (n=3)		R
		Control cells	BCRP expressing cells	
[^{14}C]Mannitol (non BCRP substrate)	30	1.0	1.1	1.1
	60	1.1	0.8	0.7
	120	0.9	0.8	0.9
[^{3}H]Prazosin (typical substrate)	60	1.8	15.0	8.3
5 µmol/L E7389	30	1.3	1.4	1.1
	60	1.3	1.2	0.9
	120	1.4	0.8	0.6
10 µmol/L E7389	30	2.1	0.7	0.3
	60	1.3	0.9	0.7
	120	2.4	1.0	0.4

Table 14: OAT1, OAT3, OATP1B1 and OCT1 uptake assays

Transporters	Compounds	Incubation time (min)	Cleared volume (µL/mg protein) [a]	
			Control cells	Transporter expressing cells
OAT1	5 µmol/L [^{3}H]-p-Aminohippuric acid	2	0.645	46.4
	5 µmol/L E7389	1	11.563	11.537
		2	15.162	15.006
		5	25.851	28.565
	10 µmol/L E7389	1	7.282	10.040
		2	9.414	15.105 [b]
		5	14.291	29.703 [b]
OAT3	0.05 µmol/L [^{3}H]-Estrone sulfate	2	2.05	20.8
	5 µmol/L E7389	1	11.563	8.582
		2	15.162	9.084 [c]
		5	25.851	17.768 [c]
	10 µmol/L E7389	1	7.282	6.162
		2	9.414	8.817
		5	14.291	11.461
OATP1B1	0.05 µmol/L [^{3}H]-Estradiol glucuronide	2	0.623	14.0
	5 µmol/L E7389	1	12.215	11.610
		2	19.380	15.963
		5	19.330	23.379
	10 µmol/L E7389	1	10.831	10.938
		2	13.973	13.988
		5	30.272	32.933
OCT1	5 µmol/L [^{14}C]-Tetraethylammonium	15	2.40	10.5
	5 µmol/L E7389	5	20.028	32.090
		10	25.487	50.852 [b]
		15	35.944	56.481 [b]
	10 µmol/L E7389	5	12.856	18.178 [b]
		10	22.915	48.637 [b]
		15	24.172	46.634 [b]

a: n=3.
b: Significantly higher compared to the controls with p-value < 0.05 by Student's t-test.
c: Significantly lower compared to the controls with p-value < 0.05 by Student's t-test.

2.3.3. PK/PD modelling

The population PK/PD (exposure-efficacy) analysis for eribulin tumour growth inhibition, OS efficacy analysis and graphical eribulin exposure-safety and exposure-efficacy analysis were based on data from Studies 217 and 309. Time-to-event analysis for OS was performed for studies 217 and 309 separately. Due to the low number of patients in study 217, only results from study 309 will be discussed here.

The population PK/PD (exposure-safety) analysis for eribulin-induced neutropenia was based on data from Studies 207, 217 and 309. The population PK/PD analysis for eribulin exposure-QTcF relationship was based on data from studies 217 and 309.

In all three studies, the starting dose was 1.4 mg/m^2 on Days 1 and 8 of every 21-day cycle.

Tumour growth inhibition model

For the tumour growth inhibition model, data of the sum of the longest diameter for target lesions by independent review from Studies 217 and 309 was used. Subjects only for which both tumour size and PK information was available were evaluated.

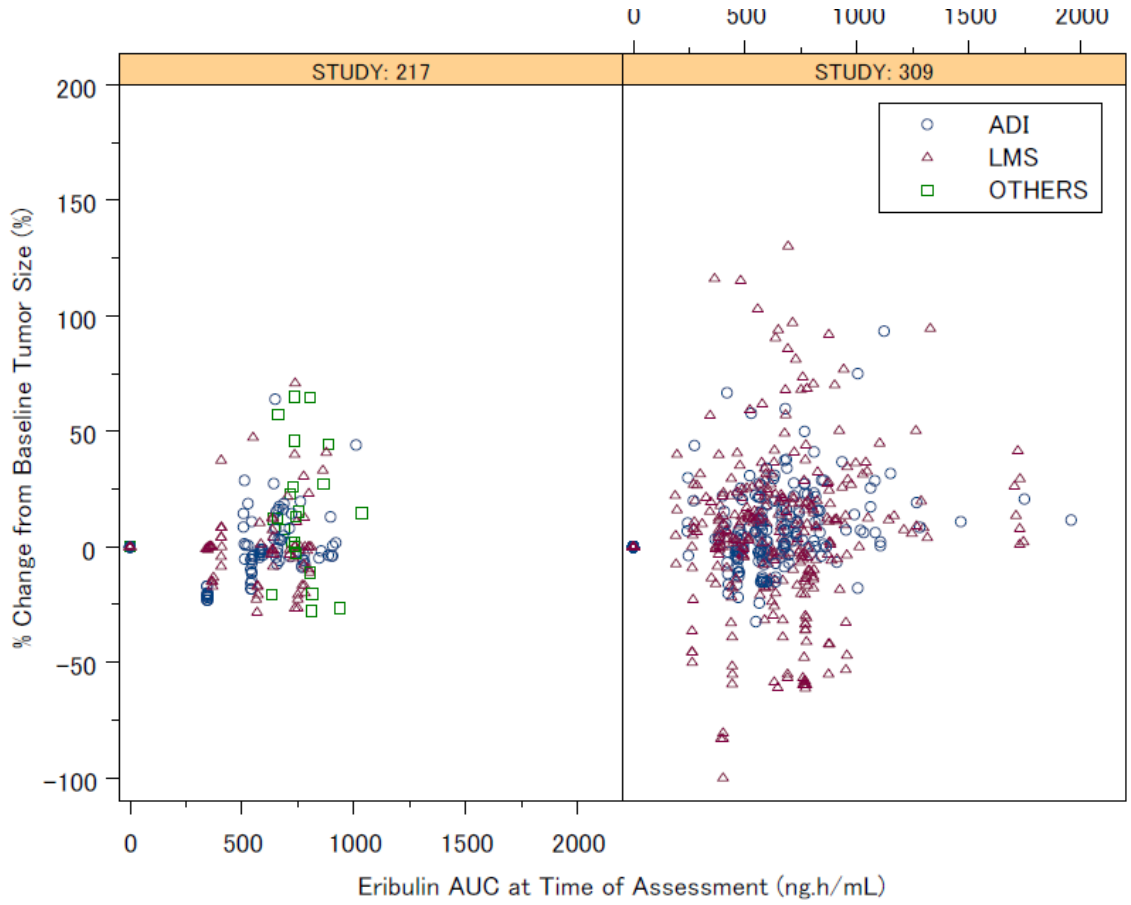
The final PK/PD study 217 and 309 dataset for tumour growth inhibition had 938 observations from 241 subjects.

The drug exposure parameter tested in the tumour growth inhibition model was individual eribulin AUC at the time of the assessment and was calculated as:

$$Tumor\ Size\ PK\ Exposure\ \left(AUC\ (ng.\frac{h}{mL})\right) = \frac{\text{Dose (µg) at time of assessment}}{\text{Individual Clearance}}$$

where Dose is in µg on the day of tumour assessment and clearance in L/h is the population PK model predicted individual clearance.

Tumour size appeared to decrease with time but not with increasing eribulin exposure.



ADI=adipocytic, LMS=leiomyosarcoma

Figure 1: Change in tumour size from baseline vs. eribulin predicted AUC at time of assessment

OS analysis

For study 309 out of the 226 subjects dosed with eribulin mesylate with available OS and PFS data, PK parameters to calculate eribulin exposure were available from 215 subjects. PFS week 12 data were available for 75 subjects. Time-to-event analysis for OS was performed on data from subjects in the eribulin arm. OS data was explored using Kaplan-Meier and Cox regression analyses using survfit() and coxph() functions, respectively in S-plus v 8.1.

For the PK/PD analysis of OS, PFS and BOR the exposure parameter used was individual eribulin AUC based on the starting dose as for Tumour size above.

The results from the univariate ($p \leq 0.05$) Cox regression analysis for the effect of eribulin exposure and other covariates on OS in study 309 (assessed in subjects receiving eribulin mesylate) are presented in the table below. Significant predictors are shown in bold type.

Table 15: Study 309 univariate-OS relationship: Cox regression analysis results

Predictor	p-value (Chi-Sq)	Estimate	Standard Error	Hazard Ratio
Eribulin Exposure $\log_e$ AUC	0.39	0.176	0.206	1.19
$\log_e$ %Change in tumor size Week 6	**4.2e-007**	**2.02**	**0.399**	**7.52**
Bodyweight	0.26	-0.00473	0.00424	0.995
BSA	0.16	-0.448	0.321	0.639
Age	1	-0.0000126	0.00707	1
Race (Caucasian vs. Black/Asian/ Chinese, Japanese/Others)	0.15	-0.246	0.171	0.782
Race (Others vs. Caucasian/Black/Asian/ Chinese/Japanese)	0.35	-0.031	0.0332	0.97
Gender (Male vs. Female)	0.9	0.0218	0.166	1.02
ECOG status (≥1 vs. 0)	**1e-005**	**0.681**	**0.154**	**1.98**
Years since diagnosed	**0.0085**	**-0.0633**	**0.024**	**0.939**
Previous radiography (Yes vs. No.)	0.46	-0.113	0.152	0.839
$\log_e$ Baseline tumor size	**1.1e-007**	**0.638**	**0.12**	**1.89**
Histology (LMS vs. ADI)	0.52	0.0529	0.0817	1.05

The significant predictors of OS from the above univariate analysis were identified to be loge % change tumor size at Week 6, ECOG status, years since diagnosed, and loge baseline tumour size. These predictors were carried forward to the multivariate analysis where all significant predictors for OS from the univariate analysis were assessed simultaneously. Multivariate Cox regression analysis ($p \leq 0.01$) results are presented in the table below.

Table 16: Study 309 multivariate-OS relationship: Cox regression analysis results (n ≤ 226)

Predictor	p-value (Chi-Sq)	Estimate	Standard Error	Hazard Ratio
$\log_e$ %Change in tumor size Week 6	**1.5e-011**	**3.21**	**0.476**	**24.7**
ECOG status (≥1 vs. 0)	0.14	0.254	0.172	1.29
Years since diagnosed	**0.0093**	**-0.0636**	**0.0245**	**0.938**
$\log_e$ Baseline tumor size	**2.7e-009**	**0.879**	**0.1476**	**2.41**

A check for confounding between baseline tumour size with % change in tumour size at Week 6 was performed. Percentage change in tumour size at Week 6 was not confounded with baseline tumour size confirming the results of the multivariate.

Neutropenia model

For the neutropenia model, eribulin concentration at the time of ANC assessment was predicted using the final population PK model in all subjects participating in studies 207, 217 and 309 with post-dose ANC measurements. The PK/PD dataset for the neutropenia model development consisted of 6602 records from 402 subjects.

Absolute neutrophil count data following eribulin mesilate administration in Studies 207, 217 and 309 was best described by a PK/PD model for haematological toxicity where model predicted eribulin concentrations reduced the neutrophil proliferation rate or induced cell loss. The results of the neutropenia PK/PD analyses for eribulin, including 24% greater inhibition of neutrophil proliferation in Japanese subjects, were consistent with previous analyses (Study 221). Parameters for the final eribulin neutropenia PK/PD model are presented in the table below.

Table 17: Population parameter estimates for neutropenia final PKPD model

		NONMEM Estimates		
Parameter [Units]	**Point Estimate**	**%RSE**	**95% CI**	
BASE = Θ_{BASE} * Θ_{ECOG}^{ECOG} * Θ_{BT}^{BT} * Θ_{GCSF}^{GCSF}				
Basal Neutrophil Count [x 10^9 /L]	4.47	3.09	4.20 – 4.74	
Effect of ECOG≥1 on basal	1.07	2.27	1.02 – 1.12	
Effect of BT on basal	1.26	6.54	1.10 – 1.42	
Effect of G-CSF on basal	0.702	5.61	0.625 – 0.779	
MTT = Θ_{MTT} * Θ_{GCSF}^{GCSF}*(ALB/0.5)$^{\Theta ALB}$				
Mean transit time [MTT; h]	53.5	3.87	49.4 – 57.6	
Effect of G-CSF on MTT	0.769	2.78	0.727 – 0.811	
Effect of albumin on MTT	0.377	6.74	0.327 – 0.427	
GAMMA = Θ_{GAMMA}				
Feedback Parameter (γ)	0.208	2.83	0.196 – 0.220	
SLOPE = Θ_{SLOPE} * Θ_{RACE}^{RACE}* Θ_{GCSF}^{GCSF}				
Effect of eribulin on ANC	0.174	4.14	0.160 – 0.188	
Effect of Japanese race on drug effect	1.24	6.59	1.08 – 1.40	
Effect of G-CSF on drug effect	1.22	6.25	1.07 – 1.37	
Inter-individual variability (ω^2)				**CV%**
ω^2BASE	0.120	10.3		34.6
ω^2MTT	0.0314	27.5		17.7
ω^2GAMMA	0.00758	114		8.71
ω^2SLOPE	0.0898	49.1		30.0
Residual variability (σ^2)				**CV%**
σ^2 prop	0.214	6.50		46.3

Abbreviations: %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, ω^2_{BASE}, ω^2_{MTT}, ω^2_{GAMMA}, ω^2_{SLOPE} = covariance of random effect of BASE, MTT, GAMMA and SLOPE, respectively, σ^2prop = proportional component of the residual error model, $\Theta ECOG^{ECOG}$ = ECOG≥1 effect on BASE, $\Theta GCSF^{GCSF}$ = GCSF effect on MTT, ΘALB = ALB effect on MTT, Θ_{RACE}^{RACE} = Japanese race effect on SLOPE

QTcF model

For the dQTcF model, observed eribulin concentrations during Cycle 1 and Cycle 2 were used with post-dose dQTcF measurements in studies 217 and 309. The PK/PD dataset for the QTcF model development consisted of 463 records from 127 subjects.

The relationship between observed eribulin concentration and change from baseline QTcF (dQTcF) during Cycle 1 and Cycle 2 was assessed using the following linear relationship, where the slope of the relationship was estimated:

$$dQTcF = Intercept + Eribulin\ Conc.\ (ng/mL) * Slope$$

The analysis showed that QTcF was not influenced by eribulin concentrations.

Evaluation of safety parameters:

No change in laboratory values for haematology, blood biochemistry and renal function with eribulin exposure was detected. Median cumulative eribulin exposure appears to be higher in subjects with AEs of Grade ≥3 compared to subjects not having these AEs. However, of the 253 subjects with PK and AE data, only 6 had Grade ≥3 neuropathy. No PK/PD relationship between average or cumulative eribulin exposure and occurrence of Grade ≥3 fatigue, nausea, anaemia and febrile neutropenia was observed.

2.3.4. Discussion on clinical pharmacology

The results of the new population pharmacokinetic analysis are fully in line with previous analyses. The data do not indicate a different pharmacokinetic behaviour of eribulin in patients with STS compared to patients with breast cancer. No changes to the pharmacokinetic information in the SmPC are therefore needed.

The MAH submitted a number of new *in vitro* studies on protein binding and interaction potential. Protein binding results were in line with previous data and warrants no changes to the SmPC.

The induction studies submitted with the original MAA had some flaws. Data were however considered sufficient to exclude a strong induction potential of eribulin and additional inductions studies were not requested by the CHMP. However, the MAH submitted further drug interaction studies. The new study investigating the eribulin induction potential on CYP1A2, 2B6 and 3A4 provides further reassurance. No changes to the SmPC are indicated.

A CYP inhibition study previously not submitted indicated a potential of eribulin to inhibit CYP3A4. The results of this study have been discussed previously, as they were used in a Physiologically-based Pharmacokinetic (PBPK) modelling, submitted and discussed in variation EMEA/H/C/002084/II/011 (EC decision on 27 June 2014). The PBPK model indicated that an in vivo inhibitory potential on CYP3A4 cannot be completely ruled out, although strong inhibition is not expected.

Several studies on eribulin as a substrate and/or inhibitor of different transporters were submitted. Overall the study setups were acceptable. The investigations were somewhat overlapping and the results are summarised below.

Eribulin as a SUBSTRATE	**Test system (Study)**					
Transporter:	**Transfected cells (2013-121)**	**Transfected cells (EISAI)**	**Transwell insert (2013-139)**	**Membrane vesicle (2013-139)**	**Membrane vesicle (EISAI)**	**Transfected cells (XS-0085)**
OATP1B1	No	-	-	-	-	No
OATP1B3	No	No	-	-	-	-
OAT1	No	-	-	-	-	No
OAT3	No	-	-	-	-	No
OCT1	No	No	-	-	-	**Yes**
OCT2	No	No	-	-	-	-
MATE1	No	-	-	-	-	-
BCRP	-	-	No	-	-	No
MRP2	-	-	-	No	No	-
MRP4	-	-	-	No	No	-
BSEP	-	-	-	No	No	-

Yes= transport observed
No= no significant transport observed
- = not studied

Eribulin as INHIBITOR	Test system (Study)				
Transporter:	Transfected cells (2013-121)	Transfected cells (EISAI)	Membrane vesicle (EISAI)	Membrane vesicle (XS-0084)	Transfected cells (XS-0084)
OATP1B1	-	-	-	-	No
OATP1B3	-	No	-	-	-
OAT1	-	-	-	-	No
OAT3	-	-	-	-	No
OCT1	-	No	-	-	No
OCT2	-	No	-	-	-
MATE1	No	-	-	-	-
BCRP	-	-	-	No	-
MRP2	-	-	No	-	-
MRP4	-	-	No	-	-
BSEP	-	-	No	-	-

Overall, eribulin appeared to be neither substrate nor inhibitor of the tested transporters. Eribulin has previously been concluded to be eliminated primarily via biliary excretion and the approved SmPC includes a general warning to avoid concomitant administration of inhibitors of transport proteins such as OATP or MRP. Based on the results of the new in vitro studies, indicating that eribulin is not a substrate of transporters known to be involved in drug-drug interactions, this warning has been removed.

A previous DDI study with rifampicin showed no effect on eribulin exposure. However, as it was then unknown whether eribulin was an OATP substrate, it could not be absolutely excluded that an inducing effect of rifampicin was counteracted by OATP inhibition, and the results from the rifampicin study could not be extrapolated to other inducers. Therefore, a warning of a potential effect of CYP3A4 inducers on eribulin was included in the SmPC. Since eribulin has now been shown not to be a substrate of OATP transporters, this warning has been removed.

2.3.5. Conclusions on clinical pharmacology

An updated PPK model, with addition of data from Study 207, 217 and 309, and a new PK/PD model including data from study 301 only have been submitted. The updated PPK model does not alter the conclusion drawn on eribulin pharmacokinetics as compared with previous PPK models. Results of the PK/PD modelling are also in line with what has been previously observed and do not have implications for the benefit/risk assessment of the currently applied indication.

New in vitro data on eribulin protein binding and on eribulin as an inducer of CYPs confirms previous results.

New in vitro data indicate that eribulin is not a substrate of breast cancer resistance protein (BCRP),

organic anion (OAT1, OAT3, OATP1B1, OATP1B3), multi-drug resistance-associated protein (MRP2, MRP4) and bile salt export pump (BSEP) transporters. Neither has it inhibited BCRP, OCT1, OCT2, OAT1, OAT3, OATP1B1 and OATP1B3 transporter-mediated activity at relevant clinical concentrations. The SmPC has been updated in line with these results (see section 4.5 of the SmPC).

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No formal dose response study has been submitted.

Two phase II studies were conducted with eribulin in STS using the 1.4 mg/m^2 of eribulin mesylate (please see section below on supportive studies).

The eribulin dose regimen (1.4 mg/m^2 IV on Days 1 and 8 of every 21-day cycle) administered in study 309 was established in the E7389-G000-305 study (EMBRACE) performed in metastatic breast cancer which constituted the basis for licensure for eribulin. The dose regimen is considered justified.

It is to be noted that the dose 1.4 mg/m^2 used in e.g. EMBRACE and the 309 study refers to the salt form (eribulin mesilate) which is equivalent to 1.23 mg/m^2 of the base of the active substance (eribulin). This is adequately highlighted in the Halaven SmPC section 4.2.

2.4.2. Main study(ies)

E7389-G000-309 (study 309): A Randomized, Open-label, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Eribulin with Dacarbazine in Subjects with Soft Tissue Sarcoma

Methods

Study participants

Inclusion Criteria (abbreviated)

1. Histologically confirmed diagnosis of STS of high or intermediate grade with one of the following histological subtypes:

a. Adipocytic sarcoma including dedifferentiated-, myxoid-, round cell- or pleomorphic liposarcoma

b. Leiomyosarcoma.

2. Documented evidence of advanced (locally recurrent, locally advanced and/or metastatic) adipocytic sarcoma (restricted to subtypes listed above) or leiomyosarcoma, incurable by surgery or radiotherapy.

3. Subjects should have received standard therapies for advanced soft tissue sarcoma which **must have included an anthracycline** (unless contraindicated) with or without ifosfamide and then at least one additional regimen after failure of the anthracycline.

One regimen will consist of the following:

• Any single agent, or combination therapy consisting of cytotoxic, hormonal, biological (including humanized antibodies) and targeted agents, scheduled to be administered as a pre-planned treatment, given concomitantly, sequentially or both, is considered one regimen.

• Neo-adjuvant plus subsequent postoperative adjuvant chemotherapy will be considered as one regimen.

• If the dose of one or more of the components must be reduced or one or more of the components of the regimen must be omitted, or one of the components must be replaced with another similar drug due to toxicity, the changed version of the original regimen is not considered a new regimen. However, if a new component, dissimilar to any of the original components is added to the regimen, the new combination is considered a new regimen.

4. Radiographic evidence of disease progression by RECIST criteria on or after the last anti-cancer therapy within the 6 months prior to randomization.

5. Presence of measurable disease meeting the following criteria:

a. At least one lesion of ≥ 1.0 cm in long-axis diameter for non-lymph nodes or ≥ 1.5 cm in short-axis diameter for lymph nodes which is serially measurable according to RECIST 1.1 using either computed tomography (CT)/magnetic resonance imaging (MRI) or panoramic and close-up colour photography.

b. Lesions that have had radiotherapy must show evidence of progressive disease based on RECIST 1.1 to be deemed a target lesion.

6. Eastern Cooperative Oncology Group [ECOG], performance status of 0, 1 or 2.

7. Adequate renal function defined as calculated creatinine clearance ≥ 50 mL/min per the Cockroft and Gault formula.

8. Adequate bone marrow function, defined as:

a. Absolute neutrophil count (ANC) ≥ 1,500/mm^3 or ≥ 1.5 x 10^9/L.

b. Platelet count ≥ 100,000/mm^3 or ≥ 100 x 10^9/L.

c. Haemoglobin (Hb) ≥ 10g/dL at baseline (blood transfusions, hematopoietic growth factors and haematinics are allowed during the Pre-randomization Phase to correct Hb values < 10g/dL).

9. Adequate liver function, defined as:

a. Bilirubin ≤ 1.5 times the upper limit of normal (ULN) except for unconjugated hyperbilirubinemia of Gilbert's syndrome.

b. Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 3 times ULN. For total ALP > 3 times ULN, the ALP liver isoenzyme must be ≤ 3 times ULN.

10. Female subjects of child-bearing potential must agree to use two forms of highly effective contraception from the last menstrual period prior to randomization, during study treatment, and for 3 months after the final dose of study treatment.

11. Male subjects and their female partner who are of child-bearing potential (as defined in Inclusion 10), and are not practicing total abstinence must agree to use two forms of highly effective contraception from the last menstrual period of their female partner prior to randomization, during study treatment, and for 3 months (or 6 months if they received dacarbazine) after the final dose of study treatment.

12. Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol.

13. Males or females aged ≥ 18 years at the time of informed consent.

Exclusion Criteria (abbreviated)

1. Subjects who have received any anti-cancer therapy, including radiotherapy, cytotoxic, hormonal,

biological (including humanized antibodies) and targeted agents within 21 days, or any investigational agent within 30 days, prior to randomization.

2. Subjects who have not recovered from acute toxicities as a result of prior anti-cancer therapy to ≤ Grade 1, according to CTCAE, except for peripheral neuropathy (see Exclusion 6) and alopecia.

3. Subjects that have previously been treated with dacarbazine or participated in a study with eribulin (whether treated with eribulin or not).

4. Radiation therapy encompassing > 30% of bone marrow.

5. Major surgery within 21 days prior to randomization.

6. Pre-existing peripheral neuropathy > CTCAE Grade 2.

7. Significant cardiovascular impairment defined as:

    a. Cardiac failure > NYHA Class II according to the NYHA Functional Classification;

    b. Unstable angina or myocardial infarction within 6 months of enrolment;

    c. Serious cardiac arrhythmia or cardiac arrhythmia requiring treatment.

8. Subjects with a high probability of Long QT Syndrome.

9. Subjects with known CNS metastases.

10. Any serious concomitant illness or infection requiring treatment.

11. Any malignancy that required treatment or has shown evidence of recurrence (except for soft tissue sarcoma, non-melanoma skin cancer or carcinoma in situ of the cervix) during the 5 years prior to randomisation.

12. Female subjects must not be pregnant as documented by a negative ß-hCG test with a minimum sensitivity 25 IU/L or equivalent unit of ß-hCG at Screening and Baseline, or breastfeeding.

13. Hypersensitivity to either HalA or HalB chemical derivatives or both, or to dacarbazine or to any of the dacarbazine excipients (refer to the dacarbazine prescribing information).

14. Any medical or other condition which, in the opinion of the PI or designee, will preclude participation in a clinical trial.

Treatments

Arm A: Eribulin mesilate at a dose of 1.4 mg/m^2 as an IV infusion over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.

Arm B: Dacarbazine (DTIC), either 1200 mg/m^2, 1000 mg/m^2, or 850 mg/m^2 (each administered once every 3 weeks) as starting dose could be chosen at the discretion of the investigator depending on the individual clinical status of the patient at entry. The selection of the starting dose of dacarbazine for each subject had to be confirmed prior to randomization.

Outcomes / endpoints

Primary Efficacy Endpoint

• OS measured from the date of randomisation until date of death from any cause.

Secondary Efficacy Endpoints

• PFS, defined as the time from the date of randomisation to the date of first documentation of disease

progression, or date of death (whichever occurs first).

• PFR_{12wks}, defined as the proportion of subjects alive and progression-free at 12 weeks from the date of randomisation.

• CBR, defined as the proportion of subjects who had best overall response of CR or PR or dSD (duration > 11 weeks).

• Safety endpoints included AEs according to CTCAE v4.0 grades and serious AEs, haematology and clinical chemistry, urinalysis, regular measurement of vital signs, 12-lead ECGs and performance of physical examinations.

• Population PK profile of eribulin in the subjects with STS.

Exploratory Endpoints

• ORR, the proportion of subjects who had overall response of CR or PR.

• DCR, the proportion of subjects who had best overall response of CR, or PR, or SD.

• dSD, defined as the proportion of subjects who had the duration of SD ≥11 weeks.

• QoL scores measured using the QLQ-C30 and EQ-5D questionnaires.

• The following exploratory PK/PD endpoints:

- Relationship between exposure to eribulin and pharmacodynamic biomarkers and efficacy.
- Relationship between exposure to eribulin and AEs.
- Blood and tumour biomarkers which may be correlated with safety and efficacy endpoints.

Sample size

The sample size determination was estimated and based upon the required number of target events to detect a treatment difference in the comparison of OS. The estimated median OS of Arm B was assumed to be approximately 6 months, based on historical controls (Anderson et al., 2006). An improvement of 2.5 months or more was considered to be of clinical importance, which translated to a median OS in Arm A of 8.5 months and a hazard ratio of 0.706. Alpha was set at 0.05 assuming a two-sided test and the power at 90%. The required number of deaths for the assumed effect size was projected to be 353 events. It was estimated that approximately 450 subjects would need to be randomized and with a randomization ratio of 1:1 this would be a minimum of 225 subjects per treatment arm.

Randomisation

Randomization was conducted in a 1:1 ratio (Arm A, eribulin; Arm B, dacarbazine) and stratified by histology (ADI or LMS), region (Region 1: USA and Canada; or Region 2: Western Europe, Australia and Israel; or Region 3: Eastern Europe, Latin America and Asia), and number of prior regimens for advanced STS (2 or >2 prior regimens).

Blinding (masking)

Study 309 was open-label.

Statistical methods

The study was designed to provide evidence to either support the null hypothesis:

H0: Seribulin(t)=Sdacarbazine(t) (the survival distributions in the two arms are equal) or to reject it in

favour of the alternative hypothesis:

H1: Seribulin(t)≠Sdacarbazine(t)

where Seribulin(t) is the survival function in the eribulin arm and Sdacarbazine(t) is the survival function in the dacarbazine arm.

Stratified log-rank test was used to compare the primary efficacy endpoint OS between treatment arms on the Full Analysis Set. Subjects who were lost to follow-up and the subjects who were alive at the date of data cut-off were censored at either the date the subject was last known to be alive, or the date of data cut-off, whichever was earliest. Subjects who died on the date of randomization had a survival time of 0.5 day. The significance levels were as follows:

• 0.0148 for the interim analysis when 70% of the target events have been observed,

• 0.0455 for the final analysis.

ECOG Performance Status (PS) were considered as additional stratification factors (0/1 vs. 2 or above) in primary analysis if baseline ECOG PS imbalance rate between two arms were more than 10%.

Three sensitivity analyses were performed on the final primary analysis.

• An analysis same as the final primary analysis but on per-protocol set.

• An analysis similar to the final primary analysis except without any stratification.

• Subjects starting new anti-cancer treatment were censored at the date of the new treatment

Subgroup analyses, via stratified Cox proportional model, were performed by age (<65, or ⩾65), sex, race, ethnicity, number of prior regimens for advanced STS, region, histology, baseline ECOG performance status , prior anti-cancer therapy type and AJCC (American Joint Committee on Cancer) Sarcoma tumor stage at the date of histological diagnosis. If it was applicable, the stratified factors would be histology, geographic region, and number of prior regimens for advanced STS.

PFS was compared between the treatment arms using two-sided stratified log-rank test, stratified by histology, geographic region and number of prior regimens for advanced STS on both Full Analysis Set and Per-Protocol Analysis set.

Results

Participant flow

Table 18: Subject Disposition and Primary Reason for Discontinuation from Study Treatment (Study 309: All Randomized Subjects)

	Eribulin (N=228) n (%)	Dacarbazine (N=224) n (%)	Total (N=452) n (%)
All screened subjects			594
Randomized, n	228	224	452
Not treated, n	1 (0.4)	1(0.4)	2 (0.4)
Treated, n (%)	227 (99.6)	223 (99.6)	450 (99.6)
Survival status at data cutoff date, n (%)			
Alive	44 (19.3)	35 (15.6)	79 (17.5)
Dead	176 (77.2)	181 (80.8)	357 (79.0)
Subject withdrew consent	8 (3.5)	8 (3.6)	16 (3.5)
Lost to follow-up	0	0	0
Number of subjects on treatment after data cutoff	1 (0.4)	1 (0.4)	2 (0.4)
Discontinued study treatment, n (%)	226 (99.1)	222 (99.1)	448 (99.1)
Primary reason for discontinuation, n (%)			
Disease progression[a]	173 (75.9)	165 (73.7)	338 (74.8)
Clinical progression	24 (10.5)	27 (12.1)	51 (11.3)
Adverse event[b]	14 (6.1)	10 (4.5)	24 (5.3)
Subject choice	5 (2.2)	10 (4.5)	15 (3.3)
Administrative/Other:	10 (4.4)	10 (4.5)	20 (4.4)
Withdrawal of consent from study	2 (0.9)	4 (1.8)	6 (1.3)
Other	8 (3.5)	6 (2.7)	14 (3.1)
Deaths due to disease progression	156 (68.4)	150 (67.0)	306 (67.7)
Death during study or within 30 days of last dose	15 (6.6)	9 (4.0)	24 (5.3)

Percentages are based on the number of subjects randomized and treated in the relevant treatment group.
CRF = case report form.
a: According to RECIST criteria.
b: Corresponding adverse event(s) leading to discontinuation from the study/study drug were reported on the Adverse Event CRF.

Recruitment

Study 309 was conducted between 10 Mar 2011 and 02 Jan 2015 at 110 study sites in three geographical regions: the United States and Canada (Region 1); Western Europe, Australia, and Israel (Region 2); and Eastern Europe, Latin America, and Asia (Region 3).

Conduct of the study

An interim analysis on efficacy data was conducted when 247 deaths (70% of the events) were observed, and was performed by an independent statistical reporting team. The data cut-off date for the interim analysis was 20 Oct 2013 (the date of the 247th event). The DMC reviewed the interim efficacy and safety data on 18 Feb 2014 and recommended that the study continue without modification.

Dry runs were conducted on hypothetical data to test the statistical programs on the datasets to ensure

they would work properly for the final analysis. However, unintentionally interim results from study 309 were used for these dry runs. Once the final analysis was conducted, it became obvious that the final KM curves and those from the dry runs were almost identical.

The Applicant conducted an internal investigation and concluded that there was no evidence that the exposure of the interim results had any impact on the final results. The first dry run was conducted on June 19, 2014, one year after the last patient was enrolled (May 28, 2013). The last dry run was conducted in November 2014. At the time of the first dry run, 82% of survival endpoints had been accrued. The MAH did not make any major amendments to the protocol after the dry runs.

Amendments and Protocol Deviations

There were two amendments to the protocol. Amendment 01 was issued on 25 May 2012 and pertained mainly to revisions of inclusion/exclusion criteria. Amendment 02 was issued on 08 Aug 2012 and pertained to study drug permanently discontinued in the event of Grade 3 or 4 QTc interval prolongation. An initial review of all protocol deviations identified 22 subjects who had a major protocol violation based on the following protocol specified criteria:

- Deviation from inclusion criteria 1 – 3

- Treated with the incorrect study drug versus the randomized treatment.

Following review of the analysis, an additional 16 subjects were identified as having a major protocol violation on the basis of inclusion/exclusion criteria, study drug dosing error, or other criteria that could potentially affect the safety or efficacy analyses. Therefore, a total of 38 subjects (8.4%) were excluded from the Per Protocol Analysis Set and a larger percentage of subjects in the dacarbazine arm (11.2%) had a major protocol violation than subjects in the eribulin arm (5.7%).

Baseline data

Table 19: Demographic Characteristics (Study 309: FAS)

Category	Eribulin (N=228) n (%)	Dacarbazine (N=224) n (%)	Total (N=452) n (%)
Age (year)[a]			
n	228	224	452
Mean (SD)	55.6 (11.01)	55.7 (10.35)	55.7 (10.68)
Median	56	56	56
Min, Max	28, 83	24, 83	24, 83
Age group, n (%)			
<65 years	178 (78.1)	178 (79.5)	356 (78.8)
≥65 years	50 (21.9)	46 (20.5)	96 (21.2)
Sex, n (%)			
Male	67 (29.4)	82 (36.6)	149 (33.0)
Female	161 (70.6)	142 (63.4)	303 (67.0)
Race, n (%)			
White	162 (71.1)	168 (75.0)	330 (73.0)
Black or African American	6 (2.6)	6 (2.7)	12 (2.7)
Japanese	1 (0.4)	0 (0.0)	1 (0.2)
Chinese	2 (0.9)	1 (0.4)	3 (0.7)
Other Asian	15 (6.6)	15 (6.7)	30 (6.6)
Native Hawaiian or other Pacific Islander	1 (0.4)	0 (0.0)	1 (0.2)
Other	6 (2.6)	4 (1.8)	10 (2.2)
Not applicable[b]	35 (15.4)	30 (13.4)	65 (14.4)
Ethnicity			
Hispanic or Latino	23 (10.1)	27 (12.1)	50 (11.1)
Not Hispanic or Latino	170 (74.6)	167 (74.6)	337 (74.6)
Not applicable	35 (15.4)	30 (13.4)	65 (14.4)
Geographic region			
Region 1: USA and Canada	87 (38.2)	86 (38.4)	173 (38.3)
Region 2: Western Europe, Australasia and Israel	106 (46.5)	105 (46.9)	211 (46.7)
Region 3: Eastern Europe, Latin America and Asia	35 (15.4)	33 (14.7)	68 (15.0)

Percentages are based on the total number of subjects with nonmissing values in relevant treatment group.
Max = maximum, Min = minimum, SD = standard deviation.
a: Age is calculated at date of informed consent.
b: Race was not collected in all countries (eg, France).
Data Source: Study 309 CSR, Table 14.1.3.1.

Table 20: Baseline Characteristics (Study 309: FAS)

Category	Eribulin (N=228) n (%)	Dacarbazine (N=224) n (%)	Total (N=452) n (%)
ECOG PS status			
0	111 (48.7)	90 (40.2)	201 (44.5)
1	114 (50.0)	121 (54.0)	235 (52.0)
2	3 (1.3)	13 (5.8)	16 (3.5)
Weight (kg)			
n	228	224	452
Mean (SD)	74.50 (20.252)	76.14 (20.176)	75.31 (20.209)
Median	71.8	71.6	71.8
Min, Max	42.0, 214.5	41.7, 157.2	41.7, 214.5
NYHA cardiac disease classification			
Class I	147 (64.5)	133 (59.4)	280 (61.9)
Class II	15 (6.6)	20 (8.9)	35 (7.7)
Not applicable	65 (28.5)	71 (31.7)	136 (30.1)
Not done	1 (0.4)	0 (0.0)	1 (0.2)
Height (cm)			
n	228	224	452
Mean (SD)	166.10 (9.786)	166.71 (10.301)	166.40 (10.038)
Median	165.1	166.0	165.6
Min, Max	144.8, 193.0	139.9, 192.5	139.9, 193.0
BSA (m^2)			
n	228	224	452
Mean (SD)	1.82 (0.255)	1.84 (0.244)	1.83 (0.250)
Median	1.80	1.82	1.81
Min, Max	1.34, 3.09	1.40, 2.84	1.34, 3.09
Histology of primary tumor			
Adipocytic (total)	75 (32.9)	78 (34.8)	153 (33.8)
Adipocytic dedifferentiated	32 (14.0)	37 (16.5)	69 (15.3)
Adipocytic myxoid	26 (11.4)	25 (11.2)	51 (11.3)
Adipocytic pleomorphic	13 (5.7)	15 (6.7)	28 (6.2)
Adipocytic round cell	4 (1.8)	1 (0.4)	5 (1.1)
Leiomyosarcoma	152 (66.7)	145 (64.7)	297 (65.7)
Other	1 (0.4)	1 (0.4)	2 (0.4)
Tumor grade			
High	150 (65.8)	152 (67.9)	302 (66.8)
Intermediate	77 (33.8)	69 (30.8)	146 (32.3)
Not done	1 (0.4)	3 (1.3)	4 (0.9)

Percentages are based on the total number of subjects with nonmissing values in relevant treatment group.
BSA = body surface area, ECOG = Eastern Cooperative Oncology Group, Max = maximum, Min = minimum, NYHA = New York Heart Association, SD = standard deviation.
Data Source: Study 309 CSR, Table 14.1.3.1.

Disease characteristics and prior treatment:

Table 21: Disease History and Characteristics at Study Entry: Randomization Phase – FAS

Category	Eribulin (N=228) n (%)	Dacarbazine (N=224) n (%)	Total (N=452) n (%)
Time between the original histological diagnosis and randomization (months)			
Mean (SD)	50.6 (48.07)	47.9 (39.45)	49.3 (43.98)
Median	36.5	34.4	35.3
Min, Max	3, 307	1, 217	1, 307
< 6 months, n (%)	2 (0.9)	2 (0.9)	4 (0.9)
≥ 6 months, n (%)	226 (99.1)	222 (99.1)	448 (99.1)
Age at diagnosis (years)			
Mean (SD)	51.4 (11.15)	51.8 (10.50)	51.6 (10.82)
Median	52.0	52.0	52.0
Min, Max	22, 82	23, 82	22, 82
< 65 years, n (%)	200 (87.7)	199 (88.8)	399 (88.3)
≥ 65 years, n (%)	28 (12.3)	25 (11.2)	53 (11.7)
Time since most recent (last) disease progression to the randomization (days			
Mean (SD)	36.0 (26.73)	39.9 (33.68)	37.9 (30.40)
Median	27.0	31.0	28.0
Min, Max	6, 143	2, 224	2, 224
Target lesions at baseline, n (%)			
Lymph node only	1(0.4)	1 (0.4)	2 (0.4)
Non-lymph node only	211 (92.5)	207 (92.4)	418 (92.5)
Lymph node and non-lymph node	16 (7.0)	16 (7.1)	32 (7.1)
Non-Target Lesions at Baseline, n(%)			
Yes	155 (68.0)	175 (78.1)	330 (73.0)
No	73 (32.0)	49 (21.9)	122 (27.0)

Max = maximum, Min = minimum, SD = standard deviation.
Percentages are based on the total number of subjects with nonmissing values in relevant treatment arm.
Source: Table 14.1.3.2.

Table 22: Previous Anticancer Therapy: Randomization Phase – FAS

	Eribulin (N=228) n (%)	Dacarbazine (N=224) n (%)	Total (N=452) n (%)
Previous Anticancer therapy regimens (including adjuvant and neoadjuvant)[a]			
0	0	0	0
1	2 (0.9)	3 (1.3)	5 (1.1)
2	113 (49.6)	103 (46.0)	216 (47.8)
3	62 (27.2)	66 (29.5)	128 (28.3)
4	26 (11.4)	29 (12.9)	55 (12.2)
>4	25 (11.0)	23 (10.3)	48 (10.6)
Number of previous neoadjuvant therapy regimens			
1	13 (5.7)	9 (4.0)	22 (4.9)
2	2 (0.9)	1 (0.4)	3 (0.7)
Number of previous adjuvant therapy regimens			
1	41 (18.0)	44 (19.6)	85 (18.8)
2	3 (1.3)	7 (3.1)	10 (2.2)
Number of previous therapeutic regimens			
1	21 (9.2)	27 (12.1)	48 (10.6)
2	115 (50.4)	100 (44.6)	215 (47.6)
3	48 (21.1)	58 (25.9)	106 (23.5)
4	22 (9.6)	17 (7.6)	39 (8.6)
5	9 (3.9)	12 (5.4)	21 (4.6)
6	1 (0.4)	2 (0.9)	3 (0.7)
7	4 (1.8)	3 (1.3)	7 (1.5)
8	2 (0.9)	0	2 (0.4)
9	2 (0.9)	0	2 (0.4)
Number of previous maintenance therapy regimens			
1	7 (3.1)	7 (3.1)	14 (3.1)
2	1 (0.4)	4 (1.8)	5 (1.1)
4	0	1 (0.4)	1(0.2)
Duration of the most recent chemotherapy (months)			
N	228	224	452
Mean (SD)	4.3 (4.98)	4.2 (4.02)	4.3 (4.52)
Median	3.0	3.0	3.0
Min, Max	0, 39	0, 23	0, 39
Best response to last therapy			
Complete response	0	0	0
Partial response	13 (5.7)	25 (11.2)	38 (8.4)
Stable disease	84 (36.8)	72 (32.1)	156 (34.5)
Progressive disease	117 (51.3)	118 (52.7)	235 (52.0)
Not evaluable	2 (0.9)	3 (1.3)	5 (1.1)
Not applicable	3 (1.3)	2 (0.9)	5 (1.1)
Unknown	9 (3.9)	4 (1.8)	13 (2.9)
Time from end of last therapy to randomization (days)			
N	228	224	452
Mean (SD)	143.7 (272.84)	148.8 (469.19)	146.2 (382.53)
Median	52.0	58.0	57.0
Min, Max	1, 2542	1, 6349	1, 6349
Type of previous anticancer therapy			
Neoadjuvant	15 (6.6)	10 (4.5)	25 (5.5)
Adjuvant	44 (19.3)	51 (22.8)	95 (21.0)
Therapeutic	224 (98.2)	219 (97.8)	443 (98.0)
Maintenance[b]	8 (3.5)	12 (5.4)	20 (4.4)
Unknown	3 (1.3)	1 (0.4)	4 (0.9)
Previous radiotherapy			
Yes	118 (51.8)	118 (52.7)	236 (52.2)
No	110 (48.2)	106 (47.3)	216 (47.8)
Type of prior chemotherapy received in ≥5% of subjects	224 (98.2)	219 (97.8)	443 (98.0)
Doxorubicin	179 (78.5)	173 (77.2)	352 (77.9)
Gemcitabine	119 (52.2)	122 (54.5)	241 (53.3)
Ifosfamide	114 (50.0)	112 (50.0)	226 (50.0)
Trabectedin	107 (46.9)	112 (50.0)	219 (48.5)
Docetaxel	97 (42.5)	91 (40.6)	188 (41.6)
Pazopanib	18 (7.9)	17 (7.6)	35 (7.7)
Investigational drugs	18 (7.9)	21 (9.4)	39 (8.6)
Epirubicin	13 (5.7)	14 (6.3)	27 (6.0)
Cisplatin	12 (5.3)	13 (5.8)	25 (5.5)
Cyclophosphamide	12 (5.3)	9 (4.0)	21 (4.6)

Max = maximum, Min = minimum, SD = standard deviation
Percentages are based on the total number of subjects in the relevant treatment arm.
a: Previous therapy excludes radiotherapy and surgery.
b: For the purposes of eligibility, maintenance therapy was considered therapeutic.

Numbers analysed

Table 23: Analysis Sets – Study 309

Analysis Set	Eribulin n (%)	Dacarbazine n (%)	Total n (%)
Full analysis set	228 (100.0)	224 (100.0)	452 (100.0)
Safety analysis set[a]	226 (99.1)	224 (100.0)	450 (99.6)
Per protocol analysis set	215 (94.3)	199 (88.8)	414 (91.6)

PK = pharmacokinetics, PD = pharmacodynamics.
Percentages are based on the number of randomized subjects in the relevant treatment arm.
a: Excluded 2 subjects (ID 11071006, 48101003) who were randomized (1 in each treatment arm) but did not receive at least 1 dose of study treatment; 1 subject (ID 19081008) was randomized in eribulin but was treated with dacarbazine, this subject is analyzed in Dacarbazine arm.
Source: Table 14.1.2.1.

Outcomes and estimation

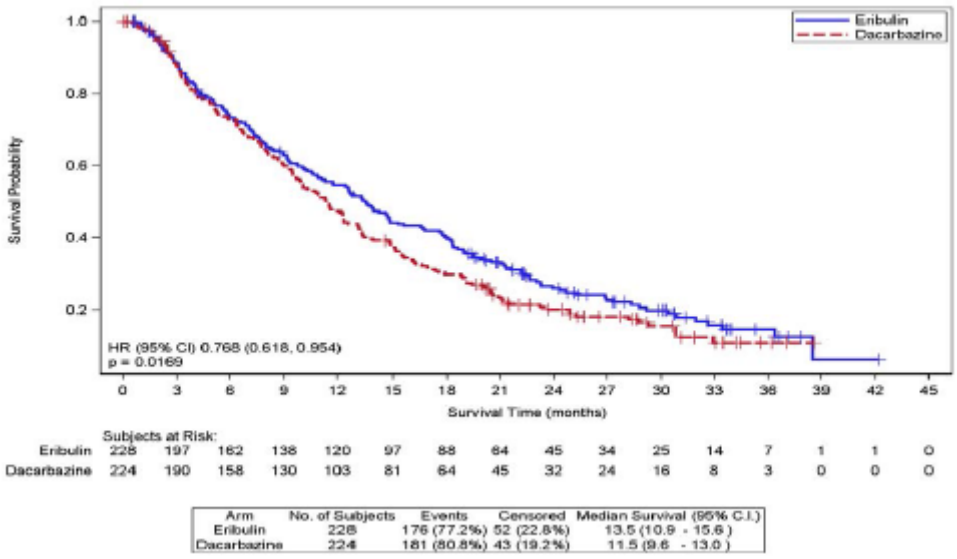
Primary endpoint

Overall survival

Table 24: Summary of Overall Survival (FAS) – Study 309

	Eribulin (N=228)	Dacarbazine (N=224)
Deaths, n (%)	176 (77.2)	181 (80.8)
Censored, n (%) Withdrew consent Alive at database cut-off	52 (22.8) 8 (3.5) 44 (19.3)	43 (19.2) 8 (3.6) 35 (15.6)
Overall survival (months)[a]		
Median (95% CI)	13.5 (10.9, 15.6)	11.5 (9.6, 13.0)
Q1 (95% CI)	5.8 (4.2, 7.2)	5.2 (4.0, 6.7)
Q3 (95% CI)	24.7 (22.1, 30.9)	20.5 (17.4, 24.9)
Stratified *P*-value[b]	0.0169	
Hazard ratio (95% CI)[c]	0.768 (0.618, 0.954)	
Overall survival rate (95% CI)[c]		
3 months 6 months 12 months 18 months 24 months	0.888 (0.838, 0.923) 0.734 (0.671, 0.787) 0.548 (0.481, 0.611) 0.402 (0.337, 0.466) 0.260 (0.202, 0.322)	0.876 (0.825, 0.914) 0.729 (0.665, 0.783) 0.475 (0.407, 0.540) 0.299 (0.239, 0.361) 0.202 (0.150, 0.259)

a: The median, first and third quartile of overall survival, the cumulative probability of overall survival at 3, 6, 12, 18, 24 months and the corresponding two-sided 95% CIs are based on Kaplan-Meier product-limit method and Greenwood formula, respectively, for each treatment arm.
b: P-value is calculated two-sided log-rank test, stratified by histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2). Significant level is alpha= 0.0455.
c: Hazard ratio is based on a stratified Cox regression model including treatment as covariate, and histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2) as strata
Source: Table 14.2.2.1.



Arm	No. of Subjects	Events	Censored	Median Survival (95% C.I.)
Eribulin	228	176 (77.2%)	52 (22.8%)	13.5 (10.9 - 15.6)
Dacarbazine	224	181 (80.8%)	43 (19.2%)	11.5 (9.6 - 13.0)

HR = hazard ratio. HR is based on a stratified Cox regression model, including treatment as covariate, and histology, geographic region and number of prior regimens for advanced STS as data.
P-value is calculated by 2-sided log-rank test, stratified by histology (ADI or LMS), geographic region (1, 2 or 3) and number of prior regimens for advanced STS (2 or >2).
Source: Figure 14.2.1.4.

Figure 2: Kaplan-Meier Plot of Overall Survival (FAS) – Study 309

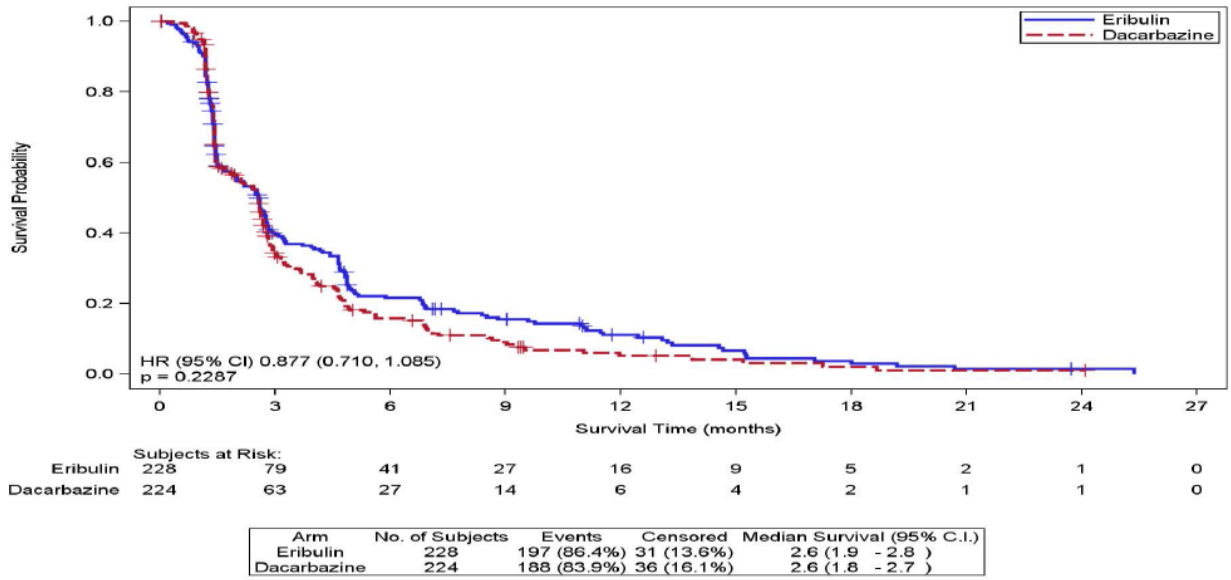
Secondary endpoints

Progression-free survival

Table 25: Summary of Progression-Free Survival (FAS) – Study 309

	Eribulin (N=228)	Dacarbazine (N=224)
Subjects with Events (PD + death), n (%)	197 (86.4)	188 (83.9)
Progressive disease (PD)[a]	183 (80.3)	173 (77.2)
Death, without documented PD	14 (6.1)	15 (6.7)
Censored, n (%)	31 (13.6)	36 (16.1)
No baseline or post baseline tumor assessment	0	0
Alive without progression at database cut-off	7 (3.1)	8 (3.6)
New anticancer treatment started	18 (7.9)	18 (8.0)
Death or PD after 2 or more missed tumor assessments	6 (2.6)	10 (4.5)
Progression-free survival (months)[b]		
Median (95% CI)	2.6 (1.9, 2.8)	2.6 (1.8, 2.7)
Q1 (95% CI)	1.3 (1.2, 1.4)	1.4 (1.2, 1.4)
Q3 (95% CI)	4.9 (4.7, 6.9)	4.2 (3.3, 4.9)
Stratified P-value[c]	0.2287	
Hazard ratio (95% CI)[d]	0.877 (0.710, 1.085)	
Progression-free survival rate (95% CI)[b]		
3 months	0.400 (0.334, 0.466)	0.343 (0.278, 0.409)
6 months	0.216 (0.162, 0.275)	0.158 (0.110, 0.214)
12 months	0.111 (0.070, 0.162)	0.052 (0.024, 0.096)

a: If a subject had both progressive disease and death, only progressive disease data will be included.
b: Progression Free Survival and Progression Free Survival rate at 3, 6 and 12 months (95% CI) is calculated using Kaplan-Meier product-limit method and Greenwood Formula.
c: P-value is calculated two-sided log-rank test, stratified by histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2). Significant level is alpha= 0.0455.
d: Hazard ratio is based on a stratified Cox regression model including treatment as covariate, and histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2) as strata
Source: Table 14.2.3.1.



Source: Table 14.2.3.1 and Listing 16.3.1.2
The tumor assessment is based on RECIST 1.1. P-value is calculated by two-sided log-rank test, stratified by histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2).

Figure 3: Kaplan-Meier Plot of Progression Free Survival (FAS) – Study 309

Progression-free rate at 12 weeks (PFR_{12WKS})

The PFR_{12wks} in the FAS was 33.3% (95% CI: 27.2, 39.9) in the eribulin arm and 28.6% (95% CI: 22.8, 35.0) in the dacarbazine arm (P = 0.253).

The results in the PP analysis were similar.

Exploratory endpoints

Objective response rate (ORR)

The exploratory efficacy endpoints of the study included ORR, DCR and dSD rate between the treatment arms.

Table 26: Summary of Tumour Response per Investigator Assessment (FAS) – Study 309

	Eribulin (N=228)	Dacarbazine (N=224)
Best overall response category, n (%)		
Complete response (CR)	0	0
Partial response (PR)	9 (3.9)	11 (4.9)
Stable disease (SD)	119 (52.2)	107 (47.8)
Progressive disease (PD)	89 (39.0)	88 (39.3)
Not evaluable (NE)	2 (0.9)	3 (1.3)
Unknown (UNK)	9 (3.9)	15 (6.7)
Objective response (CR + PR), n (%)	9 (3.9)	11 (4.9)
95 % CI[a]	1.8, 7.4	2.5, 8.6
P-value[b]	0.616	
Disease control rate (CR + PR + SD), n (%)	128 (56.1)	118 (52.7)
95% CI[a]	49.4, 62.7	45.9, 59.4
P-value[b]	0.438	
Durable SD, n (%)	96 (42.1)	96 (42.9)
95% CI[a]	35.6, 48.8	36.3, 49.6
P-value[b]	0.900	

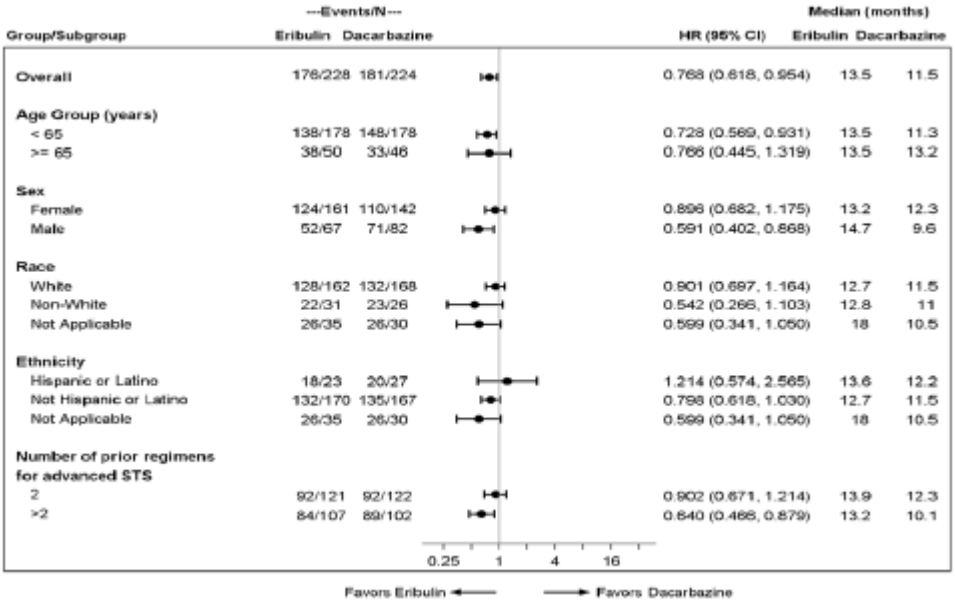
CI = confidence interval. The tumor assessment is based on RECIST 1.1.
ORR = objective response rate, is the proportion of PR+CR. DCR = disease control rate, is the proportion of PR+CR+SD.
Durable SD = stable disease ≥ 11 weeks. Best overall response of SD must be at least 6 weeks after first dose.
a: 95% CI is calculated using exact Pearson Clopper two-sided 95% confidence limits.
b: P-value is calculated using the stratified Cochran Mantel-Haenszel method, the stratified factors are histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2).
Source: Table 14.2.6.1.

Ancillary analyses

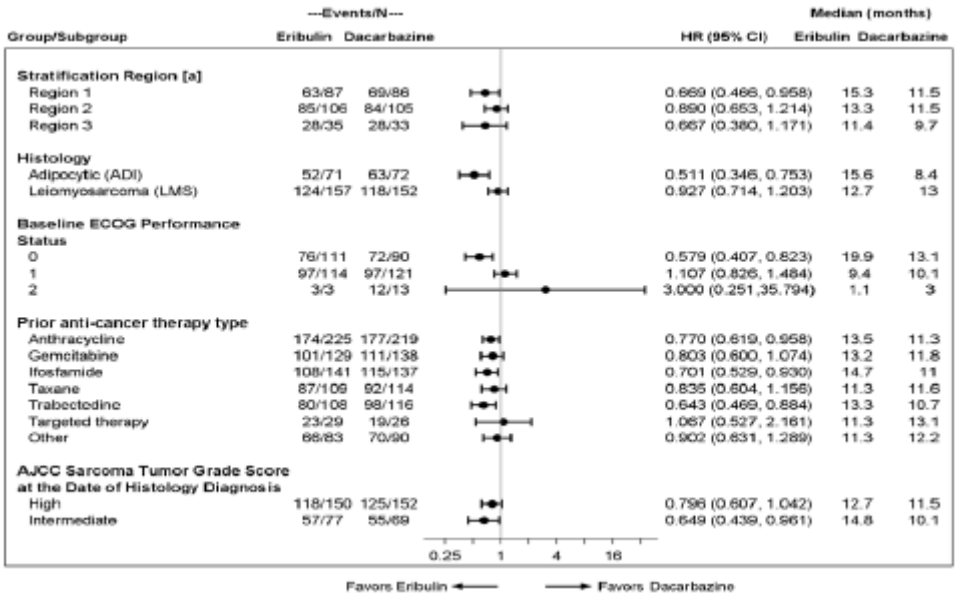
Subgroup Analysis of OS

Planned subgroup analyses for the primary endpoint of OS were conducted for subjects in the FAS population based on age group, sex, race, ethnicity, number of prior regimens, geographic region, tumour histology, baseline ECOG PS, prior anticancer therapy type and AJCC sarcoma tumour grade at the date of histology diagnosis.

OS Forest Plot of HR by Subgroup (FAS)



Note: Information on race or ethnicity is not collected in some countries (eg France) and is recorded as "Not applicable".

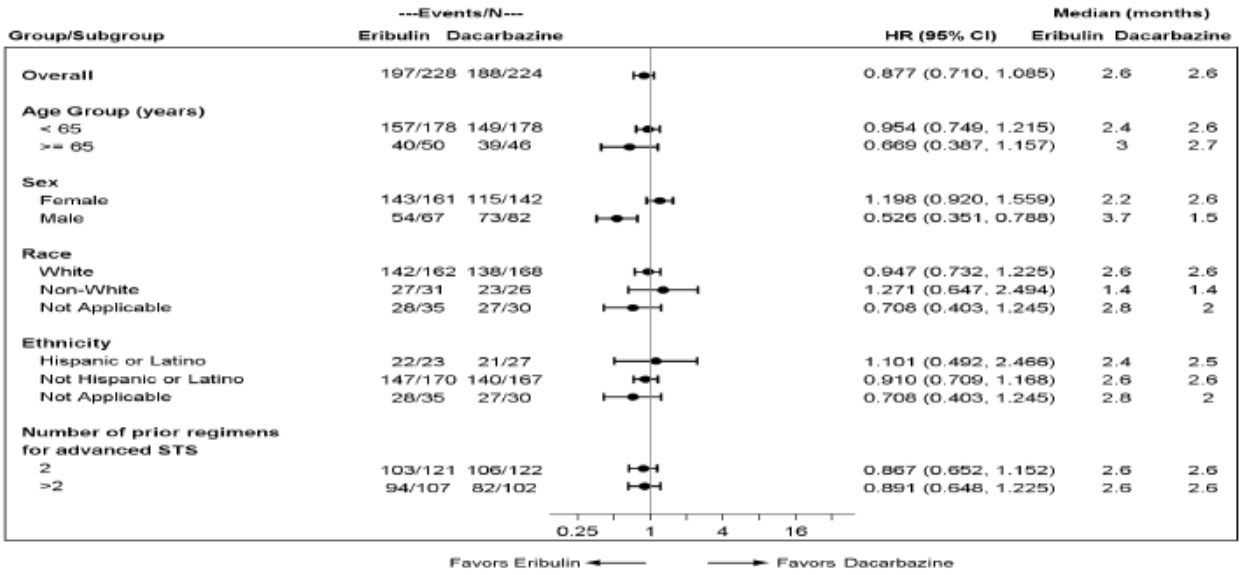


a: Region 1: USA and Canada; Region 2: Western Europe, Australia and Israel; Region 3: Eastern Europe, Latin America and Asia.

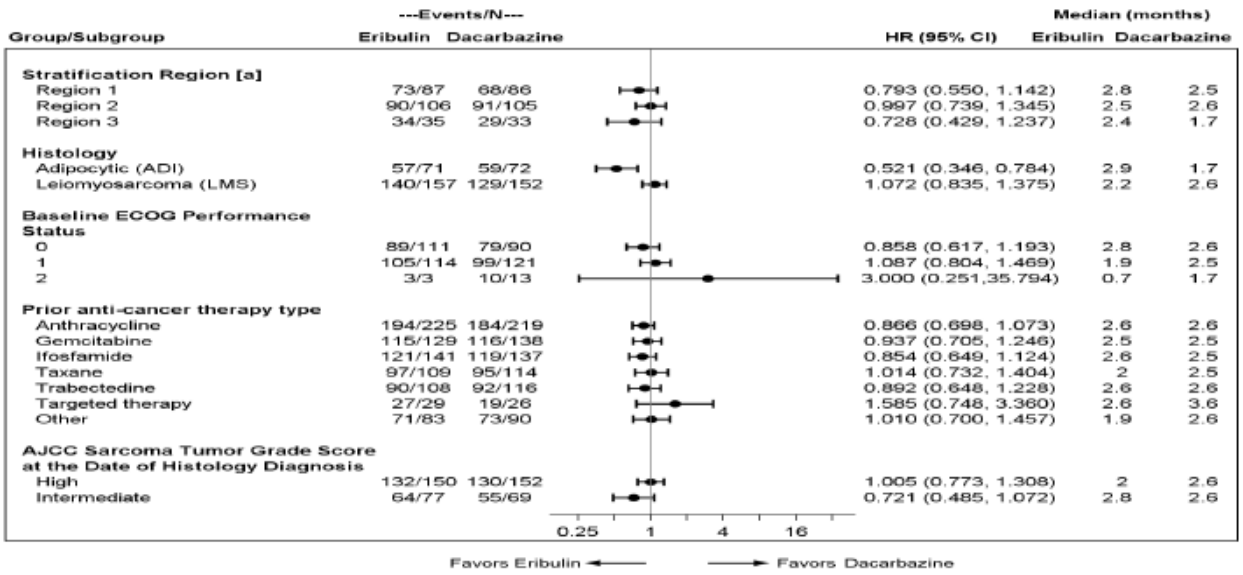
Figure 4: Overall survival forest plot of Hazard Ratio randomisation phase – FAS (Study 309)

PFS

PFS Forest Plot of HR (Full Analysis Set) is presented below.



Source: Table 14.2.3.1 and Table 14.2.3.1.1
The tumor assessment is based on RECIST 1.1. Hazard ratio is defined as the ratio of Eribulin to Dacarbazine
[a]: Region 1: USA and Canada; Region 2: Western Europe, Australasia and Israel; Region 3: Eastern Europe, Latin America and Asia.
X:/projects/E7389/E7389-G000-309/CSR/PROD/pg/Figures/f_forest_pfs.sas FINAL/DATA CUTOFF: 02JAN2015 07MAY2015:23:06



Source: Table 14.2.3.1 and Table 14.2.3.1.1
The tumor assessment is based on RECIST 1.1. Hazard ratio is defined as the ratio of Eribulin to Dacarbazine
[a]: Region 1: USA and Canada; Region 2: Western Europe, Australasia and Israel; Region 3: Eastern Europe, Latin America and Asia.
X:/projects/E7389/E7389-G000-309/CSR/PROD/pg/Figures/f_forest_pfs.sas FINAL/DATA CUTOFF: 02JAN2015 07MAY2015:23:06

Figure 5: PFS forest plot of Hazard Ratio randomisation phase – FAS (Study 309)

As the subgroup analyses for OS and PFS indicated a differential benefit between the ADI and LMS (ADI [OS HR 0.51; PFS HR 0.52] vs. LMS [OS HR 0.93; PFS HR 1. 07]), separate baseline and outcome data for the two subtypes including subgroup analyses were requested:

Study Outcomes by Histology

Adipocytic (ADI)

OS for ADI subjects is shown in the figure below.

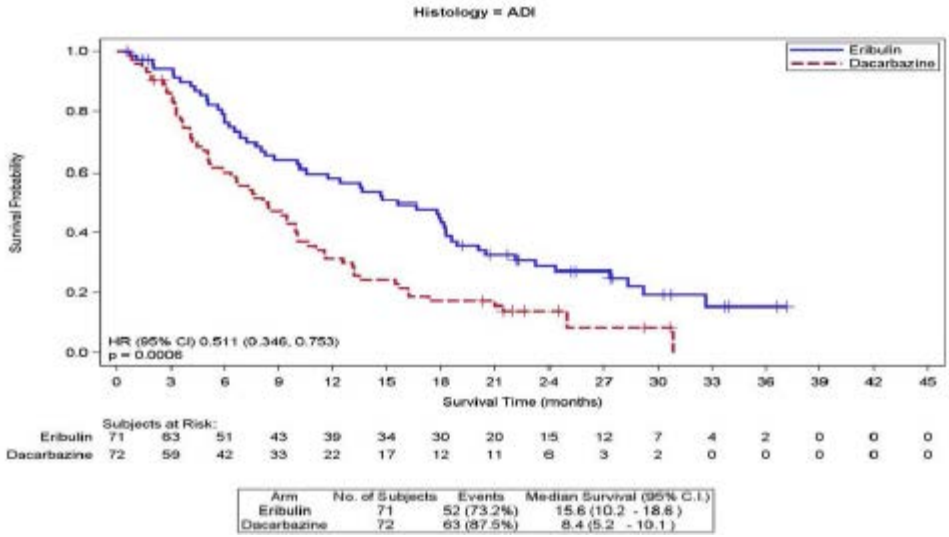


Figure 6: Overall survival by treatment for adipocytic (ADI) subjects - Study 309

PFS for ADI subjects is shown in the figure below.

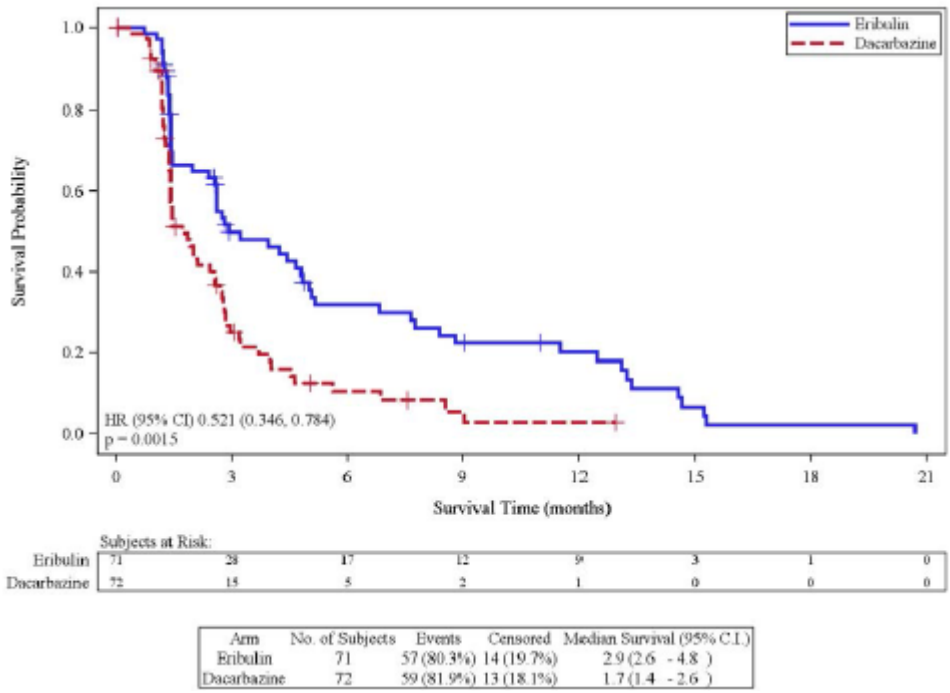


Figure 7: PFS by treatment for adipocytic (ADI) subjects – Study 309

From these analyses it is apparent that the OS benefit for eribulin over dacarbazine is entirely driven by the patients with the ADI subtype (HR 0.51 (95% CI 0.346, 0.753), P=0.0006) with a median OS of about 16 months for the eribulin arm compared with approximately 8 months for the dacarbazine arm. In

addition, a benefit in PFS for this subtype can be observed (median 2.9 months vs. 1.7 months in the dacarbazine arm with a HR of 0.52 (95% CI 0.346; 0.784, P=0.0015).

Leiomyosarcoma

OS for LMS is shown in the figure below.

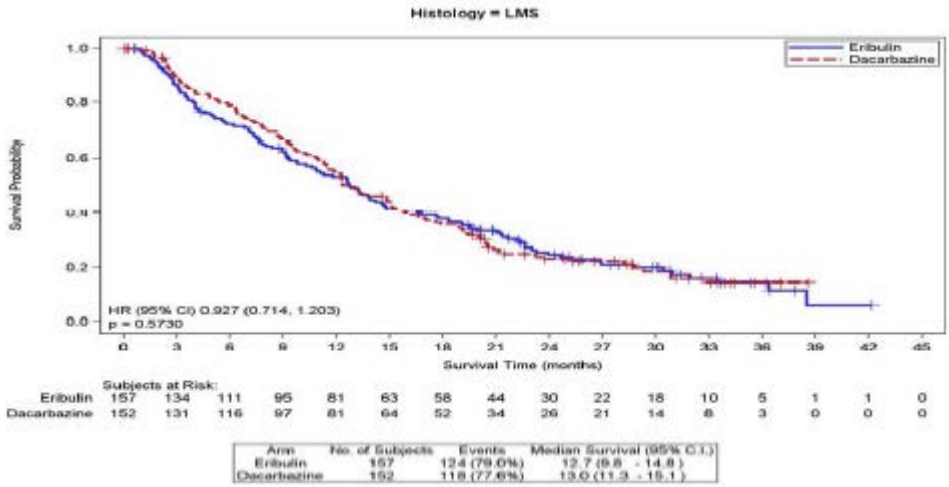


Figure 8: Overall survival by treatment for Leiomyosarcoma subjects – Study 309

PFS for LMS subjects is shown in the figure below.

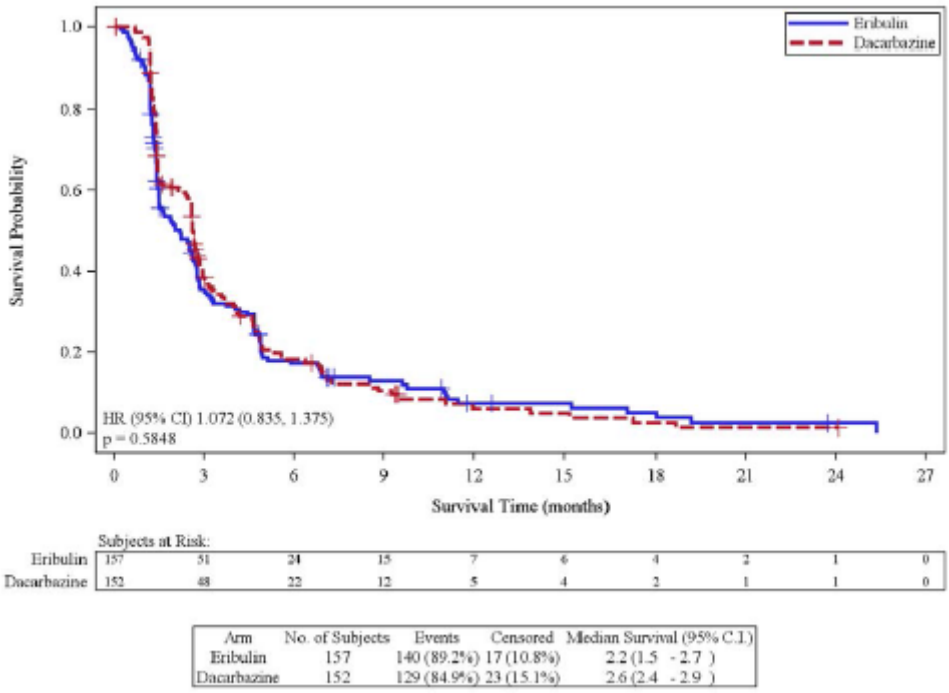


Figure 9: PFS by treatment for Leiomyosarcoma subjects – Study 309

A Forest Plot of OS and PFS by histology subtype are summarized in the figures below.

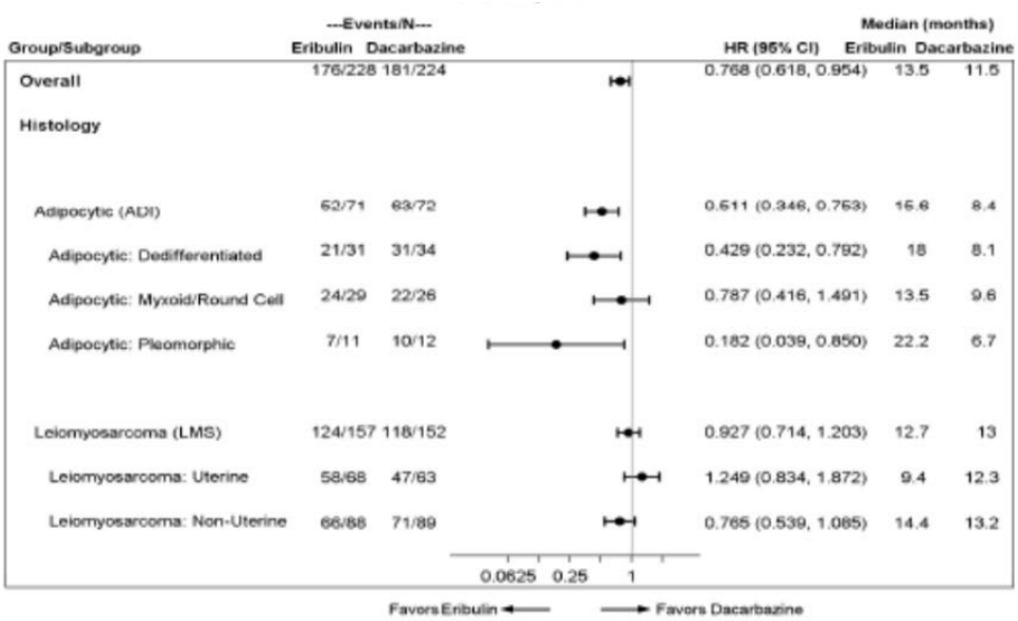


Figure 10: Overall Survival - Forest Plot of Hazard Ratio by Histology Subtype

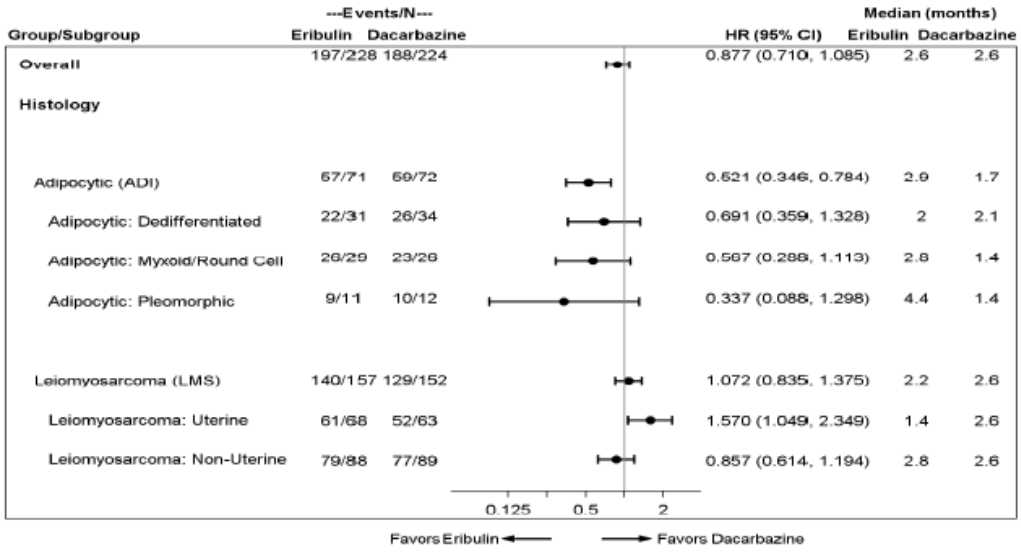
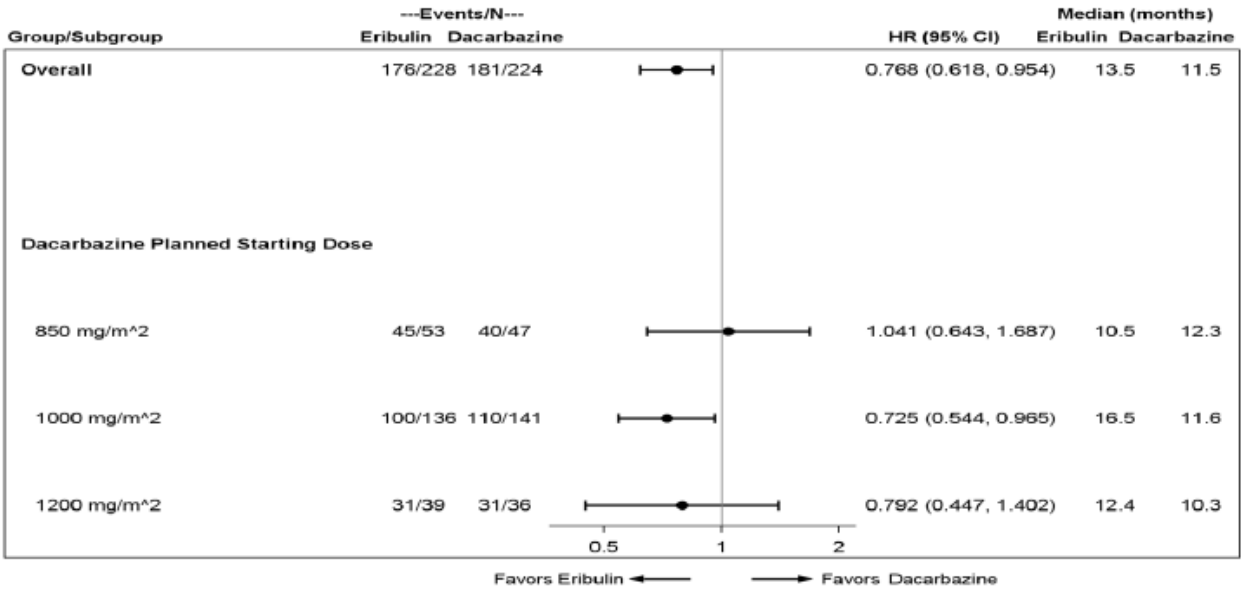


Figure 11: Progression-free Survival - Forest Plot of Hazard Ratio by Histology Subtype

Analysis of OS by dacarbazine dose level

Since the starting dose of dacarbazine was allowed to be determined by the treating investigator, OS by planned dacarbazine dose was evaluated.



Hazard ratio is defined as the ratio of Eribulin to Dacarbazine
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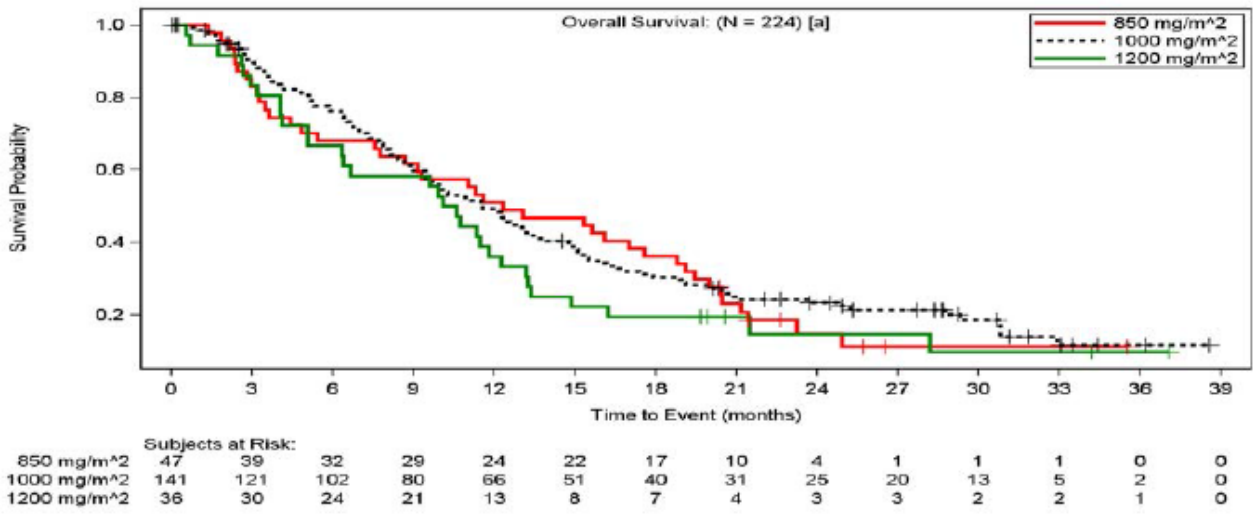
Figure 12: Overall survival forest plot of Hazard ratio with dacarbazine planned starting dose as subgroup – FAS (Study 309)



Planned Dose	n	Events	Censored	Median Survival (95% C.I.)
850 mg/m^2	47	40 (85.1%)	7 (14.9%)	12.3 (7.8 - 17.6)
1000 mg/m^2	141	110 (78.0%)	31 (22.0%)	11.6 (9.5 - 13.5)
1200 mg/m^2	36	31 (86.1%)	5 (13.9%)	10.3 (5.1 - 12.3)

Figure 13: Kaplan Meier Plot of OS in Dacarbazine Arm by Planned Dose: Randomization Phase (FAS) – Study 309

Analysis of post-study therapy

Table 26: Post-Treatment Therapies by Histology (IVRS) (FAS) – Study 309

	Eribulin (ADI + LMS) n (%)	Dacarbazine (ADI + LMS) n (%)
N	228 (100.0)	224 (100.0)
Post treatment		
Surgery		
No	192 (84.2)	186 (83.0)
Yes	36 (15.8)	38 (17.0)
Radiotherapy		
No	175 (76.8)	180 (80.4)
Yes	53 (23.2)	44 (19.6)
Chemotherapy[a]		
Yes	158 (69.3)	141 (62.9)
No	70 (30.7)	83 (37.1)
1	57 (25.0)	58 (25.9)
2	43 (18.9)	34 (15.2)
3	29 (12.7)	25 (11.2)
4	13 (5.7)	9 (4.0)
>4	16 (7.0)	15 (6.7)
Frequency of chemotherapy[a]		
Dacarbazine	78 (34.2)	17 (7.6)
Docetaxel	17 (7.5)	23 (10.3)
Doxorubicin	26 (11.4)	16 (7.1)
Gemcitabine	48 (21.1)	47 (21.0)
Ifosfamide	27 (11.8)	22 (9.8)
Pazopanib	58 (25.4)	62 (27.7)
Trabectedin	36 (15.8)	27 (12.1)
Other	8 (3.5)	17 (7.6)

ADI = adipocytic, LMS = leionyosarcoma.
a: If a subject has the same preferred term 2 or more times, the subject will be counted only once for that preferred term.
Source: Table 12-5.

Analysis of PFS including clinical progression as an event

Clinical progression was determined by the investigator and these were instances where either clinical deterioration of a patient (performance status deterioration without objective evidence of disease progression) or objective evidence of disease progression but did not meet the RECIST criteria.

Table 27: Analysis of PFS – Study 309

	Eribulin (N=228) n (%)	Dacarbazine (N=224) n (%)
Subjects With Events (PD + Death + CP), n (%)	211 (92.5)	197 (87.9)
Progressive Disease (PD) [a]	181 (79.4)	171 (76.3)
Death, without documented PD	6 (2.6)	3 (1.3)
Clinical Progression	24 (10.5)	23 (10.3)
Censored, n (%)	17 (7.5)	27 (12.1)
No baseline or post baseline tumor assessment	0	0
Alive without progression at database cut-off	6 (2.6)	7 (3.1)
New anti-cancer treatment started	6 (2.6)	14 (6.3)
Death or PD after two or more missed tumor assessment	5 (2.2)	6 (2.7)
Progression-Free Survival (months)[d]		
Median (95% CI)	2.2 (1.5 , 2.6)	2.4 (1.4 , 2.6)
Q1 (95% CI)	1.3 (1.2 , 1.3)	1.2 (1.2 , 1.4)
Q3 (95% CI)	4.9 (4.4 , 6.8)	4.0 (3.1 , 4.7)
Stratified P-value [b]	0.2436	
Hazard Ratio (95% CI) [c]	0.884 (0.720, 1.086)	
Progression-Free Survival Rate (95% CI) [d]		
At 3 months	0.366 (0.303, 0.430)	0.321 (0.258, 0.385)
At 6 months	0.200 (0.150, 0.256)	0.136 (0.092, 0.189)
At 12 months	0.092 (0.057, 0.137)	0.040 (0.017, 0.077)

Summary of Progression-Free Survival (PFS) - Investigator Assessment. The tumor assessment is based on RECIST 1.1.
[a]: If a subject had both progressing disease and death, only progressing disease data will be included. If a subject had clinical progression before progressing disease or censoring, only clinical progression at last dose date will be included. [b]: P-value is calculated from a two-sided Log-rank test stratified by histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2).
[c]: Hazard ratio is based on a Cox regression model including treatment as covariate, and histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2) as strata.
[d]: Progression Free Survival and Progression Free Survival rate at 3, 6 and 12 months (95% CI) is calculated using Kaplan-Meier product-limit method and Greenwood Formula.
X:/projects/E7389/E7389-G000-309/CSR/PROD/pg/Tables/tef pfs cpd2 fas.sas FINAL/DATA CUTOFF: 02JAN2015 21MAY2015:10:02

Analysis of PRO and QoL

Two PROs were included for the analysis of QoL (exploratory analyses). These were the EORTC questionnaire QLQC30 and the EQ-5D-3L (administered at baseline, pre-dose on Day 1 of each treatment cycle and at the Off-treatment Visit).

Compliance

Overall study compliance was good for both measures throughout the course of the study and did not fall below 70%.

No absolute differences in PRO compliance were observed between treatment arms.

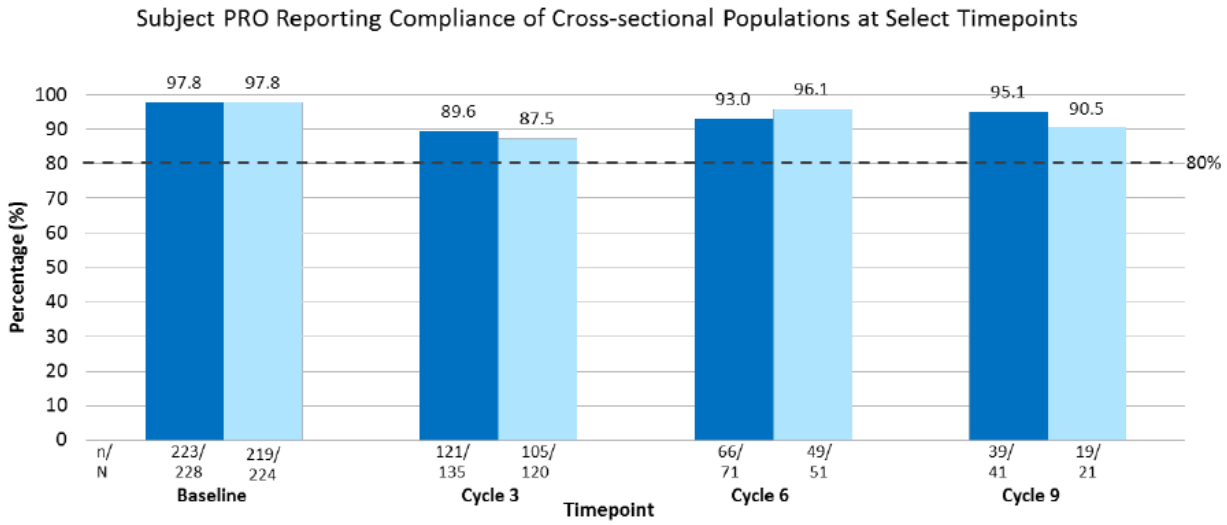


Figure 13: Patient Reported Compliance at Select Timepoints (Overall, ⩾ 1 QLQ-C30 Items, and ⩾ 1 EQ-5D Items) – Study 309

Cross-sectional Analyses

The cross sectional analysis of the EORTC QLQ-C30 domain indicated equivalent scores between the eribulin and dacarbazine treatment arms in the majority of domains.

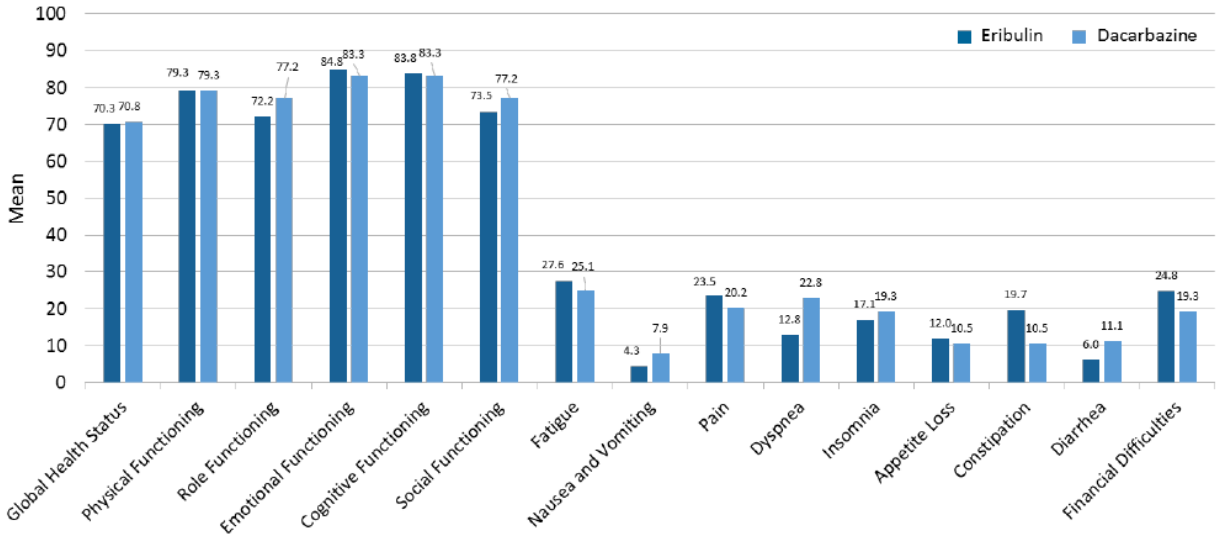


Figure 14: QLQ-C30 Mean Symptom and Profile Scores at Cycle 9 – Study 309

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28: Summary of Efficacy for trial E7389-G000-309

Title: A Randomized, Open-label, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Eribulin with Dacarbazine in Subjects with Soft Tissue Sarcoma			
Study identifier	E7389-G000-309		
Design	Randomised, open label, 1:1 design		
Hypothesis	Superiority		
Treatments groups	Experiment	Eribulin mesilate 1.4 mg/m2 IV on Days 1 and 8 of every 21-day cycle	
	Reference	Dacarbazine (DTIC) IV 1200 mg/m^2, 1000 mg/m^2 **or** 850 mg/m^2 Q 3w	
Endpoints and definitions	Primary endpoint	OS	
	Secondary endpoints	PFS (Investigator), PFR_{12wks}, CBR	
Database lock	02 January 2015		
Results and Analysis			
		Eribulin	Dacarbazine
OS	Event rate Median (mo) (95%CI) HR (95%) P-value	176/228 (77.2 %) 13.5 (10.9, 15.6) 0.768 (0.618, 0.954) 0.0169	181/224 (80.8 %) 11.5 (9.6, 13.0)
PFS (Investigator)	Event rate Median, m. (95%CI) HR (95%) P-value	197/228 86.4 %) 2.6 (1.9, 2.8) 0.877 (0.710, 1.085) 0.2287	188/224 (83.9 %) 2.6 (1.8, 2.7)
$PFR_{12weeks}$	(95%CI) P-value	33.3% (27.2, 39.9) 0.253	28.6% (22.8, 35.0)
CBR	(95%CI) P-value	46.1% (39.5, 52.8) 0.741	47.8% (41.1, 54.5)

Supportive studies

Study E7389-E044-207 (study 207): A Phase II Study of E7389 Administered as an IV Infusion Day 1 and 8 Every 3 weeks in Pretreated Patients with Advanced and/or Metastatic Soft Tissue

Sarcoma

A multicenter, open-label, nonrandomized study conducted in Belgium, Denmark, Germany, Poland and France. A total of 128 subjects were enrolled between13 Dec 2006 to 28 Jun 2012.

The study was an EORTC conducted study.

The study enrolled subjects who had histologically confirmed and measurable (RECIST) advanced and/ or metastatic STS of the following histology: leiomyosarcoma (LMS), adipocytic (ADI), synovial sarcoma (SYN), or other types of sarcoma (OTH) and with evidence of objective progression within the last 6 months (RECIST). No more than one prior combination regimen or two single agent cytotoxic drugs for metastatic disease were allowed (prior neoadjuvant chemotherapy or adjuvant chemotherapy included).

The subjects were treated with eribulin mesilate 1.4 mg/m² on Days 1 and 8, every 21 days.

A total of 115 patients were evaluable for efficacy and were divided into four strata: leiomyosarcoma (LMS, n=38), adipocytic (ADI, n=32), synovial sarcoma (SYN, n=19) or other types of sarcoma (OTH, n=26). The limited number of patients in each group is recognised.

Primary endpoint was $PFS_{12\ weeks}$ and secondary endpoints were Overall PFS, ORR, CRB rate, time to onset of response, duration of response and OS.

The primary endpoint showed response in 47% of the patients in the ADI stratum, 32% in the LMS stratum, 21% in the SYN stratum and 19% in the OTH stratum.

The median PFS time was similar for each of the four strata (82, 88, 81 and 72 days for the ADI, LMS, SYN and OTH strata respectively).

Only one patient (in the ADI stratum) experienced a CR at Week 12. One patient in each of the ADI, SYN, and OTH strata experienced a PR. No difference among the strata for the ORR was observed (3%, 5%, 5%, and 4% for the ADI, LMS, SYN and OTH strata respectively).

Study E7389-J081-217 (study 217): An Open-label, Multi-centre, Phase 2 Study to Evaluate the Efficacy and Safety of Eribulin in Previously Treated Subjects with Advanced or Metastatic Soft Tissue Sarcoma

Study 217 was initiated to investigate the efficacy and safety of eribulin in the treatment of subjects with advanced or metastatic STS in Japan.

The study was conducted between 14 November 2011 and 14 November 2014 (date of database cut-off) at 13 study sites in Japan. A total of 51 patients were evaluable for efficacy in this study (35 patients in the ADI (n=16)/LMS (n=19) stratum and 16 patients in the OTH stratum. The inclusion/ exclusion criteria and eribulin dose regimen are in line with that of the pivotal study 309.

Primary endpoint was PFR_{12wks} and secondary endpoints were PFS, OS, ORR, DCR, CBR and dSDR.

The primary endpoint showed progression-free survival at Week 12 in 60 % of the patients (95% CI: 42.1, 76.1) in the ADI/ LMS stratum and 31 % (95% CI: 11.0, 58.7) in the OTH stratum.

The median PFS time was 5.5 months (95% CI: 2.79, 8.18) in the ADI/LMS stratum and 2 months (95% CI: 1.22, 4.07) in the OTH stratum.

The median OS was 17 months (95% CI: 11.01, 20.47) in the ADI/LMS stratum and about 8 months (95% CI: 3.84, 16.13) in the OTH stratum.

There were no complete or partial responses observed. DCR was 80 % and 50 %, CBR was 74 % and 50 % and dSDR was 74 % and 50 % for ADI/ LMS and OTH strata respectively.

2.4.3. Discussion on clinical efficacy

The MAH is applying for an extension of the indication for eribulin in the treatment of patients with locally advanced and/or metastatic soft tissue sarcoma (STS).

Design and conduct of clinical studies

The application formally rests on the pivotal 309 study, a randomized, open-label, multi-centre, Phase III study comparing the efficacy and safety of eribulin to that of dacarbazine in patients previously treated for locally advanced and/or metastatic tumours of either the adipocytic subtype (liposarcoma [ADI]) or of smooth muscle origin (leiomyosarcoma [LMS]).

The inclusion- and exclusion criteria are considered adequately reflecting the target population for the proposed indication in terms of ADI and LMS subtypes. However, although STS may also occur in the paediatric population, it is noted that only patients aged ≥ 18 years were eligible for inclusion in the pivotal study. The safety and efficacy of Halaven in children from birth to 18 years of age have not yet been established in soft tissue sarcoma and the indication in the SmPC now refers to "adults".

In Q2 2015 the MAH informed the regulatory authorities of so-called "dry runs" where interim results from study 309 were used for these dry runs. This became clear once the final analysis was conducted, as the final KM curves and those from the dry runs were almost identical. The primary endpoint of the study is OS and it is considered robust and not easily manipulated. Thus, even though interim results were unintentionally exposed there is no evidence of any bias of the primary analysis of study 309.

The protocol was amended twice and it is considered unlikely that the amendments and protocol violations have a relevant impact on the integrity of the study.

The study enrolled 452 patients randomised in a 1:1 design (n=228 in the eribulin arm; n=224 in the dacarbazine arm) and stratified by histology (ADI or LMS), region (Region 1: USA and Canada; or Region 2: Western Europe, Australia and Israel; or Region 3: Eastern Europe, Latin America and Asia), and number of prior regimens for advanced STS (2 or >2 prior regimens).

Median time from diagnosis is about 3 years which is a common feature observed in the target population. The vast majority had non-lymph nodes as target lesions which is not unexpected since STS most commonly metastasize to the lungs and to a lesser extent to the lymph nodes.

Some imbalances in terms of baseline disease characteristics ("time between the original histological diagnosis and randomisation" and "non-target lesions at baseline") were noted. This has been adequately clarified during the procedure and there is no reason to assume that these imbalances could have an effect on OS and PFS.

The eribulin dose regimen (1.4 mg/m^2 IV on Days 1 and 8 of every 21-day cycle) was established in the E7389-G000-305 study (EMBRACE) performed in metastatic breast cancer and is considered justified. It is to be noted that the dose of 1.4 mg/m^2 refers to the salt form (eribulin mesilate) which is equivalent to 1.23 mg/m^2 of the base of the active substance (eribulin). This has been adequately highlighted in the Halaven SmPC section 4.2.

Dacarbazine as the comparator is considered acceptable. In 2010 the MAH applied for a scientific advice on the clinical development plan for eribulin in STS and the design of the future Phase III study 309 including the use of dacarbazine as the comparator. Either1200 mg/m^2, 1000 mg/m^2, or 850 mg/m^2 as starting dose could be chosen at the discretion of the investigator. The selection of the starting dose for each patient had to be confirmed prior to randomization.

Although a blinded study would have been preferred, feasibility issues, such as differences in tolerability between treatment arms could be foreseen and therefore the open-label design is acceptable.

Demographic and baseline characteristics are reasonably well balanced between the treatment arms. It is recognised that the study enrolled heavily pre-treated patients. It is noted that while STS in general show a slight predominance in the male gender, in this study the majority were female patients (67 %). This is likely due to a higher than expected proportion of patients with uterine LMS enrolled (about 30 % of the LMS stratum).

Median age at study entry was 56 years which reflects the clinical target population. About 21% of subjects were aged ≥65 years. Close to 50 % were recruited from Region 2 (Western Europe, Australia and Israel).

Approximately 1/3 of the overall population were patients with ADI and 2/3 were LMS with similar distribution between the two arms.

AEs as reasons for treatment discontinuations were low with approx. 6 % in the erbulin arm and 4.5 % in the DTIC arm. Withdrawal of consent was likewise low with about 1 % and 2 % respectively. About 10 % discontinued due to clinical progression which was similar in both arms.

In conclusion, there are no major concerns identified with respect to the conduct of the pivotal study. The population studied is considered representative for the target population in terms of ADI and LMS.

Efficacy data and additional analyses

The primary endpoint of the pivotal study was OS. The study met its primary objective with an estimated reduction of death of 23 % in the experimental arm (HR 0.77 [95% CI 0.618, 0.954]; p=0.0169) with an improved benefit favouring eribulin of a median of 2 months (13.5 months and 11.5 months respectively). The magnitude of the statistical significance with a p-value of about 0.017 is not considered overwhelming but is still within the boundaries of statistical significance.

No differences between the two arms were observed with respect to the secondary endpoints (PFS, PFR_{12wks} and CBR). In terms of PFS no difference in medians between the arms was observed with 2.6 months (HR=0.877 [95% CI 0.710, 1.085]; P=0.2287) however the HR of 0.88 may be indicative of an improved treatment effect for eribulin as compared to dacarbazine.

The PFR_{12wks} was 33 % (95% CI 27.2, 39.9) in the eribulin arm and about 29 % (95% CI 22.8, 35.0) in the control arm (p = 0.253). The CBR was 46 % (95% CI 39.5, 52.8) in the eribulin arm and 48 % (95% CI 41.1, 54.5) in the dacarbazine arm (p=0.741).

ORR was performed as an exploratory analysis. No significant differences between the two arms for either ORR, DCR or dSD rate could be observed.

There is no overall consistency in regard to HR in the subgroups analyses for either OS or PFS. In particular, the apparent discrepancy with respect to histology stands out indicating a differential benefit.

In addition to the pre-planned efficacy analysis of OS and PFS by histological subtypes, the MAH has provided as requested, post hoc analyses in terms of baseline and outcome data separately for the two histology subtypes including data on the subtypes of ADI enrolled in the study i.e. dedifferentiated, myxoid/round cell and pleomorphic liposarcoma. The OS benefit for eribulin over dacarbazine appears entirely driven by the patients with the ADI subtype (HR 0.51 (95% CI 0.346, 0.753), P=0.0006) with a median OS of about 16 months for the eribulin arm compared with approximately 8 months for the dacarbazine arm. In addition, a benefit in PFS can be observed with a median PFS of 2.9 months vs. 1.7 months in the eribulin and dacarbazine arm, respectively, with a HR of 0.52 (95% CI 0.346; 0.784, P=0.0015).

As emphasised by the MAH, the different subtypes of ADI (dedifferentiated, myxoid/round cell, pleomorphic) may be viewed as biologically different, but the small sample size and absence of preformed

hypotheses make further analyses less than meaningful. Thus it is accepted that activity has been shown irrespective of the different subtypes of ADI. On the other hand, a benefit is not shown in the LMS population as no difference at all between the two treatment arms is observed. The HR is 0.93 (95% CI 0.714, 1.203; P=0.57) for OS with a median of about 13 months in both arms. For PFS the HR is 1.07 (95% CI 0.835, 1.375; P=0.585) with a similar median of about 2.5 months.

The MAH has been unable to provide evidence that dacarbazine is meaningfully active in LMS. If this actually were the case, i.e. that similarity in PFS (HR 1.07) reflected a meaningful delay in progression for both study arms vs. a virtual placebo, then it would be expected that post progression survival would be prolonged in the eribulin arm, analogues to findings in breast cancer and ADI. This is not the case, however. Therefore the most reasonable interpretation is that neither dacarbazine nor eribulin is meaningfully active in LMS.

The apparent difference, especially in PFS between uterine and non-uterine sarcoma is noticed. This is an unexpected finding from a tumour biology perspective as currently described and from the perspective of "non-activity" of dacarbazine and eribulin is rather interpreted as reflecting differences in baseline prognostic factors.

There seemed to be an interaction between ECOG PS 0 and 1 with patients with performance status >0 having little effect of eribulin. The requested exploratory analysis shows that the interaction seems to be driven by patients with LMS and ECOG 1. Although it is recognised that patients were not stratified by ECOG score, nevertheless this analysis seems to add more evidence to the fact that the effect of eribulin in the LMS population is limited.

The overall number of events in the study at the time of the analysis (data cut-off date 02 January 2015) was about 79 % for OS and 85 % for PFS. A satisfactory level of data maturity is considered reached.

It is concluded that in isolation the two exploratory studies (207 and 217) cannot be claimed as supportive. To this effect, contextualisation of the primary endpoint $PFR_{12weeks}$ was warranted. PFR_{12wks} for ADI and LMS was compared with corresponding data in study 309. For eribulin it is agreed that there is consistency shown for the respective histology subgroups between study 309 and study 207 with 41 % and 47 % for ADI vs. 30 % and 32 % for LMS in the respective studies. An overall higher $PFS_{12weeks}$ was observed in the 217 study but with similar discrepancy pattern between the two histology subgroups as observed in the 309 and 207 studies.

For dacarbazine PFR_{12wks} for ADI and LMS in study 309 was to be compared with corresponding data from other dacarbazine studies, e.g. using the EORTC data base. The study by García-del-Muro, et al. (2011) compared gemcitabine plus dacarbazine with dacarbazine alone in 113 patients with previously treated STS (mixed). The PFR at 3 months was 56% (95% CI: 43% to 69%) for gemcitabine plus dacarbazine versus 37% (95% CI: 23.5% to 50%) for dacarbazine alone (P=0.001). The study by Demetri G, et al., (2015) compared trabectedin with dacarbazine in 518 patients with metastatic ADI or LMS. The PFR at 3 months was 34% for patients on the dacarbazine arm.

It is noted that the $PFS_{12weeks}$ for dacarbazine in the two publications is similar to the results obtained for eribulin in LMS in the 309 study. In terms of $PFS_{12weeks}$, the findings are consistent with the primary analysis i.e. no superior efficacy obtained for eribulin in regard to LMS as compared to dacarbazine.

The initially proposed indication encompassed STS not subtype specified. As no benefit has been demonstrated in LMS the indication has been revised to only include adult patients with unresectable liposarcoma. Moreover, "prior systemic therapy" has been revised to reflect that standard chemotherapy is based on anthracyclines as the 1st line treatment.

2.4.4. Conclusions on the clinical efficacy

A benefit of eribulin over dacarbazine has been shown exclusively in the ADI population and as such the indication has been restricted to the adult patient population with unresectable liposarcoma. The magnitude of the benefit is of definite high clinical relevance in this STS subtype and would meet an unmet medical need.

2.5. Clinical safety

Introduction

Existing safety profile

The current knowledge of the safety profile is based primarily on studies in breast cancer. In this setting, the major undesirable effects related to Halaven include, as per SmPC, bone marrow suppression including neutropenia (57%; grade 3/4: 50%) with associated infections (e.g. sepsis 0.5%); anaemia (21%) and thrombocytopenia (5%). New onset or worsening of pre-existing peripheral neuropathy (36%; grade 3/4: 8%). Gastrointestinal toxicities are common, including nausea (34%), vomiting (18%), diarrhoea (18%), constipation (20%), and stomatitis. Other significant adverse drug reactions (ADRs) include fatigue (48%; grade 3/4: 8%), alopecia, increased liver enzymes, pyrexia (20%), bone pain (10%) and musculoskeletal pain.

Safety analysis populations

The data to support the safety of eribulin in the soft tissue sarcoma (STS) indication are based on data from 404 subjects in 1 pivotal phase III trial and 2 phase II trials, supported by data from 1559 subjects in one of eight completed trials in metastatic breast cancer (MBC) as follows:

Table 29: Safety populations

Safety population	Phase	Trial name (Region)	Treatments	Number of eribulin-treated subjects
Soft tissue sarcoma (STS) population	Phase 3	Study 309 (Global)	Eribulin vs. dacarbazine	226
	Phase 2	Study 207 (EU)	Single-arm eribulin	127
		Study 217 (Japan)	Single-arm eribulin	51
	Total STS			**404**
Metastatic breast cancer (MBC) population	Phase 3	Study 301 (Global)	Eribulin vs. capecitabine.	544
		Study 305 "EMBRACE" (Global)	Eribulin vs. treatment of physician's choice (TPC).	503
	Phase 2	Study 201 [a] (US)	Single-arm eribulin	33
		Study 206 (US)	Single-arm eribulin	56
		Study 209 (US)	Single-arm eribulin	51
		Study 211 (North America, Europe)	Eribulin vs. ixabepilone	291
		Study 221 (North America, Europe)	Single-arm eribulin, pooled	81
		Study 224 [b] (Japan)		(6 included in 81 above)
	Total MBC			**1559**
Integrated Safety	**Total STS + MBC**			**1963**

Population				

a: Subjects who received 28-day cycles of eribulin in Study 201 have been excluded from the analysis.

b: The six subjects who continued to receive eribulin in extension Study 224 after receiving eribulin in Study 221 are included in the total of 81 treated subjects for Study 221. Data from Study 221 were pooled with the data from Study 224, once all enrolled subjects had discontinued treatment in Study 224.

The safety data in this review are based on a data cut-off date for Study 309 of 02 January 2015, a data cut-off date for Study 217 of 14 November 2014 and a data cut-off date for Study 207 of 12 June 2012.

All MBC trials except Study 206 have been previously submitted and assessed.

In all studies submitted as part of this variation application, the labelled standard dose of eribulin was used, i.e. 1.4 mg/m^2 (equivalent to 1.23 mg/m^2 in the EU SmPC) on Day 1 and 8 in a 21-day cycle.

Patient exposure

Table 30: Exposure to study treatment

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Duration of exposure (week)					
N	226	224	404	1559	1963
Mean (SD)	17.4 (18.65)	13.7 (13.35)	18.0 (20.58)	21.2 (20.44)	20.6 (20.50)
Median	10.0	9.0	12.0	15.9	15.0
Q1, Q3	6.0, 21.0	6.0, 16.6	6.0, 21.2	9.0, 27.0	7.0, 25.0
Min, Max	3, 112	3, 110	3, 178	3, 196	3, 196
Total number of cycles administered per subject					
N	226	224	404	1559	1963
Mean (SD)	5.5 (5.75)	4.2 (3.88)	5.7 (6.47)	6.7 (6.47)	6.5 (6.48)
Median	3.0	3.0	4.0	5.0	5.0
Q1, Q3	2.0, 7.0	2.0, 5.0	2.0, 7.0	3.0, 8.0	2.0, 8.0
Min, Max	1, 34	1, 30	1, 58	1, 65	1, 65
Cumulative dose (mg/m^2) per subject[d]					
n	226	224	404	1559	1963
Mean (SD)	13.44 (13.719)	3993.28 (3860.853)	14.09 (15.635)	17.00 (16.709)	16.40 (16.532)
Median	8.03	2481.10	8.41	12.40	11.21
Q1, Q3	5.56, 16.73	1990.48, 4748.65	5.58, 16.80	6.40, 20.83	5.63, 19.66
Min, Max	1.4, 84.7	849.6, 33914.5	1.3, 164.8	1.4, 182.3	1.3, 182.3
Actual dose intensity (mg/m^2/week) per subject[e]					
N	226	224	404	1558	1962
Mean (SD)	0.803 (0.1591)	305.644 (50.7909)	0.812 (0.1478)	0.799 (0.1512)	0.801 (0.1506)
Median	0.873	315.737	0.872	0.855	0.858
Q1, Q3	0.709, 0.932	280.801, 333.333	0.717, 0.930	0.702, 0.925	0.706, 0.927
Min, Max	0.32, 0.97	130.40, 405.18	0.32, 0.97	0.24, 1.04	0.24, 1.04
Relative dose intensity per subject[f]					
n	226	224	404	1558	1962
Mean (SD)	0.861 (0.1705)	0.919 (0.1202)	0.870 (0.1585)	0.856 (0.1621)	0.859 (0.1614)
Median	0.935	0.991	0.934	0.916	0.920
Q1, Q3	0.759, 0.998	0.853, 1.000	0.768, 0.998	0.752, 0.991	0.757, 0.994
Min, Max	0.35, 1.04	0.39, 1.08	0.35, 1.04	0.25, 1.12	0.25, 1.12
Any dose delay/reduction/omission					
Dose delay	70 (31.0)	79 (35.3)	165 (40.8)	632 (40.5)	797 (40.6)
Dose omission	28 (12.4)	-	49 (12.1)	209 (13.4)	258 (13.1)
Dose reduction	59 (26.1)[g]	-	104 (25.7)	475 (30.5)	579 (29.5)
Reduced to 1.1 mg/m^2	58 (25.7)	-	103 (25.5)	-	-
Reduced to 0.7 mg/m^2	24 (10.6)	-	34 (8.4)	-	-

Dose delay: Study medication was administered at least one week later than the scheduled dosing day per regular scheme of eribulin dosing on Day 1 and Day 8 of each cycle, and dacarbazine dosing on Day 1 of each cycle, over the consecutive 21-day treatment cycles.

Dose omission (applicable to eribulin Day 8): dose for Day 8 of a cycle was not administered while dose for Day 1 of the cycle had been administered.

Dose reduction (applicable to eribulin): eribulin dose was reduced to 1.1 mg/m^2 or 0.7 mg/m^2.

Max = maximum, MBC = metastatic breast cancer, Min = minimum, STS = soft tissue sarcoma.

a The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

d Cumulative dose (mg/m^2) = the sum of doses received (mg/m^2) during the entire study

e Actual dose intensity (mg/m^2/week) = Cumulative dose (mg/m^2) / Duration of exposure (week)

f Relative dose intensity = Actual dose intensity (mg/m^2/week) / Planned dose intensity (mg/m^2/week), where planned dose intensity is 1.4 mg/m^2 x 2/3 for subjects receiving eribulin mesilate and 850 (or 1000, 1200) mg/m^2 x 1/3 for subjects receiving dacarbazine.

g 58 of 59 subjects had dose reductions due to treatment-emergent adverse events (TEAEs). See Table 15

Adverse events

Treatment-Emergent Adverse Events

Table 31: Overview of Treatment-Emergent Adverse Events

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Subjects with TEAEs	224 (99.1)	218 (97.3)	399 (98.8)	1520 (97.5)	1919 (97.8)
Subjects with related[d] TEAEs	210 (92.9)	203 (90.6)	375 (92.8)	1438 (92.2)	1813 (92.4)
Subjects with severe TEAEs (CTCAE Grade ≥ 3)	152 (67.3)	126 (56.3)	267 (66.1)	1123 (72.0)	1390 (70.8)
Subject with SAEs	76 (33.6)	71 (31.7)	138 (34.2)	373 (23.9)	511 (26.0)
Subjects with fatal SAEs[e]	10 (4.4)	3 (1.3)	14 (3.5)	66 (4.2)	80 (4.1)
Subjects with non-fatal SAEs[e]	74 (32.7)	70 (31.3)	134 (33.2)	344 (22.1)	478 (24.4)
Subjects with TEAEs leading to study drug action[f] taken	107 (47.3)	89 (39.7)	125 (30.9)	423 (27.1)	548 (27.9)
Subjects with TEAEs leading to study drug withdrawn	17 (7.5)	11 (4.9)	21 (5.2)	166 (10.6)	187 (9.5)
TEAEs of special interest					
Peripheral Neuropathy[g]	83 (36.7)	34 (15.2)	166 (41.1)	637 (40.9)	803 (40.9)
Neutropenia (TEAEs only)	99 (43.8)	53 (23.7)	151 (37.4)	902 (57.9)	1053 (53.6)
Neutropenia (TEAEs and laboratory abnormalities)	156 (69.0)	96 (42.9)	307 (76.0)	1314 (84.3)	1621 (82.6)
Arthralgia/myalgia events[g]	35 (15.5)	27 (12.1)	43 (10.6)	309 (19.8)	352 (17.9)
Asthenia/fatigue events[g]	139 (61.5)	131 (58.5)	255 (63.1)	793 (50.9)	1048 (53.4)
Alopecia events	79 (35.0)	6 (2.7)	154 (38.1)	720 (46.2)	874 (44.5)

A subject with two or more TEAEs in the category of one row is counted once in that row.
Study 207 did not assess action taken with respect to the study drug through the adverse event CRF data, and is therefore not reflected in the rows for "study drug action taken" and "study drug withdrawn" for its incidence of this nature.
Adverse event terms are coded using MedDRA version 17.1.
CTCAE = Common Terminology Criteria for Adverse Events, MBC = metastatic breast cancer, MedDRA = Medical Dictionary for Regulatory Activities, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event.
a The STS includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.
b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.
c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations
d Relationship to treatment as determined by the Investigator
e A subject with both non-fatal and fatal SAEs is counted in both the non-fatal SAEs row and the fatal SAEs row
f Drug withdrawn, dose reduction, or drug interruption
g These TEAEs are reported as Sponsor Derived Query (SDQ) terms; details of groupings were provided. Alopecia and neutropenia are reported as a single terms.

Source: SCS, Table 8.

STS vs. MBC

Compared with the MBC population some differences in the overall patter of treatment-emergent adverse events TEAEs are noted. Severe TEAEs (≥CTCAE toxicity grade 3) were a few percent lower, while non-fatal SAEs were around 10% higher in the STS population, as well as in the pivotal study, compared with the MBC population. (Fatal SAEs were similar around 4%.) TEAEs leading to dose reduction, interruption or withdrawal were considerable higher in the pivotal phase III trial (47%), but only slightly higher in the full STS population (31%) compared with the MBC (27%). Withdrawals due to TEAEs were numerically lower, however; thus, the differences in the former figures reflect differences in dose adjustments.

With regard to TEAEs of special interest, most showed lower frequencies in the pivotal study (and full STS population) compared with the MBC population (potentially related to observation time, as noted above). Asthenia/fatigue was considerably more frequent in the STS studies however (61-63% vs. 51% in MBC).

Eribulin vs. dacarbazine

In Study 309, the proportion of patients with TEAEs and treatment-related TEAEs and serious adverse events (SAEs) were similar across arms (numerically around 2% higher in the eribulin arm for each item). Severe TEAEs were more frequent in the eribulin arm (67 vs. 56%). Fatal SAEs were more frequent in the eribulin arm (4.4 vs. 1.3%; n= 10 vs. 3). Dose adjustments and withdrawals due to TEAEs were more frequent in the eribulin arm. It is noted that the frequencies of dose adjustments and withdrawals due to TEAEs were higher in both study arms compared with the eribulin-treated MBC population.

For TEAEs of special interest, see further below. No new safety concern is raised.

Table 32: Incidence of Most Common (≥10% in any population) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Subjects with any TEAE	**224 (99.1)**	**218 (97.3)**	**399 (98.8)**	**1520 (97.5)**	**1919 (97.8)**
General disorders and administration site conditions	**172 (76.1)**	**153 (68.3)**	**316 (78.2)**	**1016 (65.2)**	**1332 (67.9)**
Fatigue	99 (43.8)	86 (38.4)	197 (48.8)	458 (29.4)	655 (33.4)
Pyrexia	63 (27.9)	31 (13.8)	111 (27.5)	317 (20.3)	428 (21.8)
Asthenia	47 (20.8)	51 (22.8)	47 (11.6)	342 (21.9)	389 (19.8)
Edema peripheral	27 (11.9)	17 (7.6)	54 (13.4)	129 (8.3)	183 (9.3)
Gastrointestinal disorders	**178 (78.8)**	**162 (72.3)**	**306 (75.7)**	**954 (61.2)**	**1260 (64.2)**
Nausea	91 (40.3)	106 (47.3)	157 (38.9)	544 (34.9)	701 (35.7)
Constipation	71 (31.4)	58 (25.9)	121 (30.0)	316 (20.3)	437 (22.3)
Vomiting	43 (19.0)	50 (22.3)	73 (18.1)	283 (18.2)	356 (18.1)
Diarrhea	38 (16.8)	36 (16.1)	75 (18.6)	293 (18.8)	368 (18.7)
Stomatitis	31 (13.7)	11 (4.9)	70 (17.3)	147 (9.4)	217 (11.1)
Abdominal pain	45 (19.9)	33 (14.7)	48 (11.9)	124 (8.0)	172 (8.8)
Blood and lymphatic system disorders	**137 (60.6)**	**124 (55.4)**	**199 (49.3)**	**1048 (67.2)**	**1247 (63.5)**
Neutropenia	99 (43.8)	53 (23.7)	151 (37.4)	902 (57.9)	1053 (53.6)
Anemia	67 (29.6)	69 (30.8)	92 (22.8)	335 (21.5)	427 (21.8)
Leukopenia	36 (15.9)	23 (10.3)	87 (21.5)	460 (29.5)	547 (27.9)
Thrombocytopenia	13 (5.8)	62 (27.7)	16 (4.0)	67 (4.3)	83 (4.2)
Lymphopenia	3 (1.3)	6 (2.7)	43 (10.6)	68 (4.4)	111 (5.7)
Nervous system disorders	**112 (49.6)**	**75 (33.5)**	**216 (53.5)**	**833 (53.4)**	**1049 (53.4)**
Peripheral neuropathy[d]	83 (36.7)	34 (15.2)	166 (41.1)	637 (40.9)	803 (40.9)
Headache	41 (18.1)	21 (9.4)	70 (17.3)	273 (17.5)	343 (17.5)
Dizziness	21 (9.3)	16 (7.1)	50 (12.4)	126 (8.1)	176 (9.0)
Dysgeusia	18 (8.0)	5 (2.2)	49 (12.1)	144 (9.2)	193 (9.8)
Skin and subcutaneous tissue disorders	**109 (48.2)**	**45 (20.1)**	**204 (50.5)**	**843 (54.1)**	**1047 (53.3)**
Alopecia	79 (35.0)	6 (2.7)	154 (38.1)	720 (46.2)	874 (44.5)
Musculoskeletal and connective tissue disorders	**104 (46.0)**	**90 (40.2)**	**184 (45.5)**	**744 (47.7)**	**928 (47.3)**
Back pain	35 (15.5)	31 (13.8)	43 (10.6)	208 (13.3)	251 (12.8)
Arthralgia	19 (8.4)	13 (5.8)	26 (6.4)	206 (13.2)	232 (11.8)
Pain in extremity	20 (8.8)	18 (8.0)	35 (8.7)	162 (10.4)	197 (10.0)
Myalgia	23 (10.2)	17 (7.6)	25 (6.2)	144 (9.2)	169 (8.6)
Infections and infestations	**98 (43.4)**	**62 (27.7)**	**169 (41.8)**	**606 (38.9)**	**775 (39.5)**
Urinary tract infection	25 (11.1)	12 (5.4)	33 (8.2)	133 (8.5)	166 (8.5)
Respiratory, thoracic and mediastinal disorders	**92 (40.7)**	**75 (33.5)**	**184 (45.5)**	**556 (35.7)**	**740 (37.7)**
Dyspnea	36 (15.9)	36 (16.1)	80 (19.8)	219 (14.0)	299 (15.2)
Cough	39 (17.3)	28 (12.5)	75 (18.6)	220 (14.1)	295 (15.0)
Metabolism and nutrition disorders	**83 (36.7)**	**71 (31.7)**	**157 (38.9)**	**551 (35.3)**	**708 (36.1)**
Decreased appetite	43 (19.0)	43 (19.2)	94 (23.3)	347 (22.3)	441 (22.5)
Hypokalemia	23 (10.2)	9 (4.0)	30 (7.4)	103 (6.6)	133 (6.8)
Investigations	**80 (35.4)**	**64 (28.6)**	**159 (39.4)**	**468 (30.0)**	**627 (31.9)**
Weight decreased	7 (3.1)	8 (3.6)	45 (11.1)	179 (11.5)	224 (11.4)
Psychiatric disorders	48 (21.2)	35 (15.6)	88 (21.8)	265 (17.0)	353 (18.0)
Insomnia	22 (9.7)	10 (4.5)	42 (10.4)	105 (6.7)	147 (7.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	19 (8.4)	18 (8.0)	95 (23.5)	116 (7.4)	211 (10.7)
Tumor pain	1 (0.4)	5 (2.2)	49 (12.1)	42 (2.7)	91 (4.6)

A subject with two or more TEAEs in the same system organ class is counted once for that system organ class. System organ classes are presented in descending frequency.

Adverse event terms are coded using MedDRA version 17.1.

MBC = metastatic breast cancer, MedDRA = Medical Dictionary for Regulatory Activities, SDQ = sponsor-derived query, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event.

a The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

d Peripheral neuropathy is reported as the SDQ term; see the Section entitled 'conventions' for details.

Eribulin vs. dacarbazine

TEAEs	Study 309	
Notable differences between study arms were observed for the following TEAEs (with a frequency of 10% or higher in any study arm)		
Pyrexia	28 vs. 14%	(20% in MBC population, 27% in STS population)
Nausea + vomiting	59 vs. 70%	(53% in MBC population - consistent)
Stomatitis	14 vs. 5%	(9% in MBC population, 17% in STS population)
Neutropenia (AEs)	44 vs. 24%	(58% in MBC population)
Neutropenia (AE+lab)	69.0 vs 42.9	(84.3 in MBC population, Table **31**)
Thrombocytopenia	6 vs. 28%	(4% in MBC population - consistent)
Peripheral neuropathy	37 vs. 15%	(41% in MBC population - consistent)
Headache	18 vs. 9%	(18% in MBC population - consistent)
Dysgeusia	8 vs. 2%	(9% in MBC population - consistent)
Alopecia	35 vs. 3%	(46% in MBC population)
SOC Infections	43 vs. 28%	(39% in MBC population - consistent)
Notable *similarities* between study arms were observed for the following TEAEs:		
Fatigue + asthenia	65 vs. 61%	(51% in MBC population, 60% in STS population)
Diarrhoea	17 vs 16%	(19% in MBC population - consistent)
Anaemia	30 vs. 31%	(21% in MBC population, 23% in STS population)
SOC Musculoskeletal	46 vs. 40%	(48% in MBC population - consistent)
Weight deceased	3 vs. 4%	(11% in MBC population)

The well-known major side effects of eribulin were seen as anticipated, e.g. neutropenia and related infections, peripheral neuropathy, fatigue and asthenia, nausea and vomiting, musculo-/skeletal pain, pyrexia, and alopecia.

It is noted that for some AEs related to tolerability, the frequencies were *similar* across study arms. These include fatigue/asthenia, musculo-/skeletal pain, anaemia and diarrhoea. With regard to nausea and vomiting the dacarbazine arm had higher frequencies. Other ADRs that are likely to affect the B/R balance and that occurred in higher frequency in the eribulin arm include *peripheral neuropathy, neutropenia, infections* and *stomatitis*. Alopecia may also be of some importance.

STS vs. MBC

Some TEAEs in the eribulin arm of Study 309 were less frequent compared with the MBC population, which may reflect the shorter observation time in the STS setting, differences in the underlying disease, or other differences in the study settings, including investigator's perception of the drug and the disease.

Some TEAEs were relevantly more frequent in the STS pivotal study compared with the MBC population. These include pyrexia, stomatitis, fatigue and asthenia, and anaemia. For all except anaemia, the frequencies were similar (or higher) in the full STS population including the Phase II studies, indicating that there may be a relevant difference in the safety profile in the STS indication for these AEs.

Treatment-related TEAEs

The direction of observed differences and the similarities for TEAEs across arms in study 309 noted above were consistent for the treatment-related TEAEs, although these were reported at lower absolute frequencies.

Severe TEAEs (≥ grade 3)

Table 33: *Selected TEAEs with a ≥1% incidence of CTCAE Grade ≥3 severity in any safety population**

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			

Subjects with any TEAE with CTCAE Grade ≥3	**152 (67.3)**	**126 (56.3)**	**267 (66.1)**	**1123 (72.0)**	**1390 (70.8)**
Blood and lymphatic system disorders	**97 (42.9)**	**72 (32.1)**	**155 (38.4)**	**844 (54.1)**	**999 (50.9)**
Neutropenia	80 (35.4)	35 (15.6)	126 (31.2)	777 (49.8)	903 (46.0)
Leukopenia	23 (10.2)	10 (4.5)	61 (15.1)	272 (17.4)	333 (17.0)
Febrile neutropenia	2 (0.9)	2 (0.9)	14 (3.5)	72 (4.6)	86 (4.4)
Anaemia	16 (7.1)	27 (12.1)	24 (5.9)	34 (2.2)	58 (3.0)
Lymphopenia	3 (1.3)	3 (1.3)	20 (5.0)	21 (1.3)	41 (2.1)
Thrombocytopenia	1 (0.4)	34 (15.2)	1 (0.2)	12 (0.8)	13 (0.7)
Pancytopenia	0	3 (1.3)	0	3 (0.2)	3 (0.2)
General disorders and administration site conditions	**15 (6.6)**	**16 (7.1)**	**36 (8.9)**	**182 (11.7)**	**218 (11.1)**
Asthenia	4 (1.8)	7 (3.1)	4 (1.0)	78 (5.0)	82 (4.2)
Fatigue	7 (3.1)	3 (1.3)	21 (5.2)	47 (3.0)	68 (3.5)
Pyrexia	2 (0.9)	1 (0.4)	5 (1.2)	8 (0.5)	13 (0.7)
Nervous system disorders	**13 (5.8)**	**5 (2.2)**	**26 (6.4)**	**177 (11.4)**	**203 (10.3)**
Peripheral sensory neuropathy	4 (1.8)	0	8 (2.0)	41 (2.6)	49 (2.5)
Neuropathy peripheral	0	0	0	36 (2.3)	36 (1.8)
Peripheral motor neuropathy	2 (0.9)	1 (0.4)	7 (1.7)	18 (1.2)	25 (1.3)
Paresthesia	1 (0.4)	0	1 (0.2)	18 (1.2)	19 (1.0)
Syncope	0	3 (1.3)	1 (0.2)	7 (0.4)	8 (0.4)
Metabolism and nutrition disorders	**23 (10.2)**	**16 (7.1)**	**39 (9.7)**	**108 (6.9)**	**147 (7.5)**
Hypokalaemia	6 (2.7)	4 (1.8)	10 (2.5)	29 (1.9)	39 (2.0)
Respiratory, thoracic and mediastinal disorders	**16 (7.1)**	**12 (5.4)**	**29 (7.2)**	**99 (6.4)**	**128 (6.5)**
Dyspnoea	5 (2.2)	5 (2.2)	12 (3.0)	57 (3.7)	69 (3.5)
Pulmonary embolism	4 (1.8)	1 (0.4)	7 (1.7)	14 (0.9)	21 (1.1)
Gastrointestinal disorders	**18 (8.0)**	**21 (9.4)**	**32 (7.9)**	**91 (5.8)**	**123 (6.3)**
Abdominal pain	4 (1.8)	8 (3.6)	4 (1.0)	20 (1.3)	24 (1.2)
Nausea	2 (0.9)	1 (0.4)	3 (0.7)	19 (1.2)	22 (1.1)
Vomiting	2 (0.9)	1 (0.4)	5 (1.2)	15 (1.0)	20 (1.0)
Stomatitis	2 (0.9)	1 (0.4)	6 (1.5)	13 (0.8)	19 (1.0)
Constipation	2 (0.9)	1 (0.4)	4 (1.0)	10 (0.6)	14 (0.7)
Infections and infestations	**23 (10.2)**	**11 (4.9)**	**36 (8.9)**	**83 (5.3)**	**119 (6.1)**
Pneumonia	4 (1.8)	3 (1.3)	7 (1.7)	13 (0.8)	20 (1.0)
Urinary tract infection	5 (2.2)	1 (0.4)	5 (1.2)	8 (0.5)	13 (0.7)

Musculoskeletal and connective tissue disorders	**7 (3.1)**	**10 (4.5)**	**13 (3.2)**	**103 (6.6)**	**116 (5.9)**
Back pain	4 (1.8)	3 (1.3)	4 (1.0)	26 (1.7)	30 (1.5)
Bone pain	0	1 (0.4)	0	23 (1.5)	23 (1.2)
Musculoskeletal pain	0	3 (1.3)	0	6 (0.4)	6 (0.3)
Hepatobiliary disorders	**4 (1.8)**	**2 (0.9)**	**7 (1.7)**	**24 (1.5)**	**31 (1.6)**
Hyperbilirubinemia	3 (1.3)	0	3 (0.7)	4 (0.3)	7 (0.4)
Vascular disorders	**3 (1.3)**	**8 (3.6)**	**7 (1.7)**	**21 (1.3)**	**28 (1.4)**
Deep vein thrombosis	0	3 (1.3)	1 (0.2)	6 (0.4)	7 (0.4)

If a subject had two or more treatment-emergent adverse events in the same system organ class (or with the same preferred term) with different CTCAE grades, then the event with the highest grade was used for that subject. System organ classes are presented in descending frequency.
Adverse event terms are coded using MedDRA version 17.1.
CTCAE = Common Terminology Criteria for Adverse Events, MBC = metastatic breast cancer, MedDRA = Medical Dictionary for Regulatory Activities, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event.
The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309
The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.
The Eribulin Integrated Safety Population includes all subjects in the STS and MBC
*: selected by assessor based on interest for the assessment.

The proportion of subjects with any toxicity grade 3 or higher was approximately 10% higher in the eribulin arm compared with the dacarbazine arm of Study 309. This corresponds to the approximately 10% higher frequency of haematological grade 3 events in the eribulin arm. Infections grade ≥ 3 are approximately twice as common in the eribulin compared with the dacarbazine arm (10 vs. 5%).

Grade ≥ 3 peripheral neuropathy (including sensory, motor, and paraesthesia) was more frequent in the eribulin arm (3.1%) compared with the dacarbazine arm (0.4%).

Grade ≥ 3 fatigue/asthenia was similar across arms (approximately 5%), just as the overall frequency was similar. For pyrexia a large difference in overall frequency across study arms was observed (28 vs 14%), but similar grade ≥ 3 frequencies (<1%).

For the respiratory conditions SOC, grade ≥ 3 events would be of similar frequencies if pulmonary embolism was referred to the Vascular disorders SOC (where deep vein thrombosis is the major event), which would then in turn also have similar grade ≥ 3 frequencies. Thus, no real difference of importance across arms appears to be present.

Grade ≥ 3 musculoskeletal pain, including back and bone pain, was reported somewhat more frequently in the dacarbazine arm.

In conclusion, with regard to severe TEAEs (toxicity grade ≥ 3), relevantly higher frequencies were seen in the eribulin compared with the dacarbazine arm of Study 309 for neutropenia, infections, and peripheral neuropathy. Severe anaemia and thrombocytopenia were relevantly higher in the dacarbazine arm. In other parts grade ≥ 3 toxicities were comparable across arms.

Serious adverse event / deaths / other significant events

Non-fatal SAEs

Table 34: Incidence of Most Common (≥1% in any population) Non-Fatal SAEs by System Organ Class and Preferred Term

	Study 309				STS Population[a] (N=404)		MBC Population[b] (N=1559)		Eribulin Integrated Safety Population[c] (N=1963)	
	Eribulin (N=226)		Dacarbazine (N=224)							
	All nonfatal SAEs	Related non-fatal SAEs	All nonfatal SAEs	Related non-fatal SAEs	All nonfatal SAEs	Related non-fatal SAEs	All nonfatal SAEs	Related non-fatal SAEs	All nonfatal SAEs	Related non-fatal SAEs
Subjects with any treatment-emergent, nonfatal SAE	**74 (32.7)**	**31 (13.7)**	**70 (31.3)**	**31 (13.8)**	**134 (33.2)**	**49 (12.2)**	**344 (22.1)**	**161 (10.3)**	**478 (24.4)**	**210 (10.7)**
Blood and lymphatic system disorders	**17 (7.5)**	**16 (7.1)**	**26 (11.6)**	**23 (10.3)**	**25 (6.2)**	**23 (5.7)**	**85 (5.5)**	**81 (5.2)**	**110 (5.6)**	**104 (5.3)**
Febrile neutropenia	2 (0.9)	2 (0.9)	2 (0.9)	2 (0.9)	7 (1.7)	7 (1.7)	47 (3.0)	46 (3.0)	54 (2.8)	53 (2.8)
Neutropenia	11 (4.9)	11 (4.9)	10 (4.5)	10 (4.5)	13 (3.2)	13 (3.2)	31 (2.0)	31 (2.0)	44 (2.2)	44 (2.2)
Anemia	5 (2.2)	4 (1.8)	9 (4.0)	7 (3.1)	6 (1.5)	4 (1.0)	8 (0.5)	6 (0.4)	14 (0.7)	10 (0.5)
Leukopenia	3 (1.3)	3 (1.3)	3 (1.3)	3 (1.3)	3 (0.7)	3 (0.7)	7 (0.4)	7 (0.4)	10 (0.5)	10 (0.5)
Thrombocytopenia	0	0	13 (5.8)	13 (5.8)	0	0	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
Pancytopenia	0	0	3 (1.3)	2 (0.9)	0	0	2 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)
Infections and infestations	**20 (8.8)**	**4 (1.8)**	**8 (3.6)**	**3 (1.3)**	**31 (7.7)**	**9 (2.2)**	**57 (3.7)**	**23 (1.5)**	**88 (4.5)**	**32 (1.6)**
Pneumonia	3 (1.3)	1 (0.4)	2 (0.9)	2 (0.9)	7 (1.7)	3 (0.7)	10 (0.6)	3 (0.2)	17 (0.9)	6 (0.3)
Urinary tract infection	4 (1.8)	0	1 (0.4)	0	4 (1.0)	0	6 (0.4)	2 (0.1)	10 (0.5)	2 (0.1)
General disorders and administration site conditions	**15 (6.6)**	**7 (3.1)**	**7 (3.1)**	**2 (0.9)**	**25 (6.2)**	**9 (2.2)**	**58 (3.7)**	**30 (1.9)**	**83 (4.2)**	**39 (2.0)**
Pyrexia	10 (4.4)	4 (1.8)	4 (1.8)	2 (0.1)	14 (3.5)	6 (1.5)	24 (1.5)	16 (1.0)	38 (1.9)	22 (1.1)
Asthenia	3 (1.3)	2 (0.9)	1 (0.4)	0	3 (0.7)	2 (0.5)	10 (0.6)	4 (0.3)	13 (0.7)	6 (0.3)
General physical health deterioration	1 (0.4)	0	1 (0.4)	0	5 (1.2)	0	5 (0.3)	1 (0.1)	10 (0.5)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**11 (4.9)**	**0**	**13 (5.8)**	**3 (1.3)**	**20 (5.0)**	**2 (0.5)**	**60 (3.8)**	**13 (0.8)**	**80 (4.1)**	**15 (0.8)**
Dyspnea	2 (0.9)	0	4 (1.8)	1 (0.4)	6 (1.5)	1 (0.2)	24 (1.5)	5 (0.3)	30 (1.5)	6 (0.3)
Pulmonary embolism	4 (1.8)	0	1 (0.4)	0	7 (1.7)	1 (0.2)	12 (0.8)	4 (0.3)	19 (1.0)	5 (0.3)
Pleural effusion	0	0	2 (0.9)	0	1 (0.2)	0	15 (1.0)	0	16 (0.8)	0
Respiratory failure	3 (1.3)	0	2 (0.9)	0	3 (0.7)	0	4 (0.3)	0	7 (0.4)	0
Gastrointestinal disorders	**16 (7.1)**	**3 (1.3)**	**18 (8.0)**	**2 (0.9)**	**23 (5.7)**	**4 (1.0)**	**48 (3.1)**	**22 (1.4)**	**71 (3.6)**	**26 (1.3)**
Abdominal pain	4 (1.8)	0	4 (1.8)	0	4 (1.0)	0	7 (0.4)	2 (0.1)	11 (0.6)	2 (0.1)
Intestinal obstruction	3 (1.3)	1 (0.4)	5 (2.2)	0	5 (1.2)	1 (0.2)	2 (0.1)	0	7 (0.4)	1 (0.1)
Ileus	1 (0.4)	0	0	0	4 (1.0)	0	0	0	4 (0.2)	0
Small intestinal obstruction	2 (0.9)	0	3 (1.3)	0	2 (0.5)	0	1 (0.1)	0	3 (0.2)	0
Neoplasms benign, malignant and unspecified	**7 (3.1)**	**0**	**7 (3.1)**	**0**	**18 (4.5)**	**1 (0.1)**	**18 (1.2)**	**0**	**36 (1.8)**	**1 (0.1)**
Cancer pain	2 (0.9)	0	0	0	5 (1.2)	0	1 (0.1)	0	6 (0.3)	0
Tumor pain	0	0	1 (0.4)	0	4 (1.0)	0	1 (0.1)	0	5 (0.3)	0
Vascular disorders	**2 (0.9)**	**0**	**5 (2.2)**	**1 (0.4)**	**4 (1.0)**	**0**	**11 (0.7)**	**4 (0.3)**	**15 (0.8)**	**4 (0.2)**
Deep vein thrombosis	0	0	3 (1.3)	0	1 (0.2)	0	6 (0.4)	3 (0.2)	7 (0.4)	3 (0.2)

A subject with two or more TEAEs in the same system organ class is counted once for that system organ class. System organ classes are presented in descending frequency. Relationship to treatment was assessed by the Investigator.

TEAEs include AEs that were considered by the investigator to be possibly or probably related to study drug and AEs with missing relationship to study drug

Adverse event terms are coded using MedDRA version 17.1.

AE = adverse event, MBC = metastatic breast cancer, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event.

a The STS includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

The overall incidence of non-fatal serious adverse events (SAEs) was similar across arms in Study 309, 32.7 vs. 31.3%. Similar frequencies were also seen for SAEs considered by investigators to be treatment related, 13.7 vs. 13.8%.

SAE differences of relevance across arms were confined to the Blood and lymphatic system disorders SOC, and to the TEAE pyrexia.

Neutropenia was the most common SAE in the eribulin arm at 4.9%, compared with 4.5% (1 patient less) in the dacarbazine arm; i.e. the frequency was similar. Other SAEs in this SOC were more common in the dacarbazine-treated patients. Thus, thrombocytopenia was the most common SAE in the dacarbazine arm at 5.8%, compared with 0% in the eribulin arm. Similarly, pancytopenia was a SAE in 3 patients (1.3%)

in the dacarbazine arm vs. none in the eribulin arm. Overall, dacarbazine had more SAEs in the Blood and lymphatic system disorders SOC than eribulin (11.6 vs. 7.5%).

Pyrexia was more common as an SAE in the eribulin compared with the dacarbazine arm, 4.4 vs. 1.8%.

Pulmonary embolism + deep vein thrombosis constituted SAEs in 6 patients (2.7%) in both arms.

Deaths

Table 35: Listing of TEAEs Leading to Death (Sarcoma Population: Study 309, Study 217 and Study 207)

Study		Cause of Death (Preferred Term)	TEAE Start Date/ Study Day	Relationship to Study Drug (Investigator-assessed)	Duration of Treatment[b]	Day of Death in Relation to Last Dose[c]
Eribulin						
Study 309		Neutropenic sepsis	12 February 2013 / 56	Possibly related	62	7
		Acute respiratory failure	04 June 2011 / 66	Not related	57	9
		Intestinal obstruction	04 July 2012 / 153	Not related	145	28
		Pneumonia aspiration	04 June 2013 / 92	Not related	84	21
		General physical health deterioration	03 February 2012 / 22	Not related	64	14
		Large intestine perforation	30 June 2012 / 94	Not related	64	30
		Respiratory failure[d]	10 July 2012 / 50	Not related	36	14
		Metastases to lung	16 October 2012 / 34	Not related	42	5
		Septic shock	26 March 2012 / 60	Not related	70	3
		Respiratory failure	05 March 2012 / 97	Not related	84	26
Study 207		Malignant pleural effusion	26 September 2009 /12	Not related	9	3
		General physical health deterioration	04 November 2007 / 152	Not related	134	18
		Cerebral ischemia	16 August 2008 / 66	Possibly related	57	36
Study 217		Cardiac failure	27 March 2012 / 71	Not related	57	49
Dacarba						
Study 309		Respiratory failure	20 May 2012 / 74	Not related	58	16
		General physical health deterioration	23 September 2012 / 21	Not related	1	20
		Cardiac arrest	31 March 2013 / 52	Not related	22	30

MedDRA Version 17.1
Age is age at informed consent
F = Female, J = Japanese, M = Male, MedDRA = Medical Dictionary for Regulatory Activities, UNK = unknown, TEAE = treatment-emergent adverse event, W = White, yr = year.

a Study Day of Death = date of death – date of first dose of study drug +1.

b Duration of exposure (days) = date of Day 1 of final cycle +21 – date of first dose (dose start date)

c Day of Death in Relation to Last Dose = date of death - date of last drug dose.

d A TEAE of respiratory failure was reported for Subject 22041011; however, the cause of death was given as disease progression. This subject was excluded from the listing of deaths in the Study 309 CSR.

Most of the fatal TEAEs listed above were deemed by the MAH to be due to disease progression.

In 2 cases, the Investigator and MAH opinion differed regarding relatedness to study drug: a fatal TEAE of septic shock in Study 309 was considered to be unrelated to eribulin by the Investigator, although the MAH considers the event was possibly related to eribulin; and for the fatal TEAE of cerebrovascular ischemia in Study 207, the Investigator considered the event to be possibly related to eribulin, but the MAH considers the event more likely to be related to the subject's past medical history. This included arterial hypertension, hypercholesterolemia, percutaneous transluminal angioplasty, coronary bypass, congestive heart failure, and a history of treatment with oral anticoagulants, antiplatelet drugs, hypolipidemic agents, thyroid hormone replacement therapy, and other supportive medication.

Of the reviewed deaths in the STS population, 2 cases of fatal neutropenic sepsis and septic shock, respectively, were considered related to the eribulin treatment. In the dacarbazine arm all three deaths were due to progressive disease.

Adverse events of special interest

The MAH has selected the following "adverse events of special interest" (AESI):

Peripheral neuropathy, neutropenia and febrile neutropenia, arthralgia/myalgia, asthenia/fatigue, and alopecia. Most are addressed in prior sections of this assessment report. For neutropenia and febrile neutropenia, please see under Laboratory findings below.

Peripheral neuropathy (PN)

Table 36: Summary of Peripheral Neuropathy (PN) Events

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Incidence of PN events (SDQ term)					
All PN events	83 (36.7)	34 (15.2)	166 (41.1)	637 (40.9)	803 (40.9)
Grade ≥3 PN events	7 (3.1)	3 (1.3)	16 (4.0)	131 (8.4)	147 (7.5)
Treatment-related events	75 (33.2)	19 (8.5)	153 (37.9)	566 (36.3)	719 (36.6)
Grade ≥3 treatment-related events	7 (3.1)	0	14 (3.5)	116 (7.4)	130 (6.6)
Time to onset of PN[d] event (weeks)					
Median (95% CI)	20.3 (15.3, 39.3)	NC	19.3 (15.1, 26.9)	28.4 (23.3, 42.7)	27.1 (22.7, 34.0)
1st Quartile (95% CI)	9.3 (5.1, 12.3)	NC	7.1 (5.1, 9.3)	8.1 (7.3, 9.1)	8.1 (7.1, 9.1)
3rd Quartile (95% CI)	NC	NC	58.3 (36.3, NC)	131.3 (89.3, NC)	131.3 (89.3, NC)
Resolution of PN events					
PN ongoing at last treatment	56 (24.8)	12 (5.4)	116 (28.7)	448 (28.7)	564 (28.7)
PN event resolved[e] within 60 days post treatment	9 (16.1)	4 (33.3)	26 (22.4)	91 (20.3)	117 (20.7)
PN event unresolved after 60 days post-treatment	26 (46.4)	5 (41.7)	47 (40.5)	199 (44.4)	246 (43.6)
Unknown due to starting another anti-cancer treatment within 60 days post-treatment	21 (37.5)	3 (25.0)	43 (37.1)	158 (35.3)	201 (35.6)

CI = confidence interval, MBC = metastatic breast cancer, PN = Peripheral Neuropathy, STS = soft tissue sarcoma, SDQ = sponsor derived query, TEAE = treatment-emergent adverse event.

a The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations.

d Time to onset of PN (weeks) = (start date of first PN – date of first dose + 1)/7. Subjects without PN were censored at the last safety assessment. Time to onset of PN and cumulative PN rate were estimated by the product limit method.

e A subject is counted as having resolution if all ongoing PN events had resolution.

In the 1559 breast cancer patients the most common adverse reaction resulting in discontinuation of treatment with eribulin was peripheral neuropathy (3.4%). The median time to Grade 2 peripheral neuropathy was 12.6 weeks (post 4 cycles). Out of the 404 sarcoma patients, 2 patients discontinued treatment with eribulin due to peripheral neuropathy. The median time to Grade 2 peripheral neuropathy was 18.4 weeks.

Development of Grade 3 or 4 peripheral neuropathy occurred in 7.4% of breast cancer patients and 3.5% of sarcoma patients. In clinical trials, patients with pre-existing neuropathy were as likely to develop new or worsening symptoms as those who entered the study without the condition.

In breast cancer patients with pre-existing Grade 1 or 2 peripheral neuropathy the frequency of treatment-emergent Grade 3 peripheral neuropathy was 14%.

No fatal events (Grade 5 severity) were reported in any population and there were no events of Grade 4 severity in the STS population.

The frequency of PN events was similar in the STS and MBC populations (approximately 40%).

Of the 166 patients (41%) of the STS population (n=404) who experienced a PN event, 116 (28% of all patients, 70% of those with PN) had PN ongoing at last treatment. For 26 patients (22% of those with PN) PN resolved within 60 days post treatment; for 47(41% of those with PN) PN was unresolved at 60 days post treatment, and for the remainder, 37 patients (37% of those with PN), resolution was unknown due to start of new therapy.

At an updated analysis in the STS population 180 days after the last treatment 28% (32/166) of eribulin PN events had resolved compared with 22% (26/166) at 60 days after last treatment, indicating further resolution.

Time adjusted analysis of PN

Table 37: Number of Peripheral Neuropathy Events Adjusted by Duration of Exposure

Dacarbazine Study 309 (N=224) Total Duration =58.9 years Episodes (Rate)	Eribulin Study 309 (N=226) Total Duration =75.5 years Episodes (Rate)	Eribulin Sarcoma Studies 207+217+309 (N=404) Total Duration =139.2 years Episodes (Rate)	Eribulin Breast Cancer Studies (N=1559) Total Duration =634.3 years Episodes (Rate)	Eribulin Sarcoma + Breast Cancer Studies (N=1963) Total Duration =773.5 years Episodes (Rate)
44 (0.747)	153 (2.028)	287 (2.062)	1149 (1.811)	1436 (1.857)

Arthralgia/Myalgia

Table 38: Summary of Arthralgia / Myalgia Events

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Incidence of arthralgia/myalgia events (SDQ term)					
All arthralgia/myalgia events	35 (15.5)	27 (12.1)	43 (10.6)	309 (19.8)	352 (17.9)
Grade ≥3 arthralgia/myalgia events	0	0	0	17 (1.1)	17 (0.9)
Treatment-related events	20 (8.8)	15 (6.7)	23 (5.7)	150 (9.6)	173 (8.8)
Grade ≥3 treatment-related events	0	0	0	4 (0.3)	4 (0.2)

Arthralgia/myalgia TEAEs based on the SDQ term, see 'conventions' for details.

MBC = metastatic breast cancer, SDQ = Sponsor derived query, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event.

a The STS includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

Source: SCS, Table 23.

Pyrexia

A large difference in overall frequency of pyrexia across arms in Study 309 was observed (28 vs 14%), but the grade ≥ 3 frequencies were similar (<1%). The incidence was highest (14-12%) in the first two cycles, following which the incidence decreased substantially. Median duration of pyrexia was 2 days and events were of low grade in most cases (only 1% were grade ≥3).

Laboratory findings

Table 39: Treatment-Emergent Markedly Abnormal[1] Laboratory Results – Haematology

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Hemoglobin					
Markedly abnormal high	0	0	1/404 (0.2)	4/1558 (0.3)	5/1962 (0.3)
Markedly abnormal low	16/226 (7.1)	32/221 (14.5)	32/404 (7.9)	42/1558 (2.7)	74/1962 (3.8)
Leukocytes					
Markedly abnormal low	65/226 (28.8)	33/221 (14.9)	147/404 (36.4)	583/1558 (37.4)	730/1962 (37.2)
Lymphocytes					
Markedly abnormal high	0	0	0	4/1536 (0.3)	4/1939 (0.2)
Markedly abnormal low	44/226 (19.5)	44/221 (19.9)	91/403 (22.6)	208/1536 (13.5)	299/1939 (15.4)
Neutrophils					
Markedly abnormal low	97/226 (42.9)	47/221 (21.3)	207/403 (51.4)	934/1532 (61.0)	1141/1935 (59.0)
Platelets					
Markedly abnormal low	5/226 (2.2)	46/221 (20.8)	7/404 (1.7)	17/1558 (1.1)	24/1962 (1.2)

MBC = metastatic breast cancer, STS = soft tissue sarcoma.

1 Post-baseline values were considered a markedly abnormal low or high if 1) baseline CTC grade was missing, 0, 1, or 2, and at least 1 post-baseline CTC grade was 3, 4, or 5; or if 2) baseline CTC grade was 3 or 4 and at least 1 post-baseline grade was higher than the baseline grade.

a. The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b. The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c. The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

Table 40: Neutropenia and Febrile Neutropenia - Number of Episodes Adjusted by Duration of Exposure

	Dacarbazine Study 309 (N=224) Total Duration =58.9 years Episodes (Rate)	Eribulin Study 309 (N=226) Total Duration =75.5 years Episodes (Rate)	Eribulin Sarcoma Studies 207+217+309 (N=404) Total Duration =139.2 years Episodes (Rate)	Eribulin Breast Cancer Studies (N=1559) Total Duration =634.3 years Episodes (Rate)	Eribulin Sarcoma + Breast Cancer Studies (N=1963) Total Duration =773.5 years Episodes (Rate)
Neutropenia (any PT)	125 (2.123)	276 (3.658)	620 (4.455)	2660 (4.193)	3280 (4.240)
Febrile neutropenia (any PT)	3 (0.051)	3 (0.040)	16 (0.115)	89 (0.140)	105 (0.136)

Low neutrophils and leukocytes were less frequently observed in the STS compared with the MBC setting, likely at least partly related to the shorter duration of treatment, based on the similar rates of neutropenia in time-adjusted analyses. The use of immunostimulants (such as filgrastim or pegfilgrastim) was similar in the arms of Study 309 and the STS population: 26.1% of subjects in the eribulin arm of Study 309, 25.4% in the dacarbazine arm of Study 309 and 23.8% in the STS population.

Table 41: Treatment-Emergent Markedly Abnormal Laboratory Test Values - Clinical Chemistry

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Alanine Aminotransferase					
Markedly abnormal high	6/225 (2.7)	6/219 (2.7)	14/402 (3.5)	69/1538 (4.5)	83/1940 (4.3)
Albumin					
Markedly abnormal low	2/225 (0.9)	1/219 (0.5)	9/401 (2.2)	14/1539 (0.9)	23/1940 (1.2)
Alkaline Phosphatase					
Markedly abnormal high	5/225 (2.2)	6/219 (2.7)	5/402 (1.2)	56/1540 (3.6)	61/1942 (3.1)
Aspartate Aminotransferase					
Markedly abnormal high	4/225 (1.8)	2/219 (0.9)	7/402 (1.7)	65/1538 (4.2)	72/1940 (3.7)
Calcium					
Markedly abnormal high	1/225 (0.4)	5/220 (2.3)	2/399 (0.5)	25/1556 (1.6)	27/1955 (1.4)
Markedly abnormal low	11/225 (4.9)	3/220 (1.4)	15/399 (3.8)	30/1556 (1.9)	45/1955 (2.3)
Creatinine					
Markedly abnormal high	0	0	3/403 (0.7)	13/1557 (0.8)	16/1960 (0.8)
Glucose					
Markedly abnormal high	4/106 (3.8)	1/100 (1.0)	7/157 (4.5)	35/943 (3.7)	42/1100 (3.8)
Markedly abnormal low	0	0	0	1/943 (0.1)	1/1100 (0.1)
Magnesium					
Markedly abnormal high	0	4/219 (1.8)	0	60/1385 (4.3)	60/1610 (3.7)
Markedly abnormal low	2/225 (0.9)	1/219 (0.5)	2/225 (0.9)	10/1385 (0.7)	12/1610 (0.7)
Phosphorus					
Markedly abnormal low	8/225 (3.6)	4/219 (1.8)	32/388 (8.2)	64/1524 (4.2)	96/1912 (5.0)
Potassium					
Markedly abnormal high	3/225 (1.3)	2/220 (0.9)	4/403 (1.0)	23/1555 (1.5)	27/1958 (1.4)
Markedly abnormal low	18/225 (8.0)	6/220 (2.7)	28/403 (6.9)	69/1555 (4.4)	97/1958 (5.0)
Sodium					
Markedly abnormal high	0	0	0	30/1556 (1.9)	30/1959 (1.5)
Markedly abnormal low	10/225 (4.4)	9/220 (4.1)	21/403 (5.2)	66/1556 (4.2)	87/1959 (4.4)
Total Bilirubin					
Markedly abnormal high	4/225 (1.8)	1/219 (0.5)	4/402 (1.0)	13/1556 (0.8)	17/1958 (0.9)

CTC = Common Terminology Criteria for Adverse Events, MBC = metastatic breast cancer, STS = soft tissue sarcoma.

a Post-baseline values were considered a markedly abnormal low or high if 1) baseline CTC grade was missing, 0, 1, or 2, and at least 1 post-baseline CTC grade was 3, 4, or 5; or if 2) baseline CTC grade was 3 or 4 and at least 1 post-baseline grade was higher than the baseline grade.

b The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

c The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

d The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

In Study 309, markedly-abnormally low calcium, phosphorous, and potassium occurred more frequently in the eribulin group (2.3%, 3.6%, and 8.0%, respectively), compared with the dacarbazine group (0.4%, 1.8%, and 2.7%, respectively). Markedly-abnormally high glucose, AST and bilirubin was also more common the in eribulin group (3.8%, 1.8 and 1.8%, respectively) compared with the dacarbazine group (1.0%, 0.9 and 0.5%, respectively).

Markedly-abnormally low phosphorous was also reported more commonly in the STS population (8.2%), compared with the MBC population (4.2%). Markedly-abnormally low calcium, was reported less commonly in the STS population (0.5%), compared with the MBC population (1.6%). Other clinically relevant abnormal laboratory test values occurred at a similar frequency in both the STS and MBC populations.

Hy's law

The integrated laboratory data were assessed for evidence of drug-induced liver injury. A total of 41 subjects had total bilirubin concentrations that were ≥1.5 x ULN with either concurrent AST and/or ALT ≥ 3 x ULN at least once during the study. The data showed that there were 9 subjects in the STS studies whose laboratory values met these limits. One of these subjects was in the dacarbazine arm of Study 309, and the remaining 8 subjects were treated with eribulin (4 subjects in Study 309, 3 subjects in Study 207 and 1 subject in Study 217). Metastatic disease was present in the liver for 7 of these 9 subjects, and 1 subject had hepatic necrosis (ischemic necrosis of the liver) at baseline; none of these subjects had increased total bilirubin concentrations or liver enzyme activities that were not reasonably explainable by their baseline liver conditions. No subjects in the STS population met the criteria for Hy's law (including criteria concerning cholestasis and alternative aetiologies).

The proportion of subjects in the STS population with elevated bilirubin (≥1.5 x ULN) concurrently with elevated AST and/or ALT (≥3 x ULN) was 8/404 subjects (2.0%); similar to that seen for the MBC population (36/1559 subjects [2.3%]).

Vital signs

There was no apparent pattern of changes with time on treatment for vital sign parameters (e.g. blood pressure, temperature, respiratory rate). Results were consistent with the known safety profile of eribulin and did not signal any new significant safety concerns.

QTc prolongation

In Study 309, there were no changes of clinical importance in mean ECG parameters over time.

The incidence of QT prolongation TEAEs was calculated using the following Sponsor-derived query for QT prolongation: "Broad and narrow SMQ terms for Torsade de pointes with the exception that 'Long QT syndrome congenital' was deleted. Also, broad and narrow SMQ terms for tachyarrhythmias (including supraventricular and ventricular tachyarrhythmia)."

Table 42: Summary of TEAEs within the SDQ term for QT prolongation

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Incidence of QT prolongation events (SDQ term)					
All QT prolongation events	20 (8.8)	25 (11.2)	31 (7.7)	32 (2.1)	63 (3.2)
Grade ≥3 QT prolongation events	5 (2.2)	8 (3.6)	6 (1.5)	15 (1.0)	21 (1.1)
Treatment-related QT prolongation events	14 (6.2)	11 (4.9)	16 (4.0)	9 (0.6)	25 (1.3)
Grade ≥3 treatment-related QT prolongation events	5 (2.2)	3 (1.3)	5 (1.2)	3 (0.2)	8 (0.4)

MBC = metastatic breast cancer, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event, SDQ = Sponsor derived query (see 'conventions' for details)

a The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

The 5 treatment-related TEAEs of Grade ≥3 severity in the STS population were all events of electrocardiogram QT prolonged which occurred in Study 309; all 5 events were of Grade 3 severity. The 3 treatment-related TEAEs of Grade ≥3 severity in the MBC population were: 1 event of sudden death (Grade 5), 1 event of electrocardiogram QT prolonged (Grade 3), and 1 event of syncope (Grade 3).

An analysis using a narrower SDQ term for QT prolongation was provided in response to questions. This included the TEAEs coding to the SDQ Torsades de pointes/QT prolongation SMQ narrow with the deletion of “Long QT syndrome congenital”. The only PT reported coding to this SDQ in the eribulin studies was “Electrocardiogram QT prolonged”.

Table 43: Summary of TEAEs within the narrow SMQ for QT prolongation/TdP

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Incidence of QT prolongation events (Updated SDQ term)					
All QT prolongation events	15 (6.6)	11 (4.9)	16 (4.0)	4 (0.3)	20 (1.0)
Grade ≥3 QT prolongation events	5 (2.2)	3 (1.3)	5 (1.2)	3 (0.2)	8 (0.4)
Treatment-related QT prolongation events	14 (6.2)	7 (3.1)	15 (3.7)	3 (0.2)	18 (0.9)
Grade ≥3 treatment-related QT prolongation events	5 (2.2)	1 (0.4)	5 (1.2)	1 (0.1)	6 (0.3)

MBC = metastatic breast cancer, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event, SDQ = sponsor derived query.

a: The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b: The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c: The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

There appears to be no major difference in the frequency of QT prolongation events for eribulin vs dacarbazine-treated patients in Study 309. The QT-prolongating ability of dacarbazine is unknown. The QT-prolongating ability of eribulin also remains unknown.

Tachycardia

Table 44: Treatment-Emergent Adverse Events by System Organ Class: Cardiac disorders

Dacarbazine Study 309 (N=224) n (%)	Eribulin Study 309 (N=226) n (%)	Eribulin Sarcoma Studies 207+217+309 (N=404) n (%)	Eribulin Breast Cancer Studies (N=1559) n (%)	Eribulin Sarcoma + Breast Cancer Studies (N=1963) n (%)
20 (8.9)	14 (6.2)	31 (7.7)	108 (6.9)	139 (7.1)

Safety in special populations

Intrinsic factors

Age

In the 404 sarcoma patient population, 90 patients (22.3%) treated with eribulin were ≥65 years of age. Population PK analyses showed that there was no significant effect of age on eribulin PK. Eribulin exposure in elderly subjects was similar to that in younger subjects.

Race

Table 45: Summary of Neutropenia Events in White and Asian / Pacific Islander Subjects

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
White subjects					
Number of subjects	161	167	161	1250	1411
Neutropenia TEAEs n (%)	68 (42.2)	39 (23.4)	68 (42.2)	682 (54.6)	750 (53.2)
Number of subjects with neutropenia laboratory data	161	165	161	1221	1382
Shifts from CTCAE Grade 0 to Grade ≥3 for neutrophil count decreased n (%)	66 (41.0)	35 (21.2)	66 (41.0)	689 (56.4)	755 (54.6)
Asian/Pacific Islander subjects					
Number of subjects	19	16	70	111	181
Neutropenia TEAEs n (%)	13 (68.4)	2 (12.5)	63 (90.0)	101 (91.0)	164 (90.6)
Number of subjects with neutropenia laboratory data	19	16	70	111	181
Shifts from CTCAE Grade 0 to Grade ≥3 for neutrophil count decreased n (%)	14 (73.7)	1 (6.3)	57 (81.4)	98 (88.3)	155 (85.6)

CTCAE = Common Terminology Criteria for Adverse Events, MBC = metastatic breast cancer, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event.

a The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

An increased incidence of neutropenia/neutrophil count decreased in Asian/Pacific Islander subjects is a known effect of eribulin; the increased incidence was also seen in the MBC population as well as in the STS population. This difference seems not to be a drug specific phenomenon, as several other publications (Gandara, et al., 2009; Hasegawa, et al., 2011) have discussed similar situations where the incidence of neutropenia in Asian subjects has been shown to be twice as high as in non-Asian subjects. Other than TEAEs of neutropenia, and laboratory abnormalities of neutrophil count decreased, there did not appear to be a consistent pattern of overall TEAE incidence with racial group, among eribulin-treated subjects in the STS and MBC populations. These results confirm the data seen in the breast cancer population, which indicate that, with the exception of neutropenia, race does not affect the way eribulin is tolerated.

Sex

Table 46: Overview of Treatment-Emergent Adverse Events by Sex (STS Population)

	STS Population[a]	
	Male (N = 151)	Female (N = 253)
Subjects with TEAEs	150 (99.3)	249 (98.4)
Subjects with related TEAEs	142 (94.0)	233 (92.1)
Subjects with severe TEAEs (CTCAE Grade ≥ 3)	98 (64.9)	169 (66.8)
Subject with SAEs	57 (37.7)	81 (32.0)
Subjects with fatal SAEs	2 (1.3)	12 (4.7)
Subjects with non-fatal SAEs	56 (37.1)	78 (30.8)
Subjects with TEAEs leading to study drug action[b] taken	33 (21.9)	92 (36.4)
Subjects with TEAEs leading to study drug withdrawn	3 (2.0)	18 (7.1)

A subject with two or more TEAEs in the category of one row is counted once in that row.

A subject with both non-fatal and fatal SAEs is counted in both the non-fatal SAEs row and the fatal SAEs row.

Adverse event terms are coded using MedDRA version 17.1.

CTCAE = Common Terminology Criteria for Adverse Events, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event.

a The STS includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b Drug withdrawn, dose reduction, or drug interruption.

Analyses by sex are confounded by indications (ADI/LMS) with different treatment effect and time on therapy. Thus, the eribulin-treated leiomyosarcoma subgroup of Study 309 consisted of 82% women, while the adipocytic subgroup was more balanced with 46% women. In addition, differences in baseline characteristics indicated slightly poorer prognosis in women compared with men (higher tumour grade, higher ECOG performance status, larger number of prior chemotherapy regimens). Together, these circumstances may provide explanations for the higher frequency of fatal AEs seen in women compared with men, which were mostly related to disease progression. The frequencies of treatment-*related* deaths (0.8 vs. 0.7%) were not unbalanced across sexes, however. The higher frequency of the cumulative toxicity peripheral neuropathy observed in men compared with women may be due to the imbalances in the histologic subgroups noted above. No important differences in safety profile across sexes are seen.

Histology

Table 47: Treatment-Emergent Adverse Events for System Organ Classes which have at least one Preferred Term with Frequency >= 5% within the SOC (Eribulin STS ISS Population) Safety Population

MedDRA System Organ Class	Eribulin Study 309				Eribulin STS (Studies 207+217+309)			
	ADI (N=70) n (%)	LMS (N=156) n (%)	Uterine LMS (N=68) n (%)	Non-Uterine LMS (N=87) n (%)	ADI (N=123) n (%)	LMS (N=215) n (%)	Uterine LMS (N=90) n (%)	Non-Uterine LMS (N=124) n (%)
Blood and lymphatic system disorders	37(52.9)	100(64.1)	46(67.6)	53(60.9)	56(45.5)	121(56.3)	53(58.9)	67(54.0)
Eye disorders	9(12.9)	19(12.2)	9(13.2)	10(11.5)	17(13.8)	23(10.7)	9(10.0)	14(11.3)
Gastrointestinal disorders	56(80.0)	122(78.2)	55(80.9)	66(75.9)	94(76.4)	167(77.7)	69(76.7)	97(78.2)
General disorders and administration site conditions	49(70.0)	123(78.8)	53(77.9)	69(79.3)	88(71.5)	173(80.5)	69(76.7)	103(83.1)
Infections and infestations	33(47.1)	65(41.7)	31(45.6)	33(37.9)	56(45.5)	91(42.3)	40(44.4)	50(40.3)
Investigations	25(35.7)	55(35.3)	23(33.8)	32(36.8)	53(43.1)	82(38.1)	34(37.8)	48(38.7)
Metabolism and nutrition disorders	26(37.1)	57(36.5)	28(41.2)	28(32.2)	48(39.0)	81(37.7)	36(40.0)	44(35.5)
Musculoskeletal and connective tissue disorders	28(40.0)	76(48.7)	32(47.1)	44(50.6)	52(42.3)	99(46.0)	40(44.4)	59(47.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5(7.1)	14(9.0)	7(10.3)	7(8.0)	21(17.1)	33(15.3)	15(16.7)	18(14.5)
Nervous system disorders	34(48.6)	78(50.0)	31(45.6)	46(52.9)	71(57.7)	113(52.6)	44(48.9)	68(54.8)
Psychiatric disorders	16(22.9)	32(20.5)	13(19.1)	19(21.8)	27(22.0)	46(21.4)	18(20.0)	28(22.6)
Respiratory, thoracic and mediastinal disorders	24(34.3)	68(43.6)	27(39.7)	40(46.0)	48(39.0)	98(45.6)	38(42.2)	59(47.6)
Skin and subcutaneous tissue disorders	35(50.0)	74(47.4)	27(39.7)	46(52.9)	62(50.4)	114(53.0)	41(45.6)	72(58.1)
Vascular disorders	9(12.9)	26(16.7)	11(16.2)	15(17.2)	20(16.3)	35(16.3)	16(17.8)	19(15.3)

The safety profile of eribulin appears similar in the different histologic/anatomic subgroups; observed differences may be the result of differences in exposure and/or underlying disease.

Peripheral neuropathy and related PTs were more frequent in adipocytic compared with leiomyosarcoma, particularly with regard to events ≥ grade 3, which was approximately 6 vs. 2 % in both Study 309 and the full STS population. PFS data indicate that the time on eribulin was longer in the adipocytic compared with the leiomyosarcoma subgroup.

Renal insufficiency

The eribulin sarcoma studies excluded subjects with severe renal impairment (e.g. included patients with serum creatinine ≤2.0 mg/dL or calculated creatinine clearance ≥40 mL/minutes per the Cockcroft and Gault formula).

A study in renal impairment has been previously submitted and assessed within the Variation II/23 and findings were reflected in the SmPC. A large variability was found between patients and across renal impairment groups, why a recommendation regarding starting dose could not be made; instead increased monitoring is recommended for all patients with renal impairment.

Hepatic insufficiency

Table 48: Neutropenia TEAEs and Laboratory Abnormalities by Liver Function

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Overall subject population					
Number of subjects	226	224	404	1559	1963
All neutropenia events	156 (69.0)	96 (42.9)	307 (76.0)	1314 (84.3)	1621 (82.6)
Grade 3 neutropenia events	55 (24.3)	24 (10.7)	88 (21.8)	446 (28.6)	534 (27.2)
Grade 4 neutropenia events	49 (21.7)	26 (11.6)	126 (31.2)	524 (33.6)	650 (33.1)
Subjects with baseline liver function = normal					
Number of subjects	186	190	330	949	1279
All neutropenia events	128 (68.8)	83 (43.7)	250 (75.8)	783 (82.5)	1033 (80.8)
Grade 3 neutropenia events	46 (24.7)	22 (11.6)	76 (23.0)	293 (30.9)	369 (28.9)
Grade 4 neutropenia events	38 (20.4)	23 (12.1)	96 (29.1)	251 (26.4)	347 (27.1)
Subjects with baseline liver function = Grade 1 liver toxicity					
Number of subjects	40	32	72	520	592
All neutropenia events	28 (70.0)	12 (37.5)	56 (77.8)	449 (86.3)	505 (85.3)
Grade 3 neutropenia events	9 (22.5)	1 (3.1)	12 (16.7)	137 (26.3)	149 (25.2)
Grade 4 neutropenia events	11 (27.5)	3 (9.4)	29 (40.3)	217 (41.7)	246 (41.6)
Subjects with baseline liver function = Grade ≥ 2 liver toxicity					
Number of subjects	0	2	2	86	88
All neutropenia events	0	1 (50.0)	1 (50.0)	79 (91.9)	80 (90.9)
Grade 3 neutropenia events	0	1 (50.0)	0	14 (16.3)	14 (15.9)
Grade 4 neutropenia events	0	0	1 (50.0)	55 (64.0)	56 (63.6)

Neutropenia TEAEs based on the SDQ terms, see 'conventions' for details

Liver function:

- Normal: (ALT ≤ 1 ULN) and (AST ≤ 1 ULN) and (Bilirubin ≤ 1 ULN)
- Grade 1 liver toxicity: [(ALT > 1 ULN) or (AST > 1 ULN) or (Bilirubin > 1 ULN)] and [(ALT ≤ 3 ULN) and (AST ≤ 3 ULN) and (Bilirubin ≤ 1.5 ULN)]
- Grade 2 or higher liver toxicity: (ALT > 3 ULN) or (AST > 3 ULN) or (Bilirubin > 1.5 ULN)

ALT = alanine transaminase, AST = aspartate transaminase, MBC = metastatic breast cancer, SDQ = Sponsor derived query, STS = soft tissue sarcoma, TEAE = treatment-emergent ad Aspartate transaminase verse event, ULN = upper limit of normal.

a The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309. Study 207 did not record laboratory abnormalities into adverse events data.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

Neutropenia in relation to liver function

The overall cumulative incidence of neutropenia events, including laboratory abnormalities observed in the registration of laboratory parameters, was lower in the STS compared with the MBC, as previously noted, at least partially attributable to differences in treatment duration. Similar trends were seen in both disease settings for a small increase in neutropenia events in patients with grade 1 liver toxicity compared with patients with normal liver function. In the MBC population information from patients with grade ≥ 2 liver toxicity was also available, indicting a further small increase in the frequency of neutropenia events. Lower frequencies of neutropenia were seen in pivotal Study 309, with a similar trend in relation to liver toxicity.

Peripheral neuropathy in relation to liver function

The corresponding analysis was performed for peripheral neuropathy, where no trend of increased toxicity was seen for patients with grade 1 liver toxicity in study 309 or in the STS (n=40 and 72, respectively). In the MBC, as well as in the eribulin integrated safety population (STS+MBC), a clear trend of increased frequencies of peripheral neuropathy at grade ≥ 2 liver toxicity was seen, however. The approximate frequencies of peripheral neuropathy in both these populations were 40% for normal liver function, 41-42% for grade 1 liver toxicity, and 51% for grade ≥ 2 liver toxicity.

Similar trends of increased toxicity overall depending on baseline bilirubin, ALT, or AST statuses, respectively, and for peripheral neuropathy depending on a combined liver function status, have been observed in previous Halaven submissions based on the MBC population (e.g. Variation II/11 for new indication, SCS Tables 34, 58-60) and discussed in ARs.

It has previously been established that hepatic impairment increases the exposure to eribulin, therefore these findings are expected. The increase in toxicity is overall rather limited. No new safety issue is raised.

Extrinsic factors

Safety related to drug-drug interactions and other interactions

No AEs of drug interaction were reported in Study 309, Study 207 or Study 217.

Sarcoma population (STS) adverse drug reactions

The table below is based on all adverse reactions observed for all 3 sarcoma studies and shows TEAEs by incidence rate (regardless of investigator assessment of relationship to eribulin treatment) and has been compiled according to the recommendations of CIOMS III – Core Clinical Safety Information. Detailed analysis of the source tables, including analyses of individual TEAEs and review of individual TEAE reports where necessary, have been performed in compiling the table. Events are included if the company believes there to be sufficient evidence of a relationship with eribulin mesilate; the table is thus a summary compiled using the frequencies of individual events and medical judgment in assessing the evidence for those less common individual events to be included.

Table 49: Adverse Events observed for eribulin in all sarcoma subjects

System Organ Class	Very common (≥10%)	Common (≥1% to ≤10%)	Uncommon (≤1%)
Blood and lymphatic disorders	Neutropenia (37.4% based on TEAEs only; 76.0% based on TEAEs and laboratory abnormalities) Leukopenia (21.5%) Anemia (22.8%) Lymphopenia (10.6%)	Febrile neutropenia Thrombocytopenia	
Eye disorders		Lacrimation increased	
Gastrointestinal disorders	Nausea (38.9%) Constipation (30.0%) Diarrhea (18.6%) Vomiting (18.1%) Stomatitis (17.3%) Abdominal pain (11.9%)	Dry mouth Dyspepsia	
General disorders and administrative conditions	Fatigue/Asthenia (66.3%) Pyrexia (27.5%) Peripheral edema (13.4%)	Chills	
Hepatobiliary disorders		Hypertransaminasemia	

Immune system disorders			Drug hypersensitivity
Infections and infestations		Pneumonia Herpes Zoster Urinary tract infection Oral candidiasis Upper respiratory tract infection Nasopharyngitis Rhinitis	Neutropenic sepsis Sepsis Oral herpes
Metabolism and nutrition disorders	Decreased appetite (23.3%) Weight decreased (11.1%)	Hypokalemia Hypomagnesaemia Dehydration Anorexia	
Musculoskeletal and connective tissue disorders	Arthralgia (6.4%)	Myalgia	
Nervous system disorders	Neuropathy peripheral[a] (41.1%) Headache (17.3%) Dizziness (12.4%)	Dysgeusia	
Respiratory, thoracic and mediastinal disorders	Dyspnea (19.8%) Cough (18.6%)	Oropharyngeal pain	
Skin and subcutaneous tissue disorders	Alopecia (38.1%)	Rash	
Vascular disorders			Hypotension

SDQ = Sponsor derived query, TEAE = treatment-emergent adverse event.

a. SDQ term = Sponsor Derived Queries (For definitions see SCS p. 8)

Discontinuation due to adverse events

Table 50: Treatment-Emergent Adverse Events Leading to Drug Action taken (Drug Withdrawn, Dose Reduction, or Drug Interruption) (≥ 1% subjects) by System Organ Class and Preferred Term

	Study 309		STS Population[a] (N=404)	MBC Population[b] (N=1559)	Eribulin Integrated Safety Population[c] (N=1963)
	Eribulin (N=226)	Dacarbazine (N=224)			
Subjects with any TEAE requiring dose action	**107 (47.3)**	**89 (39.7)**	**125 (30.9)**	**423 (27.1)**	**548 (27.9)**
Blood and lymphatic system disorders	**57 (25.2)**	**64 (28.6)**	**70 (17.3)**	**204 (13.1)**	**274 (14.0)**
Neutropenia	48 (21.2)	30 (13.4)	61 (15.1)	167 (10.7)	228 (11.6)
Leukopenia	6 (2.7)	8 (3.6)	7 (1.7)	39 (2.5)	46 (2.3)
Febrile neutropenia	0	1 (0.4)	1 (0.2)	29 (1.9)	30 (1.5)
Anemia	5 (2.2)	7 (3.1)	6 (1.5)	5 (0.3)	11 (0.6)
Thrombocytopenia	5 (2.2)	39 (17.4)	5 (1.2)	7 (0.4)	12 (0.6)
Nervous system disorders	**17 (7.5)**	**1 (0.4)**	**18 (4.5)**	**109 (7.0)**	**127 (6.5)**
Peripheral sensory neuropathy	10 (4.4)	0	10 (2.5)	37 (2.4)	47 (2.4)
Neuropathy peripheral	0	0	1 (0.2)	36 (2.3)	37 (1.9)
General disorders and administration site conditions	**20 (8.8)**	**5 (2.2)**	**20 (5.0)**	**49 (3.1)**	**69 (3.5)**
Fatigue	8 (3.5)	3 (1.3)	8 (2.0)	16 (1.0)	24 (1.2)
Pyrexia	8 (3.5)	1 (0.4)	8 (2.0)	8 (0.5)	16 (0.8)
Asthenia	2 (0.9)	1 (0.4)	2 (0.5)	16 (1.0)	18 (0.9)
Investigations	**18 (8.0)**	**13 (5.8)**	**18 (4.5)**	**42 (2.7)**	**60 (3.1)**
Neutrophil count decreased	10 (4.4)	7 (3.1)	10 (2.5)	4 (0.3)	14 (0.7)
ALT increased	3 (1.3)	0	3 (0.7)	10 (0.6)	13 (0.7)
WBC decreased	3 (1.3)	9 (4.0)	3 (0.7)	6 (0.4)	9 (0.5)
AST increased	3 (1.3)	0	3 (0.7)	4 (0.3)	7 (0.4)
Platelet count decreased	1 (0.4)	7 (3.1)	1 (0.2)	1 (0.1)	2 (0.1)
Infections and infestations	**23 (10.2)**	**6 (2.7)**	**26 (6.4)**	**25 (1.6)**	**51 (2.6)**
Urinary tract infection	4 (1.8)	0	4 (1.0)	2 (0.1)	6 (0.3)
Metabolism and nutrition disorders	**6 (2.7)**	**4 (1.8)**	**6 (1.5)**	**9 (0.6)**	**15 (0.8)**
Hyperglycemia	3 (1.3)	0	3 (0.7)	3 (0.2)	6 (0.3)

A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).

Adverse event terms are coded using MedDRA version 17.1.

Study 207 did not assess action taken with respect to study drug through adverse events data. Study treatment discontinuation in Study 207 is only reported in Table 2 based on subject disposition data.

ALT = alanine transaminase, AST = aspartate transaminase, MBC = metastatic breast cancer, MedDRA = Medical Dictionary for Regulatory Activities, STS = soft tissue sarcoma, TEAE = treatment-emergent adverse event, WBC = white blood cell count.

a The STS Population includes all subjects treated with eribulin in sarcoma studies 207, 217, and 309.

b The MBC Population includes all subjects treated with eribulin monotherapy in 21-day cycles in breast cancer studies 201, 206, 209, 211, 221, 224, 301, and 305.

c The Eribulin Integrated Safety Population includes all subjects in the STS and MBC Populations

With regard to TEAEs leading to drug action taken (dose reduction, dose interruption, or drug withdrawn), the Blood and lymphatic system disorders SOC was the most prominent with similar frequencies overall

across arms, but with emphasis on neutropenia in the eribulin arm and thrombocytopenia in the dacarbazine arm, in line with the safety profiles.

Peripheral neuropathy and pyrexia caused drug action to be taken in the eribulin arm (at 4.4 and 3.5%) but only in single patients in the dacarbazine arm, also in line with the known toxicity profiles.

While similar overall and grade ≥ 3 frequencies were observed for fatigue/asthenia across arms, these conditions lead to dose reduction/interruption/(withdrawal, see below) more often in the eribulin compared with the dacarbazine arm (4.4 vs 1.8%, n: 10 vs. 4).

ALT elevation, AST elevation, and hyperglycemia were each causes for dose reduction or interruption in three eribulin-treated patients (1.3%), but not for drug withdrawal apparently. No drug action was taken based on these events in the dacarbazine arm.

When only TEAEs leading to drug withdrawal were summarised it was noted that for neuropathy this was done in 2 vs. 1 patient in the eribulin vs. dacarbazine arm; fatigue lead to drug withdrawal in 2 vs 2 cases, asthenia 0 vs. 0, neutropenia 0 vs. 0, thrombocytopenia in 2 vs. 3, and infections (SOC) in 3 vs 0 patients. It is also noted that ECG QT prolongation was the cause for eribulin withdrawal in one patient in Study 309 (none in the dacarbazine arm).

The overall frequency of treatment discontinuation due to AE was higher in the eribulin arm compared with the dacarbazine arm (7.5 vs 4.9%).

Supportive safety data

This study evaluated therapy with single-agent eribulin mesylate for first-line treatment in subjects with previously untreated locally recurrent or metastatic HER2-negative breast cancer.

Table 51: Study 206 Safety summary based on TEAES ≥ 25 of patients, including SAEs, treatment-related TEAEs and TEAEs leading to discontinuation

MedDRA Preferred Term	Eribulin mesylate (N=56)			
	Total TEAEs (Grade 1-5) n (%)	Severe (Grade 3-4) TEAEs n (%)	Treatment-related TEAEs n (%)	TEAEs Leading to Treatment Discontinuation n (%)
Alopecia	47 (83.9)	NA[a]	47 (83.9)	0
Neutropenia[b]	40 (71.4)	28 (50.0)	40 (71.4)	0
Fatigue	36 (64.3)	1 (1.8)	34 (60.7)	0
Peripheral neuropathy[c]	34 (60.7)	12 (21.4)	32 (57.1)	5 (8.9)
Nausea	33 (58.9)	1 (1.8)	27 (48.2)	0
Anaemia	21 (37.5)	3 (5.4)	20 (35.7)	0
Constipation	20 (35.7)	0	15 (26.8)	0
Diarrhoea	19 (33.9)	0	14 (25.0)	0
Leukopenia	19 (33.9)	12 (21.4)	19 (33.9)	0
Decreased appetite	15 (26.8)	0	13 (23.2)	0
Vomiting	14 (25.0)	1 (1.8)	12 (21.4)	0

MedDRA version 16.0.
For each preferred term, a subject with two or more episodes was counted only once.
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.
a: Not applicable. Per NCI CTCAE v4.0, the maximum severity rating for alopecia is Grade 2.
b: The incidence of neutropenia does not include the preferred term "febrile neutropenia," which occurred in 4 subjects (7.1%); all 4 were severe (Grade ≥3).
c: SMQ analysis of peripheral neuropathy included the following pooled preferred terms: neuropathy peripheral, neuropathy, peripheral motor neuropathy, polyneuropathy, peripheral sensory neuropathy, peripheral sensorimotor neuropathy, demyelinating polyneuropathy, and paresthesia.
Source: Tables 14.3.1.2.2, 14.3.1.2.6, and 14.3.1.2.10.

Serious AEs reported in more than one subject in Study 206 were febrile neutropenia (n=3; 5.4%), neutropenia (n=3; 5.4%), and pulmonary embolism (n=2; 3.6%). Two deaths occurred. Both deaths occurred more than 30 days after the subject received her last dose of eribulin mesylate. One was attributed to disease progression. The second subject died due to pericardial and pleural effusion, reported by the investigator to be not related to study drug. Although the death occurred more than 30 days after last dose of eribulin mesylate, the onset date of the event was during the study treatment period. There were no clinically relevant trends in group mean/median lab or vital sign values over time. No subject had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of Grade 3 or 4 during the study and one subject had a shift of two grades (Grade 0 to Grade 2) from Baseline to worst value during treatment. A total of 33 subjects had an abnormal ECG finding some time during treatment, which was clinically significant in 3 subjects. A total of 23 subjects had an abnormal ECG finding at the end of treatment, which was clinically significant in 1 subject. Two subjects had QT prolongation (one Grade 2, possibly related, study drug interrupted, recovered; one Grade 3, probably related, study drug discontinued, not recovered).

2.5.1. Discussion on clinical safety

Sarcoma

STS vs MBC

The overall eribulin safety profile in the studied soft tissue sarcoma (STS) population was similar to that seen in the previously approved metastatic breast cancer (MBC) setting. No new safety concerns have been identified.

The mean and median duration of eribulin exposure are lower in the STS compared with the MBC population (median 12 vs. 16 weeks). Similarly, the cumulative eribulin dose is lower in the STS compared with the MBC population. This is most likely an effect of the efficacy in the respective indications. The absolute and relative dose intensity is slightly higher in the STS compared with the MBC population, indicating similar tolerability in the two indications. Dose reductions were slightly less frequent (25.7 vs. 30.5%), but could potentially be attributable to the shorter time on drug.

For many ADRs, the AE frequencies were numerically or significantly lower in the STS setting compared to the MBC setting. This could at least partly be explained by a shorter duration of exposure.

For a smaller number of ADRs, relevantly higher frequencies were seen in the STS compared with the MBC population. These include pyrexia (27 vs. 20%), stomatitis (17 vs 9%), and fatigue/asthenia (60 vs. 51%).

Eribulin vs. dacarbazine

The duration of study drug exposure was numerically slightly longer in the eribulin arm compared with the dacarbazine comparator arm of the pivotal Study 309 (difference in means 3.7 weeks, difference in medians 1 week), likely reflecting the difference in efficacy. The relative dose intensity was numerically higher in the comparator arm, which could potentially reflect a difference in tolerability.

Notable differences across arms in pivotal Study 309 for eribulin vs. dacarbazine (underlined when higher) included: pyrexia, 28 vs. 14%; nausea + vomiting, 59 vs. 70%; stomatitis, 14 vs. 5%; neutropenia AEs, 44 vs. 24%; thrombocytopenia, 6 vs. 28%; peripheral neuropathy, 37 vs. 15%; headache, 18 vs. 9%; dysgeusia, 8 vs. 2%; alopecia, 35 vs. 3%; and Infections and infestations SOC, 43 vs. 28%.

With regard to severe TEAEs (toxicity grade ≥ 3), relevantly higher frequencies were seen in the eribulin compared with the dacarbazine arm of Study 309 for neutropenia, infections, and peripheral neuropathy. Severe anaemia and thrombocytopenia were relevantly higher in the dacarbazine arm. In other parts grade ≥ 3 toxicities were comparable across arms.

SAE frequencies were similar across arms of Study 309. Of the fatal AEs, 2 cases of fatal neutropenic sepsis and septic shock in the STS population were considered related to eribulin treatment following review of narratives; both occurred in the pivotal Study 309. In the dacarbazine arm, all deaths were due to disease progression.

The overall frequency of treatment discontinuation due to AEs was higher in the eribulin arm compared with the dacarbazine arm (7.5 vs 4.9%).Apart from infections as a group, no meaningful differences were found between arms at the individual PT/SOC levels with regard to TEAEs leading to drug discontinuation, however.

For some of the major ADRs of eribulin, the frequencies were similar in the dacarbazine arm, e.g. fatigue/asthenia, musculo-/skeletal pain, anaemia and diarrhoea.

ADRs with higher frequency in the eribulin arm that may have major impact on the B/R assessment include peripheral neuropathy, neutropenia and infections and stomatitis. Alopecia may also be of some importance.

ADRs of specific interest

Pyrexia

In eribulin-treated patients of Study 309, the median duration of pyrexia was 2 days and events were of low grade in most cases (only 1% was grade ≥3). Pyrexia is therefore not considered likely to affect tolerability to an important extent. It is noted that while a large difference in overall frequency of pyrexia across arms in Study 309 was observed (28 vs 14%), the grade ≥ 3 frequencies were similar (<1%).

Peripheral neuropathy

The median time to onset of peripheral neuropathy appears shorter in the STS compared with the MBC population, around 20 weeks vs. 28 weeks. The reason for this is not obvious considering the similar values observed for e.g. dose intensity and relative dose intensity across the two populations, and also that breast cancer patients to a greater extent have received prior neurotoxic therapy with taxanes. However it is acknowledged that the smaller sample size in the STS (n= 226) compared with the MBC (n=1559) population may affect the estimates.

The lower frequencies of grade ≥3 events in pivotal study 309 and the STS population generally compared with the MBC population may be due to the longer exposure time in the MBC and potentially also other differences between populations such as prior therapies.

Similar to the MBC population the information on resolution of peripheral neuropathy is limited and the possibility of late reversibility of PN is still largely unknown. As part of the eribulin EU RMP, the MAH is currently conducting a study (E7389-A001-303) in order to generate information on the frequency and time to resolution of eribulin-induced or aggravated PN. The results of this study will provide more accurate data on the outcome of eribulin-induced PN (see RMP).

Neutropenia

Fatal cases of febrile neutropenia, neutropenic sepsis, sepsis and septic shock have been reported. Out of 1963 breast cancer and soft tissue sarcoma patients who received eribulin at the recommended dose in clinical trials there was one fatal event each of neutropenic sepsis (0.1%) and febrile neutropenia (0.1%). In addition there were 3 fatal events of sepsis (0.2%) and one of septic shock (0.1%).

Severe neutropenia may be managed by the use of G-CSF or equivalent at the physician's discretion in accordance with relevant guidelines. 18% and 13% of eribulin treated patients received G-CSF in the two phase 3 breast cancer studies (Studies 305 and 301, respectively). In the phase 3 sarcoma study (Study 309), 26% of the eribulin treated patients received G-CSF.

QT prolongation

A relevantly higher incidence of QT prolongation was observed in both arms of Study 309, and in the STS, compared with the MBC population. There was no obvious explanation for this finding, as pre-treatment with (cardiotoxic) anthracycline was an inclusion criterion in the pivotal breast cancer studies 305 and 301, as well as in the sarcoma Study 309. It could be hypothesised that sarcoma patients might have received generally higher doses of anthracycline due to different treatment practices in the two indications, leading to larger variability in transduction in myocardia, but no data to substantiate that notion have been presented. As the frequency in the dacarbazine arm of Study 309 is similar to the frequency in the eribulin-treated overall STS population, no strong signal is considered received by the 1.7% difference between arms in Study 309, however.

To date, the QT prolonging potential of eribulin has not been definitively investigated, since a thorough QTc study could not be performed for this cytotoxic agent and the dedicated QT Study 110, which was an uncontrolled open-label ECG study in 26 patients, could not exclude an effect on QT. In addition, the Non-Clinical data available at market authorisation were non-informative due to poor tolerability in animals. The current SmPC text regarding QT prolongation refers to Study 110 and gives precautions for use.

Electrolytes

Low potassium and low phosphorous was observed in higher frequency in the eribulin treated STS-population compared with the MBC population, as well as in eribulin-treated patients compared with dacarbazine-treated patients in the pivotal study. The causes for this are unknown.

Liver function tests

Liver function tests abnormalities were generally (i.e. for ALT, AST ALP) less common in the STS setting compared with the MBC setting. Total bilirubin was slightly more frequent in Study 309 (1.8%, n= 4), but similar in the overall STS population (1%) compared with the MBC population (0.8%). Low albumin was seen more frequently in the STS population (2.2%) compared with 0.9% in the MBC, but also in the pivotal study.

Compared with the dacarbazine control arm, AST and bilirubin abnormalities were numerically higher, and ALT and ALP abnormalities numerically lower.

In conclusion, no important differences in liver function tests were observed for eribulin vs. dacarbazine in the STS setting. Compared with the MBC setting liver function tests abnormalities were generally less frequent (possibly due to shorter duration of exposure).

Subgroups

The safety profile of eribulin appears similar in the different histologic/anatomic subgroups and observed differences may likely be the result of differences in exposure and/or underlying disease characteristics.

There were 151 male patients treated with eribulin in the STS studies, thus constituting 37% of the STS population and 8% of the combined STS+MBC population (Integrated safety population).

Analyses of AEs by sex are confounded by the indications, ADI and LMS, which had different proportions of men and women as well as different treatment effect and time on therapy. In addition, differences in baseline characteristics in the STS population indicated slightly poorer prognosis in women compared with men (higher tumour grade, higher ECOG performance status, larger number of prior chemotherapy regimens). When this is taken into account, no important differences in safety profile across sexes are seen.

In an analysis of patients divided by age < 65 years vs. ≥ 65 years of age, only small differences (0.1-3%) were seen in the overall AE frequencies in the STS and the MBC populations. The only larger differences were seen in the STS population for fatal SAEs (n= 8/314; 2.5% vs. 6/90; 6.7%) and for TEAEs leading to study drug being withdrawn (n=13; 4.1% vs. n= 8; 8.9%). The numbers are small, however, and tolerability appears overall largely similar irrespective of age. On the basis of PK and safety data, no specific dose adjustments are recommended based on the age of the subject.

As 18% (n=283/1559) of the patients in the MBC population and 22% (n=90/404) in the STS population were aged ≥ 65 years, "elderly" has now been removed as missing information in the RMP.

Study 206

The breast cancer study 206, evaluating eribulin as first-line treatment for metastatic breast cancer, was not previously submitted and was therefore assessed in this procedure.

An unusually high incidence of treatment-emergent peripheral neuropathy (61%) in Study 206 compared with the overall MBC population (41%) was noted. The relatively small increases in duration of exposure in Study 206 (median 137 days; 7 cycles) compared with studies 301 (125 days; 6 cycles) and 305 (118 days; 5 cycles) might provide an explanation. The considerably higher frequency of peripheral neuropathy in Study 206 could also, at least in part, be a chance finding due to the relatively small sample size (n= 56).

Drug-drug interactions

No AEs of drug interaction were reported in Study 309, Study 207 or Study 217. Nonclinical in vitro studies indicate CYP3A4 as the major pathway for eribulin mesilate metabolism, and a low potential for clinical drug-drug interactions caused by eribulin mesilate via inhibition or induction.

Until further data are available, concomitant medications that are metabolized through liver CYP3A4 pathways that have a narrow therapeutic window should be used with caution with eribulin mesilate. In addition, drugs (including herbal supplements or grapefruit juice) that demonstrate potent CYP3A4 inhibition or CYP3A4 induction should be administered with caution, at a low dose whenever possible.

SmPC

The new table of ADRs in the SmPC, section 4.8 is based on the combined STS and MBC populations. For some ADRs the frequencies have therefore decreased. As the STS comprises only 21% of the total safety population, the decreases are small, however. Important differences across therapeutic settings are adequately reflected in section 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

No new safety concerns were identified for eribulin in the STS setting compared with the previously approved MBC setting. Eribulin ADRs of importance to the B/R assessment include peripheral neuropathy, neutropenia and infections, stomatitis and alopecia. For some major ADRs of eribulin, the frequencies were similar in the dacarbazine arm of Study 309, e.g. fatigue/asthenia, musculo-/skeletal pain, anaemia and diarrhoea. The dacarbazine arm had more nausea and vomiting and thrombocytopenia.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and/or CHMP.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	Myelosuppresion and associated infections Peripheral neuropathy Nausea/vomiting Depression & Insomnia Tachycardia Disseminated intravascular coagulation
Important potential risks	Adverse Pregnancy Outcomes Male infertility Gastrointestinal perforation
Missing information	Hepatic impairment ~~Renal impairment~~ Cardiovascular impairment ~~Elderly~~ ~~Male patients~~ Pregnant women Paediatric and Adolescent population

The following areas of missing information have been removed:

- Study 106 in patients with different stages of renal impairment has been completed. The results of this study have been assessed in variation II/23. Thus, the area of missing information regarding renal impairment is considered filled.
- Elderly and male patients, since these are no longer considered to represent areas of missing information.

Pharmacovigilance plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
E7389-A001-303 (ACCRU): A Randomized Phase III Trial of Eribulin Compared to Standard Weekly Paclitaxel as First- or Second-Line Therapy for Locally Recurrent or Metastatic Breast Cancer (3)	To capture data on frequency of and time to resolution of eribulin-induced or aggravated peripheral neuropathy: • Clearly define the onset, frequency and time to resolution in order to ensure more comprehensive collection of data; • Time to resolution	Peripheral neuropathy	Ongoing	Expected FY 2019

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
	will be defined as the time from onset (or worsening from baseline) to the date of resolution (defined as neuropathy ended or returned to baseline); • Continue to follow up patients for peripheral neuropathy until death (follow-up every 12 weeks as per overall survival follow-up schedule), recognising that the data will be confounded due to new post-study treatment regimens.			

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Myelosuppression	Warning in section 4.4 of SmPC that dose dependent myelosuppression may occur and that monitoring of blood counts should be performed on all patients prior to each dose of eribulin. Also patients with hepatic impairment may experience a higher incidence of grade 4 neutropenia or febrile neutropenia. Information on incidence myelosuppression and associated infection also in section 4.8 of SmPC	None
Peripheral neuropathy	Warning in section 4.4 of SmPC to monitor patients for signs of peripheral and sensory neuropathy. Information on incidence and course of neuropathy also in section 4.8 of SmPC	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Nausea/vomiting	Information on use of anti-emetics as required given in section 4.2 of SmPC Information on incidence of nausea and vomiting in section 4.8 of SmPC	None
Depression and insomnia	Information on incidence of insomnia and depression in section 4.8 of SmPC	None
Tachycardia	Information on incidence of tachycardia in section 4.8 of SmPC	None
Disseminated intravascular coagulation	Information on occurrence of DIC has been added to section 4.8 of SmPC	None
Adverse pregnancy outcomes	Warning to avoid eribulin in pregnancy unless benefit outweighs the risks in section 4.6 of SmPC	None
Male infertility	Information on testicular toxicity and advice to male patients to conserve sperm prior to treatment given in section 4.6 of SmPC	None
Gastrointestinal perforation	Appropriate actions e.g. labelling updates will be taken as applicable.	None
Hepatic impairment	- The use of eribulin in patients with severe hepatic impairment (Child-Pugh C) has not been studied. Reduction of the starting dose in patients with mild hepatic impairment (Child-Pugh A) and moderate hepatic impairment (Child-Pugh B) is recommended.	None
~~**Renal impairment**~~	~~- Patients with severely impaired renal function (creatinine clearance <40 ml/min) may need a reduction of the dose. The optimal dose for this patient groups remains to be established. Caution and close safety monitoring is advised (section 4.2 of the SmPC).~~	~~None~~
Cardiovascular impairment	- Eribulin has not been studied in population with significant cardiovascular impairment and patients with history of congestive heart failure > NYHA Grade II, unstable angina or myocardial infarction within the past six months, or serious cardiac arrhythmia were excluded from the studies.- Any adverse events reported in patients with cardiac impairment will be closely monitored in the post-marketing environment	None
~~**Elderly**~~	~~- Information that no dose adjustments are recommended based for elderly patients is given in sections 4.2 and 4.8 of the SmPC.~~	~~None~~

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
~~**Male patients**~~	~~- Information on testicular toxicity and advice to male patients to conserve sperm prior to treatment is given in section 4.6 of SmPC.~~	~~None~~
Pregnant women	- Information that there are no data on the use of eribulin in pregnant women, that eribulin should not be used during pregnancy unless clearly necessary and after a careful consideration of the needs of the mother and the risk to the foetus is provided in section 4.6 of the SmPC.	None
Paediatric and adolescent population	- Information that there is no relevant use of eribulin in children and adolescents in the indication of breast cancer is given in section 4.2 of the SmPC.	None

Routine pharmacovigilance requires the monitoring of suspected adverse reactions to medicinal products. Annex I of the Risk Management Plan (RMP) template, which is to be supplied in electronic format, provides an interface between the RMP, Eudravigilance and EPITT, the European Pharmacovigilance Issues Tracking Tool, to facilitate the monitoring of identified and potential risks and related risk management activities. Please could you send an updated version of Annex I of the RMP template, reflecting the final RMP agreed with the CHMP at the time of the Opinion, to h-eurmp-evinterface@emea.europa.eu within 30 calendar days of the receipt of the Opinion.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable as the changes to the leaflet were considered minimal.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The application formally rests on the pivotal 309 study: a randomized (1:1), open-label, multi-centre, Phase III study comparing eribulin (n=228) to dacarbazine (n=224) in patients previously treated for locally advanced and/or metastatic tumours of either the adipocytic subtype (liposarcoma [ADI]) or of smooth muscle origin (leiomyosarcoma [LMS]). The primary endpoint was OS.

The study met its primary objective with an estimated reduction of death of 23 % in favour of eribulin to that of the control (HR 0.77 [95% CI 0.618, 0.954]; p=0.017) with a median gain of 2 months (13.5 months and 11.5 months respectively).

As the subgroup analyses for OS and PFS clearly indicated a differential benefit between the ADI and LMS (ADI [OS HR 0.51; PFS HR 0.52] vs. LMS [OS HR 0.9; PFS HR 1.1]), separate baseline and outcome data for the two subtypes including subgroup analyses were requested:

Adipocytic sarcoma (ADI)

It is concluded that the OS benefit for eribulin over dacarbazine is entirely driven by the patients with the ADI subtype (HR 0.51 (95% CI 0.346, 0.753), P=0.0006) with a median OS of about 16 months for the eribulin arm compared with approximately 8 months for the dacarbazine arm. In addition, a benefit in PFS for this subtype can be observed (median 2.9 months vs. 1.7 months in the dacarbazine arm with a HR of 0.52 (95% CI 0.346; 0.784, P=0.0015).

The different subtypes of ADI (dedifferentiated, mixed/round cell or pleomorphic) may be viewed as biologically different but the small sample size and absence of preformed hypotheses make further analyses less than meaningful. Thus it is accepted that activity has been shown irrespective of ADI subtype.

Leiomyosarcoma (LMS)

Evidence of a benefit of eribulin over dacarbazine has not been shown in the LMS population. No difference at all between the two treatment arms is observed. The HR is 0.93 (95% CI 0.714, 1.203; P=0.57) for OS with a median of about 13 months in both arms. For PFS the HR is 1.07 (95% CI 0.835, 1.375; P=0.585) with a similar median of about 2.5 months.

The apparent difference, especially in PFS between uterine and non-uterine sarcoma is noticed. This is an unexpected finding from a tumour biology perspective as currently described and from the perspective of “non-activity” of dacarbazine and eribulin is rather interpreted as reflecting differences in baseline prognostic factors.

The MAH has been unable to provide evidence that dacarbazine is meaningfully active in LMS. If this actually was the case, i.e. that similarity in PFS (HR 1.07) reflected a meaningful delay in progression for both study arms vs. a virtual placebo, then it would be expected that post progression survival would be prolonged in the eribulin arm, analogous to findings in breast cancer and ADI. This is however not the case. Therefore, the most reasonable interpretation is that neither dacarbazine nor eribulin is meaningfully active in LMS.

Uncertainty in the knowledge about the beneficial effects

In the overall population there is a lack of substantial support of a benefit of eribulin compared to dacarbazine in STS aside from the demonstrated OS gain. The mechanistic rationale to the differential benefit between ADI and LMS is lacking.

Risks

Unfavourable effects

The eribulin safety profile in the studied soft tissue sarcoma (STS) population (Studies 309, 217 and 207) was generally similar to that seen in the previously approved metastatic breast cancer (MBC) setting. No new safety concerns were identified.

For many ADRs, the AE frequencies were numerically or significantly lower in the STS setting compared to the MBC setting. This could at least partly be explained by a shorter duration of exposure. For a smaller

number of ADRs, relevantly higher frequencies were seen in the STS compared with the MBC population. These include pyrexia (27 vs. 20%), stomatitis (17 vs 9%), and fatigue/asthenia (60 vs. 51%).

Notable differences across arms in pivotal Study 309 for eribulin vs. dacarbazine included: pyrexia, 28 vs. 14%; nausea + vomiting, 59 vs. 70%; stomatitis, 14 vs. 5%; neutropenia, 44 vs. 24%; neutropenia including laboratory abnormalities, 70 vs 43%; thrombocytopenia, 6 vs. 28%; peripheral neuropathy, 37 vs. 15%; headache, 18 vs. 9%; dysgeusia, 8 vs. 2%; alopecia, 35 vs. 3%; and Infections and infestations SOC, 43 vs. 28%.

For some ADRs related to tolerability the AE frequencies were similar across study arms. These include fatigue/asthenia (65 vs. 61%), musculo-/skeletal pain (46 vs. 40%), anaemia (30 vs. 31%) and diarrhoea (17 vs 16%).

The incidence of pyrexia in eribulin-treated patients in Study309 was highest (14-12%) in the first two cycles, following which the incidence decreased substantially. Median duration was 2 days and only 1% was grade ≥3, making these events less likely to affect the overall tolerability.

With regard to severe TEAEs (toxicity grade ≥ 3), relevantly higher frequencies were seen in the eribulin compared with the dacarbazine arm of Study 309 for neutropenia, infections, and peripheral neuropathy. Severe anaemia and thrombocytopenia were relevantly higher in the dacarbazine arm. In other parts grade ≥ 3 toxicities were comparable across arms.

SAE frequencies were similar across arms of Study 309. There were 2 vs. 0 treatment-related deaths in the eribulin vs. dacarbazine arm. These were due to neutropenic sepsis and septic shock. Treatment discontinuation due to AEs was higher in the eribulin arm compared with the dacarbazine arm (7.5 vs 4.9%). However apart from infections as a group, no meaningful differences were found between arms at the individual PT/SOC levels with regard to TEAEs leading to drug discontinuation,.

The safety profile of eribulin appears similar in the different histologic and histologic-anatomic subgroups (ADI, LMS; Uterine LMS, Non-uterine LMS) and the observed differences across subgroups may be the result of differences in exposure and/or in the underlying disease.

Uncertainty in the knowledge about the unfavourable effects

Currently the QT prolonging potential of eribulin is unknown, since no thorough QTc study has been performed and the Non-Clinical available data at market authorisation were non-informative due to poor tolerability in animals. The current SmPC text regarding QT prolongation refers to an uncontrolled open-label ECG study in 26 patients and gives precautions for use.

Similar to the MBC population the information on resolution of peripheral neuropathy is limited and the possibility of late reversibility of peripheral neuropathy is still largely unknown. As part of the eribulin EU RMP, the MAH is currently conducting a study in order to generate information on the frequency and time to resolution of eribulin-induced or aggravated peripheral neuropathy.

Effects Table

Table 52: Effects table for HALAVEN (eribulin mesilate) for the treatment of soft tissue sarcoma (cut-off date: 02 Jan 2015)

Effect	Unit	Experimental: Eribulin	Control: Dacarbazine	Relative outcome	Comments/ Uncertainties/ Strength of evidence
Favourable Effects					
ITT		**n = 228**	**n = 224**	**HR (95%CI) p-value**	
OS	months	13.5 (95% CI: 10.9,15.6	11.5 (95% CI: 9.6, 13.0)	0.768 (95%CI 0.618, 0.954) P=0.0169	Primary endpoint. Of clinical relevance and would meet an unmet medical need. Lack of support.
PFS	months	2.6 (95% CI:1.9, 2.8)	2.6 (95% CI:1.8, 2.7)	0.877 (95%CI 0.710, 1.085) P=0.2287	Secondary endpoint HR 0.88 may be indicative of an effect although not translated in any difference in medians.
ADI		**n=71**	**n=72**		
OS	months	15.6	8.4	0.51 (95% CI 0.346, 0.753) P=0.0006	Pre-planned subgroup analysis Of definite high clinical relevance and would meet an unmet medical need.
PFS	months	2.9	1.7	0.52 (95% CI 0.346, 0.784 P=0.0015)	Pre-planned subgroup analysis HR indicative of a definite clinical relevance
LMS		**n=157**	**n=152**		
OS	months	12.7	13.0	0.93 (95% CI 0.714, 1.203) P=0.5730	Pre-planned subgroup analysis No difference
PFS	months	2.2	2.6	1.07 (95% CI 0.835, 1.375) P=0.5848	Pre-planned subgroup analysis No difference
Unfavourable Effects					
Safety set		**n= 226**	**n = 224**	**Difference**	
Severe TEAE (grade ≥ 3)	%	67.3	56.3	11.0	Corresponds to approx. 10% higher frequency of haematological grade ≥3 events in the eribulin arm.
Peripheral neuropathy	%	36.7	15.2	21.5	Grade ≥3= 3.1 %
Neutropenia (TEAE)	%	43.8	23.7	20.1	Grade ≥3= 35.4%
Infections (SOC)	%	43.4	27.7	15.7	Grade ≥3 events of infections were 10 vs. 5%
Stomatitis	%	13.7	4.9	8.8	
Alopecia	%	35.0	2.7	32.3	

*: Frequencies for fatigue and asthenia, respectively, are added together in this presentation; some patients may have reported both items, the true frequency for the combined item may therefore be smaller.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

While a statistically significant benefit in OS in the overall population has been demonstrated in favour of eribulin vs. dacarbazine with a reduction of death of 23 %, it becomes clear based on subgroup analyses per histology subtype that the OS benefit for eribulin over dacarbazine is entirely driven by the patients with the ADI subtype with a reduction of death of about 50 % and approximately 8 months median gain.

Important ADRs of eribulin that had relevantly higher incidence in the eribulin compared with the dacarbazine arm of Study 309 included peripheral neuropathy, neutropenia, infections, stomatitis and alopecia.

Neutropenia is routinely managed by oncologists and may as such be of less importance to the B/R balance, except in cases of hospitalisation due to e.g. febrile neutropenia. Infections related to neutropenia are of concern, however, and eribulin is associated with deaths due to infections in a few percent of patients; less than 1 percent in the present sarcoma setting. Peripheral neuropathy is debilitating and unpleasant (sometimes painful), and may affect patients' activities of daily living and quality of life. Stomatitis is a painful condition that affects the possibility to eat normal food and quality of life.

Benefit-risk balance

A differential benefit between ADI and LMS was identified in the pre-planned subgroup analysis. In further requested analyses, a benefit in OS and PFS favouring eribulin over dacarbazine was convincingly shown in the ADI population and it is accepted that activity has been shown irrespective of ADI subtype (dedifferentiated, mixed/round cell or pleomorphic).

There is no evidence that eribulin has a superior efficacy over dacarbazine in the LMS population.

Discussion on the Benefit-Risk Balance

Due to the overall rarity of STS and the heterogeneity within in terms of histology, the challenges in performing large randomised studies are recognised. Hence a regimen that can demonstrate an OS benefit would meet a high medical need.

Although the 309 study met its primary objective with an estimated reduction of death of 23 % in favour of eribulin in the overall population, the subgroup analysis identified a differential response between the two subtypes. A benefit of eribulin over dacarbazine has convincingly been demonstrated in the ADI subtype which is of high clinical relevance. This however, has not been shown in the LMS population. The MAH has been unable to provide evidence that dacarbazine is meaningfully active in LMS and therefore the most reasonable interpretation is that neither dacarbazine nor eribulin is meaningfully active in LMS.

As the post progression and therefore post treatment effects on survival are of major interest, further studies are strongly encouraged.

The initially proposed indication encompassed STS not subtype specified. The MAH proposed a revised indication:

HALAVEN is also indicated for the treatment of adult patients with unresectable liposarcoma or leiomyosarcoma who have received prior systemic therapy for advanced or metastatic disease (see section 5.1).

This has not been accepted as no benefit has been demonstrated in LMS. Moreover, "prior systemic therapy" should reflect that standard chemotherapy is based on anthracyclines as the 1st line treatment. The following wording has been proposed:

HALAVEN is ~~also~~ indicated for the treatment of adult patients with unresectable liposarcoma ~~or leiomyosarcoma~~ who have received prior ***anthracycline containing therapy (unless unsuitable)*** *~~systemic therapy~~ for advanced or metastatic disease (see section 5.1).*

Conclusion

The B/R is considered positive exclusively in the ADI population.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of unresectable liposarcoma in adult patients who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are updated with the PK, efficacy and safety information. The Package Leaflet and RMP are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the PI in line with the latest QRD template version 9.1.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Halaven (eribulin) is not similar to Yondelis (trabectedin) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include the treatment of unresectable liposarcoma in adult patients who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC are updated with the PK, efficacy and safety information. The Package Leaflet and RMP are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the PI in line with the latest QRD template version 9.1.

Summary

Please refer to the Scientific Discussion Halaven-H-C-2084-II-028.