Xi'an Janssen Pharmaceutical Ltd

Synoptic Clinical Study Report

Multicenter, Open-label Study of YONDELIS (Trabectedin) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma

Protocol ET743SAR3006; Phase 3 (Part 1)

JNJ-17027907 (Trabectedin)

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Protocol No.: ET743SAR3006

Title of Study: Multicenter, Open-label Study of YONDELIS (Trabectedin) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma

Name of Active Ingredient(s): JNJ-17027907 (Trabectedin)

NCT No.: NCT01692678

Clinical Registry No.: CR017269

Study Center(s): Two centers in China

Publication (Reference): None

Study Period: Part 1: 29 August 2013 to 10 October 2016

Part 2: Not started yet.

Phase of Development: 3

OBJECTIVES:

Primary Objectives

Part 1: To find the maximum tolerated dose (MTD, ie, optimal dose) of trabectedin for Chinese subjects with locally advanced or metastatic liposarcoma or leiomyosarcoma (L-sarcoma) who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen.

Part 2: To evaluate whether the overall survival (OS) of the trabectedin group is superior to dacarbazine group in the same population as Part 1.

Secondary Objectives

Part 1: To characterize the plasma pharmacokinetics (PK) of trabectedin in the Chinese patient population, and to estimate OS, progression free survival (PFS), time to progression (TTP), objective response rate (ORR) and safety of trabectedin-treated subjects.

Part 2: To estimate PFS, TTP, ORR, and safety in the trabectedin group and dacarbazine group.

METHODS:

The study consisted of 2 parts. Subjects enrolled in Part 1 were to be excluded from participation in Part 2. Part 1 was a dose-finding part and Part 2 was planned to be a randomized, active-controlled, parallel-group, open-label Phase 3 study part.

The study (both Part 1 and Part 2) consisted of a Screening Phase (baseline radiographic disease assessments within 30 days before dosing [Part 1] or randomization [Part 2]), a Treatment Phase (21-day treatment cycles until documented disease progression or unacceptable toxicity) and a Follow-up Phase (contact every 30 days for the first 2 years after last dose and every 90 days thereafter until clinical cutoff date for survival status and subsequent anticancer therapy).

A Study Evaluation Team (SET) was planned to monitor safety data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study in Part 1.

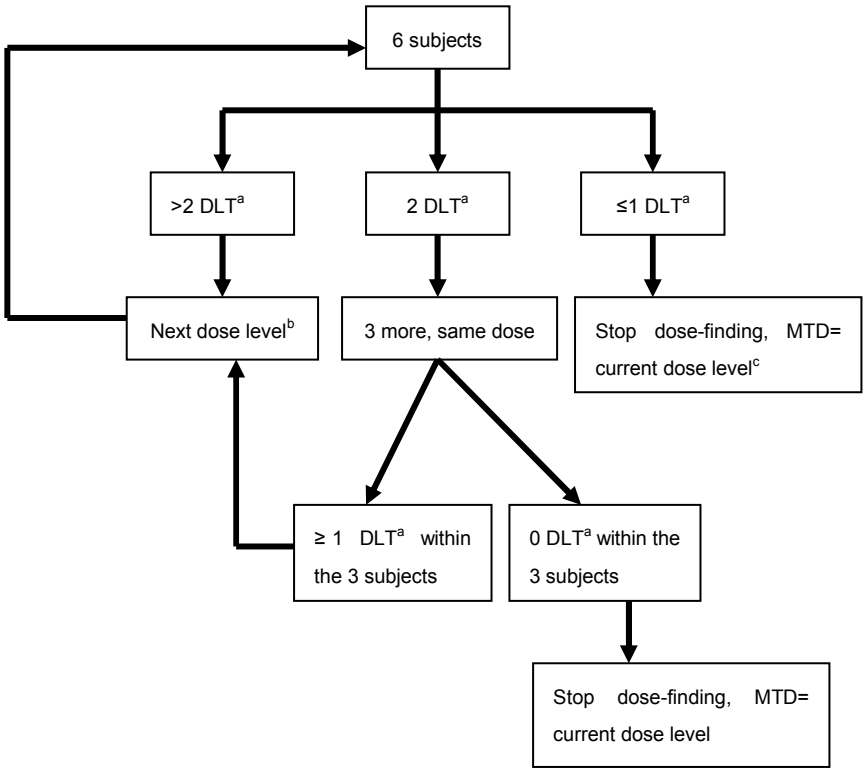
Part 1 (Dose Finding)

Part 1 was a dose de-escalation design and it was planned to investigate whether the dose of trabectedin approved for use in other countries was appropriate for use in the Chinese patient population. The initial dose was 1.5 mg/m^2 of trabectedin administered as a 24-hour intravenous (IV) infusion on Day 1 of each 21-day treatment cycle. Subsequent dose levels to be assessed, if necessary, were 1.2 mg/m^2 and 1.0 mg/m^2. Cohorts of 6 subjects were planned to be treated at each dose level. Dose-limiting toxicity (DLT) referred to any pre-defined adverse event (AE) that occurred during the first cycle (Cycle 1) of treatment, with the exception of those AEs that could be clearly defined as not related to the study drug. De-escalation to the next dose level would occur if more than 2 of the first 6 evaluable subjects (ie, subjects finishing at least one 21-day treatment cycle of trabectedin) at the current dose level experienced a DLT during Cycle 1. If $\leqslant$1 of the first 6 evaluable patients developed a DLT during Cycle 1, the current dose level would be determined as the MTD. If 2 of the first 6 evaluable patients developed a DLT during Cycle 1, 3 additional subjects would be enrolled at that dose level. If none of the 3 additional evaluable subjects developed a DLT during Cycle 1, the current dose level was determined as the MTD. Otherwise, de-escalation to the next dose level would occur. At each dose level, if $\leqslant$1 of the first 6 evaluable patients developed a DLT during Cycle 1, 4 additional subjects would be enrolled at the same dose level for PK evaluation. A SET was planned to evaluate the results from each level to decide if the study dose was acceptable or if a de-escalation dose was to be investigated. The dose de-escalation scheme is presented in Figure 1. All subjects were to have blood samples collected for full PK evaluation. A subject was to continue to receive study drug until documented disease progression or unacceptable toxicity.

During the Follow-up Phase, subjects were to be monitored for survival status and the start of subsequent anticancer therapy.

The clinical cutoff date for the final analyses of Part 1 was to be 18 months after the last subject enrollment.

Figure 1: Dose de-escalation scheme-Part 1



AE=adverse event; DLT=dose-limiting toxicity; MTD=maximum tolerated dose; PK= pharmacokinetics

a. DLT referred to any pre-defined AE that occurred during Cycle 1 of treatment, with the exception of those AEs that can be clearly defined as not related to the study drug. The numbers in this figure refers to the number of subjects who develop DLT.
b. The dose of 1.0 mg/m^2 was the lowest dose level to be investigated in this study. The whole study (including Part 2) would stop if a MTD couldn't be determined after 9 evaluable subjects on 1.0 mg/m^2 of trabectedin treatment.
c. Added 4 subjects to evaluate PK.

A DLT was defined as 1 or more of the following events: (a) absolute neutrophil count (ANC) of $<0.5\times10^9$/L lasting more than 5 days or febrile neutropenia (neutrophils $<0.5\times10^9$/L, with a temperature ≥38.5°C or a temperature ≥38°C for ≥ 1 hr); (b) platelets of $<25\times10^9$/L; (c) any Grade 3 or 4 elevations in hepatic transaminases or Grade 1 elevation of bilirubin, and not recovered to pretreatment levels by Day 21 after treatment; (d) Grade 3 to 4 nonhematologic toxicities (except for nausea/vomiting in the absence of an appropriate antiemetic regimen treatment) other than hepatic.

AE of interest was defined as kinds of AEs including thrombocytopenia-bleeding, neutropenia- selected infections, CPK elevations-rhabdomyolysis, catheter related complications, liver injury, cardiac disorders and renal disorder. Preferred Terms (PT) of these groups are attached in Attachment Copy of AE of interest.

Part 2 (Randomized Controlled Phase 3 Study)

When the MTD was determined in Part 1, Part 2 was to be initiated to compare the efficacy and safety of the optimal dose of trabectedin with another active drug, dacarbazine, in a randomized controlled Phase 3 part. If the MTD identified in Part 1 was 1.5mg/m^2, Part 2 was to be conducted as part of the ongoing global randomized Phase 3 study, ET743-SAR-3007. Data from Part 2 and the global study were planned

to be combined using weighted Z statistic to test the treatment effect for Chinese patients. If any other dose was identified in Part 1, Part 2 was to be conducted as an independent Phase 3 study within China.

In either situation, Chinese subjects with L-sarcoma were to be randomly assigned in a 2:1 ratio to either the trabectedin or dacarbazine treatment group.

Study end date (ie, Part 2 end date) was planned to be the clinical cutoff date for the final OS analysis (for the clinical study report) or 30 days after the last dose of study drug administered, whichever was later.

Part 2 of the study had not been initiated at the time of this report.

There were 2 amendments to the protocol. The first amendment (13 February 2012) included the following changes: inclusion criteria (Patients with synovial sarcoma would not be eligible to participate in the study), study title (added "following Treatment With an Anthracycline and Ifosfamide"), study design of Part 2 (Part 2 changed from a single-arm study to an active drug comparative study) and Part 1 (The dose finding design in Part 1 changed from a 3+3 dose escalation to a dose de-escalation), definition of PFS (PFS definition was revised based on RECIST [Version 1.1] criteria, which allowed disease progression to be determined by symptomatic deterioration), and DLT (deleted "Grade 2 and above cardiac or neurologic toxicity" and "cardiac or neurologic"), objectives of each part (The primary efficacy endpoint for Part 2 was changed from PFS to OS. PFS became a secondary endpoint. Study hypotheses for Part 1 and Part 2 were added.), PK blood samples collection plan (The blood sample collection for the PK evaluations changed from the first 18 subjects [in both Part 1 and Part 2] to all subjects in Part 1.), and others so that the data of this study could be combined with the global study ET743-SAR-3007. The second amendment (10 March 2014) included the study inclusion criteria (Serum pregnancy test was also acceptable) and clinical operation. For more information about protocol amendments, please refer to the study protocol.[1]

Number of Subjects (planned and analyzed):

Part 1

Nine to 28 subjects were planned to be enrolled in Part 1 of the study. At each dose level, if $\leqslant$1 of the first 6 evaluable patients developed a DLT during Cycle 1, 4 additional subjects were planned to be enrolled at the same dose level for PK evaluation. As of the Part 1 clinical cut-off date (10 October 2016), 18 subjects were enrolled and analyzed.

Part 2

If the MTD found in Part 1 was 1.5 mg/m^2, approximately 48 subjects were planned to be enrolled into the global ET743-SAR-3007 Phase 3 study. If the MTD found in Part 1 was below 1.5 mg/m^2, 123 subjects were planned to be enrolled in a separate Phase 3 study, to be conducted in China alone. No subject was enrolled in Part 2 at this time.

Main Criteria for Inclusion:

Key inclusion criteria

1. 15 years of age or older at the time of screening.
2. Histologically proven, unresectable, locally advanced or metastatic liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic), or leiomyosarcoma.
3. Treated in any order with at least:
    - an anthracycline and ifosfamide containing regimen, or
    - an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen

Previous treatment must be reviewed by the sponsor before randomization may occur.

Key exclusion criteria

1. Prior exposure to trabectedin (both Part 1 and Part 2) or dacarbazine (Only Part 2).
2. Less than 3 weeks from last dose of systemic cytotoxic therapy, radiation therapy, or therapy with any investigational agent.
3. Other malignancy within the past 3 years. Exceptions: basal or nonmetastatic squamous cell carcinoma of the skin, cervical carcinoma in situ, or Federation Internationale de Gynecologie et d'Obstetrique (FIGO) Stage 1 carcinoma of the cervix.
4. Known central nervous system metastasis.

For a full list of inclusion and exclusion criteria, please refer to study protocol[1].

Test Product, Dose and Mode of Administration, Batch No.:

Test Product	Dose	Mode of Administration	Batch No.	Expiration Date
TRABECTEDIN	1.5 mg/m^2	intravenously guttae (IV.gtt)	4367866/4367421	4367866: 30 September 2015
TRABECTEDIN	1.2 mg/m^2	IV.gtt	4367866/4367421	4367421: 31 October, 2014

Duration of Treatment:

Subjects were to receive study drug until there was documented disease progression or unacceptable toxicity.

Criteria for Evaluation:

Safety Evaluations

Safety was to be evaluated by AEs, clinical laboratory tests, multiple gated acquisition scans (MUGA), electrocardiogram, vital signs, and physical examination. The safety data in Parts 1 and 2 were not to be pooled, and were to be analyzed separately. Dose-limiting toxicity (DLT) referred to any pre-defined AE that occurred during the first cycle (Cycle 1) of treatment, with the exception of those AEs that can be clearly defined as not related to the study drug.

Please refer to the Protocol[1] Time and Events Schedule for a more detailed safety evaluation schedule.

Pharmacokinetic evaluation

In Part 1, a series of blood samples were to be obtained to evaluate the full PK profile (including C_{max} [observed maximum plasma concentration, taken directly from the plasma concentration-time profile],, t_{max} [the time when C_{max} is observed, taken directly from the plasma concentration-time profile],, λ_z [first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time],, $t_{1/2}$ [elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$],, AUC_{last} [the area under the plasma concentration-time curve from time 0 to the last quantifiable time point, calculated by linear trapezoidal summation], AUC_∞ [the area under the plasma concentration –time curve from time 0 to infinity, calculated as $AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last measurable plasma

concentration and λz is the terminal rate constant],, CL [systemic clearance after IV dose, estimated by dividing the total administered dose by the plasma AUC_{∞}] and V_{ss} [the apparent volume of distribution at steady-state]) for trabectedin during the first 2 cycles (Cycles 1 and 2) for all subjects. Venous blood samples were collected on Days 1, 2, 3, 4, 5, and 8 for PK analysis at specific time points as defined in the protocol. For all the subjects participating in the full PK sampling schedule, 3 samples of 3 mL venous blood each were to be taken over 1.5 hours during drug treatment on Day 1. On Day 2, 6 samples of 3 mL venous blood each were to be collected over 8 hours, 1 before and the rest at intervals after treatment. Additionally, subjects were to return to the clinic on Days 3, 4, 5 and 8, for a 3-mL blood collection. A total of 39 mL of blood was to be collected for full PK in each of the first 2 cycles.

The concentrations of trabectedin in plasma were determined using validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) assays.

Efficacy evaluations/Endpoints

Efficacy was to be evaluated by tumor measurements and survival status.

Part 1: The efficacy endpoints were to include OS, PFS, TTP, ORR, and duration of response (DR).

Part 2: The primary endpoint was to be OS. The secondary endpoints were to include PFS, TTP, ORR, and DR.

OS was defined as the time between dosing (Part 1) or randomization (Part 2) and death.

PFS was defined as the time from dosing (Part 1) or randomization (Part 2) to the occurrence of disease progression or death, whichever occurred first.

TTP was defined as the time between dosing (Part 1) or randomization (Part 2) and disease progression.

ORR was defined as the proportion of subjects having complete response (CR) or partial response (PR) as best overall response based on reconciled radiographic disease assessment.

DR was defined only for subjects who have CR or PR as best overall response and was calculated from the date of the first documentation of response to the date of disease progression or death, whichever occurred first.

Data Quality Assurance:

The study was monitored according to the sponsor's current Standard Operating Procedure (SOP) for the Monitoring of Clinical Trials. Steps taken to ensure the accuracy and reliability of the clinical study data included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated study-site personnel prior to study start, and periodic monitoring visits by the sponsor or their delegate. The study-specific monitoring guidelines are stored in the trial master file (TMF). The Sponsor may have also conducted investigator site audits.

During the course of this study, several activities were implemented to ensure proper operational study oversight (documented in the TMF). These activities were focused on identification and resolution of operational and quality issues to ensure data integrity, protocol compliance, and safety of the study participants.

Written instructions were provided for the collection of source documentation. Source documentation was reviewed for accuracy and completeness by the sponsor during on-site monitoring visits, except for source data directly transmitted from the selected laboratory into the sponsor's database, and internal data reviews by various functions throughout the study and at the time of database lock. Discrepancies were resolved with the investigator or designees, as appropriate.

Statistical Methods:

Part 1 (Dose Finding Part)

There was no formal sample size calculation for this part. A total of 9 to 28 subjects were to be enrolled based on the traditional modified Fibonacci design. The efficacy and safety statistics were descriptive. Subjects were monitored for survival status and the start of subsequent anticancer therapies until the clinical cutoff date. All analyses of PFS, TTP, and OS were based on the Kaplan-Meier (KM) method to summarize the survival time. Response rate and the associated 95% confidence interval (CI) were provided for ORR. For DR, descriptive statistics, ie, mean, standard deviation, median and ranges, were provided.

The safety analysis set was to be used for safety analyses. All reported AEs with onset during the treatment phase (ie, treatment-emergent adverse events [TEAE]) would be included in the analysis and would be coded with Medical Dictionary for Regulatory Activities (MedDRA) 18.0. For each AE, the percentage of subjects who experienced at least 1 occurrence of the given event would be summarized by treatment group. The National Cancer Institute-Common Toxicity Criteria (NCI-CTCAE), Version 4.0, was to be used to grade the severity of AEs and to summarize clinical laboratory results.

For PK analyses, full trabectedin concentration versus time profiles was plotted for each subject and cycle. Mean concentration-time profiles were plotted for each dose regimen and cycle. Trabectedin concentration data at each time point derived from the full PK sampling were summarized with mean, standard deviation, and coefficient of variation for each treatment. The PK parameters were estimated using standard noncompartmental analysis and were summarized with mean, median, geometric mean, minimum, maximum, standard deviation and coefficient of variation for each treatment.

Part 2 (Randomized Controlled Phase 3 Study)

A bridging design to combine the efficacy information collected in the global study (ET743-SAR-3007) was planned in Part 2.

The sample size calculation for Part 2 was based on the OS as the primary endpoint, for which the information collected in the global study and local study was to be combined. A weighted Z statistic, ie, the log-rank statistic, was to be formulated, in which the information collected in the non-Chinese subgroup of the global study was to be down-weighted. It was assumed that the hazards for the 2 treatment groups would follow a proportional hazards model for OS. The test utilizing the weighted Z statistic to detect a difference between a median OS of 10 months in the dacarbazine group and a median OS of 13.5 months in the trabectedin group (hazard ratio [HR] =0.74), assuming the same treatment effect size for both global and local studies, at an overall 2-sided significance level of 0.05 with a power of 80%, required the following number of events:

1. If the MTD dose found in Part 1 was 1.5 mg/m^2, assuming a weight of 0.5 and approximately 60 Chinese subjects enrolled in the global study, 32 events would be required.
2. If the MTD dose found in Part 1 was below 1.5 mg/m^2, assuming a weight of 0.4 and 0 Chinese subjects enrolled in the global study, 82 events would be required.

Assuming an event rate of 66% (the same as ET743-SAR-3007), approximately 48 and 123 subjects needed to be randomized to the 2 treatment groups for the above two scenarios, respectively.

Since the major characteristics, ie, the etiology and current standard treatment of soft tissue sarcoma (STS) were not significantly different between the Chinese and western populations, considering the weight of the global study should be less than the actual proportion of global subjects in the whole sample size (global and local studies combined) (570/[570+123]≈0.8), it was reasonable to consider a weight of 0.5 for the data of the global registration trial (ET743-SAR-3007) in case the MTD was 1.5 mg/m^2. In case the MTD was below 1.5 mg/m^2, it was reasonable to consider a lower weight of 0.4, given the dose difference between the global and the local studies.

Efficacy analyses for Part 2 were to be performed using the intent-to-treat analysis set. All statistical tests and CIs- would be 2-sided with a significance level of 0.05 unless otherwise specified. The analysis of OS was planned after approximately 32 deaths (MTD=1.5 mg/m^2), or 82 deaths (MTD<1.5 mg/m^2) had been observed.

The primary analysis of OS was the comparison of OS between the 2 treatment groups. The unstratified log-rank test would be performed at α=0.05 (two-sided) based on the weighted statistic which combined the efficacy information from the global study (ET743-SAR-3007) and the local study. The distribution of OS would be estimated for each treatment group using the KM method. The median times to event with 2-sided 95% CIs would be estimated. The estimate of the HR and the 95% CI would also be provided. The effect of prognostic factors such as age (continuous variable), lines of prior chemotherapy (1 versus 2 or more), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score (0 versus 1), and sarcoma subtype (liposarcoma versus leiomyosarcoma) would also be examined in the supplementary analysis using the Cox proportional hazards model.

Methods similar to those used to evaluate OS would be used to analyze PFS and TTP except that all the analyses would be based on data from the local study. Comparison of the ORR between the 2 treatment groups would be made using the Fisher's exact test. Response rate and the associated 95% CI would be provided for each treatment group. For DR, descriptive statistics would be provided. No statistical testing would be performed.

RESULTS:

As of the clinical cutoff date (10 October 2016), Part 1 of the study was completed. This report only summarizes the results of Part 1.

STUDY POPULATION:

Eighteen subjects were enrolled in Part 1 of the study. Six subjects were enrolled in the 1.5 mg/m^2 dose cohort. Twelve subjects were enrolled in the 1.2 mg/m^2 dose cohort, 7 of which were enrolled for DLT evaluation and the other 5 subjects were enrolled for PK analyses after 1.2 mg/m^2 had been chosen as the MTD. All subjects discontinued treatment. The most common reasons for treatment discontinuation were withdrawal of consent (44.4%) and disease progression (38.9%). One subject in the 1.5 mg/m^2 cohort discontinued treatment due to an AE. (Table 1)

Table 1: Subject Disposition and Withdrawal Information; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Analysis set: all treated	6	12	18
Treatment Discontinuation	6(100%)	12(100%)	18(100%)
The Subject Withdraws Consent	3(50%)	5(41.7%)	8(44.4%)
The Subject Has Disease Progression	1(16.7%)	6(50%)	7(38.9%)
Adverse Event	1(16.7%)	0(0%)	1(5.6%)
Other	1(16.7%)	0(0%)	1(5.6%)
Physician Decision	0(0%)	1(8.3%)	1(5.6%)

Table 1: Subject Disposition and Withdrawal Information; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total

Note: Percentage is based on the number of subjects treated.

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Overall, the mean age of all subjects enrolled was 48.8 (standard deviation [SD] ± 12.11) years, and the majority were female (66.7%). All subjects had ECOG-PS of 1 except for 1 subject with a missing ECOG-PS score at baseline. Two thirds (66.7%) of subjects had leiomyosarcoma and the others (33.3%) had liposarcoma. The tumor subtypes included nonuterine (33.3%) and uterine (33.3%) subtypes of leiomyosarcoma, and myxoid +/- round cell (27.8%) and pleomorphic (5.6%) subtypes of liposarcoma. The median duration from the initial diagnosis to study entry was 921.5 days. However, the median duration from the initial diagnosis to study entry of subjects in the 1.5 mg/m^2 was 760.5 days, which was far shorter than that of subjects in the 1.2 mg/m^2 (1641.0 days). The median duration from the latest disease progression to study entry was 55.5 days. However, the median duration from the latest disease progression to study entry of subjects in the 1.5 mg/m^2 was 46 days, which was shorter than that of subjects in the 1.2 mg/m^2 (61.5 days).

Table 2: Demographics at Baseline and Baseline Disease Characteristics; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Age, years			
N	6	12	18
Mean (SD)	54.2 (7.00)	46.1 (13.44)	48.8 (12.11)
Median	55.0	52.5	52.5
Range	(44; 62)	(19; 61)	(19; 62)
Sex, n (%)			
N	6	12	18
Female	5 (83.3%)	7 (58.3%)	12 (66.7%)
Male	1 (16.7%)	5 (41.7%)	6 (33.3%)
Race, n (%)			
N	6	12	18
Chinese	6 (100.0%)	12 (100.0%)	18 (100.0%)
Ethnicity, n (%)			
N	6	12	18
Han	6 (100.0%)	11 (91.7%)	17 (94.4%)
Other	-	1 (8.3%)	1 (5.6%)
Weight, kg			
N	6	12	18
Mean (SD)	65.6 (18.04)	66.8 (12.79)	66.4 (14.21)
Median	57.5	65.3	64.0
Range	(52; 100)	(50; 95)	(50; 100)
Height, cm			
N	6	12	18
Mean (SD)	162.6 (9.60)	167.3 (6.59)	165.7 (7.77)
Median	158.0	164.0	164.0
Range	(155; 178)	(158; 179)	(155; 179)
ECOG-PS, n (%)			
N	6	12	18
1	6 (100.0%)	11 (91.7%)	17 (94.4%)

Table 2: Demographics at Baseline and Baseline Disease Characteristics; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Left ventricular Ejection Fraction Methods, n (%)			
N	6	12	18
Echocardiogram	3 (50.0%)	10 (83.3%)	13 (72.2%)
MUGA	3 (50.0%)	2 (16.7%)	5 (27.8%)
Left ventricular Ejection Fraction Results,%			
N	6	12	18
Mean (SD)	64.9 (2.40)	66.3 (4.43)	65.8 (3.86)
Median	64.7	66.4	65.7
Range	(62; 69)	(57; 74)	(57; 74)
Tumor Type, n (%)			
N	6	12	18
Leiomyosarcoma	5 (83.3%)	7 (58.3%)	12 (66.7%)
Liposarcoma	1 (16.7%)	5 (41.7%)	6 (33.3%)
Tumor Subtype, n (%)			
N	6	12	18
Myxoid+/- round cell	-	5 (41.7%)	5 (27.8%)
Nonuterine	4 (66.7%)	2 (16.7%)	6 (33.3%)
Pleomorphic	1 (16.7%)	-	1 (5.6%)
Uterine	1 (16.7%)	5 (41.7%)	6 (33.3%)
Duration of Initial Diagnosis Prior to Study Entry, day			
N	6	12	18
Mean (SD)	827.8 (424.76)	1641.6 (1324.97)	1370.3 (1159.66)
Median	760.5	1641.0	921.5
Range	(266; 1533)	(152; 4184)	(152; 4184)
Duration of the Latest Disease Progression Prior to Study Entry, day			
N	6	12	18
Mean (SD)	54.5 (37.98)	83.8 (78.20)	74.0 (67.70)
Median	46.0	61.5	55.5
Range	(18; 102)	(4; 270)	(4; 270)

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Listings of demographics and baseline disease characteristics are provided in Attachment LSIDEM01A and Attachment LSIDEM01B.

Listings of previous therapies are presented in Attachment LSICM01, Attachment LSICM02, Attachment LSICM03 and Attachment LSICM04. A listing of concomitant medications is provided in Attachment LSICM05.

All subjects received at least 1 dose of study drug. A listing of study drug exposure is presented in Attachment LSIEXP01.

SAFETY RESULTS:

Dose Limiting Toxicity

In Part 1, 6 of subjects were dosed in the 1.5 mg/m^2 cohort, with 6 evaluable for DLT. A further 12 of subjects were dosed within the 1.2 mg/m^2 cohort. Six of the 7 subjects dosed within the 1.2mg cohort for DLT evaluation were evaluable (1 subject's treatment duration was less than 21 days thus not evaluable for DLT), and the other 5 subjects were enrolled for PK data collection per regulatory requirement. Within both cohorts, 4 of 6 (66.7%) evaluable patients in the 1.5 mg/m^2 cohort experienced a DLT, while 1 of 7 (14.2%) evaluable subjects in the 1.2mg/m^2 cohort experienced a DLT. Brief narratives for each subject experiencing a DLT are provided below.

In the 1.5 mg/m^2 cohort, the following 4 subjects experienced a DLT:

- Subject [redacted] is a female, 44 years old subject, who was diagnosed with nonuterine leiomyosarcoma. The subject experienced Grade 3 alanine aminotransferase (ALT) increased (495U/L) on Cycle 1 Day 8, accompanied by other Grade 2 AEs of gamma-glutamyltransferase (GGT) increased, aspartate aminotransferase (AST) increased and neutrophil count decreased. The AE of ALT increased was resolved to Grade 1 ALT increased 7 days later (84U/L). The ALT did not return to pretreatment level (19U/L) by Day 21 (50U/L on Day 21). The AE of ALT increased was considered to be very likely related to the treatment and a DLT, because it met the 3rd criterion for a DLT.

- Subject [redacted] is a female, 60 years old subject, who was diagnosed with nonuterine leiomyosarcoma. On Cycle 1 Day 4, the subject experienced Grade 3 decreased immune responsiveness and Grade 3 decreased appetite, accompanied by other Grade 3 AEs of nausea and vomiting. The subject also experienced Grade 4 ALT increased (837U/L), Grade 3 AST increased (498U/L) and Grade 1 bilirubin increased (26.5 umol/L) on Cycle 1 Day 8. The AE of Grade 1 bilirubin increased was resolved 7 days later (16 umol/L). The events of ALT and AST increased were resolved to Grade 3 (404 U/L) and Grade 2 (157 U/L) three days later. On Cycle 1 Day 15, the AEs of ALT increased and AST increased were resolved to Grade 2 (161 U/L) and Grade 1 (70 U/L) respectively. But ALT and AST did not return to pretreatment levels (32U/Land 24U/L respectively) by Day 21 (67U/L and 41U/L, respectively). These AEs were accompanied by other Grade 1 AEs of white blood cell (WBC) count decreased, neutrophil count decreased, blood creatinine increased, and blood creatine phosphokinase increased and Grade 2 AEs of platelet count decreased, GGT increased, and decreased immune responsiveness. The events of Grade 3 decreased immune responsiveness, Grade 3 decreased appetite, Grade 4 ALT increased, Grade 3 AST increased, and Grade 1 bilirubin increased were considered to be very likely related to the treatment and were DLTs, because they met the 3rd and 4th criteria for a DLT.

- Subject [redacted] is a female, 60 years old subject, who was diagnosed with pleomorphic liposarcoma. The subject experienced Grade 3 decreased appetite on Cycle 1 Day 3, accompanied by Grade 3 nausea and Grade 2 vomiting. On Cycle 1 Day 4, the subject experienced Grade 3 ALT increased (696U/L) and Grade 3 AST increased (758U/L), and the ALT and AST increased events were resolved to Grade 2 (266U/L and 125 U/L respectively) 4 days later, and events were resolved to Grade 1 on Cycle 1 Day 11(156U/L and 79 U/L respectively). The ALT and AST did not return to pretreatment levels (15U/L and 14U/L, respectively) by Day 21 (141U/L and 318U/L respectively). These AEs were accompanied by Grade 3 anemia and Grade 2 hypoalbuminemia. The subject experienced Grade 3 neutrophil count decreased (0.8 x10^9/L) on Cycle 1 Day 8, accompanied by Grade 2 AEs of AST increased and ALT increased, Grade 1 pyrexia, and Grade 3 white blood cell count decreased. The severity of the neutrophil count decreased increased to Grade 4 (0x10^9/L) 1 day later (0.4 x10^9/L on Day 9 and 0x10^9/L on Day 10). The subject's ANC of <0.5 x10^9/L lasted more than 5 days. On Cycle 1 Day 10, the subject experienced Grade 4 platelet count decreased (17 x10^9/L); until Cycle 1 Day 18, the platelet counts were <25×10^9/L consistently.

These events were considered to be very likely to the treatment and were DLTs, because they met all the criteria of a DLT.

- Subject [redacted] is a female, 52 years old subject, who was diagnosed with nonuterine leiomyosarcoma. The subject experienced Grade 3 ALT increased (721U/L) and Grade 3 AST increased (507U/L) on Cycle 1 Day 3. The ALT and AST levels increased to 1218 U/L and 530U/L two days later. The ALT increased event was resolved to Grade 2 (285 U/L) on Cycle 1 Day 15 and resolved to Grade 1 (185U/L) 6 days later. The AST increased event was resolved to Grade 2 (517 U/L) on Cycle 1 Day 10 and resolved to Grade 1 (77 U/L) 5 days later. The ALT and AST levels did not return to pretreatment levels (18U/L and 14U/L respectively) by Day 21 (185U/L and 68U/L, respectively). This subject also experienced Grade 3 decreased appetite on Cycle 1 Day 3, accompanied by Grade 1 vomiting, Grade 2 nausea, and Grade 1 hypokalemia. The ALT increased, AST increased, and decreased appetite were considered to be probably related to study the treatment and were DLTs, because they met the 3rd and 4th criteria of a DLT.

At the 1.2 mg/m^2 dose level, subject [redacted] is a male, 60 years old subject, who was diagnosed with myxoid+/-round cell liposarcoma. The subject had first line ifosfamide and epirubicin combination treatment. The subject experienced Grade 3 fatigue on Cycle 1 Day 4, accompanied by other Grade 2 AEs of vomiting, dyspnea, and abdominal distension. The Grade 3 fatigue was considered to be very likely related to the treatment and was a DLT, because it met the 4th criterion for a DLT. The event was resolved after additional treatment given.

One subject ([redacted]) was enrolled after the determination of 1.2mg/m^2 as the recommended dose by the SET, to collect additional PK data at the dose identified for use in the phase 3 study, for regulatory purposes. Therefore, although this subject had reported safety events meeting DLT criteria, the subject was not confirmed by the SET to have experienced a DLT.

Listing 1 : List of Subjects with DLT; All Treated (Study ETS743SAR3006 Part 1)

Dose Cohort	Site Id	Subject Id	Informed Consent date	Treatment Start Date	Date of Specimen Collection	Study Day of Specimen Collection	Reason for DLT
1.2 mg/m^2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22	Yes for dlt4
1.5 mg/m^2						22	Yes for dlt3
						22	Yes for dlt3
						22	Yes for dlt4
						22	Yes for dlt1
						22	Yes for dlt2
						22	Yes for dlt3
						22	Yes for dlt4
						22	Yes for dlt3
						22	Yes for dlt4

Note: dlt1:Absolute neutrophil count (ANC) of <0.5×109/L lasting more than 5 days or febrile neutropenia (neutrophils <0.5×109/L, with a temperature =38.5°C or a temperature =38°C for = 1 hr).
Note: dlt2:Platelets of <25×109/L.
Note: dlt3:Any Grade 3 or 4 elevations in hepatic transaminases or Grade 1 elevation of bilirubin, and not recover to pretreatment levels by Day 2 1 after treatment.
Note: dlt4:Grade 3 to 4 nonhematologic toxicities (except for nausea/vomiting in the absence of an appropriate antiemetic regimen) other than he patic.
Note: One subject ([redacted]) was enrolled after the determination of 1.2mg/m2 as the recommended dose by the SET, in order to collect additional PK data at the dose identified for use in the phase 3 study, for regulatory purposes. Therefore, although this subject had reported safety events meeting DLT criteria, the subject was not confirmed by the SET to have experienced a DLT.

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The dose of 1.2 mg/m^2 was determined to be the MTD in Part 1 of the study. A listing of laboratory tests abnormal records is presented in Attachment LSFLAB01.

Treatment Emergent Adverse Events

The most commonly observed TEAEs, by system organ class (SOC) (observed in ≥25% subjects) were gastrointestinal disorders (100%), investigations (100%), metabolism and nutrition disorders (61.1%), blood and lymphatic system disorders (50.0%), general disorders and administration site conditions (50.0%), immune system disorders (27.8%), nervous system disorders (27.8%) and respiratory, thoracic and mediastinal disorders (27.8%). The most frequently reported (observed in ≥25% total subjects) TEAEs by preferred term (PT) included ALT increased (94.4% subjects), AST increased (88.9%), nausea (88.3% subjects), vomiting (88.3% subjects), GGT increased (77.8%), neutrophil count decreased (77.8%), WBC decreased (77.8%), decreased appetite (55.6%), constipation (50.0%), anemia (38.9%), blood creatinine phosphokinase increased (33.3%), platelet count decreased (33.3%), and hypocalcaemia (27.8%). (Table 3 and Attachment TSFAE05) A listing of all TEAEs is provided in Attachment LSFAE01.

Table 3: Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Analysis set: all treated	6	12	18
Subjects with any adverse events	6	12	18
System organ class/ preferred term			
Gastrointestinal disorders	6 (100.0%)	12 (100.0%)	18 (100.0%)
Nausea	5 (83.3%)	10 (83.3%)	15 (83.3%)
Vomiting	6 (100.0%)	9 (75.0%)	15 (83.3%)
Constipation	4 (66.7%)	5 (41.7%)	9 (50.0%)
Abdominal distension	1 (16.7%)	3 (25.0%)	4 (22.2%)
Diarrhoea	2 (33.3%)	0	2 (11.1%)
Abdominal pain	0	1 (8.3%)	1 (5.6%)
Epigastric discomfort	1 (16.7%)	0	1 (5.6%)
Gastrointestinal disorder	1 (16.7%)	0	1 (5.6%)
Pancreatitis acute	0	1 (8.3%)	1 (5.6%)
Investigations	6 (100.0%)	12 (100.0%)	18 (100.0%)
Alanine aminotransferase increased	6 (100.0%)	11 (91.7%)	17 (94.4%)
Aspartate aminotransferase increased	6 (100.0%)	10 (83.3%)	16 (88.9%)
Gamma-glutamyltransferase increased	5 (83.3%)	9 (75.0%)	14 (77.8%)
Neutrophil count decreased	5 (83.3%)	9 (75.0%)	14 (77.8%)
White blood cell count decreased	5 (83.3%)	9 (75.0%)	14 (77.8%)
Blood creatine phosphokinase increased	2 (33.3%)	4 (33.3%)	6 (33.3%)
Platelet count decreased	3 (50.0%)	3 (25.0%)	6 (33.3%)
Blood creatinine increased	1 (16.7%)	3 (25.0%)	4 (22.2%)
Blood bilirubin increased	1 (16.7%)	2 (16.7%)	3 (16.7%)
Blood iron increased	0	3 (25.0%)	3 (16.7%)
Haemoglobin decreased	2 (33.3%)	1 (8.3%)	3 (16.7%)
High density lipoprotein increased	0	3 (25.0%)	3 (16.7%)
Bilirubin conjugated increased	0	2 (16.7%)	2 (11.1%)
Blood alkaline phosphatase increased	0	2 (16.7%)	2 (11.1%)
Blood calcium decreased	1 (16.7%)	1 (8.3%)	2 (11.1%)
Blood phosphorus decreased	0	2 (16.7%)	2 (11.1%)
Blood triglycerides increased	0	2 (16.7%)	2 (11.1%)
White blood cell count increased	1 (16.7%)	1 (8.3%)	2 (11.1%)

Table 3: Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Blood cholesterol increased	0	1 (8.3%)	1 (5.6%)
Blood creatinine decreased	0	1 (8.3%)	1 (5.6%)
Blood glucose increased	0	1 (8.3%)	1 (5.6%)
Blood iron decreased	0	1 (8.3%)	1 (5.6%)
Blood urea increased	0	1 (8.3%)	1 (5.6%)
Myoglobin blood increased	0	1 (8.3%)	1 (5.6%)
Red blood cell count decreased	0	1 (8.3%)	1 (5.6%)
Total bile acids increased	0	1 (8.3%)	1 (5.6%)
Metabolism and nutrition disorders	6 (100.0%)	5 (41.7%)	11 (61.1%)
Decreased appetite	6 (100.0%)	4 (33.3%)	10 (55.6%)
Hypocalcaemia	3 (50.0%)	2 (16.7%)	5 (27.8%)
Hypoalbuminaemia	1 (16.7%)	1 (8.3%)	2 (11.1%)
Hypokalaemia	2 (33.3%)	0	2 (11.1%)
Hypercholesterolaemia	0	1 (8.3%)	1 (5.6%)
Hypochloraemia	0	1 (8.3%)	1 (5.6%)
Hyponatraemia	0	1 (8.3%)	1 (5.6%)
Blood and lymphatic system disorders	1 (16.7%)	8 (66.7%)	9 (50.0%)
Anaemia	1 (16.7%)	6 (50.0%)	7 (38.9%)
Leukopenia	0	3 (25.0%)	3 (16.7%)
Neutropenia	0	3 (25.0%)	3 (16.7%)
General disorders and administration site conditions	2 (33.3%)	7 (58.3%)	9 (50.0%)
Fatigue	1 (16.7%)	3 (25.0%)	4 (22.2%)
Pyrexia	2 (33.3%)	2 (16.7%)	4 (22.2%)
Oedema peripheral	1 (16.7%)	2 (16.7%)	3 (16.7%)
Malaise	0	2 (16.7%)	2 (11.1%)
Asthenia	0	1 (8.3%)	1 (5.6%)
Chest discomfort	0	1 (8.3%)	1 (5.6%)
Chills	1 (16.7%)	0	1 (5.6%)
Death	0	1 (8.3%)	1 (5.6%)
Device related infection	0	1 (8.3%)	1 (5.6%)
Face oedema	1 (16.7%)	0	1 (5.6%)
Oedema	0	1 (8.3%)	1 (5.6%)
Pain	1 (16.7%)	0	1 (5.6%)
Immune system disorders	2 (33.3%)	3 (25.0%)	5 (27.8%)
Decreased immune responsiveness	2 (33.3%)	2 (16.7%)	4 (22.2%)
Hypersensitivity	0	1 (8.3%)	1 (5.6%)
Nervous system disorders	2 (33.3%)	3 (25.0%)	5 (27.8%)
Insomnia	2 (33.3%)	2 (16.7%)	4 (22.2%)
Headache	0	1 (8.3%)	1 (5.6%)
Respiratory, thoracic and mediastinal disorders	3 (50.0%)	2 (16.7%)	5 (27.8%)
Dyspnoea	1 (16.7%)	2 (16.7%)	3 (16.7%)
Cough	2 (33.3%)	0	2 (11.1%)
Upper respiratory tract infection	2 (33.3%)	0	2 (11.1%)
Hiccups	0	1 (8.3%)	1 (5.6%)
Laryngeal pain	1 (16.7%)	0	1 (5.6%)
Musculoskeletal and connective tissue disorders	0	3 (25.0%)	3 (16.7%)
Myalgia	0	2 (16.7%)	2 (11.1%)
Arthralgia	0	1 (8.3%)	1 (5.6%)

Table 3: Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (16.7%)	2 (16.7%)	3 (16.7%)
Tumour pain	1 (16.7%)	2 (16.7%)	3 (16.7%)
Eye disorders	2 (33.3%)	0	2 (11.1%)
Conjunctival haemorrhage	1 (16.7%)	0	1 (5.6%)
Conjunctivitis	1 (16.7%)	0	1 (5.6%)
Infections and infestations	0	2 (16.7%)	2 (11.1%)
Upper respiratory tract infection	0	2 (16.7%)	2 (11.1%)
Skin and subcutaneous tissue disorders	1 (16.7%)	1 (8.3%)	2 (11.1%)
Pruritus	1 (16.7%)	1 (8.3%)	2 (11.1%)
Vascular disorders	2 (33.3%)	0	2 (11.1%)
Epistaxis	1 (16.7%)	0	1 (5.6%)
Haemoptysis	1 (16.7%)	0	1 (5.6%)
purpura	1 (16.7%)	0	1 (5.6%)
Cardiac disorders	1 (16.7%)	0	1 (5.6%)
Atrial fibrillation	1 (16.7%)	0	1 (5.6%)
Hepatobiliary disorders	0	1 (8.3%)	1 (5.6%)
Hepatic pain	0	1 (8.3%)	1 (5.6%)

Note: Adverse events are coded using MedDRA version 18.0.
Percentage is based on the number of subjects treated.

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Sixteen subjects (88.9%) in total experienced Grade 3 or higher TEAEs. Subjects in the 1.5 mg/m^2 cohort had a higher incidence (100%) of Grade 3 or higher TEAEs than that of 1.2 mg/m^2 cohort (83.3%). The most common Grade 3 or higher TEAEs in 1.5 mg/m^2 cohort (observed in ≥25% subjects) included neutrophil count decreased (83.3%), ALT increased (83.3%), WBC count decreased (83.3%), AST increased (50.0%), vomiting (50.0%), decreased appetite (50.0%), GGT increased (33.3%), platelet count decreased (33.3%), nausea (33.3%), and decreased immune responsiveness (33.3%). However, the Grade 3 or higher TEAE observed in ≥ 25% subjects in 1.2 mg/m^2 cohort included neutrophil count decreased (50.0%), ALT increased (41.7%), WBC decreased (25.0%), GGT increased (25.0%), nausea (25.0%), vomiting (25.0%), and neutropenia(25.0%). (Table 4)

Table 4: Grade 3 or Higher Treatment-emergent Adverse Events; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Analysis set: all treated	6	12	18
Subjects with grade 3 or higher TE adverse events	6 (100.0%)	10 (83.3%)	16 (88.9%)
System organ class/ preferred term			
Investigations	5 (83.3%)	9 (75.0%)	14 (77.8%)
Neutrophil count decreased	5 (83.3%)	6 (50.0%)	11 (61.1%)
Alanine aminotransferase increased	5 (83.3%)	5 (41.7%)	10 (55.6%)
White blood cell count decreased	5 (83.3%)	3 (25.0%)	8 (44.4%)
Aspartate aminotransferase increased	3 (50.0%)	3 (25.0%)	6 (33.3%)
Gamma-glutamyltransferase increased	2 (33.3%)	1 (8.3%)	3 (16.7%)

Table 4: Grade 3 or Higher Treatment-emergent Adverse Events; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Blood creatine phosphokinase increased	1 (16.7%)	1 (8.3%)	2 (11.1%)
Platelet count decreased	2 (33.3%)	0	2 (11.1%)
Gastrointestinal disorders	5 (83.3%)	3 (25.0%)	8 (44.4%)
Vomiting	3 (50.0%)	3 (25.0%)	6 (33.3%)
Nausea	2 (33.3%)	3 (25.0%)	5 (27.8%)
Diarrhoea	1 (16.7%)	0	1 (5.6%)
Blood and lymphatic system disorders	1 (16.7%)	3 (25.0%)	4 (22.2%)
Neutropenia	0	3 (25.0%)	3 (16.7%)
Anaemia	1 (16.7%)	0	1 (5.6%)
Leukopenia	0	1 (8.3%)	1 (5.6%)
General disorders and administration site conditions	1 (16.7%)	3 (25.0%)	4 (22.2%)
Death	0	1 (8.3%)	1 (5.6%)
Device related infection	0	1 (8.3%)	1 (5.6%)
Fatigue	0	1 (8.3%)	1 (5.6%)
Pain	1 (16.7%)	0	1 (5.6%)
Metabolism and nutrition disorders	3 (50.0%)	1 (8.3%)	4 (22.2%)
Decreased appetite	3 (50.0%)	1 (8.3%)	4 (22.2%)
Hypokalaemia	1 (16.7%)	0	1 (5.6%)
Immune system disorders	2 (33.3%)	1 (8.3%)	3 (16.7%)
Decreased immune responsiveness	2 (33.3%)	1 (8.3%)	3 (16.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (8.3%)	1 (5.6%)
Tumour pain	0	1 (8.3%)	1 (5.6%)

Note: Adverse events are coded using MedDRA version 18.0.
Percentage is based on the number of subjects treated.

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Only 1 subject in the 1.5 mg/m^2 cohort experienced a TEAE (Grade 3 diarrhea) leading to treatment discontinuation on Cycle 4 Day 74, the event was considered as doubtfully related to study treatment. On the same day, the subject also experienced Grade 2 GGT increased and Grade 1 AST increased (60 U/L), both of which were considered as very likely related to study treatment (Attachment LSFAE02).

Of those subjects receiving at least 2 cycles of trabectedin (4 subjects in the 1.5 mg/m^2 cohort and 9 subjects in the 1.2 mg/m^2 cohort), 3 subjects (75.0%) in the 1.5 mg/m^2 cohort experienced TEAEs leading to 2 dose reductions and 2 subjects (22.2%) in the 1.2 mg/m^2 cohort experienced a TEAE leading to 1 dose reduction. (Table 5)

In the 1.5 mg/m^2 cohort, Subject [redacted] experienced Grade 3 ALT increased (355 U/L) and Grade 2 AST increased (172 U/L) leading to dose reduction on Cycle 2 Day 29. On Cycle 18 Day 430, the subject experienced Grade 4 WBC decreased (0.89 x10^9/L) and Grade 4 ANC decreased (0.42 x10^9/L) leading to the 2nd dose reduction. All the events leading to dose reduction were considered as very likely related to study treatment. Subject [redacted] experienced Grade 3 ALT increased (221 U/L) leading to dose reduction on Cycle 1 Day 8. On Cycle 3 Day 58, the subject experienced Grade 3 vomiting leading to 2nd dose reduction. Both the events were considered as very likely related to study treatment. Subject [redacted] experienced Grade 3 ALT increased (721 U/L) on Cycle 1 Day 3

leading to dose reduction, which was considered as probably related to study treatment and as DLT. On Cycle 3 Day 53, the subject experienced Grade 3 ALT increased (417 U/L) leading to a 2nd dose reduction, which was considered as very likely related to study treatment. On Cycle 4 Day 74, the subject withdrew from the study treatment due to Grade 3 diarrhea, which was considered as doubtfully related to study treatment. (Attachment LSFAE03)

In the 1.2mg/m^2 cohort, subject [redacted] reported Grade 3 ALT (294 U/L) and Grade 2 AST increased (136 U/L) on Cycle 1 Day 8 then ALT recovered to Grade 1(59 U/L) in 8 days, and AST recovered to Grade 1 (52U/L) on Cycle 1 Day 20, which leading to a dose reduction. The AE was considered to be very likely related to study treatment. Subject [redacted] experienced Grade 3 ALT increased (293 U/L) and Grade 1 bilirubin conjugated increased leading to a dose reduction on Cycle 2 Day 36, both of which were considered as very likely related to study treatment. (Attachment LSFAE03)

Table 5: Treatment Dose Reductions by Overall; All Treated (Study ETS743SAR3006 Part 1)

	1.5 mg/m^2 (N=6)	1.2 mg/m^2 (N=12)	Total (N=18)
Subjects who received at least 2 cycles of treatment	4	9	13
Dose reduction			
Yes	3 (75.0%)	2 (22.2%)	5 (38.5%)
No	1 (25.0%)	7 (77.8%)	8 (61.5%)
Number of dose reductions			
1	0	2 (22.2%)	2 (15.4%)
2	3 (75.0%)	0	3 (23.1%)

Note: Dose reductions were tabulated for subjects who received at least 2 cycles of treatment.

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Serious Adverse Events

Of all treated subjects, 3 subjects experienced serious adverse events (SAEs) (2 in the 1.5 mg/m^2 cohort [33.3%] and 1[8.3%] in the 1.2 mg/m^2 cohort) (Table 6). Of all treated subjects, 1 experienced SAEs reported as very likely related to study drug, and a further 2 experienced SAEs reported as doubtfully related to study drug. (Attachment LSFAE06) In the 1.5 mg/m^2 cohort, subject [redacted] reported Grade 3 pain during treatment discontinuation, which was considered as doubtfully related to study treatment. Subject [redacted] reported Grade 4 neutrophil count decreased (0.4x10^9/L) and Grade 4 platelet count decreased (11x10^9/L) during Cycle 1 leading to drug interruption, but was never dosed after that. Both SAEs were considered to be very likely related to study treatment and were DLTs. In the 1.2 mg/m^2 cohort, subject [redacted] was reported with death as an SAE during treatment discontinuation. This SAE was considered as doubtfully related to study treatment. A listing of subjects who experienced SAEs are presented in Attachment LSFAE06.

Table 6: Treatment-emergent Serious Adverse Events; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Analysis set: all treated	6	12	18
Subjects with serious adverse events	2 (33.3%)	1 (8.3%)	3 (16.7%)
System organ class/preferred term			
General disorders and administration site conditions	1 (16.7%)	1 (8.3%)	2 (11.1%)
Death	0	1 (8.3%)	1 (5.6%)

Table 6: Treatment-emergent Serious Adverse Events; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Pain	1 (16.7%)	0	1 (5.6%)
Investigations	1 (16.7%)	0	1 (5.6%)
Neutrophil count decreased	1 (16.7%)	0	1 (5.6%)
Platelet count decreased	1 (16.7%)	0	1 (5.6%)

Note: Adverse events are coded using MedDRA version 18.0.
Percentage is based on the number of subjects treated.

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Adverse Events of Interests

All subjects in the 1.5 mg/m^2 cohort and 11 subjects (91.7%) in the 1.2mg/m^2 cohort experienced AEs of special interest. The most frequently reported AEs of interest (observed in ≥25% subjects) included ALT increased (94.4%), AST increased (88.9%), and GGT increased (77.8%) (Table 7)Only 1 subject in the 1.5 mg/m^2 cohort experienced Grade 4 AE of interest (Grade 4 ALT increased). (Attachment TSFAE06) None of the AEs of interest were SAEs. A listing of subjects who experienced an AE of special interest is presented in Attachment LSFAE05.

Table 7: Incidence of Treatment-emergent AEs of Special Interest; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total
Analysis set: all treated	6	12	18
Subjects with AEs of Special Interest	6 (100.0%)	11 (91.7%)	17 (94.4%)
Group of AE of Special Interest/Preferred Term			
Liver injury	6 (100.0%)	11 (91.7%)	17 (94.4%)
Alanine aminotransferase increased	6 (100.0%)	11 (91.7%)	17 (94.4%)
Aspartate aminotransferase increased	6 (100.0%)	10 (83.3%)	16 (88.9%)
Gamma-glutamyltransferase increased	5 (83.3%)	9 (75.0%)	14 (77.8%)
Blood bilirubin increased	1 (16.7%)	2 (16.7%)	3 (16.7%)
Blood alkaline phosphatase increased	0	2 (16.7%)	2 (11.1%)
Hypoalbuminaemia	1 (16.7%)	1 (8.3%)	2 (11.1%)
Renal disorder	1 (16.7%)	3 (25.0%)	4 (22.2%)
Blood creatinine increased	1 (16.7%)	3 (25.0%)	4 (22.2%)
Blood urea increased	0	1 (8.3%)	1 (5.6%)
Thrombocytopenia-Bleeding	2 (33.3%)	0	2 (11.1%)
Epistaxis	1 (16.7%)	0	1 (5.6%)
Haemoptysis	1 (16.7%)	0	1 (5.6%)
Cardiac disorders	1 (16.7%)	0	1 (5.6%)
Atrial fibrillation	1 (16.7%)	0	1 (5.6%)
Catheter related complications	0	1 (8.3%)	1 (5.6%)
Device related infection	0	1 (8.3%)	1 (5.6%)
CPK elevations-Rhabdomyolysis	0	0	0
Neutropenia-Selected infections	0	0	0

Table 7: Incidence of Treatment-emergent AEs of Special Interest; All Treated (Study ETS743SAR3006 Part 1)

	Trabectedin		
	1.5 mg/m^2	1.2 mg/m^2	Total

Note: Adverse events are coded using MedDRA version 18.0.
Percentage is based on the number of subjects treated.

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PHARMACOKINETIC RESULTS:

In Part 1, a series of peripheral blood samples were obtained to evaluate the full PK profile for trabectedin during the first 2 cycles. The estimated noncompartmental PK parameters were summarized for each dosing regimen (1.5 and 1.2 mg/m^2) and Cycle (1 and 2) in Table 8 and Table 9. Trabectedin concentration data at each time point derived from the full PK sampling were summarized for each dosing regimen and cycle in Attachment PK table 1. Mean full concentration-time profiles were plotted for each dosing regimen and cycle in Attachment PK Figure 1. Individual full trabectedin concentration-time profiles were plotted for each subject and cycle in Attachment PK Figure 2.

PK of trabectedin in Chinese patients from this study confirmed previous observed PK properties for trabectedin in other studies in non-Chinese subjects. With a few exceptions the maximal concentrations were observed at the end of the 24-hr IV infusion. The decline in the plasma concentrations of trabectedin was characterized by a marked and rapid phase followed by more prolonged distribution and terminal phases. Trabectedin demonstrated a high apparent volume of distribution following intravenous administration, consistent with extensive tissue distribution. As in other populations, moderate to high PK variability was observed in Chinese patient population. Percent coefficient of variation (CV%) of Cmax were 100% (cycle 1) and 97.7% (cycle 2) at 1.5 mg/m^2; CV% of Cmax were 76.3% (cycle 1) and 63.1% (cycle 2) at 1.2 mg/m^2. CV% of AUC_{inf} were 116% (cycle 1) and 65.7% (cycle 2) at 1.5 mg/m^2; CV% of AUC_{inf} were 38.5% (cycle 1) and 64.5% (cycle 2) at 1.2 mg/m^2. In general, summary of PK parameters were similar between Cycle 1 and 2. C_{max} and AUC exposure were lower for 1.2 mg/m^2 compared to 1.5 mg/m^2. The mean Cmax at cycle 1 and 2 for 1.5 mg/m^2 were 3.70 and 4.13 ng/mL, respectively; the mean Cmax at cycle 1 and 2 for 1.2 mg/m2 were 2.02 and 1.35 ng/mL, respectively. The mean AUC_{inf} at cycle 1 and 2 for 1.5 mg/m^2 were 159 and 88.3 ng*h/mL, respectively; the mean AUC_{inf} at cycle 1 and 2 for 1.2 mg/m2 were 67.2 and 78.0 ng*h/mL, respectively.

Table 8: Summary of PK parameters for China Phase 1 Study Part 1 Dose level 1.5 mg/m2

PK parameter	cycle	T_{max}, h	C_{max}, ng/mL	AUC_{last}, ng*h/mL	AUC_{inf}, ng*h/mL	$t_{1/2, z}$	CL, L/h	$V_{ss, L}$
Mean (SD)	1		3.70 (3.71)	97.3 (84.5)	159 (185)	155 (98.5)	33.4 (23.7)	3935 (3458)
CV%			100	86.9	116	63.5	70.9	87.9
Geometric mean			2.54	72.8	104	133	24.1	2492
Median (minimum, maximum)		24.0 (1.50, 24.12)	2.18 (0.95, 10.6)	56.2 (33.2, 241)	87.5 (41.0, 534)	105.5 (72.9, 307)	31.8 (4.28, 68.5)	3316 (381.7, 9580)
Mean (SD)	2		4.13 (4.04)	75.6 (57.6)	88.3 (58.0)	126.2 (36.4)	37.8 (26.2)	4684 (5192)
CV%			97.7	76.2	65.7	28.8	69.3	111

Geometric mean			2.46	59.6	75.2	123	30.7	2451
Median (minimum, maximum)		23.7 (22.8, 24.0)	3.37 (0.67, 9.12)	62.4 (26.1, 151)	73.3 (40.1, 167)	112 (102, 180)	33.8 (13.5, 70.0)	3203 (617, 11714)

Table 9: Summary of PK parameters for China Phase 1 Study Part 1 Dose level 1.2 mg/m2

PK parameter	cycle	T_{max}, h	C_{max}, ng/mL	AUC_{last}, ng*h/mL	AUC_{inf}, ng*h/mL	$T_{1/2}$	CL, L/h	Vss, L
Mean (SD)	1		2.02 (1.54)	45.2 (11.8)	67.2 (25.9)	182 (224)	33.6 (10.7)	4570 (4554)
CV%			76.3	26	38.5	123	31.8	97.5
Geometric mean			1.63	43.8	63.5	131	32	3506
Median (minimum, maximum)		24.2 (1.52, 28.7)	1.33 (0.765, 5.79)	44.8 (26.4, 60.7)	65.3 (41.4, 132)	127 (50.9, 849)	32.4 (15.0, 53.8)	2997 (1724, 17120)
Mean (SD)	2		1.35 (0.853)	44.6 (16.9)	78.0 (50.4)	191 (87.4)	33.2 (16.2)	5066 (2311)
CV%			63.1	38	64.5	45.8	48.7	45.6
Geometric mean			1.17	42.3	67.7	173.8	29.1	4593
Median (minimum, maximum)		23.9 (1.47, 24.9)	1.01 (0.679, 2.72)	38.1 (25.8, 81.6)	57.5 (36.2, 190)	154 (86.8, 316)	32.2 (8.93, 609)	4611 (2452, 8063)

EFFICACY RESULTS

Overall Survival

As of the clinical cut-off date (10 October 2016), 1 (16.7%) subject in the 1.5 mg/m^2 cohort and 6 (50.0%) subjects in the 1.2 mg/m^2 cohort died (Table 10). The median survival duration was 19.38 months (95% CI: 9.86, NE) for all subjects. A KM plot of OS is presented in Attachment GEFSUR01. A listing of time to event endpoints is presented in Attachment LEFTTE01.

Table 10: Overall Survival

	1.5 mg/m^2 (N=6)	1.2 mg/m^2 (N=12)	Total (N=18)
Subjects treated	6	12	18
Death	1 (16.7%)	6 (50.0%)	7 (38.9%)
Censored	5 (83.3%)	6 (50.0%)	11 (61.1%)
Overall survival (months) [a]			
25th percentile (95% CI)	27.76 (27.76, NE)	9.86 (0.53, 18.10)	12.25 (0.53, 19.38)
Median (95% CI)	NE (27.76, NE)	18.10 (2.63, NE)	19.38 (9.86, NE)
75th percentile (95% CI)	NE (27.76, NE)	NE (12.25, NE)	27.76 (19.38, NE)
Range	(1.1+, 44.2+)	(0.5, 25.4+)	(0.5, 44.2+)
6-month event-free rate (95% CI)	1.000 (1.000, 1.000)	0.786 (0.361, 0.944)	0.866 (0.552, 0.966)
12-month event-free rate (95% CI)	1.000 (1.000, 1.000)	0.655 (0.253, 0.878)	0.770 (0.428, 0.922)

Table 10: Overall Survival

	1.5 mg/m^2 (N=6)	1.2 mg/m^2 (N=12)	Total (N=18)
18-month event-free rate (95% CI)	1.000 (1.000, 1.000)	0.524 (0.164, 0.793)	0.673 (0.333, 0.867)
24-month event-free rate (95% CI)	1.000 (1.000, 1.000)	0.262 (0.039, 0.575)	0.462 (0.159, 0.722)
30-month event-free rate (95% CI)	0.500 (0.006, 0.910)	0.262 (0.039, 0.575)	0.231 (0.015, 0.599)
p-value [b]	0.0538		
Hazard ratio (95% CI) [c]	NE (NE, NE)		

Note: + = censored observation, NE = not estimable.
[a] Overall survival (OS) is defined as the time between dosing and death. Subject who die, regardless of the cause of death, will be considered to have had an event. All subjects who are lost to the follow-up prior to the end of the trial or who are withdrawn from the trial will be censored at the time of last contact.
Subjects who are still being treated will be censored at the last available date where the subject is known to be alive.
[b] p value is from a nonstratified log-rank test and is only for reference.
[c] Hazard ratio is from nonstratified proportional hazards model. Hazard ratio < 1 favors 1.5 mg/m2.

[TEFSUR01.rtf] [JNJ-17027907\SAR3006\DBR_CSR\RE_SET1\TEFSUR01.sas] 30MAR2017, 03:47

Progression Free Survival

As of the clinical cut-off date, 3 (50.0%) subjects in the 1.5 mg/m^2 cohort and 7 (58.3%) subjects in the 1.2 mg/m^2 cohort died or had progressive disease. A further 8 subjects (3 in the 1.5mg/m^2 cohort, and 5 in the 1.2 mg/m^2 cohort) were censored for these events due to withdraw of consent (Table 11). The median PFS duration was 2.99 months (95% CI: 1.45, 19.38). A KM plot of PFS is presented in Attachment GEFSUR02.

Table 11: Progression Free Survival

	1.5 mg/m^2 (N=6)	1.2 mg/m^2 (N=12)	Total (N=18)
Subjects treated	6	12	18
Progressive disease or died	3 (50.0%)	7 (58.3%)	10 (55.6%)
Censored	3 (50.0%)	5 (41.7%)	8 (44.4%)
Progression free survival (months) [a]			
25th percentile (95% CI)	5.04 (2.99, 27.76)	1.41 (0.30, 1.51)	1.45 (0.30, 2.99)
Median (95% CI)	7.10 (2.99, 27.76)	1.48 (0.30, 19.38)	2.99 (1.45, 19.38)
75th percentile (95% CI)	27.76 (2.99, 27.76)	11.17 (1.45, NE)	19.38 (2.96, 27.76)
Range	(0.0+, 27.8)	(0.0+, 19.8+)	(0.0+, 27.8)
6-month event-free rate (95% CI)	0.750 (0.128, 0.961)	0.250 (0.037, 0.558)	0.440 (0.168, 0.684)
12-month event-free rate (95% CI)	0.375 (0.011, 0.808)	0.250 (0.037, 0.558)	0.330 (0.092, 0.597)
p-value [b]	0.1078		
Hazard ratio (95% CI) [c]	NE (NE, NE)		

Table 11: Progression Free Survival

	1.5 mg/m^2 (N=6)	1.2 mg/m^2 (N=12)	Total (N=18)

Note: + = censored observation, NE = not estimable.
[a] Disease progression based on RECIST Version 1.1 guidelines will be used to calculate PFS, which is defined as the time from dosing to the occurrence of disease progression or death, whichever occurs first. If a subject has not progressed and is still alive as of the clinical cutoff date, the subject will be censored at the date of his or her last radiographic assessment. If a subject starts subsequent anticancer therapy without prior disease progression, he or she will be
censored at the last disease assessment date before or on the first day of the start of the first subsequent anticancer therapy.
[b] p value is from a nonstratified log-rank test and is only for reference.
[c] Hazard ratio is from nonstratified proportional hazards model. Hazard ratio < 1 favors 1.5 mg/m2.

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Time to Progression

As of the clinical cut-off date, 2 (33.3%) subjects in the 1.5 mg/m^2 cohort and 6 (50.0%) subjects in the 1.2 mg/m^2 cohort had progressive disease (Table 12). The median TTP was 2.99 months (95% CI: 1.45, NE) for all subjects. A KM plot of TTP is presented in Attachment GEFSUR03.

Table 12: Time to Progression

	1.5 mg/m^2 (N=6)	1.2 mg/m^2 (N=12)	Total (N=18)
Subjects treated	6	12	18
Progression	2 (33.3%)	6 (50.0%)	8 (44.4%)
Censored	4 (66.7%)	6 (50.0%)	10 (55.6%)
Time to progression (months) [a]			
25th percentile (95% CI)	5.04 (2.99, NE)	1.45 (0.30, 1.51)	1.45 (0.30, 2.99)
Median (95% CI)	7.10 (2.99, NE)	1.51 (0.30, NE)	2.99 (1.45, NE)
75th percentile (95% CI)	NE (2.99, NE)	NE (1.45, NE)	NE (2.96, NE)
Range	(0.0+, 14.7+)	(0.0+, 19.8+)	(0.0+, 19.8+)
6-month event-free rate (95% CI)	0.750 (0.128, 0.961)	0.254 (0.038, 0.564)	0.442 (0.170, 0.687)
12-month event-free rate (95% CI)	0.375 (0.011, 0.808)	0.254 (0.038, 0.564)	0.295 (0.060, 0.589)
p-value [b]	0.1156		
Hazard ratio (95% CI) [c]	NE (NE, NE)		

Note: + = censored observation, NE = not estimable.
[a] Time-to-progression (TTP) is defined as the time between dosing and disease progression. Subjects who progressed or died with documented disease progression will be considered to have had an event. Subjects who died without evidence of disease progression will be considered censored at time of last tumor assessment prior to death. Subjects who are lost to follow-up or still being treated without documented disease will be censored at the date of the last tumor assessment.
[b] p value is from a nonstratified log-rank test and is only for reference.
[c] Hazard ratio is from nonstratified proportional hazards model. Hazard ratio < 1 favors 1.5 mg/m2.

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Objective Response Rate

Among all the 13 subjects with post-baseline disease assessment, 1 (12.5 %) subject in the 1.2 mg/ m^2 cohort had a PR as the best overall response. (Table 13, Attachment LEFRESP02). A listing of tumor assessment is presented in Attachment LEFRESP01.

Table 13: Objective Response Rate for Subjects with overall response; All Treated Subjects (Study ETS743SAR3006 Part 1)

	1.5 mg/m^2 (N=6)	1.2 mg/m^2 (N=12)	Total (N=18)
Subjects with overall response	5	8	13
Responder [a]	0	1 (12.5%)	1 (7.7%)
Non-Responder	5 (100.0%)	7 (87.5%)	12 (92.3%)

[a] Responder is defined as having CR or PR as best overall response based on reconciled radiographic disease assess ment.
Percentage is based on the number of subjects with overall response.

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Duration of Response

Duration of response couldn't be analyzed, as only 1 subject had PR as the best overall response.

Table 14: Duration of Response

	1.5 mg/m^2 (N=6)	1.2 mg/m^2 (N=12)	Total (N=18)
Subjects with CR or PR	0	1	1

Note: Duration of response (DR) is defined only for subjects who have complete response (CR) or partial response (PR) as best overall response and is calculated from the date of the first documentation of response to the date of disease progression or death, whichever occurs first. Subjects who have neither progressed nor died will be censored at their last disease assessment date. If a subject starts subsequent anticancer therapy without prior disease progression, then he or she will be censored at the
last disease assessment date before or on the first day of the start of the first subsequent anticancer therapy.

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LIMITATIONS

This is a summary of Part 1 of the study and Part 1 was designed to identify the MTD according to the traditional dose de-escalation design. Therefore the total sample size is not pre-defined and small. With only 6 subjects treated at the dose of 1.5mg/m^2 and 12 subjects treated at 1.2mg/m^2, making the evaluation of the safety and clinical efficacy of trabectedin at the two different doses is very preliminary. Consistent with other populations, moderate to high PK variability was observed in Chinese patient population and it is difficult to correlate PK with toxicity. Further confirmation of the clinical efficacy and safety profile of 1.2mg/m^2 in Chinese patients with advanced leiomyosarcoma and liposarcoma will be done in Part 2 of the study.

CONCLUSION(S):

In Part 1 of Study ET743-SAR-3006, 2 doses were studied and the MTD was declared as 1.2 mg/m^2. Compared with subjects in the 1.2 mg/m^2 dose group, the incidences of SAEs, AEs leading to a dose

reduction and AEs of interest in the 1.5 mg/m^2 dose group were higher. While the toxicity observed in the trabectedin 1.5 mg/m^2 group was higher than the 1.2 mg/m^2 group, they were generally transient and managed by dose reductions and treatment discontinuations, according to protocol-specified criteria. The most frequently reported DLTs were ALT increased, AST increased and decreased appetite, which were consistent with the known safety profile of trabectedin.

Due to the small sample size, no efficacy conclusion can be mad. However, there was one subject treated with the initial dose of 1.2 mg/m^2 who experienced a documented PR at the 1.2mg/m^2 , and another subject treated within the 1.5mg/m^2 cohort who experienced prolonged disease stabilization through 19 Cycles.

As in other populations, moderate to high PK variability was observed in Chinese patient population. Percent coefficient of variation (CV%) of Cmax were 100% (cycle 1) and 97.7% (cycle 2) at 1.5 mg/m^2; CV% of Cmax were 76.3% (cycle 1) and 63.1% (cycle 2) at 1.2 mg/m^2. CV% of AUC_{inf} were 116% (cycle 1) and 65.7% (cycle 2) at 1.5 mg/m^2; CV% of AUC_{inf} were 38.5% (cycle 1) and 64.5% (cycle 2) at 1.2 mg/m^2. In general, PK parameters were similar between Cycle 1 and 2. C_{max} and AUC exposure were lower for 1.2 mg/m^2 compared to 1.5 mg/m^2. The mean Cmax at cycle 1 and 2 for 1.5 mg/m^2 were 3.70 ng/mL and 4.13 ng/mL, respectively; the mean Cmax at cycle 1 and 2 for 1.2 mg/m^2 were 2.02 ng/mL and 1.35 ng/mL, respectively. The mean AUC_{inf} at cycle 1 and 2 for 1.5 mg/m^2 were 159 ng*h/mL and 88.3 ng*h/mL, respectively; the mean AUC_{inf} at cycle 1 and 2 for 1.2 mg/m2 were 67.2 ng*h/mL and 78.0 ng*h/mL, respectively. At the 1.2 mg/m^2 dose cohort, trabectedin is generally tolerated and safe in Chinese subjects.

REFERENCES

1. Protocol, ET743SAR3006/ JNJ-17027907 (trabectedin). Multicenter, Open-label Study of YONDELIS (Trabectedin) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma. Document No. EDMS-ERI-30724363.
2. Christophe Le Tourneau, J. Jack Lee, and Lillian L. Siu. Dose Escalation Methods in Phase I Cancer Clinical Trials, J Natl Cancer Inst. 2009 May 20; 101(10): 708–720.
3. Demetri GD, von Mehren M, Jones RL and ect. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol. 2016 Mar 10;34(8):786-93

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STUDY TITLE:	**Multicenter, Open-label Study of YONDELIS (Trabectedin) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma**
REPORT CONTRIBUTORS:	[redacted] MS; [redacted], MD; [redacted], PhD; [redacted] PhD

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NAME:	Hongmei Li, MD
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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SIGNATURES

Signed by	Date	Justification
Hongmei Li	02Jun2017, 14:06:21 PM, UTC	Document Approval

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