Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Eribulin Mesilate

Proprietary Product Name: Halaven

Sponsor: Eisai Australia Pty Ltd

Date of first round report: 06 May 2016

Date of second round report: Not applicable

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

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List of common abbreviations

Abbreviations	Meaning
AE	Adverse Event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALKP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute neutrophil count
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate Transaminase
AUC	Area under the curve
BIL	Bilirubin
BUN	Blood urea nitrogen
CBR	Clinical Benefit Rate
CI	Confidence interval
Cmax	Maximum concentration
Cmin	Minimum concentration
CMI	Consumer Medicines Information
CL	Clearance
CR	Complete Response
CrCl	Creatinine clearance
CT	X-Ray Computed Tomography
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
DCR	Disease Control Rate
dSD	Durable stable disease

Abbreviations	Meaning
ECG	Electrocardiograph
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIT	Gastrointestinal tract
ICH	International Conference on Harmonisation
L	Litre(s)
LDH	Lactate Dehydrogenase
LFTs	Liver function tests
MBC	Metastatic breast cancer
MEDRA	Medical dictionary for regulatory activities
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall Survival
PD	Pharmacodynamics
PFR12wks	Progression-free survival rate at 12 weeks
PFS	Progression free survival
PI	Product Information
PK	Pharmacokinetics
PR	Partial Response
PS	Performance status
QoL	Quality of Life
RECIST	Response evaluation criteria in solid tumours

Abbreviations	Meaning
SAE	Serious Adverse Event
SD	Stable Disease
STS	Soft Tissue Sarcoma
TGA	Therapeutic Goods Administration
Tmax	Time of maximum concentration
WHO	World Health Organisation

1. Introduction

This is an abbreviated submission to extend the indications of the product.

1.1. Drug class and therapeutic indication

Eribulin is a cytotoxic agent, which acts by binding to tubulin, thereby blocking formation of microtubules and preventing mitosis and cell proliferation.

The currently approved indication is:

> *'For the treatment of patients with locally advanced or metastatic breast cancer, who have progressed after at least one chemotherapeutic regimen for advanced disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting unless these are contraindicated.'*

The proposed additional indication is:

> *'For the treatment of patients with unresectable soft tissue sarcoma (STS), who have received prior chemotherapy for advanced or metastatic disease. Efficacy and safety have been established primarily in patients with leiomyosarcoma and liposarcoma.'*

1.2. Dosage forms and strengths

The only dosage form/strength currently registered is a 1 mg in 2 mL solution for injection. No new dosage forms or strengths are proposed.

1.3. Dosage and administration

The proposed starting dose for the new indication is 1.4 mg/m^2 administered IV over 2 to 5 minutes on Days 1 and 8 of a 21 day cycle. This is the same dose currently approved for use in breast cancer.

1.4. Other proposed changes to the PI

Most of the proposed changes to the PI are based on new clinical data submitted in support of the new indication. Some additional minor editorial changes are also proposed throughout the PI.

2. Clinical rationale

Soft tissue sarcomas (STS) are a heterogeneous group of malignant tumours arising in tissues derived from the embryonic mesoderm (for example, skeletal muscle, smooth muscle, adipose tissue and blood vessels). The 2002 World Health Organisation (WHO) classification of soft tissue tumours (both benign and malignant) lists over 50 separate soft tissue malignancies. The most common of these subtypes in adults are undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma and synovial sarcoma (1).

Comment: The WHO classification system was revised in 2013. However, the 2002 system would have been current at the time the studies in this submission were performed.

STS can develop anywhere in the body but most commonly occurs in the limbs and limb girdles and in the abdomen. They are rare, comprising about 1% of all malignancies in adults and 7-10% of paediatric cancers. The tumours usually present as a painless slowly enlarging mass (1,

2). There are various systems used for the grading and staging of STS. A commonly used one is that produced by the American Joint Committee on Cancer (AJCC). The AJCC system used for the pivotal study in this submission is shown in Table 1: American Joint Committee on Cancer Staging of Soft Tissue Sarcoma. Peripheral STS most commonly metastasize to the lungs while those arising in the abdomen commonly spread to the liver and peritoneum (1).

Table 1: American Joint Committee on Cancer Staging of Soft Tissue Sarcoma

Tumour Grade (G)		
GX	Grade cannot be assessed	
G1	Well differentiated	
G2	Moderately differentiated	
G3	Poorly differentiated	
G4	Poorly differentiated or undifferentiated	
Primary Tumour (T)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Tumour 5 cm or less in greatest dimension	
	T1a	Superficial tumour
	T1b	Deep tumour
T2	Tumour 5 cm or larger in greatest dimension	
	T2a	Superficial tumour
	T2b	Deep tumour
[Note: Superficial tumour is located exclusively above the superficial fascia without invasion of the fascia; deep tumour is located either exclusively beneath the superficial fascia, or superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumours.]		
Regional lymph nodes (N)*		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastases	
N1	Regional lymph node metastasis [Note: Presence of positive nodes (N1) is considered stage IV]	
Distant Metastasis (M)		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	

AJCC Stage Groupings				
Stage I	G1	T1a	N0	M0
	G1	T1b	N0	M0
	G1	T2a	N0	M0
	G1	T2b	N0	M0
	G2	T1a	N0	M0
	G2	T1b	N0	M0
	G2	T2a	N0	M0

AJCC Stage Groupings				
	G2	T2b	N0	M0
Stage II	G3	T1a	N0	M0
	G3	T1b	N0	M0
	G3	T2a	N0	M0
	G4	T1a	N0	M0
	G4	T1b	N0	M0
	G4	T2a	N0	M0
Stage III	G3	T2b	N0	M0
	G4	T2b	N0	M0
Stage IV	Any G	Any T	N1	M0
	Any G	Any T	N0	M1

AJCC, American Joint Committee on Cancer; TNM, tumour node metastasis.

**Laterality does not affect the N classification. If a lymph node dissection is performed, then pathologic evaluation would ordinarily include at least eight nodes.*

Soft tissue sarcoma. In: American Joint Committee on Cancer. AJCC Cancer Staging Manual. 6th Ed. New York, NY: Springer, 2002, pp 193-197.

Adverse prognostic factors in subjects with STS include large tumour size, high grade, advanced stage, older age and histological subtype (3).

2.1. Treatment

A number of current clinical practice guidelines provide evidence-based recommendations regarding appropriate treatment of STS in adults. These include guidelines produced by:

- The National Comprehensive Cancer Network (NCCN) in the United States (2016) (1);
- The Cancer Council of Australia in collaboration with the Australasian Sarcoma Study Group (2014) (1).
- The European Society of Medical Oncology (2014)(2);

The mainstay of treatment for STS is surgery. Radiotherapy improves local control in subjects with resectable disease and can be used alone in subjects in whom surgery is considered inappropriate (2, 3). Systemic chemotherapy is used in subjects with unresectable disease.

The current clinical practice guidelines generally recommend anthracycline-based chemotherapy as first-line treatment for unresectable/ metastatic STS. The Australian guideline recommends doxorubicin, either alone or in combination with ifosfamide. There is no standard second or later line treatment. The various guidelines refer to a large number of agents that can be considered for second or later-line therapy. These include ifosfamide (if not used in first line), trabectedin (not registered in Australia), gemcitabine, dacarbazine and pazopanib (excluding subjects with adipocytic sarcomas). The Australian guidelines recommend ifosfamide (if not used in first-line) and then dacarbazine.

In Australia, agents registered for the treatment of STS include various grandfathered agents such as doxorubicin, epirubicin, ifosfamide and dacarbazine. These agents all have a broad STS indication, not restricted by line of therapy or histological subtype. The tyrosine kinase inhibitor pazopanib is registered for use as second or later line therapy of STS, excluding GIST and adipocytic sarcomas.

The rationale for the submission is based on the lack of established therapies for STS after failure of first line therapy.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- One pivotal Phase III randomised controlled trial in subjects with STS (Study 309);
- Two single-arm Phase II studies in subjects with STS (studies 207 and 217);
- One single-arm Phase II study in subjects with breast cancer (Study 206). This study contained safety data not previously reviewed by the TGA.
- Two population pharmacokinetic analyses.
- Literature references.

3.2. Paediatric data

The submission did not include paediatric data. The sponsor has a paediatric investigation plan (PIP) agreed with the EMA, which involves the conduct of three clinical studies in children with STS. The plan is due to be completed by 2029 (10). According to the TGA submission, an initial report is due to be submitted by September 2017.In the United States, the sponsor has a waiver from the FDA for paediatric data. The waiver was granted on the grounds that the FDA has designated eribulin as an orphan drug for the treatment of STS.

3.3. Good clinical practice

The clinical study reports included in the submission all included an assurance that the studies were conducted in compliance with the ICH E6 Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The submission included three clinical studies in STS: 207, 217 and 309. In each of these studies sparse PK sampling was performed as follows:

- Study 207: a total of 7 samples were collected from each subject in Cycle 1 only. Time points for collection were: prior to eribulin administration, and then at any time within each of the following time windows after the end eribulin administration – 5-10 minutes, 15-90 minutes, 2-4 h, 4-7 h, 7-14 h and 16-50 h.
- Study 217: trough samples were collected prior to eribulin administration on Days 1 and 8 of cycles 1 and 2.
- Study 309 (eribulin arm only): samples were collected on Cycle 1/Day 1 (end of infusion, and at 0.5-6 h and 24-120 h after the end of the infusion), Cycle 1/Day 8 (pre-dose and at the end of the infusion), Cycle 2/Day 1 (end of infusion, and at 0.5-6 h and 24-120 h after the end of the infusion), and Cycle 2/Day 8 (pre-dose and at the end of the infusion).

Eribulin was quantified using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

The PK data collected were used in two population PK and PK/PD analyses:

- Report No CPMS-E7389-003R (dated 17 April 2013) combined data from Study 207 with data from eight previously evaluated Phase I and Phase II studies.
- Report No CPMS-E7389-005R (dated 18 June 2015) combined data from studies 207, 217 and 309 with data from seven other previously evaluated Phase I and Phase II studies.

4.2. Evaluator's overall conclusions on pharmacokinetics

The PK properties of eribulin as described by the population PK analyses were consistent with those previously determined. Findings included the following:

- Typical clearance was estimated to be approximately 2.8 L/h.
- Markers of impaired hepatic function (decreased albumin, increased LFTs) were associated with increased exposure to eribulin.
- Tumour type (sarcoma versus other tumours) or type of sarcoma did not affect eribulin PK.
- Eribulin PK was not affected by age, gender, race, ECOG status or creatinine clearance.

A number of population PK/PD analyses were also undertaken. Findings of these analyses included the following:

- No relationship was identified between eribulin exposure and efficacy endpoints (PFS, overall survival, overall response or reduction in tumour size);
- Subjects who developed certain AEs (neuropathy, fatigue) had higher eribulin exposure compared to other subjects;
- A model was developed that adequately described the effect of eribulin on absolute neutrophil count. Inhibition of neutrophil proliferation by eribulin was higher in Japanese subjects and in subjects receiving G-CSF treatment.
- No relationship was identified between eribulin exposure and QT interval.

5. Pharmacodynamics

Apart from the PK/PD analyses, no new clinical pharmacodynamic data were included in the submission.

6. Dosage selection for the pivotal studies

The dose of eribulin selected for all the STS studies was 1.4 mg/m^2 IV over 2-5 minutes on Days 1 and 8 of a 21 day cycle.

The choice was based on findings of Phase I and Phase II studies conducted prior to the STS studies. The maximum tolerated dose (MTD) of eribulin was determined to be 1.4 mg/m^2 when administered as a bolus on Days 1, 8, and 15 of a 28 day cycle. However, in subsequent Phase II studies, the Day 15 dose in the 28 day cycle had to be omitted in more than 50% of cases due to hematologic toxicity. Efficacy was not affected by skipping the Day 15 dose. It was therefore concluded that 1.4 mg/m^2 on Days 1 and 8 of a 21 day cycle was likely to be the optimal dose and schedule. This was the dosage regimen approved for use in breast cancer.

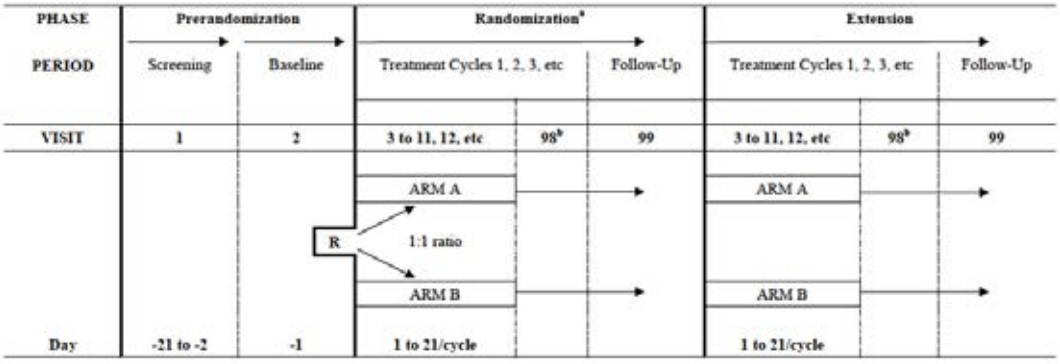
7. Clinical efficacy

7.1. Pivotal efficacy study (Study 309)

7.1.1. Study design, objectives, locations and dates

Study 309 was a randomised, open-label, Phase III trial with two parallel groups; eribulin (Arm A) versus dacarbazine (Arm B). A study schema is shown in Figure 1.

Figure 1: Study 309 Study schema



R = randomization.
Arm A = Eribulin mesilate 1.4 mg/m^2 IV on Days 1 and 8, every 21 days.
Arm B = Dacarbazine IV on Day 1, every 21 days. The starting dose must be selected from one of the following doses: 850 mg/m^2 or 1,000 mg/m^2, or 1,200 mg/m^2.
a. The Randomization Phase will end at the time of data cut-off for the primary analysis when the target number of events has been observed. All subjects still on treatment with study treatment or are in survival follow-up will then enter the Extension Phase.
b. Off-treatment Visit.

The study included:

- A pre-randomisation phase, consisting of a screening visit (between days -21 and -2) and a baseline visit (either Day -1 or Day 1 of Cycle 1);
- A randomisation phase during which subjects in both arms received treatment in 21 day cycles until disease progression or unacceptable toxicity. Clinic visits occurred on Days 1, 8 15 of each 21 day cycle. Subjects who discontinued treatment had an 'off treatment visit' within 30 days following their final dose of study treatment. They then entered a follow-up period.

The 'randomisation phase' lasted until the time of data cut-off for the primary analysis (that is, until the target number of events had been observed). Subjects were then considered to be in an 'extension phase'. However, the visit schedule etc. did not change from that used in the randomisation phase.

The primary objective of the study was to compare overall survival (OS) in subjects with advanced STS (adipocytic sarcoma or leiomyosarcoma) when treated with eribulin (Arm A) or dacarbazine (Arm B).

Secondary objectives were to:

- Compare progression-free survival (PFS) between Arm A and Arm B;
- Compare PFS rate at 12 weeks (PFR12wks) between Arm A and Arm B;
- Compare the clinical benefit rate (CBR) between Arm A and Arm B;
- Compare the safety and tolerability between Arm A and Arm B;
- Characterize the population PK of eribulin in subjects with STS.

Exploratory objectives were to:

- Compare objective response rate (ORR), disease control rate (DCR), and durable stable disease (dSD) rate, between Arm A and Arm B;
- Explore the relationship between exposure to eribulin and pharmacodynamics biomarkers and efficacy;
- Explore the relationship between exposure to eribulin and AEs;
- Investigate and identify blood and tumour biomarkers which can be correlated with safety and efficacy endpoints;
- Compare quality of life (QoL) scores between Arm A and Arm B.

The study was conducted at 110 centres in 22 countries: USA (31 centres) Canada (3), Australia (3), Austria (2), Belgium (3), Denmark (1), France (8), Germany (7), Israel (4), Italy (9), Netherlands (2), Spain (7), UK (4), Argentina (1), Brazil (8), Czech Republic (4), Poland (1), Korea (5), Romania (2), Russia (1), Singapore (1) and Thailand (3).

The trial commenced in March 2011. The date for data cut-off for inclusion in the study report was 2 January 2015 and the study report itself was dated 22 June 2015. The study has been published (1).

7.1.2. Inclusion and exclusion criteria

Enrolment was restricted to adult subjects with liposarcoma or leiomyosarcoma, who had received at least two prior lines of therapy and had advanced disease incurable by surgery or radiotherapy. The restriction to subjects with liposarcoma or leiomyosarcoma was based on the findings of earlier phase II studies (see below). A subject was required to have tumour samples or slides available for an independent histological review (IHR). Enrolment was also restricted to subjects with good performance status (ECOG performance status of 0, 1 or 2; Table 2).

Table 2: Study 309 - Eastern Cooperative Oncology Group (ECOG) Performance Status

Scale	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Comment: The proposed indication is not restricted to subjects with liposarcoma or leiomyosarcoma. It also does not restrict treatment to subjects who have received at least two prior lines of systemic therapy.

7.1.3. Study treatments

Subjects were randomised (1:1) to receive one of the following two treatments:

- Eribulin 1.4 mg/m^2 IV over 2-5 minutes on Days 1 and 8 of a 21 day cycle. The dose could be injected as the undiluted solution (0.5 mg/ mL) or diluted in up to 100 mL of normal saline.
- Dacarbazine IV over 15-60 minutes on Day 1 of a 21 day cycle. The investigator could choose one of three starting doses: 850, 1,000 or 1,200 mg/m^2. The dose had to be selected for each subject prior to randomisation. The chosen dose was diluted to a final volume of 200-500 mL in normal saline or 5% glucose. The sponsor provided a commercially available formulation of dacarbazine (powder for injection) that was manufactured in Germany.

Doses of eribulin could be delayed or permanently reduced in the event of toxicity. Two levels of dose reduction were permissible: to 1.1 mg/m^2 and then to 0.7 mg/m^2. For dacarbazine, dose delays and dose reductions were in accordance with the prescribing information.

Treatment was to be continued until disease progression, development of unacceptable toxicity, withdrawal of consent, or sponsor discontinuation of the study. Subjects in the dacarbazine arm who developed progressive disease were not permitted to receive eribulin.

The sponsor justified the choice of dacarbazine as the comparator agent on the following grounds:

- Dacarbazine has been demonstrated to have activity in STS in several published studies;
- The drug is widely available and hence appropriate for a multinational trial;
- It was listed as a treatment option in both the NCCN and ESMO clinical practice guidelines for STS;
- The sponsor convened a global advisory board of experts in the field of sarcoma who agreed that dacarbazine was an acceptable comparator in the setting of advanced STS in subjects who have failed other standard therapies;
- The use of dacarbazine as the comparator was agreed with the FDA and EMA prior to the initiation of the study.

Comment: Published studies that have used dacarbazine as monotherapy in the treatment of STS are summarised in Table 3. The drug's reputation for efficacy in STS appears to have been based on early single-arm Phase II studies where the drug produced response rates of up to 18%. The drug has not been shown to produce a survival benefit. More recent studies have used dacarbazine as the comparator arm in trials of novel therapies. Response rates obtained with dacarbazine in these studies have been less impressive.

Dacarbazine continues to be listed in the NCCN and ESMO guidelines as an option for 2nd or later line chemotherapy. In addition, the current Australian guideline recommends the following: *For patients who have been exposed to both doxorubicin and ifosfamide, dacarbazine is considered the next most active approved agent.*
It is also noteworthy that other regulatory authorities with similar standards to the TGA, such as the FDA and EMA, have accepted dacarbazine monotherapy as an acceptable comparator given their approvals for trabectedin and eribulin.
As noted above, dacarbazine is registered in Australia for the treatment of STS.
Overall it is considered that the sponsor's choice of dacarbazine monotherapy as the comparator agent in the pivotal study is acceptable.

Table 3: Published studies of dacarbazine monotherapy in STS

Study	Design	Indication	N	Dacarbazine regimen	ORR	Median PFS	Median OS
Gottlieb 1976	Phase II Single-arm	STS	53	Various	**17%**	-	-
Buesa 1991	Phase II Single-arm	STS – various 2nd line	44	1200 mg/m^2 Day 1 of a 21-day cycle	**18%** (95% CI: 7-29%)	-	-
Holstein	Retrosp	STS –	14	1200 mg/m^2	**0%**	-	5 mths

Study	Design	Indication	N	Dacarbazine regimen	ORR	Median PFS	Median OS
1996	ective Case series	various 2nd line		Day 1 of a 21-day cycle			
Zucali 2008	Retrospective Case series	STS – various 2nd line	40	800 mg/m² on day 1; or 400 mg/m² on days 1 and 2; or 300 mg/m² on days 1, 2 and 3. 21-day cycle for all	**7.5%**	2 mths	13 mths
Garcia-del-Muro 2011	Phase II RCT Vs. gemcitabine + dacarbazine	STS – various 2nd line	52	1200 mg/m² Day 1 of a 21-day cycle	**4%** (95% CI: 0-13%)	2 mths	8.2 mths
Demetri 2016	Phase III RCT Vs. trabectedin	Liposarcoma Leimyosarcoma 2nd line	173	1000 mg/m² Day 1 of a 21-day cycle	**6.9%**	1.5 mths	12.9 mths

The design of the study was unusual in that it allowed investigators to choose one of three doses of dacarbazine. The sponsor justified this design on the following grounds:

- There is no generally accepted global consensus among physicians treating STS patients regarding the appropriate dose for dacarbazine;
- Although the highest response rate with dacarbazine was obtained with 1200 mg/m², haematological toxicity was dose limiting in some patients. Therefore investigators were provided with the option of using lower starting doses depending upon the subject's clinical status on entry to the study.
- The dacarbazine dosing was agreed with the FDA and EMA prior to the initiation of the study.

Comment: As shown in Table 3, a variety of dosage regimens have been used in published studies. None of the studies compared efficacy results between doses. Using cross-trial comparison there does not appear to be any obvious pattern of reduced efficacy with lower doses.

7.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Survival;
- Change in tumour size;
- Quality of life.

The primary efficacy outcome was overall survival (OS), measured from the date of randomisation until the date of death from any cause.

Secondary efficacy outcomes were:

- Progression-free survival (PFS), defined as the time from the date of randomisation to the date of first documentation of disease progression or date of death from any cause (whichever occurs first).
- The progression-free rate at 12 weeks (PFR12wks), defined as the proportion of subjects who are still alive without disease progression at 12 weeks from the date of randomization. Subjects were considered to be progression-free if the tumour assessment performed during Week 12 indicated stable disease (SD), partial response (PR), or complete response (CR). Anything else including a missing value was considered as not meeting progression-free status;
- Clinical benefit rate (CBR) defined as the proportion of subjects who had a best overall response of CR or PR or dSD (durable SD; that is, SD ≥ 11 weeks) during study.

Exploratory efficacy outcomes were:

- Objective response rate (ORR) defined as the proportion of subjects who have overall response of CR or PR.
- Disease control rate (DCR) defined as the proportion of subjects who have best overall response of CR, or PR, or SD.
- The durable stable disease (dSD) rate, defined as the proportion of subjects who have duration of SD ≥ 11 weeks.
- Quality of life (QoL) scores measured using the QLQ-C30 and the EQ-5D questionnaires.

Disease progression and response were assessed using the Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1 (1), as assessed by the investigators. There was no central or blinded assessment of imaging.

PFR12wks is a novel endpoint originally proposed by the EORTC Soft Tissue and Bone Sarcoma Group in 2002[13]. It is intended for use in Phase II studies to identify activity in new drugs, including those that may have only a *cytostatic* effect (that is, inhibition of tumour growth). Conventional response rate criteria typically only identify activity in drugs that have a *cytoreductive* effect (that is, cause tumour shrinkage). Based on previously published data the EORTC Group estimated that for second-line therapy in STS, a PFR12wks of ≥ 40% would suggest drug activity, and ≤ 20% would suggest inactivity.

Comment: PFR12wks was used as the primary endpoint in the Phase II studies of eribulin (see below), and was presumably included as a secondary endpoint in the pivotal study to allow comparison between trials.

The EORTC QLQ-C30 questionnaire is a validated cancer-specific 30-item questionnaire. It incorporates five functional scales (physical, role, cognitive, emotional and social) covered by 16 questions, three symptom scales (fatigue, pain and nausea/vomiting) covered by 6 questions, six single-question items (constipation, diarrhoea, sleep, dyspnoea, appetite and financial difficulties) and two questions addressing global health status. All scales and single-item measures range in score from 0 to 100. A high score on a functional scale represents a high level of functioning. A high score on global quality of life represents a high quality of life. A high score on the symptom scale or item represents a high level of symptomatic problems. A minimal clinically important difference is considered to be 5-10 points on the 100-point scale.

The EQ-5D is a generic measure of QoL. It consists of a questionnaire and a visual analogue scale (VAS). The questionnaire has five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each domain consists of one question for which the subject can choose one of three responses (for example, no problems, some problems, severe problems). Responses to the five domains were used to generate the Health Utility Index (HUI) which is scored

between -1 (worst imaginable health state) and 1 (best imaginable health state). The VAS asks the subject to rate his or her current health state from 0 ('worst imaginable health state') to 100 ('best imaginable health state').

Tumour assessments (CT or MRI of chest/abdomen/pelvis and other areas of known disease at screening plus any areas of newly suspected disease) were to be performed every 6 weeks (for the 1st 12 weeks), and then every 9 weeks, or sooner if clinically indicated, until disease progression was confirmed. Subjects who discontinued study treatment without disease progression underwent tumour assessment according to the same schedule, until disease progression or commencement of another anticancer therapy. Subjects were followed up for survival every 12 weeks after the off-treatment visit. The QoL questionnaires were administered at baseline, on Day 1 of each treatment cycle and at the off-treatment visit.

Comment: Apart from PFS12wks the endpoints chosen for the study were standard for oncology studies. Assessment of disease response and progression was not blinded to treatment allocation and hence the secondary endpoints may have been open to some bias.

7.1.5. Randomisation and blinding methods

Subjects were randomised (1:1) to either eribulin or dacarbazine. Randomisation was stratified by:

- Histology (adipocytic sarcoma or leiomyosarcoma);
- Geographical 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).

An independent statistician provided the randomisation schedule. Subjects were allocated via an interactive voice/web response system (IV/WRS).

There was no blinding to treatment allocation in the study.

7.1.6. Analysis populations

The following analysis sets were defined:

- The Full Analysis Set (Intent-to-treat [ITT] Analysis Set) included all subjects who were randomised. This was the primary analysis set for all efficacy evaluations. For analyses subjects were included in the treatment arm to which they were randomised.
- The Per Protocol Analysis Set included those subjects who received at least one dose of study treatment, and had no major protocol violations, which included but were not limited to the following:
- Deviation from inclusion criteria #1 to 3[1];
- Treated with the incorrect study treatment instead of the randomised treatment;
- Subjects who were found to be ineligible based upon independent histologic review were excluded from this analysis set.

[1] 1. Histologically confirmed diagnosis of STS of high or intermediate grade with one of the following histological subtypes: Adipocytic sarcoma, including i) dedifferentiated, ii) myxoid, iii) round cell, iv) pleomorphic subtype; or leiomyosarcoma, Tumour histology performed at diagnosis for study entry, although formalin-fixed paraffin embedded (FFPE) tumour blocks and/or representative slides must be available and provided to the sponsor for independent histological review (IHR). IHR is not required prior to randomisation. 2. Documented evidence of advanced (locally recurrent, locally advanced and/or metastatic) adipocytic sarcoma (restricted to subtypes listed in Inclusion 1) or leiomyosarcoma, incurable by surgery or radiotherapy. 3. Subjects should have received at least two standard systemic regimens for advanced STS, one of which must have included an anthracycline (unless contraindicated).

- This was the secondary analysis set for all efficacy evaluations.
- The Safety Analysis Set included all subjects who were randomised, received at least one dose of the study treatment and had at least one post-baseline safety evaluation. Subjects were analysed in the treatment arm for the study drug they actually received (in Cycle 1) if it was different from the treatment to which they had been randomised. This was the analysis set for all safety evaluations.

7.1.7. Sample size

The survival time in the dacarbazine arm was estimated to be approximately 6 months. An increase by 2.5 months to 8.5 months in the eribulin arm was considered to be clinically important. This correlated to an estimated hazard ratio of 0.706. With a significance level of 0.05 using a two-sided test and a power of 90%, it was estimated that a total of 353 deaths would be required. Assuming an enrolment rate of 20 subjects per month, it was estimated that a total of 450 subjects (225 in each arm) would have to be randomised in order to observe the required number of deaths.

7.1.8. Statistical methods

Overall survival was summarised using Kaplan-Meier estimates. A stratified log-rank test was used to compare the two treatment arms. A hazard ratio (with 95% CI) was estimated using a stratified Cox regression model. Three sensitivity analyses were planned (an analysis using the per-protocol set, analysis without any stratification and an analysis with censoring of subjects starting new anticancer treatment). Subgroup analyses were also planned.

An interim analysis of overall survival was planned after approximately 70% (247) of the required 353 deaths had occurred. Significance levels were 0.0148 for the interim analysis and 0.0455 for the final analysis.

PFS was analysed using similar methods to OS. PFR12wks and CBR were analysed using a stratified Cochran-Mantel-Haenszel (CMH) Chi-square test. No statistical adjustment of the secondary endpoint analyses was performed to allow for multiple comparisons. No subgroup analyses of secondary endpoints were performed. There were no formal statistical analyses planned for the exploratory endpoints.

7.1.9. Participant flow

A total of 594 subjects were screened for the study and 452 subjects were randomised. Failure to meet inclusion and exclusion criteria was the most common reason for non-randomisation (106/142). A total of 228 subjects were randomised to eribulin and 224 to dacarbazine.

Subject disposition is summarised in Table 4. At the time of data cut-off only 2 subjects were still receiving randomised treatment and 79% of subjects had died. Analysis sets are summarised in Table 5.

Table 4: Study 309 Subject disposition

	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 arm.
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.

Table 5: Study 309 Analysis sets

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.

7.1.10. Major protocol violations/deviations

Protocol deviations resulting in exclusion from the per-protocol set was summarised: The incidence of violations was higher in the dacarbazine arm (11.2% versus 5.7%). Violations that occurred with a notably higher incidence in the dacarbazine arm were failure to meet inclusion criteria #3 (at least two prior systemic regimens) and failure to meet exclusion criteria #3 (no previous treatment with dacarbazine, temozolomide or eribulin). The only violation that occurred with a notably higher incidence in the eribulin arm was failure to meet exclusion criteria #1 (anticancer therapy in the 21 days prior to randomisation).

Comment: The differences between treatment arms were small and it is unlikely that they would have affected interpretation of the efficacy outcomes.

7.1.11. Baseline data

Approximately 66% of subjects had leiomyosarcoma and 34% had adipocytic sarcoma. Median age was 56 years and most subjects were White (73.0%). The two arms were generally well balanced although the eribulin arm had slightly better ECOG performance status (PS=0: 48.7% versus 40.2%).

The enrolled population was a heavily pre-treated one with 98.9% of subjects having received at least 2 prior lines of therapy and 51.1% having received 3 or more lines of therapy. The most commonly previously used chemotherapy agents were doxorubicin (77.9%), gemcitabine (53.3%), ifosfamide (50.0%) and trabectedin (48.5%). A total of 52.2% had received previous radiotherapy. An analysis of prior surgery for STS was not provided.

Comment: Overall the two arms were generally well balanced with respect to baseline characteristics, although the eribulin arm had slightly better ECOG performance status (PS=0: 48.7% versus 40.2%).

7.1.12. Results for the primary efficacy outcome

The interim analysis of efficacy was conducted after 247 deaths, with a data cut-off of 20 October 2013. The data monitoring committee for the trial recommended that the study continue without modification.

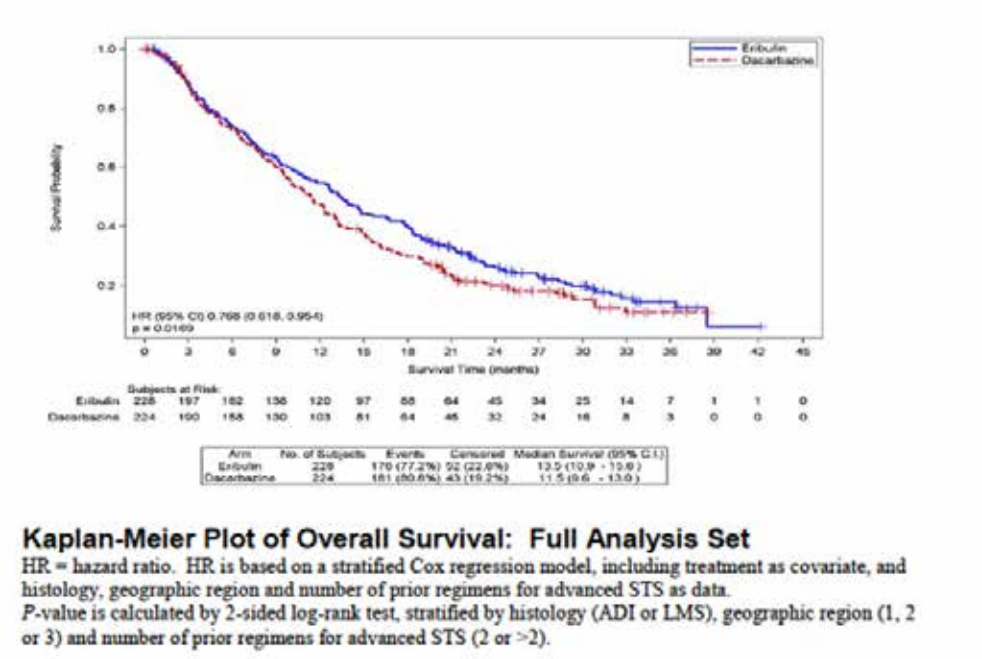
The final analysis was conducted after a total of 357 deaths had occurred. Results are summarised in Table 6and Figure 2. Treatment with eribulin was associated with a statistically significant improvement in overall survival compared with dacarbazine treatment (Hazard Ratio [HR] = 0.768 [95%CI: 0.618 – 0.954]; p = 0.0169). Median OS was improved by approximately 2 months (13.5 versus 11.5 months). The estimated proportion of subjects alive after 12 months was increased from 47.5% to 54.8%.

Table 6: Study 309 Overall survival (primary endpoint)

	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

Figure 2: Study 309 Overall survival (primary endpoint)



Kaplan-Meier Plot of Overall Survival: Full Analysis Set
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).

Results of the sensitivity analyses were:

- The per-protocol analysis gave results consistent with the primary analysis (HR = 0.747 [95%CI: 0.596 – 0.937]; p = 0.0115);
- When subjects were censored at the time of commencement of new anticancer therapy, the analysis also gave results consistent with the primary analysis (HR = 0.645 [95%CI: 0.442 – 0.941]; p = 0.0223);
- Using an unstratified analysis, the difference between treatments was *not* statistically significant (HR = 0.843 [95%CI: 0.685 – 1.038]; p = 0.1087)

Table 7shows therapies received by subjects after randomised treatment. 69.3% of subjects in the eribulin arm and 62.9% of subjects in the dacarbazine arm received further chemotherapy. Post –trial therapy with dacarbazine was used in 34.2% of subjects in the eribulin arm compared with only 7.6% in the dacarbazine arm. This imbalance could have theoretically favoured the eribulin arm with respect to survival. However, the above sensitivity analysis suggested a survival benefit with eribulin regardless of post-trial therapy. Post–trial therapy with eribulin was used in 1.3% of subjects in the eribulin arm compared with 2.7% in the dacarbazine arm.

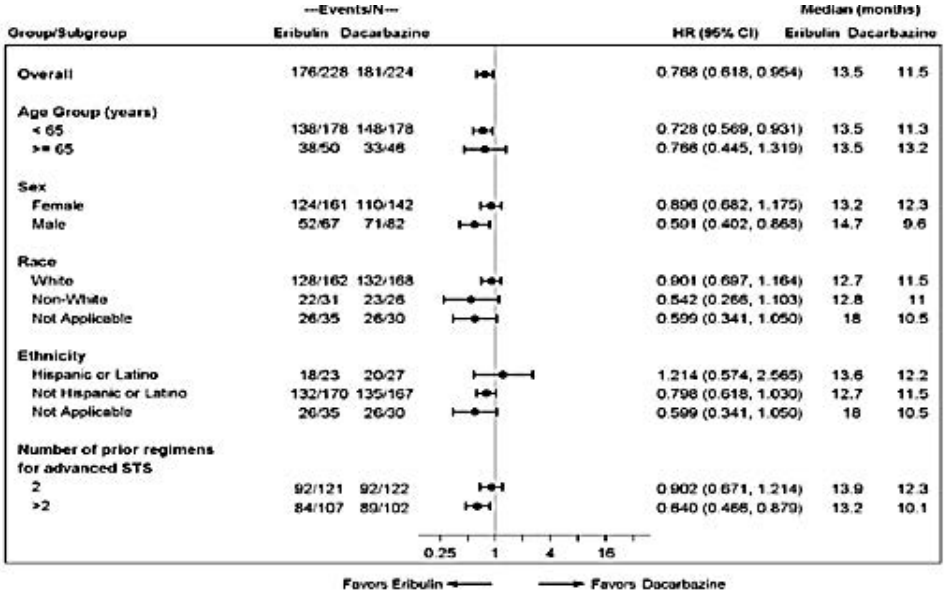
Results of pre-planned subgroup analyses are shown in Figure 3.

Table 7: Study 309 Post-study anticancer therapy

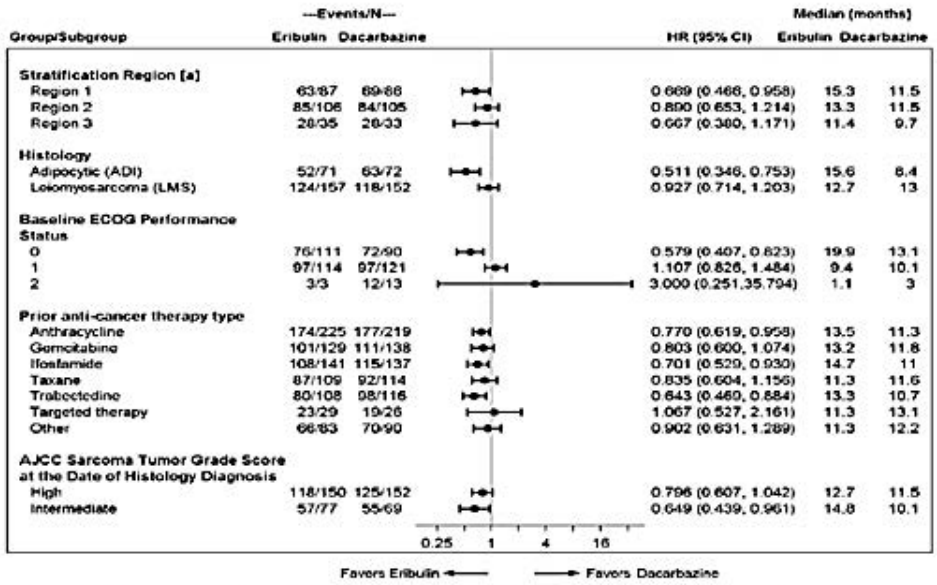
	Eribulin (ADI + LMS) n (%)	Dacarbazine (ADI + LMS) n (%)
N	228 (100.0)	224 (100.0)
Post treatment		
Surgery		
No	192 (84.2)	186 (83.0)
Yes	36 (15.8)	38 (17.0)
Radiotherapy		
No	175 (76.8)	180 (80.4)
Yes	53 (23.2)	44 (19.6)
Chemotherapy[a]		
Yes	158 (69.3)	141 (62.9)
No	70 (30.7)	83 (37.1)
1	57 (25.0)	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 = leiomyosarcoma.
a: If a subject has the same preferred term 2 or more times, the subject will be counted only once for that preferred term.

Figure 3: Study 309 Subgroup analyses of overall survival



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



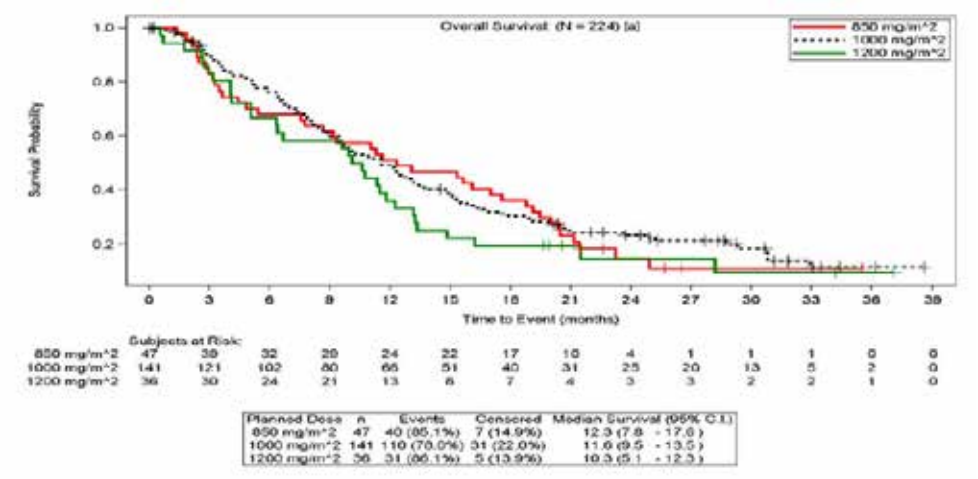
a: Region 1: USA and Canada; Region 2: Western Europe, Australia and Israel; Region 3: Eastern Europe, Latin America and Asia

Comment: The study was not powered to detect significant differences between treatments within subgroups. However, in general, the analyses suggested efficacy in most subgroups in that hazard ratios were less than 1.0. In most subgroups that had a HR > 1.0, subject numbers were small. An exception was the group of subjects with ECOG PS=1 (n=235) - HR = 1.107 (95%CI: 0.826 – 1.484).

Even though the study was not powered to detect significant differences in subgroups, a significant effect was demonstrated for the subgroup of subjects with adipocytic sarcoma (HR = 0.511 [95%CI: 0.346 – 0.753]). In this subgroup median survival was prolonged by approximately 7 months (15.6 versus 8.4 months). In contrast, the HR in the leiomyosarcoma subgroup was 0.927 (95%CI: 0.714 – 1.203), with no increase in median survival.

Kaplan-Meier curves for OS by dacarbazine starting dose are shown in Figure 4. Lower doses were not associated with reduced survival.

Figure 4: Study 309 – Overall survival by dacarbazine dose



7.1.13. Results for secondary efficacy outcomes

7.1.13.1. Progression-free survival

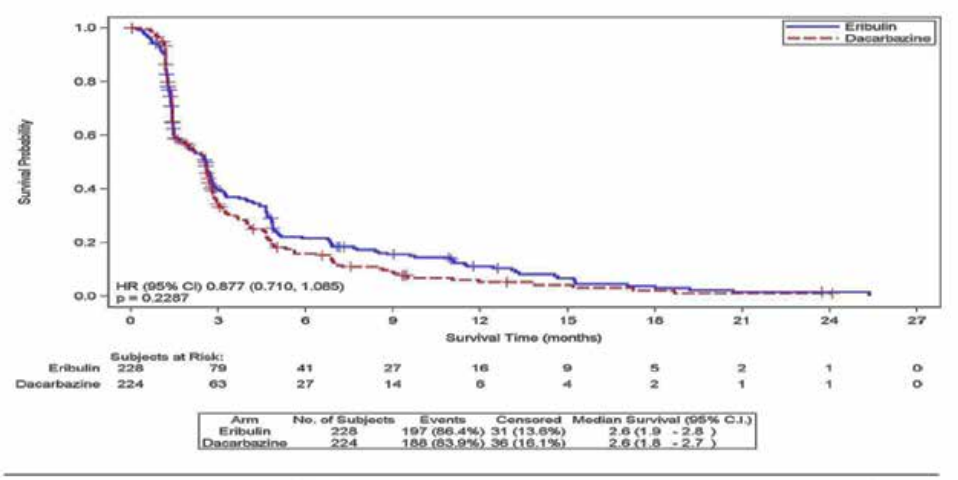
Results for PFS are summarised in Table 8and Figure 5. There were no significant differences between the two treatments. Subgroup analysis by histology subgroups demonstrated a statistically significant benefit for eribulin treatment in liposarcoma subjects, but not in leiomyosarcoma subjects (Table 9).

Table 8: Study 309 Progression-free survival

	Eribulin (N=228)	Dacarbazine (N=224)
Subjects with Events (PD + death), n (%)	197 (86.4)	188 (83.9)
Progressive disease (PD)[a] Death, without documented PD	183 (80.3) 14 (6.1)	173 (77.2) 15 (6.7)
Censored, n (%) No baseline or post baseline tumor assessment Alive without progression at database cut-off New anticancer treatment started Death or PD after 2 or more missed tumor assessments	31 (13.6) 0 7 (3.1) 18 (7.9) 6 (2.6)	36 (16.1) 0 8 (3.6) 18 (8.0) 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 6 months 12 months	0.400 (0.334, 0.466) 0.216 (0.162, 0.275) 0.111 (0.070, 0.162)	0.343 (0.278, 0.409) 0.158 (0.110, 0.214) 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

Figure 5: Study 309 Progression-free survival



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).

Table 9: Study 309 Progression-free survival by histology subgroup

	Eribulin (N=228)			Dacarbazine (N=224)			Hazard Ratio	P-value [d]
	N	Events [a]	Median (95% CI) (Months) [b]	N	Events [a]	Median (95% CI) (Months) [b]	HR [c] 95% CI	
Histology								
Adipocytic (ADI)	71	57	2.9 (2.6, 4.8)	72	59	1.7 (1.4, 2.6)	0.521 (0.346, 0.784)	0.0015
Leiomyosarcoma (LMS)	157	140	2.2 (1.5, 2.7)	152	129	2.6 (2.4, 2.9)	1.072 (0.835, 1.375)	0.5848

Source: Listing 16.2.1.2, Listing 16.2.8.1, Listing 16.2.8.2 and Listing 16.2.4.2
[a]: Subjects who have progressive disease or died. [b]: Median was estimated with Kaplan-Meier product-limit method and 95 % confidence interval was constructed with Greenwoods formula. [c]: Hazard ratio is based on a Cox regression model including treatment as covariate, and if applicable, the stratified factor will be histology (ADI or LMS), geographic region (1,2 or 3) and number of prior regimens for advanced STS (2 or >2); if the stratified factor is the same within the subgroup, the related factor will be excluded from the Cox regression model.
[d]: P-value is calculated using a two-sided stratified log-rank test within each category of the subgroup, if it is applicable, the stratified factor will be the same as for Hazard ratio; if the stratified factor is the same within the subgroup, the related factor will be excluded from the Log-rank test. NE = Not Estimable.

7.1.13.2. PFR12wks

The rate was 33.3% in the eribulin group and 28.6% in the dacarbazine group. The difference was not statistically significant.

Comment: It is of note that the PFR12wks in both groups was < 40%, the level proposed by the EORTC for determining drug activity in 2nd line therapy. Subjects in this trial were receiving 3rd or later line therapy, so this finding may not be relevant. However, it would be of interest to know the PFR12wks for each of the two histological groups included in the trial.

7.1.13.3. Clinical Benefit Rate

The rate was 46.1% in the eribulin group and 47.8% in the dacarbazine group. The difference was not statistically significant.

7.1.14. Results for exploratory efficacy outcomes

7.1.14.1. Objective response rate, disease control rate and durable stable disease

Results for these endpoints are summarised in Table 10. There were no significant differences between treatment groups. Objective response rates were low in both groups (3.9% with eribulin and 4.9% with dacarbazine). All responses were partial responses.

Table 10: Study 309 ORR, DCR and dSD results

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

7.1.14.2. Quality of life

The sponsor provided a separate report on the QoL variables, which contained a large number of analyses. Patient numbers remaining in the trial decreased over time and hence many of the analyses focussed on results up to and including Cycle 9 of treatment. Compliance rates were high with > 80% of subjects completing questionnaires during the first 9 cycles.

There were no significant differences between the two study arms at baseline. The overall conclusions of the QoL analyses were that there were no significant differences in outcomes between treatment arms. There were sporadic statistically significant differences between treatments on various measures but these were not consistent over time. For example, Figure 6 shows results for mean scores for the QLQ C-30 at Cycle 3, and Figure 6B shows results for the EQ-5D Health Utility Index and VAS over time. Subgroup analyses of the QoL outcomes were presented for the two histological subgroups enrolled in the trial. No consistent differences were demonstrated between the treatment groups.

Figure 6A: Study 309 EORTC QLQ-C30 results (at Cycle 3). QLQ-C30 Mean symptom and profile scores at Cycle 3

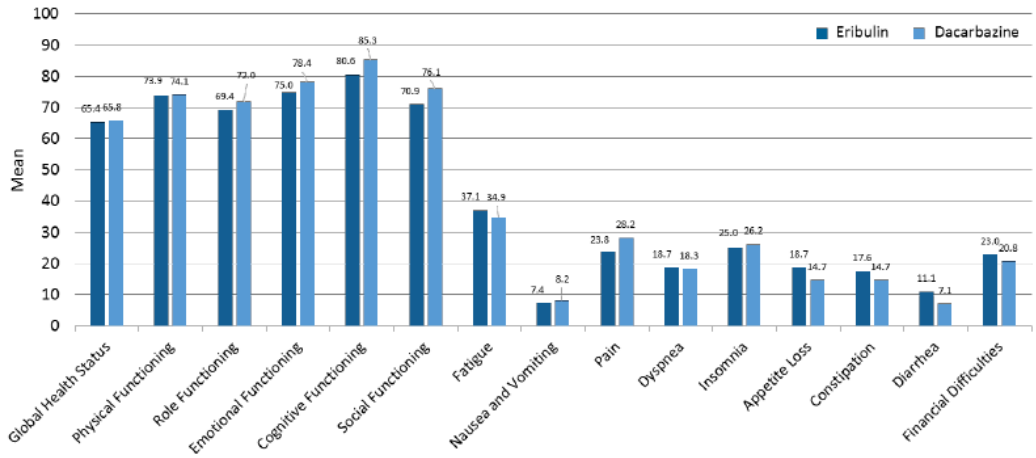
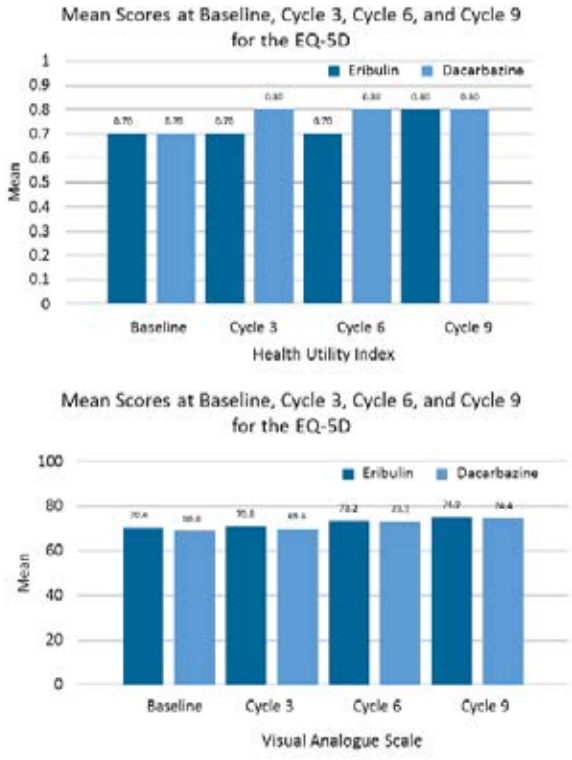


Figure 6B: Study 309 EQ-5D results



7.2. Other efficacy studies

7.2.1. Study 207

Study 207 was an open-label, single-arm, Phase II trial. The primary objective of the study was to evaluate the therapeutic activity and safety of eribulin in subjects with advanced and/or metastatic STS who had relapsed following standard therapies. It was conducted at 14 centres in Europe between December 2006 and June 2012. The study report provided was dated 24 June 2013. The study has been published.[14]

The study enrolled subjects with histologically confirmed advanced or metastatic STS, with evidence of disease progression in the previous 6 months. Subjects could have received only one prior combination regimen or two single agent cytotoxic drugs for metastatic disease. Subjects were all treated with eribulin 1.4 mg/m^2 IV over 2-5 minutes on Days 1 and 8 of a 21 day cycle. Treatment was continued until disease progression or unacceptable toxicity.

The primary endpoint was the rate of progression-free survival at 12 weeks (PFR12wks). Secondary endpoints included overall PFS, overall survival and response rate. Tumour response and progression were assessed using RECIST version 1.0 criteria. The trial enrolled subjects into one of four strata: leiomyosarcoma, adipocytic sarcoma, synovial sarcoma and 'other' sarcoma. With each stratum, a two-stage design was applied. A total of 17 subjects would be enrolled in each stratum, and if 4 of the initial 17 subjects (23.5%) were progression-free at 12 months, enrolment would continue up to 37 subjects in each stratum. If 11 of the 37 subjects (30%) were progression-free at 12 months, it would be concluded that eribulin would warrant further investigation in that histological subtype.

A total of 128 subjects were enrolled in the study. One subject did not receive treatment and 12 subjects received treatment but were subsequently deemed ineligible on central histology review. Therefore 115 subjects were evaluable for efficacy. The analysis sets in the study are summarised in Table 11. In all four strata there were at least 4 of the initial 17 subjects who

were progression-free at 12 weeks. Further enrolment therefore proceeded in all four strata however a total of 37 subjects were only reached for leiomyosarcoma and adipocytic sarcoma.

Table 11: Study 207 Analysis sets.

	Eribulin mesilate				
	Strata				
Analysis Set	ADI (N=37) n (%)	LMS (N=40) n (%)	SYN (N=19) n (%)	OTH (N=32) n (%)	Total (N=128) n (%)
Enrolled	37	40	19	32	128
Safety Analysis Set[a]	37 (100.0)	40 (100.0)	19 (100.0)	31 (96.9)	127 (99.2)
Full Analysis Set[a]	37 (100.0)	40 (100.0)	19 (100.0)	31 (96.9)	127 (99.2)
Efficacy Evaluable Set[b]	32 (86.5)	38 (95.0)	19 (100.0)	26 (81.3)	115 (89.8)

ADI = adipocytic tumors, LMS = leiomyosarcoma, OTH = other types of sarcoma, SYN = synovial sarcoma.
a Subjects who received at least one dose of study drug.
b Subjects who received at least one dose of study drug and were eligible for the study by central review.

For the 127 treated subjects median age was 56.0 years and 52% were female. 55.9% had received 2 prior anticancer regimens and 12.6% had received more than 2. The most commonly used prior chemotherapy agents were doxorubicin (89.8% of subjects), ifosfamide (52.0%), trabectedin (6.3%), dacarbazine (5.5%) and gemcitabine (5.5%).

Results for the primary endpoint (PFR12wks) are summarised in Table 12. The predefined efficacy rate of >30% was reached in the adipocytic sarcoma (46.9%) and leiomyosarcoma (31.6%) strata. PFS rate was lower in the other two strata however the number of subjects enrolled was low.

Table 12: Study 207 PFS at 12 weeks (primary endpoint)

	Eribulin mesilate				
	Strata				
	ADI (N=32)	LMS (N=38)	SYN (N=19)	OTH (N=26)	Total (N=115)
Subjects with Events, n (%)					
Progressive Disease	15 (46.9)	22 (57.9)	14 (73.7)	19 (73.1)	70 (60.9)
Dead with PD	4	0	0	3	7
Alive with PD	11	22	14	16	63
Death without PD	1 (3.1)	0	0	0	1 (0.9)
Unknown	1 (3.1)	4 (10.5)	1 (5.3)	2 (7.7)	8 (7.0)
Progression Free at Week 12, n (%)	15 (46.9)	12 (31.6)	4 (21.1)	5 (19.2)	36 (31.3)
95% 2-sided CI	(29.1, 65.3)	(17.5, 48.7)	(6.1, 45.6)	(6.6, 39.4)	(23.0, 40.6)

The tumor assessment is based on RECIST.
ADI = adipocytic tumors, CI = confidence interval, LMS = leiomyosarcoma, OTH = other types of sarcoma, RECIST = Response Evaluation Criteria In Solid Tumors, SYN = synovial sarcoma

Results for overall PFS are summarised in Table 13. Median PFS for the whole efficacy population was 82 days (2.7 months). The synovial sarcoma and other sarcoma groups had lower PFS rates at most time points. Results for overall survival are summarised in Table 14. Median OS for the whole efficacy population was 359 days (11.8 months). As with PFS, the synovial sarcoma and other sarcoma groups had lower survival rates at most time points. Results for objective response rate are summarised in Table 15. Response rates were low (<5.5%) in all strata.

Table 13: Study 207 Overall progression-free survival

	Eribulin mesilate				
	Strata				Total (N=115)
	ADI (N=32)	LMS (N=38)	SYN (N=19)	OTH (N=26)	
Subjects with Events, n (%)					
Progressive Disease	32 (100)	37 (97.4)	19 (100.0)	26 (100)	114 (99.1)
Dead (PD)	28	33	18	25	104
Alive (PD)	4	4	1	1	10
Progression Free at Last Follow-Up, n (%)	0	1 (2.6)	0	0	1 (0.9)
95% 2-sided CI	(0.0, 10.9)	(0.1, 13.8)	(0.0, 17.6)	(0.0, 13.2)	(0.0, 4.7)
Progression-Free Survival (days)					
Median (95% CI)	82 (44, 175)	88 (69, 114)	81 (43, 101)	72 (42, 87)	82 (69, 90)
1st Quartile (95% CI)	43 (37, 57)	43 (39, 73)	43 (36, 80)	42 (36, 43)	43 (42, 44)
3rd Quartile (95% CI)	201 (124, 309)	162 (95, 295)	121 (81, 211)	94 (83, 204)	163 (121, 204)
Progression-free Survival Rate (95% CI)					
At 3 months[a]	46.9 (29.1, 62.8)	47.4 (31.0, 62.1)	31.6 (12.9, 52.2)	26.9 (11.9, 44.5)	40.0 (31.0, 48.8)
At 6 months	31.3 (16.4, 47.3)	23.7 (11.8, 37.9)	10.5 (1.8, 28.4)	15.4 (4.8, 31.5)	21.7 (14.7, 29.6)
At 9 months	12.5 (3.9, 26.2)	20.7 (9.6, 34.8)	5.3 (0.4, 21.4)	3.8 (0.3, 16.4)	11.7 (6.6, 18.4)
At 12 months	9.4 (2.4, 22.3)	8.9 (2.3, 21.0)	0	3.8 (0.3, 16.4)	6.3 (2.8, 11.9)
Status at Week 12, n (%)					
Alive, without PD	15 (46.9)	12 (31.6)	4 (21.1)	5 (19.2)	36 (31.3)
Alive, with PD	11 (34.4)	22 (57.9)	14 (73.7)	16 (61.5)	63 (54.8)
Dead, without PD	1 (3.1)	0	0	0	1 (0.9)
Dead, with PD	4 (12.5)	0	0	3 (11.5)	7 (6.1)
Unknown	1 (3.1)	4 (10.5)	1 (5.3)	2 (7.7)	8 (7.0)

The tumor assessment is based on RECIST.
Overall PFS rate at x months (95% CI) was calculated using Kaplan-Meier estimate.
ADI = adipocytic tumors, CI = confidence interval, LMS = leiomyosarcoma, OTH = other types of sarcoma, PD = progressive disease, RECIST = Response Evaluation Criteria In Solid Tumors, SYN = synovial.
[a]Three month results are based on the Kaplan-Meier estimate and are estimated at Day 84 across all subjects.

Table 14: Study 207 Overall survival

	Eribulin mesilate				
	Strata				Total (N=115)
	ADI (N=32)	LMS (N=38)	SYN (N=19)	OTH (N=26)	
Subjects with Events, n (%)					
Deaths	28 (87.5)	33 (86.8)	18 (94.7)	25 (96.2)	104 (90.4)
Alive at End of Study	4 (12.5)	5 (13.2)	1 (5.3)	1 (3.8)	11 (9.6)
95% 2-sided CI	(3.5%, 29.0%)	(4.4%, 28.1%)	(0.1%, 26.0%)	(0.1%, 19.6%)	(4.9%, 16.5%)
Overall Survival (days)					
Median (95% CI)	363 (234, 495)	466 (392, 697)	293 (170, 371)	204 (149, 312)	359 (262, 426)
1st Quartile (95% CI)	174 (70, 273)	260 (117, 423)	170 (105, 237)	125 (72, 179)	171 (137, 222)
3rd Quartile (95% CI)	565 (395, -)	922 (617, 1888)	416 (324, 602)	560 (231, 1047)	602 (479, 926)
Overall Survival Rate (95% CI)					
At 3 months	81.3 (62.9, 91.1)	100.0 (100.0, 100.0)	100.0 (100.0, 100.0)	84.6 (64.0, 93.9)	91.2 (84.3, 95.2)
At 6 months	75.0 (56.2, 86.6)	86.8 (71.2, 94.3)	66.7 (40.4, 83.4)	57.7 (36.8, 73.9)	73.7 (64.6, 80.8)
At 9 months	62.5 (43.5, 76.7)	73.7 (56.6, 84.9)	50.0 (25.9, 70.1)	38.5 (20.4, 56.3)	58.8 (49.2, 67.2)
At 12 months	50.0 (31.9, 65.7)	68.4 (51.1, 80.7)	38.9 (17.5, 60.0)	30.8 (14.6, 48.5)	50.0 (40.5, 58.7)
At 24 months	21.9 (9.6, 37.2)	30.1 (16.4, 45.1)	5.6 (0.4, 22.4)	15.4 (4.8, 31.5)	20.5 (13.6, 28.4)
At 36 months	18.8 (7.6, 33.7)	16.4 (6.7, 29.9)	5.6 (0.4, 22.4)	5.1 (0.4, 20.2)	13.1 (7.6, 20.1)

Subjects who had not died were censored at the date last known to be alive.
Overall Survival rate at x months (95% CI) was calculated using Kaplan-Meier estimate.
ADI = adipocytic tumors, CI = confidence interval, LMS = leiomyosarcoma, OTH = other types of sarcoma, SYN = synovial sarcoma.

Table 15: Study 207 Response rates

	Eribulin mesilate				
	Strata				
	ADI (N=32)	LMS (N=38)	SYN (N=19)	OTH (N=26)	Total (N=115)
Response at Week 12, n (%)					
Complete Response	1 (3.1)	0	0	0	1 (0.9)
Partial Response	1 (3.1)[a]	0	1 (5.3)	1 (3.8)	3 (2.6)
Stable Disease	13 (40.6)	12 (31.6)	3 (15.8)	4 (15.4)	32 (27.8)
Progressive Disease	14 (43.8)	22 (57.9)	14 (73.7)	19 (73.1)	69 (60.0)
Early Death	1 (3.1)	0	0	0	1 (0.9)
Not Evaluable	2 (6.3)	4 (10.5)	1 (5.3)	2 (7.7)	9 (7.8)
Best Overall Response, n (%)					
Complete Response	1 (3.1)	0	0	0	1 (0.9)
Partial Response	0[a]	2 (5.3)	1 (5.3)	1 (3.8)	4 (3.5)
Stable Disease	18 (56.3)	20 (52.6)	8 (42.1)	11 (42.3)	57 (49.6)
Progressive Disease	11 (34.4)	14 (36.8)	9 (47.4)	13 (50.0)	47 (40.9)
Early Death	1 (3.1)	0	0	0	1 (0.9)
Due to malignant disease	1(100.0)	0	0	0	1(100.0)
Due to toxicity	0	0	0	0	0
Due to other cause	0	0	0	0	0
Not Evaluable	1 (3.1)	2 (5.3)	1 (5.3)	1 (3.8)	5 (4.3)
Status at Last Follow-Up, n (%)					
Alive, without progressive disease	0	1 (2.6)	0	0	1 (0.9)
Alive, with progressive disease	4 (12.5)	4 (10.5)	1 (5.3)	1 (3.8)	10 (8.7)
Dead, without progressive disease	2 (6.3)	3 (7.9)	0	1 (3.8)	6 (5.2)
Dead, with progressive disease	26 (81.3)	30 (78.9)	18 (94.7)	24 (92.3)	98 (85.2)
Objective Response Rate (CR + PR)	3.1%	5.3%	5.3%	3.8%	4.3%
95% CI of Objective Response Rate	(0.1%, 16.2%)	(0.6%, 17.7%)	(0.1%, 26.0%)	(0.1%, 19.6%)	(1.4%, 9.9%)
Clinical Response Benefit (CR + PR + SD)	59.4%	57.9%	47.4%	46.2%	53.9%
95% CI of Clinical Response Benefit	(40.6%, 76.3%)	(40.8%, 73.7%)	(24.4%, 71.1%)	(26.6%, 66.6%)	(44.4%, 63.2%)

95% CIs were calculated using the exact method of binomial distribution.
ADI = adipocytic tumors, BOR = best overall response, CI = confidence interval, CR = complete response, LMS = leiomyosarcoma, OTH = other types of sarcoma, PR = partial response, SD = stable disease, SYN = synovial sarcoma.
[a] A CR and a PR were recorded at Week 12 but only a CR as BOR, this was because the PR assessment for one subject was not confirmed and was therefore counted in the analysis of response at Week 12 but not in the BOR analysis.

7.2.2. Study 217

Study 217 was an open-label, single-arm, Phase II trial. The primary objective of the study was to evaluate the efficacy of eribulin, as measured by PFR12wks, in subjects with advanced STS previously treated with chemotherapy. It was conducted at 12 sites in Japan between November 2011 and November 2014. The study report provided was dated 25 May 2015. The study has not been published.

The study enrolled subjects with histologically confirmed advanced or metastatic STS of high or intermediate grade, with evidence of disease progression in the previous 6 months. Subjects should have received at least one prior standard chemotherapy regimen (an anthracycline or ifosfamide as monotherapy, or a combination regimen). Subjects were all treated with eribulin 1.4 mg/m^2 IV over 2-5 minutes on Days 1 and 8 of a 21 day cycle. Treatment was continued until disease progression or unacceptable toxicity.

The primary endpoint was the rate of progression-free survival at 12 weeks (PFR12wks). Secondary endpoints included overall PFS, overall survival and response rate. Tumour response and progression were assessed using RECIST version 1.1 criteria. The trial enrolled subjects into one of two strata: 1) leiomyosarcoma or adipocytic sarcoma and 2) 'other' sarcomas. It was planned to enrol 35 subjects in the first stratum and 16-20 in the second.

A total of 51 subjects were enrolled and treated in the study: 35 subjects in the first stratum (adipocytic sarcoma n=16 and leiomyosarcoma n=19) and 16 subjects in the other sarcoma stratum. For the entire population median age was 52 years and 54.9% were female. 66.7% had received 2 prior anticancer regimens and 33.3% had received more than 2. The most commonly used prior chemotherapy agents were anthracyclines (100% of subjects, predominantly doxorubicin), ifosfamide (70.6%), docetaxel (43.1%) and gemcitabine (41.2%).

Results for the primary endpoint (PFR12wks) are summarised in Table 16.

In PFR12wks was 81.3% for adipocytic sarcoma, 42.1% for leiomyosarcoma and 31.3% for other sarcomas. Results for objective response rate are also summarised in Table 16. No responses were observed.

Table 16: Study 217 PFS at 12 weeks (primary endpoint) and Objective Response Rate

Category	ADI (N=16)	LMS (N=19)	ADI or LMS (N=35)	OTH (N=16)	Total (N=51)
Progression-Free Rate at 12 Weeks (PFR_{12wks}), n (%)	13 (81.3)	8 (42.1)	21 (60.0)	5 (31.3)	26 (51.0)
90% CI of PFR_{12wks} (1-sided) [a]	62.9, 100.0	26.3, 100.0	47.8, 100.0	16.1, 100.0	41.1, 100.0
90% CI of PFR_{12wks} (2-sided) [a]	58.3, 94.7	23.0, 63.2	44.7, 74.0	13.2, 54.8	38.7, 63.2
95% CI of PFR_{12wks} [a]	54.4, 96.0	20.3, 66.5	42.1, 76.1	11.0, 58.7	36.6, 65.2
P-value (1-sided) [b]			<0.0001	0.0790	
Complete Response (CR), n (%)	0	0	0	0	0
Partial Response (PR), n (%)	0	0	0	0	0
Stable Disease (SD), n (%)	15 (93.8)	13 (68.4)	28 (80.0)	8 (50.0)	36 (70.6)
Progressive Disease (PD), n (%)	1 (6.3)	6 (31.6)	7 (20.0)	8 (50.0)	15 (29.4)
Not Evaluable (NE), n (%)	0	0	0	0	0
Unknown, n (%)	0	0	0	0	0
Objective Response Rate (CR + PR), n (%)	0	0	0	0	0
95% CI of Objective Response Rate [a]	0.0, 20.6	0.0, 17.6	0.0, 10.0	0.0, 20.6	0.0, 7.0
Disease Control Rate (CR + PR + SD), n (%)	15 (93.8)	13 (68.4)	28 (80.0)	8 (50.0)	36 (70.6)
95% CI of Disease Control Rate [a]	69.8, 99.8	43.4, 87.4	63.1, 91.6	24.7, 75.3	56.2, 82.5
Clinical Benefit Rate (CR + PR + durable SD), n (%)	15 (93.8)	11 (57.9)	26 (74.3)	8 (50.0)	34 (66.7)
95% CI of Clinical Benefit Rate [a]	69.8, 99.8	33.5, 79.7	56.7, 87.5	24.7, 75.3	52.1, 79.2
Durable SD Rate, n (%)	15 (93.8)	11 (57.9)	26 (74.3)	8 (50.0)	34 (66.7)
95% CI of Durable Stable Disease Rate [a]	69.8, 99.8	33.5, 79.7	56.7, 87.5	24.7, 75.3	52.1, 79.2
Progression-Free Survival Rate at 12 Weeks (%)	93.8	56.4	73.8	37.5	62.2
90% CI of Progression-Free Survival Rate at 12 Weeks [c]	71.6, 98.8	35.5, 72.9	59.0, 83.9	18.5, 56.5	49.9, 72.3
95% CI of Progression-Free Survival Rate at 12 Weeks [c]	63.2, 99.1	31.3, 75.4	55.7, 85.4	15.4, 59.8	47.3, 74.0

The tumor assessment is based on RECIST 1.1 criteria.
Objective response = CR + PR, disease control = CR + PR + SD (SD >= 5 wks), clinical benefit = CR + PR + durable SD, durable SD = duration of SD >= 11wks
CI = confidence interval
a: 1-sided, 2-sided 90% and 95% CI is calculated using exact method of binomial distribution.
b: The 1-sample exact test (1-sided) against the threshold of 20% for ADI or LMS, 15% for OTH.
c: Progression Free Survival rate at 12 weeks (2-sided 90% and 95% CI) are calculated using Kaplan-Meier estimate and Greenwood Formula.

Results for overall PFS are summarised in Table 17. Median PFS for the whole efficacy population was 4.07 months. Patients with leiomyosarcoma or adipocytic sarcoma had longer PFS than those with other sarcomas. Results for overall survival are summarised in Table 18. Median OS for the whole population was 13.17 months. As with PFS, subjects in the other sarcoma stratum had lower survival rates.

Table 17: Study 217 Overall progression-free survival

	Eribulin mesilate		
	Strata		
Category	ADI or LMS (N=35)	OTH (N=16)	Total (N=51)
Subjects with events, n (%)	28 (80.0)	14 (87.5)	42 (82.4)
Progressive disease	28 (80.0)	13 (81.3)	41 (80.4)
Death	0	1 (6.3)	1 (2.0)
Censored subjects, n (%)	7 (20.0)	2 (12.5)	9 (17.6)
Subjects censored before database cutoff, n (%)	6 (17.1)	2 (12.5)	8 (15.7)
No progression	0	1 (6.3)	1 (2.0)
New anticancer treatment started	5 (14.3)	1 (6.3)	6 (11.8)
Death or PD after more than 1 missing assessment	1 (2.9)	0	1 (2.0)
Alive without progression at database cutoff, n (%)	1 (2.9)	0	1 (2.0)
Progression-free survival (months)			
Median (95% CI)[a]	5.52 (2.79, 8.18)	2.01 (1.22, 4.07)	4.07 (2.56, 5.55)
1st Quartile (95% CI)[a]	2.66 (1.18, 5.09)	1.29 (1.18, 1.45)	1.41 (1.18, 2.66)
3rd Quartile (95% CI)[a]	8.41 (6.83, 15.18)	4.07 (1.45, 6.37)	8.18 (5.52, 15.18)
Range of event/Censoring time	0.2, 35.8+	1.2, 6.4	0.2, 35.8+
Progression-free survival rate (95% CI)[a]			
At 3 months	61.7 (43.3, 75.7)	30.0 (10.2, 53.0)	51.5 (36.8, 64.4)
At 6 months	42.2 (25.2, 58.3)	10.0 (0.7, 34.5)	32.9 (19.9, 46.5)
At 9 months	22.7 (10.1, 38.4)	0.0 (NE, NE)	16.5 (7.3, 28.8)
At 12 months	18.2 (6.8, 34.0)	0.0 (NE, NE)	13.2 (4.9, 25.5)

The tumor assessment is based on RECIST 1.1 criteria.
ADI = adipocytic sarcoma, CI = confidence interval, LMS = leiomyosarcoma, OTH = other types of eligible soft tissue sarcoma, RECIST = Response Evaluation Criteria in Solid Tumor.
a: Progression-free survival rate (95% CI) was calculated using Kaplan-Meier estimate and Greenwood Formula. A generalized Brookmeyer and Crowley method is used to construct a log-log-transformed 95% CI.
+: censored information
NE = Not estimable due to insufficient events or no subjects at risk. And CIs cannot be estimated if rate is 100% or 0%.

Table 18: Study 217 Overall survival

Category	Eribulin mesilate		
	Strata		
	ADI or LMS (N=35)	OTH (N=16)	Total (N=51)
Subjects with events, n (%)	25 (71.4)	13 (81.3)	38 (74.5)
Death, n (%)	25 (71.4)	13 (81.3)	38 (74.5)
Censored subjects, n (%)	10 (28.6)	3 (18.8)	13 (25.5)
Subjects censored before database cutoff[a], n (%)	1 (2.9)	0	1 (2.0)
Subjects censored at database cutoff, n (%)	9 (25.7)	3 (18.8)	12 (23.5)
OS (months)			
Median (95% CI)[b]	16.95 (11.01, 20.47)	7.64 (3.84, 16.13)	13.17 (9.49, 18.33)
1st Quartile (95% CI)[b]	9.49 (3.38, 11.53)	3.88 (1.74, 7.29)	6.83 (3.38, 9.59)
3rd Quartile (95% CI)[b]	31.15 (19.38, NE)	16.76 (7.29, NE)	31.15 (17.38, NE)
Range of event/Censoring time	2.0, 35.8+	1.7, 33.5+	1.7, 35.8+
OS rate (95% CI)[b]			
At 6 months	82.9 (65.8, 91.9)	68.8 (40.5, 85.6)	78.4 (64.4, 87.4)
At 12 months	57.1 (39.3, 71.5)	43.8 (19.8, 65.6)	52.9 (38.5, 65.5)
At 18 months	45.7 (28.9, 61.0)	18.8 (4.6, 40.2)	37.3 (24.3, 50.2)
At 24 months	31.4 (17.1, 46.8)	18.8 (4.6, 40.2)	27.5 (16.1, 40.0)

ADI = adipocytic sarcoma, CI = confidence interval, LMS = leiomyosarcoma, OS = overall survival, OTH = other types of eligible soft tissue sarcoma.
a: Subjects censored before database cutoff includes subjects who are lost to follow up and consent withdraw.
b: OS rate (95% CI) are calculated using Kaplan-Meier estimate and Greenwood Formula. A generalized Brookmeyer and Crowley method is used to construct a log-log-transformed 95% confidence interval.
+: censored information
NE = Not estimable due to insufficient events or no subjects at risk. And CIs cannot be estimated if rate is 100% or 0%.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

There were no pooled analyses or meta-analyses of efficacy data presented in the submission. The sponsor's summary of Clinical Efficacy included a summary tabulation of efficacy results across the three STS studies. This is shown in Table 19.

Table 19: Summary of efficacy results

	Study 309		Study 207	Study 217
	Eribulin ADI + LMS (N=228)	Dacarbazine (N=224)	Eribulin ADI +LMS (N=77)	Eribulin ADI + LMS (N=35)
OS (months)[a,g], median (95% CI)	13.5 (10.9, 15.6)	11.5 (9.6, 13.0)	14.6 (10.7, 17.9)	16.95 (11.01, 20.47)
$PFR12_{wks}$[b,c], % (95% CI)	33.3% (27.2, 39.9)	28.6% (22.8, 35.0)	39.0% (28.0, 50.8)	60.0% (42.1, 76.1)
PFS (months)[g] median (95% CI)	2.6 (1.9, 2.8)	2.6 (1.8, 2.7)	2.8 (2.3, 4.0)	5.52 (2.79, 8.18)
CBR[d], % (95% CI)	46.1% (39.5, 52.8)	47.8% (41.1, 54.5)	57.1% (45.4, 68.4)	74.3% (56.7, 87.5)[c]
ORR[e,c], % (95% CI)	3.9% (1.8, 7.4)	4.9% (2.5, 8.6)	3.9% (0.8, 11.0)	0% (0.0, 10.0)
Time to onset of response (months)[f], median	-	-	3.9	-
DOR[f], median	-	-	5.7	-
DCR[h], % (95% CI)	56.1% (49.4, 62.7)	52.7% (45.9, 59.4)	-	80.0% (63.1, 91.6)
dSDR	42.1% (35.6, 48.8)[c]	42.9% (36.3, 49.6)[c]	-	74.3% (56.7, 87.5)[c]

Abbreviations: ADI = adipocytic tumors, CBR = clinical benefit rate, CI = confidence interval, CSR = clinical study report, CR = complete response, DCR = disease control rate, DOR = duration of response, dSD = durable stable disease, dSDR = durable stable disease rate, FAS = Full Analysis set, LMS = leiomyosarcoma, ORR = objective response rate, OS = overall survival; PFR = progression-free rate; PFS = progression-free survival, PR = partial response, SD = stable disease.

Note: Data in bold refer to Primary Efficacy endpoints.

a In Study 309, 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 PFR_{12wks} = PFS as assessed 12 weeks after start of treatment.

c For Study 309 the 95% CI was calculated using exact Pearson Clopper two-sided 95% confidence limits, and for Study 217 the 95% CI was calculated using the exact method of binomial distribution.

d Study 309: the proportion of subjects who had best overall response of CR or PR or dSD (duration ≥11 weeks). Study 207: CR + PR + SD. Study 217: CR + PR + dSD.

e ORR = CR + PR.

f In Study 207 this parameter was only calculated for subjects who had a best overall response of CR or PR (n=1 and n=2, respectively, for ADI and LMS strata).

g In Study 217, PFS and OS rate (95% CI) were calculated using Kaplan-Meier estimate and Greenwood Formula. A generalized Brookmeyer and Crowley method was used to construct a log-log-transformed 95% CI.

h DCR = CR + PR + SD.

7.4. Evaluator's conclusions on clinical efficacy for STS

The pivotal study in the submission was well designed and well executed. The design complied with the recommendations of the EMA guideline on anticancer agents (6) that has been adopted by the TGA. The choice of dacarbazine as the comparator agent was reasonable.

The study demonstrated a statistically significant increase in survival with eribulin compared to dacarbazine (HR = 0.768 [95%CI: 0.618 – 0.954]; p = 0.0169). Median survival was increased by approximately 2 months. The magnitude of the survival benefit is clinically significant. The TGA has in recent years approved pazopanib for advanced STS, and the pivotal study for this drug demonstrated a prolongation of PFS by approximately 3 months compared with placebo, with no demonstrated improvement in overall survival.

Eribulin was not associated with significant benefits on the other efficacy endpoints studied such as PFS or response rates. These endpoints are generally considered to be surrogates for the gold standard of overall survival. In the presence of a demonstrated overall survival benefit, the absence of a demonstrated effect of eribulin on these endpoints is not considered important. Eribulin treatment was not associated with any improvement or impairment of QoL compared to dacarbazine.

The indication proposed by the sponsor would permit use of eribulin in all forms of STS. Enrolment in the pivotal study was restricted to subjects with liposarcoma or leiomyosarcoma, as the Phase II study did not demonstrate convincing evidence of activity for eribulin in other histological subtypes. There is therefore no adequate evidence to support use of eribulin in histological subtypes other than liposarcoma or leiomyosarcoma. If a new STS indication is to be approved the other subtypes should be excluded.

Although a statistically significant effect on overall survival was demonstrated in the pivotal study, subgroup analysis indicated that there was a notable difference between the two STS subtypes. The overall survival benefit was driven by a marked survival benefit in the liposarcoma subgroup. (HR = 0.511 [95%CI: 0.346 – 0.753]). In this subgroup median survival was prolonged by approximately 7 months (15.6 versus 8.4 months). In contrast, the HR in the leiomyosarcoma subgroup was 0.927 (95%CI: 0.714 – 1.203), with no increase in median survival. However, the study was not powered to demonstrate a significant effect on survival in the leiomyosarcoma subgroup. It might be concluded that the efficacy of eribulin in leiomyosarcoma is approximately comparable to that of dacarbazine. However, dacarbazine has not been demonstrated to produce a survival benefit in STS. Evidence of efficacy in liposarcoma is therefore convincing, while evidence for efficacy in leiomyosarcoma is uncertain.

The two Phase II studies used the novel endpoint of PFR12wks and were single-arm, non-comparative studies. In both studies PFR12wks was higher among liposarcoma subjects than among leiomyosarcoma subjects, a finding that is consistent with the efficacy results of the pivotal study. According to the EORTC Sarcoma group a PFR12wks > 40% indicates activity of a drug in the 2nd line STS setting. Using this criterion, activity in liposarcoma was demonstrated in both studies (46.9% in Study 207 and 81.3% in Study 217) and activity in leiomyosarcoma was demonstrated in one of the studies (31.6% in Study 207 and 42.1% in Study 217). It should be noted that most subjects in these studies were receiving eribulin as 3rd or later line therapy and therefore the cut-off of 40% may not be applicable.

The indication proposed by the sponsor would permit use of eribulin as 2nd or later line therapy. In the pivotal study only 9.2% of eribulin-treated subjects had received only one line of prior treatment for their advanced disease. In Study 207 the proportion was 30.7% and in Study 217 it was 35.3%. Therefore the majority of patients in the clinical trial program received eribulin as 3rd or later line therapy, and it could be argued that the proposed indication should be revised to reflect this. However, this reviewer would support an indication that does not exclude 2nd line use for the following reasons:

- There is no generally agreed standard for 2nd line therapy of STS;
- The current Australian clinical practice guideline for STS (4) recommends the use of dacarbazine after failure of doxorubicin and ifosfamide. Doxorubicin and ifosfamide are often used in combination as first-line therapy, and in this scenario dacarbazine would be recommended as 2nd line therapy. The pivotal study would suggest that eribulin is clearly superior to dacarbazine, at least for liposarcoma;
- Cytotoxic agents generally have greater efficacy in less heavily pre-treated subjects.

The submission for the new indication is based on a single pivotal study and the TGA has adopted an EMA guideline that deals with this situation (7). This guideline sets out certain 'prerequisites' that must be met for approval of such a submission. In the opinion of this reviewer, the design and results of the pivotal study allow the conclusion that these prerequisites have been met, at least for liposarcoma.

Overall the evidence submitted to support the efficacy of eribulin for liposarcoma is considered acceptable. Evidence for efficacy in leiomyosarcoma is uncertain. There is no adequate evidence for efficacy in other histological subtypes.

8. Clinical safety

Eribulin is known to be associated with the following toxicities, as described in the current PI:

- Myelosuppression, mainly manifesting as neutropaenia but also including anaemia, thrombocytopaenia and febrile neutropaenia;
- Peripheral neuropathy;
- QT prolongation;
- Gastrointestinal toxicity including anorexia, nausea, vomiting, diarrhoea, constipation, and stomatitis;
- Liver function test abnormalities;
- Fatigue, alopecia, and musculoskeletal pain.

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

8.1.1. Pivotal efficacy study (Study 309)

In the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs) were recorded throughout the study. AEs were coded into standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA) and were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.
- Comprehensive physical examinations were conducted at baseline, on Day 1 of each cycle and at the off-treatment visit. Symptom-directed examinations were conducted at other study visits.
- Laboratory tests were performed at baseline, Days 8 and 15 of Cycle 1, Days 1, 8 15 of Cycle 2, Days 1 and 8 of subsequent cycles and at the off-treatment visit. Parameters tested were:

- Haematology: haematocrit, haemoglobin, RBC, platelet count, WBC with differential count (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils, [ANC]), MCH, MCHC and MCV.
- Biochemistry: chloride, potassium, sodium, BUN or urea, serum creatinine, magnesium, phosphorus, calcium, albumin, total protein, ALP, ALT, AST, conjugated (direct) and total bilirubin, LDH.
- Urinalysis (glucose, haemoglobin (or blood), ketones, pH, protein and specific gravity) was performed on Day 1 of each cycle.
- ECGs were collected at baseline, Cycle 1/Day 1 pre-dose and end of infusion (Arm A and Arm B), Cycle 1/ Day 8 pre-dose and end of infusion (Arm A only), Cycle 2/Day 1 pre-dose and end of infusion (Arm A and Arm B), Cycle 2/Day 8 pre-dose and end of infusion (Arm A only), Cycle 3 and all subsequent cycles on Day 1 pre-dose (Arm A and Arm B), and Day 8 pre-dose (Arm A only) and at the off-treatment Visit (Arm A and Arm B).

8.1.2. Phase II efficacy studies (studies 207 and 217)

Safety data collected in the two Phase II studies was similar in nature and extent to that collected in the pivotal study.

8.1.3. Other safety data

The sponsor's Summary of Clinical Safety (SCS) presented safety data for the following populations:

- The pivotal study (Study 309 - eribulin versus dacarbazine);
- A pooled population of sarcoma patients who received eribulin in Studies 207, 217 and 309 (n=404);
- A pooled population of metastatic breast cancer (MBC) patients who had received eribulin (n=1559). Most of these patients had participated in studies previously evaluated by the TGA. However the population included 56 subjects who had participated in a single-arm Phase II study (Study 206) that had not been reviewed previously by the TGA. The safety findings from this study are reviewed in section *Study 206*.
- A pooled population of sarcoma and MBC subjects (n=1963).

The data presented in the SCS has been used for the review of safety in this report. The SCS also analysed a collection of adverse events of special interest (AESI), based on MedDRA terms. These are listed in Table 20.

Table 20: Adverse events of special interest A number of sponsor derived queries) SDQs) have been used in this document to describe AEs of special interest (AESIs). These SDQs are described below.

AESI	Terms used in SDQ
Alopecia	Alopecia, alopecia areata, alopecia scarring, alopecia syphilitic, alopecia totalis, alopecia universalis, androgenic alopecia, application site alopecia, diffuse alopecia and radiation alopecia
Arthralgia/myalgia	Arthralgia and myalgia
Asthenia/fatigue	Asthenia, decreased activity, fatigue, lethargy, listless, malaise and sluggishness
Febrile neutropenia	Febrile neutropenia, neutropenic infection and neutropenic sepsis
Liver events	Alanine aminotransferase increased, anorectal varices haemorrhage, ascites, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, cholestasis, drug-induced liver injury, gamma-glutamyltransferase increased, haemorrhagic ascites, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatic pain, hepatic steatosis, hepatitis, hepatitis A, hepatitis acute, hepatitis toxic, hepatocellular injury, hepatomegaly, hepatotoxicity, hyperbilirubinaemia, hypoalbuminaemia, jaundice, liver abscess, liver disorder, liver function test abnormal, ocular icterus, oesophageal varices haemorrhage, transaminases increased.
Neutropenia	Granulocyte count decreased, granulocytopenia, neutropenia, and neutrophil count decreased
Peripheral neuropathy	Broad and narrow Standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) terms for peripheral neuropathy plus allodynia, dysgeusia and hyperesthesia.
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).

8.2. Patient exposure

Patient exposure is summarised in Table 21. A total of 404 subjects with STS were treated with eribulin in the submitted studies. The median duration of exposure was 12 weeks or 4 cycles. Median relative dose intensity was 93.4% of the planned dose. 40.8% of subjects require a dose delay and 25.7% required a dose reduction.

Table 21: Extent of exposure

	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

8.3. Adverse events

An overall summary of the incidence of AEs, SAEs etc. is shown in Table 22.

Table 22: Overview of AEs, SAEs etc.

	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. Study drug discontinuation in study 207 is reflected in the subject disposition summary Table 2.

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; see the Section entitled 'conventions' for details of groupings. Alopecia and neutropenia are reported as a single terms.

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal study

AEs occurred in 99.1% of subjects in the eribulin arm and 97.3% of subjects in the dacarbazine arm. AEs that were notably more common in the eribulin arm included neutropaenia (43.8% versus 23.7%), peripheral neuropathy (36.7% versus 15.2%), alopecia (35.0% versus 2.7%), pyrexia (27.9% versus 13.8%), stomatitis (13.7% versus 4.9%) and headache (18.1% versus 9.4%). Thrombocytopaenia was notably more common with dacarbazine treatment (27.7% versus 5.8%).

Grade 3 or higher AEs occurred in 67.3% of subjects in the eribulin arm and 56.3% of subjects in the dacarbazine arm. Grade ≥ 3 AEs occurring in at least 1% of subjects are summarised in Table 23. The pattern of these events was similar to that observed for all AEs with neutropaenia, infections and peripheral neuropathy being more common in the eribulin arm and thrombocytopaenia more common with dacarbazine.

Table 23: Grade ≥ 3 AEs (incidence ≥ 1%)

	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)
Anemia	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)
Pain	0	0	0	15 (1.0)	15 (0.8)
Mucosal inflammation	0	0	0	16 (1.0)	16 (0.8)
General physical health deterioration	2 (0.9)	1 (0.4)	7 (1.7)	7 (0.4)	14 (0.7)
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)
Investigations	**35 (15.5)**	**31 (13.8)**	**43 (10.6)**	**114 (7.3)**	**157 (8.0)**
ALT increased	3 (1.3)	4 (1.8)	6 (1.5)	32 (2.1)	38 (1.9)
Neutrophil count decreased	16 (7.1)	6 (2.7)	16 (4.0)	15 (1.0)	31 (1.6)
AST increased	1 (0.4)	2 (0.9)	3 (0.7)	25 (1.6)	28 (1.4)
White blood cell count decreased	8 (3.5)	8 (3.6)	8 (2.0)	16 (1.0)	24 (1.2)
GGT increased	3 (1.3)	2 (0.9)	3 (0.7)	15 (1.0)	18 (0.9)
ECG QT prolonged	5 (2.2)	3 (1.3)	5 (1.2)	3 (0.2)	8 (0.4)
Hemoglobin decreased	0	3 (1.3)	0	7 (0.4)	7 (0.4)
Platelet count decreased	2 (0.9)	7 (3.1)	2 (0.5)	1 (0.1)	3 (0.2)
Lymphocyte count decreased	0	4 (1.8)	0	2 (0.1)	2 (0.1)

Table 23 continued: Grade ≥ 3 AEs (incidence ≥ 1%)

	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)			
Metabolism and nutrition disorders	**23 (10.2)**	**16 (7.1)**	**39 (9.7)**	**108 (6.9)**	**147 (7.5)**
Hypokalemia	6 (2.7)	4 (1.8)	10 (2.5)	29 (1.9)	39 (2.0)
Hyperglycemia	7 (3.1)	3 (1.3)	7 (1.7)	20 (1.3)	27 (1.4)
Hypophosphatemia	2 (0.9)	1 (0.4)	7 (1.7)	9 (0.6)	16 (0.8)
Hyponatremia	4 (1.8)	4 (1.8)	4 (1.0)	8 (0.5)	12 (0.6)
Hypoalbuminemia	2 (0.9)	1 (0.4)	5 (1.2)	3 (0.2)	8 (0.4)
Hypocalcaemia	3 (1.3)	0	3 (0.7)	5 (0.3)	8 (0.4)
Respiratory, thoracic and mediastinal disorders	**16 (7.1)**	**12 (5.4)**	**29 (7.2)**	**99 (6.4)**	**128 (6.5)**
Dyspnea	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)
Pleural effusion	1 (0.4)	1 (0.4)	2 (0.5)	15 (1.0)	17 (0.9)
Respiratory failure	4 (1.8)	2 (0.9)	4 (1.0)	8 (0.5)	12 (0.6)
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)
Intestinal obstruction	4 (1.8)	4 (1.8)	6 (1.5)	2 (0.1)	8 (0.4)
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)
Device related infection	2 (0.9)	1 (0.4)	5 (1.2)	5 (0.3)	10 (0.5)
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)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**10 (4.4)**	**6 (2.7)**	**26 (6.4)**	**42 (2.7)**	**68 (3.5)**
Cancer pain	2 (0.9)	0	5 (1.2)	3 (0.2)	8 (0.4)
Tumor pain	1 (0.4)	1 (0.4)	10 (2.5)	6 (0.4)	16 (0.8)

Table 23 continued: Grade ≥ 3 AEs (incidence ≥ 1%)

	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)			
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.

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.

8.3.1.2. Other studies

The incidence of AEs in the pooled STS population was 98.8%. The pattern of AEs was similar to that observed in the pivotal study. The incidence of Grade ≥ 3 AEs in the pooled STS population was 66.1%, with a pattern of events similar to the pivotal study. The incidence of Grade ≥ 3 AEs in the STS population appeared slightly lower than the incidence in the pooled MBC population (66.1% versus 72.0%).

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal study

Treatment-related AEs occurred in 92.9% of subjects in the eribulin arm and 90.6% of subjects in the dacarbazine arm. Grade 3 or higher treatment-related AEs occurred in 54.4% of subjects in the eribulin arm and 40.2% of subjects in the dacarbazine arm. The pattern of treatment-related AEs was very similar to that observed for all AEs.

8.3.2.2. Other studies

In the pooled STS population the incidence of treatment-related AEs was 92.8% and the incidence of Grade ≥ 3 treatment-related AEs was 50.5%. The pattern of treatment-related AEs was again very similar to that observed for all AEs.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Deaths

Pivotal study

The overall incidence of death (in the safety analysis set) was 77.0% (174/226) for the eribulin arm and 81.3% (182/224) in the dacarbazine arm. Most deaths were due to progressive disease (68.1% for eribulin and 67.4% for dacarbazine).

There were 10 subjects in the eribulin arm and 3 subjects in the dacarbazine arm who had AEs leading to death. All of these deaths occurred within 30 days of the last dose of study drug.

None of the 3 deaths in the dacarbazine arm were assessed as being related to study drug. One of the deaths in the eribulin arm was investigator-assessed by the as being possibly treatment-related. This subject [information redacted] White female with uterine leiomyosarcoma who presented with Grade 4 neutropaenia and sepsis on Day 54 of treatment and died 9 days later. Another subject [information redacted] White female with liposarcoma, presented with Grade 4

neutropaenia and septic shock on Day 59 of treatment and died on Day 60. Although the investigator did not consider the death to be treatment-related, the sponsor considered it was possibly related.

Other studies

In Study 207, 113/127 subjects (89.0%) had died by the date of data cut-off. Three subjects had an adverse event leading to death. Only one of these was assessed as being related to eribulin. This was a 76 year-old female with leiomyosarcoma who received 3 cycles or eribulin. She developed cerebral ischaemia on Day 66 of treatment and died approximately 1 month later. Prior to enrolment in the study she had a past history of hypertension, hypercholesterolaemia and ischaemic heart disease. The investigator considered that the event was possibly related to eribulin. The sponsor considered that a relationship was unlikely given the subject's previous medical history.

In Study 217, 39/51 subjects (76.5%) had died by the date of data cut-off. Of these, 36 were due to progressive disease. One subject had an adverse event that led to death (cardiac failure). The event was assessed as being unrelated to eribulin.

AEs leading to death in the Phase II studies are summarised in Table 24.

Table 24: Studies 207 and 217 AEs leading to death

Study	Subject ID	Age(yr), Sex, Race	Date of Death/ Study Day of Death[a]	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]
Study 207			26 September 2009 /12	Malignant pleural effusion	26 September 2009 /12	Not related	9	3
			04 November 2007 / 152	General physical health deterioration	04 November 2007 / 152	Not related	134	18
			13 September 2008 / 94	Cerebral ischemia	16 August 2008 / 66	Possibly related	57	36
Study 217			01 May 2012 / 106	Cardiac failure	27 March 2012 / 71	Not related	57	49

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.

8.3.3.2. Serious AEs (SAEs)

An SAE was defined as any adverse experience that resulted in death; was life threatening; required inpatient hospitalization or prolongation of a hospitalization; resulted in persistent or significant disability/incapacity; resulted in a congenital anomaly/birth defect; or was an important medical event that could jeopardize the subject and required medical or surgical intervention to prevent any of the outcomes listed above.

Pivotal study

The overall incidence of SAEs (other than AEs leading to death) was similar in the two arms (32.7% versus 31.3%). Non-fatal SAEs occurring in at least 1% of subjects are summarised in Table 25.

Serious infections were more common with eribulin (8.8% versus 3.6%) as were serious events of pyrexia (4.4% versus 1.8%). Serious haematological events were slightly more common in the dacarbazine arm (7.5% versus 11.6%) mainly due to a higher incidence of severe thrombocytopaenia (0% versus 5.8%).

Table 25: Serious AEs (Incidence ≥ 1%)

	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)	83 (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

Other studies

In the pooled STS population the overall incidence of non-fatal SAEs was 33.2%. SAEs appeared to be more common in the pooled STS population than in the pooled MBC population (33.2% versus 22.1%). However, the incidence of related SAEs was comparable (12.2% versus 10.3%). The pattern of SAEs in these populations was similar to that observed in the pivotal study.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal study

The overall incidence of AEs leading to discontinuation was slightly higher in the eribulin arm (7.5% versus 4.9%). Infections were a more common cause of discontinuation with eribulin (3 versus 0). Discontinuations due to haematological toxicity and neuropathy occurred with comparable frequency in the two arms.

8.3.4.2. Other studies

In the pooled STS population the overall incidence of AEs leading to discontinuation was 5.2%. This compared favourably with the incidence in the pooled MBC population (10.6%).

8.3.5. AEs of special interest

8.3.5.1. Peripheral neuropathy

Peripheral neuropathy events occurred more frequently with eribulin than with dacarbazine (36.7% versus 15.2%). With eribulin, approximately 10% of cases were assessed as being Grade ≥ 3 AEs. Median time to onset was approximately 20 weeks and only a minority of subjects had resolution of the event at 60 days post treatment.

8.3.5.2. Neutropaenia

Neutropaenia occurred more commonly with eribulin than with dacarbazine. However, the incidence of febrile neutropaenia was comparable. In the pooled STS population, 87.3% of subjects who developed grade 3 or 4 neutropaenia recovered to grade 0 or 1. Median recovery time was 8.0 days.

8.3.5.3. Arthralgia/myalgia

AEs of arthralgia/myalgia were slightly more common with eribulin than with dacarbazine. However, no events of Grade 3 or higher were reported in the STS studies.

8.3.5.4. Asthenia/fatigue

AEs of asthenia/fatigue occurred with similar frequency in the two arms of the pivotal study.

8.3.5.5. Alopecia

AEs of alopecia occurred more frequently with eribulin.

8.3.5.6. Liver events

In the pivotal study liver events were reported in 19.5% of subjects in the eribulin arm and 12.1% of subjects in the dacarbazine arm. Grade 3 or higher events were reported in 5.8% and 3.1% of subjects respectively. Most of the events were abnormal LFT results. Results of LFTs are summarised in *Laboratory tests, Liver fu*nction below.

8.3.5.7. QT prolongation

AEs of QT prolongation are summarised in Table 26. Treatment-related AEs of QT prolongation were slightly more common with eribulin in the pivotal study (6.2% versus 4.9%). Most of the events were ECG abnormalities. There were no episodes of sudden death, cardiac arrest etc. in the STS studies. ECG findings with respect to QT prolongation are summarised in section *Laboratory tests*, *Electrocardiograph*.

Table 26: AEs 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

8.4. Laboratory tests

8.4.1. Liver function

The incidences of Grade 3 or 4 abnormalities of liver function tests were infrequent and occurred with comparable frequency in the two treatment arms in the pivotal study. Dacarbazine is known to be associated with hepatic toxicity.

In the STS studies there were a total of 8 eribulin-treated subjects with concurrent elevations of bilirubin (≥ 1.5 x ULN) and AST or ALT (≥ 3 x ULN). Six of these subjects had hepatic disease involvement (at baseline), 1 had ischaemic hepatic necrosis and 1 had hepatic congestion associated with cardiac failure. None of the cases met Hy's law criteria for severe drug-induced liver injury.

8.4.2. Kidney function

In the pivotal study there was no Grade 3 or 4 increases in serum creatinine in either treatment group. Grade 1 and 2 abnormalities occurred with similar frequency in the two groups. The incidence of grade 3 or 4 increases in serum creatinine in the pooled STS population was 0.7%, which is similar to that observed in the pooled MBC population (0.9%).

8.4.3. Other clinical chemistry

Decreased calcium, decreased potassium and hyperglycaemia occurred more commonly in the eribulin arm of the pivotal study.

Comment: Hypokalaemia, hypomagnesaemia, hyperglycaemia and hypophosphataemia are currently listed in the eribulin PI as common adverse reactions. Hypocalcaemia is not currently listed.

8.4.4. Haematology

Grade 3 or 4 abnormalities of haematology parameters: Neutropaenia and leukocytopaenia were more common with eribulin in the pivotal study. Thrombocytopaenia was more common with dacarbazine.

8.4.5. Urinalysis

According to the Summary of Clinical Safety, eribulin had no notable effects on urinalysis parameters. The study report for Study 309 did not present any analyses of urinalysis parameters.

8.4.6. Electrocardiograph

Events of QT interval prolongation on ECG occurred with comparable frequency in the two arms of the pivotal study. The comparator dacarbazine is not known to be associated with significant QT prolongation.

Comment: These data do not clearly demonstrate an effect of eribulin on the QT interval. Also, a PK/PD analysis did not demonstrate a relationship between eribulin systemic exposure and QT interval. However, the current PI contains a warning statement regarding QT prolongation. In the absence of a 'Thorough QT study' an effect has not been excluded and it is appropriate to retain the warning.

8.4.7. Vital signs

Over the course of the pivotal study there were no clinically significant differences between the treatment arms in average values for blood pressure (systolic and diastolic), pulse rate, temperature or weight.

8.4.8. Study 206

The current submission included a study report for a Phase II trial in breast cancer (Study 206) that had not previously been reviewed by the TGA. The safety findings of this study are briefly reviewed here for completeness.

The study was a Phase II, single-arm trial of eribulin as monotherapy in the first line treatment of locally recurrent or metastatic human epidermal growth factor receptor two (HER2) negative breast cancer. It was conducted between 2011 and 2013 at 16 centres in the United States. All subjects received eribulin 1.4 mg/m^2 IV over 2-5 minutes on Days 1 and 8 of a 21 day cycle until progressive disease occurred.

A total of 56 subjects were treated. Median duration of treatment was 4.5 months. An overall summary of AEs, SAEs etc. is shown in Table 27. The pattern of toxicity was consistent with that previously associated with eribulin treatment, with cytopaenias, peripheral neuropathy, GIT events, fatigue, alopecia and musculoskeletal events being common. Neutropaenia was the most common serious AE. There were two deaths during the study. One subject died after developing a pericardial effusion, which was secondary to disease progression. The other died of disease progression. Neither death was assessed as being related to eribulin. Laboratory testing results were consistent with the known adverse event profile of eribulin.

Comment: Overall the safety findings of this study were consistent with the toxicity profile previously identified for eribulin in patients with breast cancer.

Table 27: Study 206 Overall incidence of AEs, SAEs etc

Category	Eribulin mesylate (N=56) n (%)
All TEAEs	56 (100.0)
Grade ≥3 TEAEs	44 (78.6)
Grade 3-4 TEAEs	43 (76.8)
Treatment-related TEAEs[a]	56 (100.0)
Treatment-related Grade 3-4 TEAEs	36 (64.3)
Serious TEAEs, including deaths	17 (30.4)
Treatment-related serious TEAEs	5 (8.9)
All Deaths	2 (3.6)
Deaths >30 days after last dose	2 (3.6)[b]
Disease progression	1 (1.8)
Adverse event	1 (1.8)[b]
TEAEs leading to study drug dose modification:	33 (58.9)
Withdrawal	6 (10.7)
Dose reduction	20 (35.7)
Dose delay	25 (44.6)
Related TEAEs leading to study drug dose modification	30 (53.6)
TEAEs of special interest	
Alopecia	47 (83.9)

MedDRA version 16.0.
For each category, a subject with two or more TEAEs in that category is counted only once.
Only rows with nonzero values are shown.
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
a: Includes TEAEs reported by the investigator to be possibly or probably related to study drug or TEAEs with missing causality.
b: TEAEs that led to death occurred during study treatment.

8.5. Post-marketing experience

No post-marketing data were included in the clinical module of the submission.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

Eribulin is known to be associated with hepatic toxicity. In the pivotal study the incidence of LFT abnormalities was comparable to that observed with dacarbazine, another agent known to be associated with hepatotoxicity. In the STS studies there were no cases meeting the criteria for Hy's law, which is predictive of severe drug-induced liver injury. There was one case of serious hepatotoxicity in the eribulin arm of the pivotal study. This was found to be due to disease progression with biliary obstruction and was assessed as unrelated to study drug. There were no serious hepatic AEs in Study 206.

8.6.2. Haematological toxicity

Bone marrow suppression is a known adverse reaction with eribulin and was very common in the STS studies and Study 206. There were no cases of serious pancytopaenia reported in the STS studies or Study 206.

8.6.3. Serious skin reactions

The current PI for eribulin lists Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) as adverse reactions that have been observed with eribulin in the post-market setting. There was no serious skin AEs reported in the STS studies or in Study 206.

8.6.4. Cardiovascular safety

The current PI for eribulin lists QT prolongation, tachycardia, hot flushes, deep venous thrombosis and pulmonary embolism as cardiovascular adverse reactions associated with eribulin.

Data from the STS studies on QT prolongation are described in *Laboratory tests, Electrocardiograph* above. In the pivotal study serious cardiac disorders occurred in 0.9% of subjects in both arms. Serious cardiac events in the eribulin arm were atrial fibrillation (1) and pericardial effusion (1). In the Phase II studies there was one additional report of serious pericardial effusion and one of serious cardiac failure.

Serious vascular disorders were more common with dacarbazine (2.2% versus 0.9%). Serious vascular events in the eribulin arm were superior vena cava syndrome (1) and vena cava thrombosis (1). In the Phase II studies there were two additional serious AEs of thrombosis.

8.6.5. Unwanted immunological events

Two subjects in the STS studies experienced a Grade 1 hypersensitivity reaction to eribulin. One event was classified as serious. This subject had symptoms of cough, sweating and hot flashes. The event resolved in one day and the subject continued further treatment with the drug.

8.7. Other safety issues

8.7.1. Safety in special populations

The sponsor's Summary of Clinical Safety presented analyses of safety in various subgroups. For the pooled STS population, findings included the following:

- Incidence of AEs, SAEs etc. was generally similar in subjects aged < 65 years (n=314) and those aged ≥ 65 years (n=90). However, discontinuations due to AEs were more common in the elderly (8.9% versus 4.1%).
- The incidence of Grade 3 or higher neutropaenia was more common in Asian/Pacific Islander subjects (n=70) than in white subjects (n=161) – 81.4% versus 41.0%.

- Incidence of AEs, SAEs etc. was generally similar in male (n=151) and female (n=253) subjects. However, discontinuations due to AEs were more common in women (7.1% versus 2.0%).

8.8. Evaluator's overall conclusions on clinical safety

In STS subjects, the toxicity profile of eribulin was consistent with that previously documented in breast cancer subjects. No new safety issues were identified in the STS studies. Common adverse events observed in STS subjects treated with eribulin were haematological toxicities (especially neutropaenia), peripheral neuropathy, GIT events, fatigue and alopecia.

The drug was moderately more toxic than dacarbazine with a higher incidence of Grade ≥ 3 AEs (67.3% versus 56.3%) and AEs leading to withdrawal (7.5% versus 4.9%). Also, there were 2 deaths in the pivotal study that appeared to be related to eribulin, compared to none related to dacarbazine. Both deaths followed the development of severe neutropaenia. However, the overall effect of eribulin on mortality is favourable compared to dacarbazine, at least in the subpopulation of patients with liposarcoma.

The relatively low incidence of discontinuation due to AEs (7.5%) suggests that the toxicity of eribulin was manageable.

Previously treated unresectable STS is a serious, life-threatening condition, as evidenced by a median survival of only 11.5 months with dacarbazine treatment in the pivotal study. For such a patient group the toxicity of eribulin, as described above, is considered acceptable.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of eribulin in subjects with liposarcoma are:

- A statistically and clinically significant reduction in the risk of death, with a hazard ratio of 0.511 (95%CI: 0.346 – 0.753) and a prolongation of median survival by approximately 7 months (15.6 versus 8.4 months), compared to dacarbazine treatment.

The benefits of eribulin in subjects with leiomyosarcoma are uncertain. The evidence to support a beneficial effect of eribulin in other histological subtypes of STS, compared to dacarbazine, is inadequate.

Eribulin is not associated with significant quality of life benefits compared to dacarbazine.

9.2. First round assessment of risks

The risks of eribulin in the treatment of soft tissue sarcoma are:

- Various risks previously documented with use of the drug. These include haematological toxicities, peripheral neuropathy, GIT events, fatigue and alopecia.

The overall risks with eribulin treatment for STS are moderately greater than those for dacarbazine.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of eribulin in the treatment of liposarcoma is favourable. Given the uncertainty of the drug's efficacy in leiomyosarcoma, a favourable benefit-risk balance for this

indication cannot be concluded. The benefit-risk balance of eribulin for other subtypes of STS is unfavourable.

10. First round recommendation regarding authorisation

It is recommended that eribulin be approved for the following indication only:

> *For the treatment of patients with unresectable liposarcoma, who have received prior chemotherapy for advanced or metastatic disease.*

11. Clinical questions

11.1. Efficacy

1. In Study 309, what was the PFS rate at 12 weeks for the two histological groups included in the trial (for both eribulin and dacarbazine)?

12. Second round evaluation of clinical data submitted in response to questions

Not applicable.

13. Second round benefit-risk assessment

Not applicable.

14. Second round recommendation regarding authorisation

Not applicable.

15. References

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