

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207953Orig1s000

MEDICAL REVIEW(S)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 207953

Applicant: Janssen

Stamp Date: November 24, 2014

Drug Name: Trabectedin

NDA/BLA Type: Priority

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			Sponsor submitted revised clinical overview in 2.5 and revised summary of clinical efficacy and safety in 2.7.3 and 2.7.4, respectively, that contain appropriate links to CSR and ISS/ISE
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				Application is a 505 (b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X			The attempt is appropriate based on the serious and life-

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Number: ET743-SAR-3007 Study Title: A randomized controlled study of Yondelis (trabectedin) or dacarbazine for the treatment of advanced liposarcoma or leiomyosarcoma Sample Size: 517 Arms: Trabectedin: 1.5 mg/ m ² as a 24-hour IV infusion every 3 weeks Dacarbazine: 1 g/m ² administered as a 20-120 minute IV infusion every 3 weeks Location in submission: Module 5, Clinical Study Report				threatening indication.
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: Phase 3 study of a randomized controlled Study of trabectedin or dacarbazine for the treatment of locally advanced or metastatic liposarcoma or leiomyosarcoma Indication: patients with (b) (4) [REDACTED] [REDACTED] Pivotal Study #2: N/A Indication: N/A	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Yes, data consistent with discussion at pre-NDA meeting.
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Integrated STS safety analysis set (n=865) and Integrated STS and other solid tumor

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					safety analysis set (n=1681).
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			Adverse events are coded using MedDRA version 16.0.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Granted orphan drug designation for patients with soft tissue sarcoma on September 30, 2004.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes._____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jennie Chang (efficacy) and Dow-Chung Chi (safety) January 20, 2015

 Reviewing Medical Officer Date

Marc Theoret January 20, 2015

 Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIE T CHANG
01/20/2015

DOW-CHUNG CHI
01/21/2015

MARC R THEORET
01/22/2015

CLINICAL REVIEW

Application Type	New Drug Application / New Molecular Entity
Application Number(s)	NDA 207953
Priority or Standard	Priority
Submit Date(s)	11/24/2014
Received Date(s)	11/24/2014
PDUFA Goal Date	7/24/2015 (Major Amendment: 10/24/2015)
Division / Office	DOP2/OHOP
Reviewer Name(s)	Amy Barone, MD Dow-Chung Chi, MD
Review Completion Date	
Established Name	Trabectedin
(Proposed) Trade Name	YONDELIS [®]
Therapeutic Class	DNA alkylator
Applicant	Janssen Research & Development LLC
Formulation(s)	1 mg sterile lyophilized powder in a single-use vial
Dosing Regimen	1.5 mg/m ² body surface area as a 24-hour intravenous infusion, every 3 weeks through a central venous line. Premedicate with dexamethasone 20 mg

intravenous 30 minutes before infusion.

Indication(s) YONDELIS[®] is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma, who have received a prior anthracycline-containing regimen

Intended Population(s) ^{(b) (4)} patients with metastatic liposarcoma or leiomyosarcoma

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	10
1.1	Recommendation on Regulatory Action	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ..	13
1.4	Recommendations for Postmarket Requirements and Commitments	13
2	INTRODUCTION AND REGULATORY BACKGROUND	14
2.1	Product Information	14
2.2	Tables of Currently Available Treatments for Proposed Indications	15
2.3	Availability of Proposed Active Ingredient in the United States	16
2.4	Important Safety Issues With Consideration to Related Drugs.....	17
2.5	Summary of Pre-submission Regulatory Activity Related to Submission	17
2.6	Other Relevant Background Information	18
3	ETHICS AND GOOD CLINICAL PRACTICES.....	19
3.1	Submission Quality and Integrity	19
3.2	Compliance with Good Clinical Practices	21
3.3	Financial Disclosures.....	22
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	23
4.1	Chemistry Manufacturing and Controls (CMC).....	23
4.2	Clinical Microbiology.....	23
4.3	Preclinical Pharmacology/Toxicology (Nonclinical)	23
4.4	Clinical Pharmacology	24
4.4.1	Mechanism of Action.....	24
5	SOURCES OF CLINICAL DATA.....	25
5.1	Tables of Studies/Clinical Trials	25
5.2	Review Strategy	27
5.3	Discussion of Individual Studies/Clinical Trials.....	27
6	REVIEW OF EFFICACY	38
6.1	Indication	39
6.1.1	Methods	39
6.1.2	Demographics	39
6.1.3	Subject Disposition.....	42
6.1.4	Analysis of Primary Endpoint(s).....	46
6.1.5	Analysis of Secondary Endpoints(s)	54
6.1.6	Other Endpoints	55
6.1.7	Subpopulations	56
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	58
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	58

6.1.10 Additional Efficacy Issues/Analyses	58
7 REVIEW OF SAFETY.....	58
Safety Summary	58
7.1 Methods.....	60
7.1.1 Studies/Clinical Trials Used to Evaluate Safety	62
7.1.2 Categorization of Adverse Events	65
7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence.....	66
7.2 Adequacy of Safety Assessments	68
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	68
7.2.2 Explorations for Dose Response.....	71
7.2.3 Special Animal and/or In Vitro Testing	71
7.2.4 Routine Clinical Testing	71
7.2.5 Metabolic, Clearance, and Interaction Workup	71
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	71
7.3 Major Safety Results	71
7.3.1 Deaths.....	71
7.3.2 Nonfatal Serious Adverse Events	93
7.3.3 Dropouts and/or Discontinuations	99
7.3.4 Significant Adverse Events	104
7.3.5 Submission Specific Primary Safety Concerns	109
7.4 Supportive Safety Results	109
7.4.1 Common Adverse Events	109
7.4.2 Laboratory Findings	117
7.4.3 Vital Signs	118
7.4.4 Electrocardiograms (ECGs)	119
7.4.5 Special Safety Studies/Clinical Trials	120
7.4.6 Immunogenicity.....	120
7.5 Other Safety Explorations.....	120
7.5.1 Dose Dependency for Adverse Events	120
7.5.2 Time Dependency for Adverse Events.....	121
7.5.3 Drug-Demographic Interactions	121
7.5.4 Drug-Disease Interactions.....	122
7.5.5 Drug-Drug Interactions.....	122
7.6 Additional Safety Evaluations	122
7.6.1 Human Carcinogenicity	122
7.6.2 Human Reproduction and Pregnancy Data.....	122
7.6.3 Pediatrics and Assessment of Effects on Growth	123
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	123
7.7 Additional Submissions / Safety Issues	123
8 POSTMARKET EXPERIENCE.....	124

9	APPENDICES	125
9.1	Labeling Recommendations	125
9.2	Advisory Committee Meeting	125
9.3	Financial Disclosure	125
9.4	Literature Review/References	126
9.5	Definitions of Adverse Events of Special Interest	127

Table of Tables

Table 1. Chemotherapy Regimens Commonly Used for the Treatment of Non-GIST STS in the U.S.	15
Table 2. Key Regulatory History for Trabectedin and Development Program in STS ..	17
Table 3. Division of Scientific Integrity (DSI) Inspection Sites	20
Table 4. Clinical Trials Supporting the Proposed Indication and Dosing Regimen, Total L-type sarcoma q3 wk; 24-h treatment group evaluable for efficacy (n=581)	25
Table 5. Clinical Trials Included in the Integrated Safety Database, Supporting Safety (n=755)	26
Table 6. Censoring rules for rPFS	35
Table 7. Patient Population (ITT)	40
Table 8. Baseline Demographics in Trial 3007 at the Time of PFS Analysis	40
Table 9. Disease Characteristics in Trial 3007 at the Time of the PFS Analysis	41
Table 10. Primary Reason for Treatment Discontinuation at the Time of PFS Analysis	42
Table 11. Previous Chemotherapy in at least 5% of Subjects in Either Treatment Group	43
Table 12. Subsequent Anti-Cancer Therapy in 5% of patients (trabectedin included regardless of frequency)	43
Table 13. Major Protocol Deviations (adapted from CSR).....	44
Table 14. Study Medication Administration	45
Table 15. Treatment Cycle Delays and Dose Reductions for Patients Who Received at Least 2 Cycles of Treatment	46
Table 16. FDA PFS Analysis per INV Assessment (ITT).....	47
Table 17. FDA PFS Sensitivity Analyses of ITT population by Investigator and BRIC assessments	49
Table 18. Reasons for Event/Censored in the rPFS Analysis by Independent Radiologist Assessment; Audited Subset (Source: adapted from applicant response to FDA request).....	50
Table 19. Reasons for Event/Censored in the rPFS Analysis by Investigator Assessment; Audited Subset (source: adapted from applicant response to FDA request)	51
Table 20. OS Interim Analysis (ITT)	51
Table 21. OS Final Analysis Results (ITT)	53
Table 22. Confirmed ORR Results in Sensitivity Analysis 1	54
Table 23. Confirmed ORR Results for Sensitivity Analysis 2	54
Table 24. DOR Analysis based on Sensitivity Analysis 1 (described in ORR section) .	55
Table 25. DOR Analysis based on Sensitivity Analysis 2 (described in ORR section)	55
Table 26. FDA PFS Subgroup Analysis by Baseline Demographics	57
Table 27. FDA Subgroup Analysis by Disease Characteristics	57
Table 28. Trials included in the Integrated Safety Summary (ISS) Database.....	60
Table 29. Selected Studies Excluded from Safety Datasets	63
Table 30. Additional Trials Identified from Investigator's Brochure.....	64

Table 31. Enumeration of Patients for Safety Datasets 1, 2, and 3 by Treatment Regimen	65
Table 32. Incidence of Common (≥10%) Treatment-Emergent Adverse Events in Trabectedin-Treated Patients. ET743-SAR-3007 – Safety Population and ISS Database	67
Table 33. Exposure to Study Drug. ET743-SAR-3007 – Safety Population and ISS ..	68
Table 34. Demographics and Baseline Characteristics. ET743-SAR-3007 – Safety Population and ISS	69
Table 35. Primary Causes of Death by Treatment Group. ET-743-SAR-3007 – Safety Population	72
Table 36. Summary of Case Narratives of Deaths within 30 Days of Last Dose– ET743-SAR-3007 – Safety Population	73
Table 37. Incidence of Grade 5 Adverse Events by Preferred Term. ET743-SAR-3007 – Safety Population and ISS Database	81
Table 38. Summary of Case Narratives of Cardiac-Related SAE. ET743-SAR-3007 – Safety Population.....	83
Table 39. Change from Baseline for LVEF. ET743-SAR-3007 – Safety Population....	88
Table 40. Incidence of Neutropenia-Related Adverse Events. ET743-SAR-3007 – Safety Population.....	90
Table 41. Summary of Selected Case Narratives of Rhabdomyolysis-Related SAE. ET743-SAR-3007 – Safety Population.....	91
Table 42. Incidence of Non-Fatal Serious Adverse Event (Occurring in ≥2 Trabectedin-Treated Patient) by Preferred Term. ET743-SAR-3007 – Safety Population and ISS Population	93
Table 43. Incidence of Dyspnea and Dyspnea-Related Adverse Events. ET743-SAR-3007 – Safety Population.....	96
Table 44. Incidence of Renal Failure and Renal-Related Adverse Events. ET743-SAR-3007 – Safety Population.....	97
Table 45. Incidence of Multi-Organ Failure-Related Adverse Events. ET743-SAR-3007 – Safety Population.....	98
Table 46. Reason for Treatment Discontinuations. ET743-SAR-3007 – Safety Population.....	99
Table 47. Frequency of Adverse Events Leading to Treatment Modification. ET743-SAR-3007 – Safety Population	99
Table 48. Incidence of Adverse Events Leading to Treatment Discontinuation (Occurring in ≥2 Trabectedin-Treated Patient) by Preferred Term. ET743-SAR-3007 – Safety Population and ISS.....	100
Table 49. Incidence of Liver Injury-Related Adverse Events. ET743-SAR-3007 – Safety Population.....	101
Table 50. Frequency of Liver Injury-Related Adverse Events Leading to Treatment Modification. ET743-SAR-3007 – Safety Population.....	102
Table 51. Summary of Case Narratives of that Met Hy’s Law. ET743-SAR-3007 – Safety Population.....	103

Table 52. Incidence of Liver Enzyme Elevations (All Grades and Grade 3-4). ET743-SAR-3007 – Safety Population.	103
Table 53. Incidence of Grade 3 & 4 AE in >3 Patients. ET743-SAR-3007 – Safety Population.....	104
Table 54. Incidence of Adverse Events Leading to Dose Reduction (Occurring in ≥2 Trabectedin-Treated Patient) by Preferred Term. Safety Population ET743-SAR-3007 and ISS Population.....	106
Table 55. Incidence of Adverse Events Leading to Treatment Interruption/Delay Reduction (Occurring in ≥2 Trabectedin-Treated Patient) by Preferred Term. ET743-SAR-3007 – Safety Population and ISS.....	107
Table 56. Incidence of TEAE (>5% of Trabectedin-Treated Patients) by Treatment Group. ET743-SAR-3007 – Safety Population.....	109
Table 57. Incidence of TEAE (≥10% of Trabectedin-Treated Patients or ≥5% Higher in Trabectedin Treatment Group by System Organ Class. ET743-SAR-3007 – Safety Population.....	112
Table 58. Incidence of TEAE (≥10% of Trabectedin-Treated Patients or ≥5% Higher in Trabectedin Treatment Group by High Group Level Term. ET743-SAR-3007 – Safety Population.....	112
Table 59. Incidence of TEAE (>10% of Trabectedin-Treated Patients or >5% Higher in Trabectedin Treatment Group by High Level Term. ET743-SAR-3007 – Safety Population.....	114
Table 60. Analysis of Narrow-Based Standardized MedDRA Queries by Treatment Group. ET743-SAR-3007 – Safety Population.....	115
Table 61. Incidence of Treatment-Emergent Grade 1-4 Laboratory Abnormality (≥10% of YONDELIS-Treated Patients). ET743-SAR-3007 – Safety Population ...	118
Table 62. Change from Baseline for ECG. ET743-SAR-3007 – Safety Population ...	119
Table 63. Summary of Safety Analyses by Age (< 65 vs. ≥65) and Gender Subgroups. ET743-SAR-3007 – Safety Population.....	121
Table 64. Dose Reduction Due to Hematologic Toxicity (adapted from CSR)	127
Table 65. Dose Reduction Due to Non-Hematologic Toxicity (adapted from CSR)....	127
Table 66. Cardiac Disorders as Defined by Applicant	127
Table 67. Neutropenia – Selected Infections as Defined by Applicant.	128
Table 68. CPK Elevations / Rhabdomyolysis as Defined by Applicant.....	129
Table 69. Liver Injury as Defined by Applicant.	129
Table 70. Renal Disorders as Defined by Applicant.	131
Table 71. Thrombocytopenia-Bleeding as Defined by Applicant.	131
Table 72. Multi-Organ Failure as Defined by Applicant.	134

Table of Figures

Figure 1. Structural formula of trabectedin (adapted from labeling)	15
Figure 2. Treatment Scheme.....	29
Figure 3. Event Scheduling and Monitoring.....	33
Figure 4. FDA's analysis of Investigator PFS, radiographic and clinical progression (where chemotherapy =dacarbazine and experimental =trabectedin)	48
Figure 5. FDA's Kaplan-Meier Curve for Interim OS Analysis (ITT)	52
Figure 6. FDA's Kaplan-Meier Curve for Final OS Analysis (ITT).....	53

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This new drug application (NDA 207953) for trabectedin, a new molecular entity, was submitted by Janssen on November 24, 2014, for the following indication:

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

The reviewers have examined the submitted data and study reports and found that the application provided substantial evidence of efficacy and safety to support the use of trabectedin in patients with unresectable or metastatic liposarcoma or leiomyosarcoma. The reviewers concur with the applicant's conclusions about trabectedin in support of the proposed indication.

The reviewers recommend regular approval of trabectedin at the proposed dosing schedule for the treatment of patients with unresectable or metastatic, liposarcoma or leiomyosarcoma subtypes of soft tissue sarcoma (STS). This is based on the totality of evidence, including an improvement in progression-free survival of significant magnitude to represent clinical benefit. The safety profile of trabectedin in patients with leiomyosarcoma and liposarcoma, as demonstrated in the submitted clinical studies performed in this patient population, is generally consistent with the safety profile of trabectedin based on post-marketing safety data in countries where trabectedin has been approved for patients with advanced soft tissue sarcoma and patients with relapsed ovarian cancer.

1.2 Risk Benefit Assessment

The benefit-risk analysis of the use of trabectedin for the treatment of liposarcoma and leiomyosarcoma is based on the totality of evidence included in the applicant's submission as well as review of current literature and consideration of expert opinion.

Unresectable or metastatic STS is a rare, heterogeneous disease with a devastating prognosis. Approximately 12,020 new cases of adult STS are diagnosed per year and 4,740 deaths are projected per year. The median overall survival from time of diagnosis is typically no more than 8 to 13 months. Liposarcoma and leiomyosarcoma represent 40-50% of STS and approximately half of these patients present with metastatic disease. Doxorubicin is the only chemotherapeutic agent approved for the first-line treatment of STS, and unfortunately, treatment is restricted to use for only six cycles due to treatment related toxicity. In 2012, pazopanib was approved for patients with advanced STS but its use is limited based on histologic subtype; no efficacy was seen in patients with liposarcoma. Other chemotherapeutic agents such as dacarbazine, gemcitabine, and ifosfamide have shown evidence of anti-tumor activity; however, none have demonstrated an improvement in overall survival. Patients with advanced L-type sarcoma are often referred to participate in clinical trials based on the lack of available therapy.

The main efficacy endpoint for this trial is an improvement in PFS. Because of the limited number of therapeutic options for STS, the clinical meaningfulness of PFS has evolved in discussion with key opinion leaders and expert advice over the past decade.

In 2012, pazopanib was presented to the Oncologic Drugs Advisory Committee (ODAC) to discuss the clinical meaningfulness of PFS. The primary trial supporting registration of pazopanib was a double-blind, placebo-controlled, multicenter study of pazopanib compared to placebo in patients with metastatic STS who had received prior systemic therapy that included anthracyclines. The primary analysis of PFS demonstrated a 3 month improvement in median PFS with pazopanib based on efficacy assessments by a blinded independent radiology review (HR 0.35; 95% CI 0.26, 0.48; p-value <0.001). The Kaplan-Meier estimated median PFS was 4.6 months in patients treated with pazopanib as compared to a median PFS of 1.6 months in patients receiving placebo. The hazard ratio of the final OS analysis was 0.87 (95% CI: 0.67-1.12; p=0.26). Generally, ODAC committee members agreed that a treatment effect that results in stabilizing the disease burden in patients rendering them to be free of progression is valuable in that patients can harbor very large, bulky disease that can impinge on vital structures. Patients can live with bulky disease and relatively minor morbidity, but rapid progression can lead to increased morbidity. Several ODAC members discussed that other agents used routinely off-label do not achieve a real, measurable improvement in PFS in patients with advanced STS. Members also discussed the value of patients who remained on treatment for one year as indication of clinical benefit. In this context, some members felt that an improvement in PFS represents a benefit to these patients. In addition, the rarity and heterogeneity of STS make accrual challenging. To power a

study for OS could take many years, limiting access of a potentially valuable drug to patients. Based on this ODAC and the general community practice, FDA accepted PFS as a clinically meaningful primary endpoint in patients with metastatic soft tissue sarcoma.

This application for trabectedin is primarily supported by Trial ET743-SAR-3007, a randomized (2:1), open-label, active-controlled multicenter study of trabectedin compared to dacarbazine in patients with unresectable or metastatic L-type sarcoma who had received prior systemic therapy that included anthracyclines. Randomization was stratified by type of sarcoma, ECOG performance status (0 vs. 1), and number of prior chemotherapy regimens (1 vs. ≥ 2). The efficacy outcome measures were investigator-assessed progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), overall survival (OS), objective response rate (ORR), and duration of response (DOR). Patients in the dacarbazine arm were not offered trabectedin at the time of disease progression. At the time of the final PFS analysis, a total of 518 patients were randomized, 345 to the trabectedin arm and 173 patients to the dacarbazine arm. The baseline demographic and disease characteristics were similar between the trabectedin and the control arm. The median patient age was 56 years (range 17 to 81); 30% were male; 76% Caucasian, 12% African American, and 4% Asian; 73% had leiomyosarcoma and 27% liposarcoma; 49% had an ECOG PS of 0; and 89% received ≥ 2 prior chemotherapy regimens. The most common ($\geq 20\%$) pre-study chemotherapeutic agents administered were doxorubicin (90%), gemcitabine (81%), docetaxel (74%), and ifosfamide (60%). Approximately 10% of patients had received pazopanib.

Treatment with trabectedin resulted in a statistically significant 45% reduction in the risk of progressive disease or death compared with dacarbazine treatment (HR= 0.550; 95%: 0.43 ,0.696; $p < 0.0001$). The median PFS by the unstratified analysis as determined by the investigator was 4.21 months for the patients treated with trabectedin compared to 1.54 months for patients treated with dacarbazine. An analysis of PFS as assessed by a blinded independent central review (BICR) per RECIST v1.1 was conducted on a retrospective audit plan of 60% of patients at 19 sites with at least 9 patients randomized. The BIRC analysis was conducted to evaluate for the introduction of bias in the investigator-assessed PFS analysis; the results of this BICR-assessed PFS analysis were consistent with investigator determination. The magnitude of the treatment effect on PFS was consistent across multiple subgroups.

The review of safety primarily focused on analyses of data submitted for the ET743-SAR-3007 trial because it is the only randomized, comparative trial submitted by the Applicant to support the safety of trabectedin. The size of the Integrated Summary of Safety (ISS) database and duration of trabectedin exposure were sufficient to characterize the safety of trabectedin for the treatment of a serious and life-threatening condition, i.e., recurrent, metastatic leiomyosarcoma and liposarcoma. In the ET743-SAR-3007 trial, the most common adverse reactions ($\geq 20\%$) are nausea, fatigue,

vomiting, diarrhea, constipation, decreased appetite, dyspnea, headache, fever, and cough. The most common laboratory abnormalities ($\geq 20\%$) are increases in AST or ALT, neutropenia, and anemia. The most common ($\geq 3\%$) serious adverse events are nausea, vomiting, abdominal pain, dyspnea, anemia, febrile neutropenia, pyrexia, and dehydration.

In the ET743-SAR-3007 trial, adverse reactions resulting in permanent discontinuation of trabectedin occurred in 98/378 (26%) patients. The most common adverse reactions ($\geq 2\%$) resulting in permanent discontinuation of trabectedin are elevated liver enzymes and thrombocytopenia. Adverse reactions that led to dose reductions occurred in 158/378 (42%) patients treated with trabectedin. The most common adverse reactions ($\geq 2\%$) resulting in dose reduction of trabectedin are elevated liver enzymes, neutropenia, including febrile neutropenia, thrombocytopenia, and fatigue. Adverse reactions led to dose interruptions in 198/378 (51%) patients treated with trabectedin. The most common adverse reactions ($\geq 2\%$) that led to dose interruptions are neutropenia, thrombocytopenia, anemia, elevated liver enzymes, and fatigue.

Overall, the efficacy and safety results demonstrated in this application suggest that trabectedin has a favorable benefit-to-risk profile in patients with unresectable or metastatic liposarcoma or leiomyosarcoma who have received prior therapy. This patient population represents an area of unmet medical need as there is only one approved therapy for advanced STS, and its activity has not been demonstrated in patients with liposarcoma. Although overall survival was initially defined as the primary efficacy endpoint to evaluate clinical benefit, the clinical reviewers consider the magnitude of improvement in PFS clinically meaningful benefit in this rare disease population with no therapeutic options that improve overall survival. The reliability of the improvement in PFS is supported by the consistency of the treatment effect, including the magnitude of PFS, across multiple subgroups; the PFS results based on an audit performed by an independent radiologic review committee, blinded to treatment assignment that was consistent with the investigator determination; and the conduct of the trial.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

The reviewer recommends the following Postmarket Requirement.

Submit integrated safety analyses and supporting data from an adequate number of clinical trial(s) to characterize the risk of cardiomyopathy and its sequelae in patients receiving trabectedin; to identify risk factors for development of these sequelae; and to

support labeling instructions for dose modification and monitoring. The design of the trial should include a patient population with previous exposure to anthracyclines and have sufficient cardiac monitoring to achieve these objectives.

2 Introduction and Regulatory Background

2.1 Product Information

Product: Trabectedin (Yondelis)

Chemical Class: New molecular entity

Pharmacologic class: DNA alkylating drug

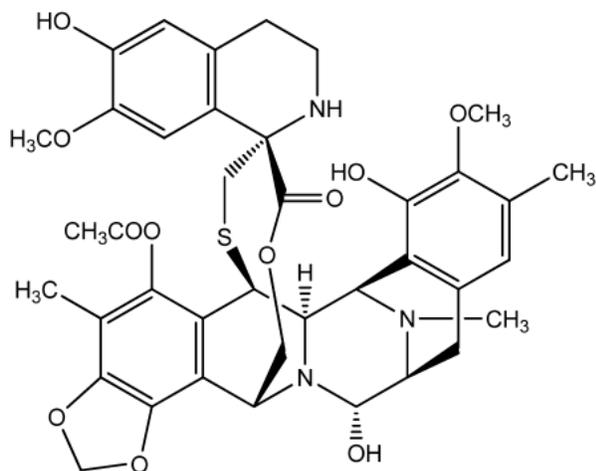
Proposed Dose: 1.5 mg/m² as an intravenous infusion over 24 hours given every 3 weeks

Trabectedin is a new chemical entity firstly isolated, identified and characterized from the marine tunicate *Ecteinascidia turbinata*. (b) (4)



Trabectedin injection (1-mg) is a sterile, lyophilized white powder containing 1 mg of trabectedin formulated with sucrose, potassium dihydrogen phosphate, phosphoric acid, and potassium hydroxide. The individual vials of drug product are reconstituted with Water for injection, USP to a nominal concentration of 50 ug/mL of drug substance, and then further diluted with intravenous infusion solution of 0.9% Sodium Chloride Injection, USP or 5% dextrose Injection, USP. The supplies used in the study were Batch Nos: 364429, 365836, 4367083, 436274, and 4367722 (Expiration dates: June 30 2013, November 30 2013, April 30 2014, October 31 2014, and December 13 2014, respectively).

Figure 1. Structural formula of trabectedin (adapted from labeling)



2.2 Tables of Currently Available Treatments for Proposed Indications

Soft tissue sarcoma (STS) is a heterogeneous group of malignancies arising from mesodermal tissue, accounting for approximately 1% of adult solid tumor malignancies. The National Cancer Institute estimates that there will be 11,930 new cases and 4,870 deaths from soft tissue sarcoma in the United States in 2015[1]. The reported international incidence rates range from 1.8 to 5 per 100,000 persons per year. Approximately 40-50% of these patients will present with unresectable or metastatic disease and have a median survival of 8 to 13 months from time of diagnosis. Doxorubicin with or without ifosfamide is the standard systemic treatment option for patients with metastatic STS, however, its use is limited to a maximum of 6 cycles due to treatment related toxicity. Pazopanib is the only FDA-approved treatment for recurrent soft tissue sarcoma that has progressed after doxorubicin, although efficacy has not been demonstrated for the treatment of liposarcoma. A list of chemotherapy regimens commonly used for the treatment of STS is summarized below (Table 2). None of these agents have been shown to increase overall survival.

Table 1. Chemotherapy Regimens Commonly Used for the Treatment of Non-GIST STS in the U.S.

Product	Approved for treatment of STS	Evidence of activity in STS
Doxorubicin	Yes	<ul style="list-style-type: none"> Activity against multiple histologies of STS first described in 1970s. Response rates in the range of 10-25% have been reported[2] When administered as part of combination regimens, response rates of up to 46% are seen although with inferior toxicity profile [2]

Product	Approved for treatment of STS	Evidence of activity in STS
		<ul style="list-style-type: none"> Unclear if liposomal doxorubicin has similar activity against STS although toxicity profile is better. Limited to a maximum of 6 cycles due to cumulative treatment-related toxicities.
Pazopanib	Yes	<ul style="list-style-type: none"> Approved for use in STS after relapse from anthracycline therapy Based on improved PFS in a double-blind, placebo-controlled, multicenter study of pazopanib compared to placebo in patients with metastatic STS who had received prior systemic therapy that included anthracyclines. Median PFS was 4.6 months in patients treated with pazopanib as compared to 1.6 months in patients receiving placebo (HR 0.35, 95% CI 0.26, 0.48 p<0.001). [3] Limitation: efficacy for the treatment of adipocytic soft tissue sarcoma has not been demonstrated.
Ifosfamide	No	<ul style="list-style-type: none"> Response rates of ≥ 25% have been reported in multiple trials[2] Typically administered in combination with doxorubicin. Combination chemotherapy for front-line treatment failed to improve overall survival [4] Active against multiple STS histologies, particularly synovial sarcoma.
Dacarbazine	No	<ul style="list-style-type: none"> Response rates of ≤18% have been reported in multiple histologies of STS
Gemcitabine	No	<ul style="list-style-type: none"> Higher response rates have been reported when administered in combination regimens [2] In a randomized phase 2 study comparing gemcitabine with gemcitabine and docetaxel, response rate (16% vs. 9%), PFS (6.2 vs. 3.0 months) and OS (17.9 vs. 11.5 months) were all superior in the combination arm[5]
Paclitaxel	No	<ul style="list-style-type: none"> Response rates of > 50% have been reported in patients with angiosarcoma.[6]

2.3 Availability of Proposed Active Ingredient in the United States

Trabectedin is a new molecular entity. It is not commercially available in the United States.

Trabectedin was granted marketing authorization under “exceptional circumstances” by the EMA in 2007 for the treatment of patients with soft tissue sarcomas who have progressed after both anthracycline and ifosfamide treatment or for whom these treatments are unsuitable. As of July 10, 2014, trabectedin is approved in 75 countries for the treatment of STS and in 68 countries for the treatment of relapsed ovarian cancer in combination with pegylated liposomal doxorubicin.

2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Since discussions began in October 2000 regarding the development of trabectedin, trabectedin has been approved outside of the U.S. for the treatment of patients with advanced STS. In 2006, several meetings were held to discuss Trial ET743-ST5-201 as a registration trial to support approval in the US. ET743-ST5-201 was the basis for EMA approval under Exceptional Circumstances of trabectedin for the treatment of relapsed/refractory locally advanced or metastatic liposarcoma or leiomyosarcoma. The trial was an open-label, randomized (1:1), multicenter trial designed to compare trabectedin in 2 different treatment regimens (0.58 mg/m² given as a 3-hour intravenous infusion every week versus 1.5 mg/m² given as a 24-hour intravenous infusion every 3 weeks) in patients with relapsed or refractory locally advanced or metastatic L-type sarcoma who had been previously treated with an anthracycline and ifosfamide containing regimen (n=270 patients total). The primary endpoint was initially a point estimate of clinical benefit (a composite rate of confirmed CR or PR or stable disease lasting for at least 24 weeks) but it was changed to time-to-progression (TTP) after early descriptive data in 80 patients led to extension of the study to expand the sample size. A meeting was held April 14, 2006, where FDA did not agree that (b) (4) would support an application for regular approval (b) (4).

FDA stated a confirmatory study would likely be required. Trial ET743-SAR-3007, the primary trial in this application, is intended to be the confirmatory trial.

Table 2. Key Regulatory History for Trabectedin and Development Program in STS

Date	Action
October 18, 2000	FDA held a Type B, End-of-Phase 2 (EOP2) meeting with the sponsor (Pharma Mar) to discuss the development of trabectedin (b) (4). FDA stated that the primary endpoint of the trial should be overall survival to support full approval.
March 5, 2002	FDA held an EOP2 meeting with Pharma Mar to discuss (b) (4).
May 21, 2004	FDA held an EOP2 meeting with the new sponsor (Johnson & Johnson) to discuss the development of trabectedin (b) (4). The sponsor proposed to submit the ORR results from Trial ET743-ST5-201 (b) (4).
March 10, 2005	FDA held a pre-NDA meeting with Johnson & Johnson to discuss the organization, content and format of an NDA for the proposed indication treatment of patients with (b) (4) metastatic liposarcoma or leiomyosarcoma after previous

Date	Action
	treatment.
November 4, 2005	FDA held a Type A meeting with Johnson & Johnson, FDA did not agree with the proposed (b) (4) analysis or with a modification (b) (4).
December 15, 2005	FDA issued a Special Protocol Assessment (SPA) – No Agreement letter for protocol (b) (4).
April 14, 2006	FDA held a Type A meeting with Johnson & Johnson to discuss ET743-STS-201. FDA did not agree that (b) (4) would support an application (b) (4). FDA stated a confirmatory study would likely be required.
November 23, 2010	FDA held a Type C meeting with Johnson & Johnson to discuss the design of the proposed Phase 3 study ET743-SAR-3007. FDA agreed with OS as the primary endpoint and with dacarbazine as the active comparator. Sponsor stated that patients would not be allowed to crossover to trabectedin arm.
July 23, 2012	During an EOP2 meeting (b) (4), FDA proposed that Janssen (formerly Johnson & Johnson) R&D share the mature PFS and response rate results from the ET743-SAR-3007 study with FDA as a basis for possible accelerated approval.
June 7, 2013	In a Type C, Written Response Only, FDA recommended that if Janssen sought approval based on PFS and ORR, an independent analysis of tumor-based assessments to determine tumor response should be conducted by an independent radiologic review committee blinded to treatment assignment. Alternatively, FDA stated that Janssen may propose a detailed auditing plan including a strategy to detect potential assessment bias.
January 9, 2014	Janssen submitted interim results for OS, PFS and response rates for Study ET743-SAR-3007 as well as a proposed auditing plan for the PFS endpoint.
July 7, 2014	FDA held a Type C meeting with Janssen to discuss the audit results of the investigatory assessed PFS endpoint for Study ET743-SAR-3007 as assessed by independent radiologic review.

2.6 Other Relevant Background Information

Trabectedin was reviewed under

(b) (4)
 (u) (4)
 (b) (4)

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission contained the debarment certificate, sufficient datasets and relevant case report forms. DSI audited the following sites for data integrity. Issues identified during the review and conveyed to the sponsor included:

- Incomplete submission of rationale for censoring differences from the Independent Radiologist (IR) Assessment and Investigator (INV) Assessment.
- Incomplete submission of date of subsequent anti-cancer therapy
- Inaccurate data in the adverse events datasets leading to modifications of historical entries from the Interim Analysis and the 120-Day Safety Update
- Insufficient data to confirm the certain reported adverse events, such as febrile neutropenia.
- Insufficient data to assess the onset, duration, and recovery of cardiomyopathy.
- Missing data, or classified as “other,” “not applicable,” “unknown”
- Laboratory datasets missing key variables, such as potassium, sodium, blood urea nitrogen, bicarbonate, chloride.
- Vital signs datasets missing body temperature, blood pressure, heart rate, respiratory rate, pulse oximetry for each study cycle.
- ECG and LVEF assessment datasets missing significant amounts of data.

Not all of these issues were satisfactorily addressed by the applicant. In many instances, the data was not collected on the eCRFs and will not be possible to retrieve missing information in a systematic manner.

A Form 438 was issued to Janssen on March 26, 2015, due to discrepancies in in audited adverse events and serious adverse events. On April 17 and 27, 2015, FDA received formal amendments to the application which constituted a major amendment. A Review Extension Major Amendment letter was issued May 1, 2015.

Table 3. Division of Scientific Integrity (DSI) Inspection Sites

Planned inspections:	Scheduled dates for inspection	Status	Site Number
Sponsor: Janssen LLC	March 16-26 th , 2015	Completed	Site 1013
CI: Demetri, George (MA)	March 30-April 2 nd , 2015	Completed	Site 1001
CI Patel, Shreyaskumar (TX)	March 23-April 2 nd , 2015	Completed	Site 1028
CI: Schuetze, Scott (MI)	March 9-20, 2015	Completed	Site 1033

DSI inspections found several instances noted where adverse events (AEs) were either not reported to the sponsor or misreported. The inspection reviewer reported that the AEs found during the inspection represent a small proportion of all AEs reported. The inspection reviewer concluded that the observations appear to be isolated and non-systemic and should not impact the overall study outcome for safety. The inspection reviewer concluded that the safety data appear reliable based on upon available information for the four sites audited.

On April 17, 2015, The Applicant submitted updated safety datasets with a database cutoff date of July 10, 2014 as part of its 120-Day Safety Update (120DSU) (NDA 207953, SDN22) and an updated Clinical Study Report submitted on March 24, 2015 (NDA 207953, SDN17). Comparison of the ae.xpt dataset from the Interim Analysis with a database cutoff date of September 16, 2013, (November 24, 2014, NDA 207953, SDN 01) with the ae.xpt dataset submitted as part of the 120-Day Safety Update, using an imposed cutoff date of September 16, 2013. This modification of the 120DSU dataset was performed so that it would have the same cutoff date as the Interim Analysis dataset. Comparison of the two datasets revealed several discrepancies, as a result of retroactive modification of historical adverse events data.

Discussions between the FDA and the Applicant uncovered that the underlying cause of the discrepancies was that there was a major backlog of data entry that was not completed before the database was locked for the Interim Analysis. As a result, many adverse events that occurred prior the database lock were added, deleted, or modified after the original NDA submission. On April 30, 2015, the Applicant submitted results of the comparison between the 2 safety databases (NDA 207953, SDN 25) . Changes to the 120DSU safety database included:

- addition of 67 new TEAEs that changed the safety profile for 33 patients.
 - 55 new TEAE
 - 10 new lab-based toxicities
 - 2 TEAE with more severe toxicity
 - 15 were
- reclassification of seriousness for 21 / 9532 TEAEs (0.2%), in 10 patients.
- changes in toxicity grading for 31 TEAEs (0.3%) in 18 patients

- changes in relationship to drug for 51 TEAEs (0.5%) in 22 patients
- changes in action taken for 20 TEAEs (0.2%) in 16 patients
- no TEAE leading to discontinuation
- no changes in TEAE leading to death

The Applicant also agreed to conduct a Re-Verification process to ensure data integrity of the 120DSU datasets. This process included:

- conduct focused re-verification visits to 9 high enrolling sites.
- review of all source documents to verify completeness of data entry
- review of all source documents to verify the accuracy of data entry with a focus on correct toxicity grade, relationship to the study drug
- emphasis on TEAE leading to treatment termination, death or significant clinical outcome
- medical review of re-verification findings

Results of the Re-Verification Process was submitted on June 16, 2015, to NDA 207953 SDN 31 which involved 9 high enrolling sites, representing 214 patients, and 4,118 treatment-emergent adverse events (TEAEs). The results of the process identified several changes to both groups of the Safety population in the new dataset in the 120DSU, including:

- addition of 38 TEAEs of any grade (0.91%) in 25 patients
 - 24 Grade 1 TEAEs
 - 3 Grade 2 TEAEs
 - 1 Grade TEAE
 - 10 TEAEs had missing toxicity grade in the source documentation
- changes to the toxicity grading in 10 TEAEs (0.24%)
- changes to relationship to treatment of 34 TEAEs (0.83%)

FDA review of the Applicant's Re-verification Process and results, as well as completion of its own internal assessment of the data integrity datasets submitted under the Interim Analysis and 120DSU, and deemed that new submissions, constituted a Major Amendment, resulting in the extension of review deadlines.

3.2 Compliance with Good Clinical Practices

According to the ethics sections of the NDA,

- The study protocol and amendments were reviewed by an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB)
- The submitted study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices (GCP) guidelines and applicable regulatory requirements.

- Known instances of nonconformance were documented and not considered to have had an impact on the overall conclusions of the study.
- Patients or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions and risks and benefits of treatment.

3.3 Financial Disclosures

This submission contained the required financial disclosure information for clinical investigators who participated in studies (b) (6) (See Section 9.3 for Financial Disclosure form). In accordance with 21 CFR part 54, the applicant required the disclosure statement to be completed at the beginning of the study, at any point when changes were made the financial interests of the investigators during the course of the trial, and 1-year post-completion of the study. The applicant defines other financial interests as payments/arrangements in excess of \$25,000. A significant equity interest is defined as ownership, stock options or other equity interest in either the Sponsor or Applicant in excess of \$50,000. The applicant conducted a vendor search for any payments made to the any individuals who participated in conduct and data collection from 2003 through 2014. Vendors were searched against three databases (Beacon, Totality and Sustain). The applicant relied on the self-disclosure process for all instances of significant equity or proprietary interests in Johnson & Johnson and/or Yondelis. Three instances of disclosable financial information were identified, all which were self-disclosures pertained to equity interest greater than \$50,000. There were no investigators who are or were sponsor employees (including both full-time and part-time employees).

Financial Disclosures identified:

(b) (6)

One principal investigator, (b) (6), self-disclosed equity interest greater than \$50,000 in the form of publically traded stock. Another principle investigator's financial disclosure form was not obtainable.

(b) (6)

Two investigators from study (b) (6), principle investigator (b) (6) and sub-investigator (b) (6) self-disclosed equity interest greater than \$50,000 in the form of publically traded stock.

Both studies were randomized studies performed at multiple centers by multiple investigators and radiographic images were independently reviewed. The investigators identified as having financial disclosable information provided minimal contributions to the overall study data: (b) (6)

(b) (6) For these reasons, the integrity of the data from both studies likely remains intact.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

Sufficient stability data was submitted in this application to support approval and there are no pending approvability issues from CMC. No facilities need to be inspected for drug product.

4.2 Clinical Microbiology

Microbial Challenge studies demonstrated that the reconstituted, diluted trabectedin can support microbial growth. Clinical Microbiology suggested three options that are available to mitigate the risk of microbial bioburden: 1) (b) (4) (b) (4) 2) Labeling to direct health care professionals to change the bag every 8 hours, or 3) recommend the use of an in-line filter. Regarding option (1), many diluents were tested and all supported microbial growth. Clinical Microbiology recommended the use of an in-line filter.

4.3 Preclinical Pharmacology/Toxicology (Nonclinical)

All studies required to support the approval of trabectedin for the treatment of patients (b) (4) were previously reviewed under (b) (4). During the original nonclinical review of trabectedin, the discovery of high levels of drug loss due to adsorption to some types of tubing was a serious complicating factor in the determination of exposure margins of the drug compared to human exposures. While this issue makes dose comparisons for some endpoints problematic, the animal studies adequately demonstrated the toxicity profile for trabectedin. In repeat dose general toxicology studies in rats and monkeys the Applicant was able to estimate the actual trabectedin delivered dose based on concentrations before and after infusion and exposure margins in the trabectedin label are based on the corrected doses from these studies. One additional study, a study of placental transfer in rats, that was initiated by the sponsor and not required by FDA was included in this application. The nonclinical reviewer concluded that based on the mechanism of action (alkylating drug), trabectedin has the potential to cause embryofetal harm and recommends a warning and precaution in labeling for embryofetal toxicity. The FDA nonclinical reviewer did not identify any issues in this application that would preclude approval.

4.4 Clinical Pharmacology

The majority of Clinical Pharmacology studies required to support the approval of trabectedin for the treatment of patients (b) (4) were previously reviewed under NDA (b) (4). Studies requested under NDA (b) (4) that were submitted with this application include OVC-1001, a QT/QTc study that did not demonstrate QT interval prolongation, OVC-1002 (Rifampin) which demonstrated a decrease in C_{max}/AUC_{last} , and OVC-1003 (Ketoconazole) which demonstrated an increase in C_{max}/AUC_{last} . Clinical Pharmacology recommends avoiding strong (b) (4) inducers; this is reflected in the proposed labeling. A hepatic impairment study is expected to be completed by 1/28/2015 and will be reviewed as a PMR.

The clinical pharmacology of trabectedin is summarized as below (adapted from Clinical Pharmacology Review under IND (b) (4)):

- The PK of trabectedin is dose proportional and cycle independent. The concentration of trabectedin decreased in a multi-exponential manner with a terminal half-life of approximately 175 hours. The trabectedin plasma clearance was approximately 31 L/hr with an intersubject variability of 51% and intra-patient variability of 28%.
- Mass balance study suggested that 57.6% of the total radioactivity was eliminated in the feces and 5.8% recovered in the urine. Trabectedin is extensively metabolized by hepatic CYP3A (b) (4). Trabectedin is a P-gp substrate. *In-vitro*, trabectedin is not an inhibitor of major CYP enzymes.
- Clear exposure-response relationships were identified for neutropenia, elevation in serum transaminases, and hyperbilirubinemia using trabectedin monotherapy data. The sponsor's proposed dose adjustment from 1.1 mg/m² to 0.9 mg/m² and then to 0.75 mg/m² appears reasonable as it moderately decreases the toxicities in the trabectedin arm.

4.4.1 Mechanism of Action

Trabectedin, formerly known as ecteinascidin 743 (ET-743) is a natural marine tetrahydroisoquinoline compound with antitumor properties first isolated from the Caribbean tunicate *Ecteinascidia turniata*, a colony-forming tunicate that grows in coastal temperate seas. (b) (4)

(b) (4) Trabectedin is a DNA alkylator with a that binds to the N2 position of guanine minor groove of DNA which results in a bending of the DNA helix to the major groove; this binding triggers a cascade of events that affect several transcription factors, DNA binding proteins, and DNA repair pathways resulting in slowing of progression through the S and G2/M of the cell cycle and p53 independent apoptosis. Trabectedin also prevents the binding of translocation-related fusion oncogenic proteins to DNA promoter region which interferes with the function of proteins known to impact growth and progression. Trabectedin also influences the

tumor microenvironment by targeting tumor associated macrophages and histiocytes in both preclinical models and biopsy samples from trabectedin-treated STS patients.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

This submission is based upon data from a confirmatory, randomized, open-label, active-controlled, parallel group, multicenter trial (ET743-SAR-3007) which investigated the activity and safety of the 1.5 mg/m², every 3 weeks (q3wk) 24-hour trabectedin dosage regimen in patients with liposarcoma or leiomyosarcoma. In addition, the results of one open-label, randomized, multicenter trial (ET743-ST5-201) and the results of three open-label single-arm activity-finding trials (ET-B005-98, ET-B-008-98, ET-B017-99) are included which each investigated the activity of the 1.5 mg/m² q3wk 24 hour trabectedin regimen in patients with unselected soft tissue sarcoma (STS). These studies are summarized in Table 4. No pediatric patients were enrolled in any of these trials.

Table 4. Clinical Trials Supporting the Proposed Indication and Dosing Regimen, Total L-type sarcoma q3 wk; 24-h treatment group evaluable for efficacy (n=581)

	Study	Design	Dosing Schedule	Patients		
Primary	ET743-SAR-3007	Randomized, open label	Trabectedin: q3wk 24-h dose	345*		
			Dacarbazine: q3wk 20- to 120- min dose	173*		
Supportive	ET743-ST5-201	Randomized, open label	Trabectedin qwk 3-h dose group	134*		
			q3wk 24-h dose group	136*		
				L-type sarcoma	Other	All
	ET-B-005-98	Single arm	Trabectedin: q3wk 24-h dose	49*	50	99
ET-B-008-98	Single arm	Trabectedin: q3wk 24-h dose	28*	22	50	

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

	Study	Design	Dosing Schedule	Patients		
	ET-B-017-99	Single arm	Trabectedin: q3wk 24-h dose	23*	11	34
Additional	ET743-SAR-3002 (Expanded Access Program)	Single arm	Trabectedin: q3wk 24-h dose	1803 (previously treated)		
	10045030	Randomized, open label	Trabectedin: q3wk 24-h dose Best Supportive Care		Translocation-Related Sarcoma 37 36	

* L-type sarcoma evaluable for efficacy

The clinical review of the safety of trabectedin was based primarily on the ET743-SAR-3007 clinical trial with a data cutoff date of 7/10/2014 that was used for the 120 Day Safety Update. This database represented 378 patients randomized to trabectedin and 172 patients randomized to dacarbazine. In addition, an Integrated Summary of Safety (ISS) database also supported the clinical review of safety. The ISS database comprises 755 patients in 7 clinical trials, who had a diagnosis of soft tissue sarcoma and received the trabectedin regimen of 1.5 mg/m² as a 24 hour infusion every three weeks. Table 5 summarizes the clinical trials used to form the ISS database.

Table 5. Clinical Trials Included in the Integrated Safety Database, Supporting Safety (n=755)

	Study	Design	Dosing Schedule	Patients		
				L-type sarcoma	Other	All
	ET743-SAR-3007	Refer to Table 4				
	ET743-ST-201	Refer to Table 4				
	ET-B-005-98	Refer to Table 4				
	ET-B-008-98	Refer to Table 4				
	ET-B-016-99	Single-arm	Trabectedin: q3wk 24-h dose	33	12	36

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

	Study	Design	Dosing Schedule	Patients		
	ET-B-017-99	Refer to Table 4				
	ET-B-028-06	Single-arm	Trabectedin: q3wk 24-h dose	29	0	29

Source: adsl.xpt and Module 5.2

5.2 Review Strategy

The clinical review of efficacy and safety primarily focused on trial ET743-SAR-3007. Supportive safety and efficacy data from the trials outlined in Table 5 were also reviewed. The electronic submission, with the CSRs, and other relevant portions of ET743-SAR-3007 were reviewed and analyzed. The key review materials and activities are outlined below:

- Electronic submission of the NDA
- Relevant published literature
- Relevant submissions in response to the medical officer's questions
- Sponsor presentation to FDA on January 16, 2015
- Major efficacy and safety analyses reproduced or audited using the datasets

The majority of efficacy and safety analyses were reproduced or audited using the raw and analysis datasets submitted electronically with the NDA.

5.3 Discussion of Individual Studies/Clinical Trials

ET743-SAR-3007 (Trial 3007) is the primary trial submitted to support the efficacy and safety review of trabectedin in patients with STS and is reviewed in detail below. The following summary of the protocol for Trial 3007 is based on Amendment 3. A summary of the amendments is included at this end of this section. The supportive trials submitted in this application are summarized after the detailed review of the design of Trial 3007.

Study Title

A Randomized Controlled Study of Yondelis (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma

Objectives

The main efficacy objectives for Trial 3007 were to evaluate overall survival (OS) and progression-free survival (PFS). Additional objectives included evaluation of time-to-progression (TTP), objective response rate (ORR), duration of response (DOR),

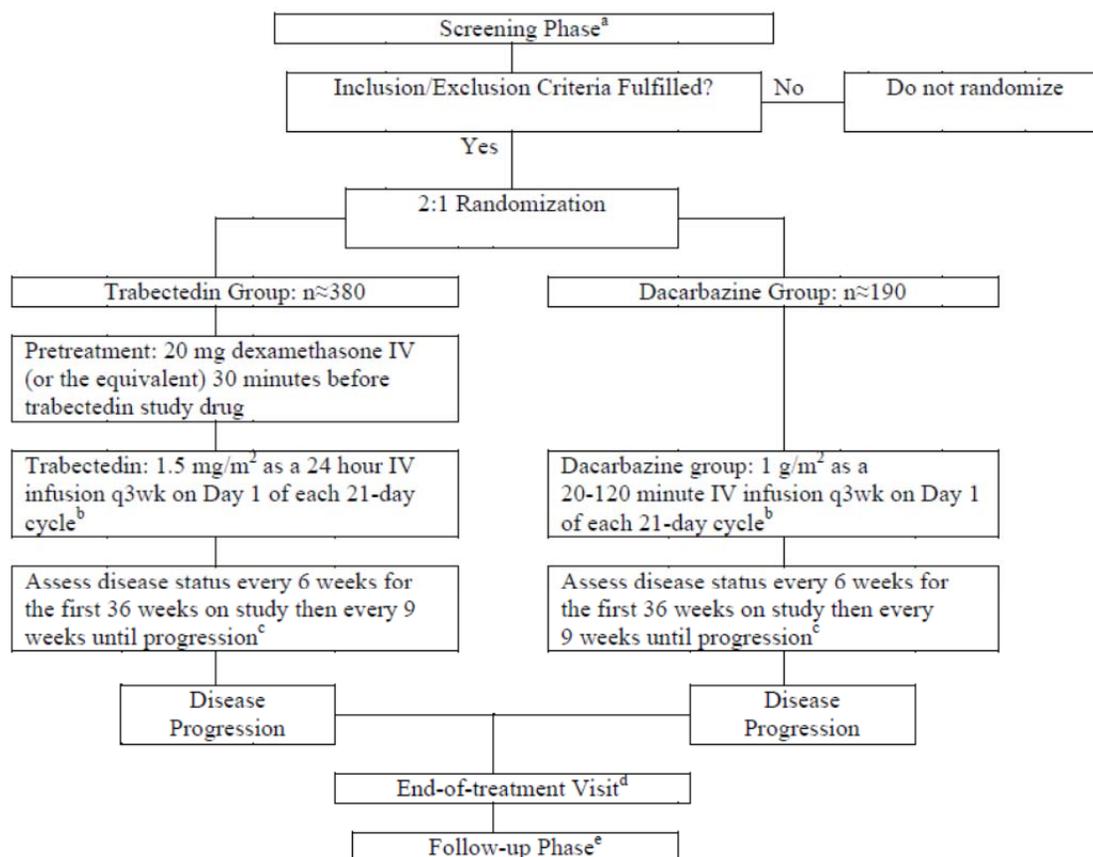
symptom severity (through the MD Anderson Symptom Inventory [MDASI] score as a patient-reported outcome [PRO] measure). The clinical benefit rate (CBR; complete response [CR] +partial response [PR] + stable disease for at least 18 weeks) and duration of stable disease were planned analysis.

Study Design

This study was a randomized, open-label, active-controlled, parallel-group, multicenter trial. An Independent Data Monitoring Committee (IDMC) was established to monitor data and ensure the safety the patients throughout the study and to assess if efficacy objectives had been achieved. Patients were not allowed to cross-over from dacarbazine to trabectedin during the study. After consultation with FDA, an audit plan was instituted to perform an independent radiological assessment of all available scans from the site that enrolled 9 or more patients at the time of the interim analysis of OS.

Number of patients: Approximately 570 patients were to be randomized (2:1) to trabectedin or dacarbazine treatment groups.

Figure 2. Treatment Scheme



ECG=electrocardiogram; MUGA=multigated acquisition scan; q3wk=every 3 weeks

^a Performed disease status assessment, ECG, and MUGA scan (or echocardiograms if MUGA was not available) to determine subject eligibility within 30 days before randomization; all other eligibility assessments within 14 days before randomization.

^b Study drug administration: Day 1 (with a dosing window of up to +2 days) of each 21-day treatment cycle (with each treatment cycle being at least 21 days apart).

^c Performed for all subjects, including those who discontinued study drug before disease progression.

^d Completed within 30 days after treatment discontinuation or withdrawal from the study.

^e Follow-up for survival status and use of subsequent anticancer therapy every 60 days for the first 2 years; every 90 days, thereafter.

Source: adapted from Clinical Study Report

Eligibility

Inclusion criteria

Subjects enrolled were required to meet the following acceptance criteria:

1. Criterion modified per amendment
 - 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. Patients must have a pathology report indicating the diagnosis of liposarcoma or leiomyosarcoma that has been reviewed by the sponsor before randomization may occur.
3. Criterion modified per amendment
 - 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.
4. Measurable disease at baseline in accordance with RECIST Version 1.1
5. Pathology specimens (e.g., tumor blocks or unstained slides) for potential centralized pathology review and biomarker studies.
6. ECOG Performance Status score of 0 or 1
7. Adequate recovery from prior therapy; all side effects (except alopecia) have resolved to Grade 1 or less according to the National Cancer Institute – Common Terminology Criteria of Adverse Events (NCI-CTCAE) Version 4.0
8. Criterion modified per amendment
 - Adequate organ function as evidenced by the following peripheral blood counts or serum chemistry values:
 - Hemoglobin ≥ 9 g/dL
 - absolute neutrophil count (ANC) $\geq 1,500/\mu\text{L}$
 - platelet count $\geq 100,000/\mu\text{L}$
 - serum creatinine ≤ 1.5 x the upper limit of normal (ULN)
 - creatine phosphokinase (CPK) ≤ 2.5 x ULN.
9. Criterion modified per amendment
 - Adequate hepatic function as evidenced by the following serum chemistry values:
 - total bilirubin \leq ULN. If total bilirubin is $>$ ULN, measure indirect bilirubin to evaluate for Gilbert's syndrome (if direct bilirubin is within normal range, subject may be eligible).
 - ALP ≤ 2.5 x ULN; if the ALP is >2.5 x ULN, then an ALP liver fraction or 5' nucleotidase must be obtained and \leq ULN
 - AST and ALT ≤ 2.5 x ULN.
10. Negative pregnancy test (urinary or serum β -HCG) at screening (applicable to women of child bearing potential who are sexually active).
11. Criterion modified per amendment
 - Female patients must be postmenopausal (no spontaneous menses for at least 2 years), surgically sterile (have had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), abstinent (at the discretion of the investigator), or if sexually active, be

practicing an effective method of birth control (e.g., prescription hormonal contraceptive, intrauterine device, double-barrier method [e.g., condoms and occlusive cap (diaphragm or cervical/vault caps)] with spermicidal foam, cream, gel, film, suppository), before entry, and must agree to continue to use the same method of contraception throughout the study and for 3 months thereafter. Male patients must agree to use an adequate contraception method as deemed appropriate by the investigator (e.g., vasectomy, double-barrier, partner using effective contraception) and to not donate sperm for a minimum of 5 months after treatment discontinuation.

12. Criterion modified per amendment

- Sign (or their legally-acceptable representative must sign) an informed consent document indicating they understand the purpose of and the procedures required for the study and are willing to participate in the study. Assent is also required for patients who are 15 years of age and up to the age of legal consent in the jurisdiction in which the study is to take place and who are capable of understanding the nature of the study (see Section 16.2.3, Informed Consent).

Exclusion Criteria

Subjects who met any of the following criteria were excluded from participating in the study:

1. Prior exposure to trabectedin or dacarbazine
2. Less than 3 weeks from last dose of systemic cytotoxic therapy, radiation therapy, or therapy with any investigational agent
3. Other malignancy within 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
5. Known significant chronic liver disease, such as cirrhosis or active hepatitis (potential patients who test positive for hepatitis B surface antigen or hepatitis C antibodies are allowed provided they do not have active disease requiring antiviral therapy).
6. Myocardial infarct within 6 months before enrollment, New York Heart Association Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities
7. Uncontrolled intercurrent illness including, but not limited to, poorly controlled hypertension or diabetes, ongoing active infection, or psychiatric illness/social situation that may potentially impair the subject's compliance with study procedures

8. Unwilling or unable to have a central venous catheter
9. Known allergies, hypersensitivity, or intolerance to trabectedin, dacarbazine, dexamethasone, or their excipients
10. Pregnant or breast-feeding
11. Any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements

Treatment Plan

Eligible patients were randomized to 1 of 2 treatment groups in a 2:1 ratio within 96 hours before Day 1 of Cycle 1 as follows:

- Trabectedin group: 1.5 mg/m² as a 24-h i.v. infusion q3 week
- Dacarbazine group: 1000 mg/m² as a 20-120 minute i.v. infusion q3week

Study drug dose was dependent on the subject's body surface area (BSA), which was calculated on Day 1 of Cycle 1 before the first dose of study drug using the subject's body weight and height. For patients who were obese (body mass index >30), BSA was calculated using the ideal body weight throughout the study.

Trabectedin and dacarbazine study drug were provided by the sponsor. The following treatment regimens were used:

Trabectedin Group

Trabectedin was administered at a dose of 1.5 mg/m² via a central venous catheter as a 24-hour infusion on Day 1 (with a dosing window of up to +2 days) of each 21-day treatment cycle (i.e., each treatment cycle being at least 21 days apart). All patients were pretreated with 20 mg of dexamethasone i.v. on Day 1 of each treatment cycle 30 minutes prior to each infusion of study drug. If dexamethasone was not available, an equivalent was allowed to be substituted. Patients could receive multiple cycles of trabectedin as long as there is no documented disease progression or unacceptable toxicities.

Dacarbazine Group

Dacarbazine was administered at a dose of 1000 mg/m² as a 20-120 minute infusion on Day 1 (with a dosing window of up to +2 days) of each 21-day treatment cycle (i.e., each treatment cycle being at least 21 days apart). Patients could receive multiple cycles of dacarbazine as long as there is no documented disease progression or unacceptable toxicities, as determined by the investigator.

Monitoring

Figure 3. Event Scheduling and Monitoring

Assessment/ Activity	Screening ^a Phase	Each Treatment Cycle				Every 6 wks for 36 wks; then every 9 wks until PD	Treatment Discontinuation ^b	Follow-up Phase
		Day 1	Day 2	Day 8	Day 15			
Informed consent/assent	X							
Inclusion and exclusion criteria	X							
Medical history	X							
Physical examination ^c	X							
Vital signs ^c	X							
Body surface area (BSA) ^d		X						
ECOG Performance Status	X						X	
MUGA ^e /ECG	X ^f						X	
Adverse events ^c	X	X	X	X	X	X	X	X ^g
Concomitant medications	X	X	X	X	X	X	X	
LABORATORY								
Hematology	X	X ^h		X ⁱ	X ⁱ		X	
Chemistry and liver panels	X	X ^h		X ⁱ	X ⁱ		X	
Urine pregnancy test ^j	X							
Pharmacogenomic blood sample (10 mL) ^k		X						
Archived tumor sample ^l	X							
PREMEDICATION								
Dexamethasone 20 mg i.v.		X ^m						
STUDY DRUG ADMINISTRATION								
YONDELIS i.v. formulation 1.5 mg/m ² , 24-hour infusion		X ⁿ						
DTIC 1 g/m ² , 20-120 minute infusion		X ⁿ						
PATIENT REPORTED OUTCOMES								
MDASI questionnaire		X ^o					X ^o	
EFFICACY								
Tumor measurements	X ⁱ					X ^p	X	X ^q
Survival status / anticancer therapy								X ^r

BSA=body surface area; DTIC= dacarbazine; ECG=electrocardiogram; MDASI= M.D. Anderson Symptom Inventory; MUGA=multiple gated acquisition scan; PD=progressive disease; wks=weeks.

^a Informed consent/assent is to be obtained within 30 days before randomization. Complete screening assessments within 14 days before randomization, except as noted for MUGA/ECG and tumor measurements (footnote "f"). Echocardiogram can be used if MUGA is not available (footnote "e")

^b End-of-Treatment Visit should be performed within 4 weeks after the last dose of study drug and will document adverse events that occur within 30 days after the last dose of study drug.

^c Document any clinically significant abnormal change in physical findings, including vital signs and ECOG Performance Status score, as an adverse events. PD should not be reported as an adverse event.

^d BSA may be calculated during screening for ordering vials of drug. It is not necessary to recalculate BSA each cycle unless required to comply with institutional guidelines or a subject has a weight gain or loss >10% of body weight. For obese subjects (body mass index [BMI] >30), calculate BSA using the ideal body weight throughout the study.

^e Echocardiogram can be used if MUGA is not available. The same procedure should be used for the screening and end-of-treatment evaluations.

^f Obtained within 30 days before randomization.

^g Record adverse events that occur within 30 days after the date of the last dose of study drug. Drug-related Grade 3 or Grade 4 toxicities will be monitored until Grade 2 or less, or for a maximum of 6 months after the last dose of study drug, whichever, occurs first. Grade 2 - 4 liver or cardiac toxicities will be monitored until Grade 1 or less, or for a maximum of 6 months after the last dose of study drug, whichever occurs first.

^h Laboratory results must be obtained within 48 hours before dosing.

ⁱ To be completed on Day 8 (±2 days) and Day 15 (±2 days).

^j Only for women of child bearing potential who are sexually active.

^k Only for subjects who are eligible for the study and who provide separate informed consent/assent to participate in the pharmacogenomic analyses.

^l Tumor specimen (eg, unstained slides or FFPE tumor block) will be collected before randomization. The specimen will be archived for possible review of diagnosis and biomarker analysis. In the event a pathology specimen is not available, a biopsy may be conducted during screening to obtain a specimen.

^m Only for subjects in the trabectedin group. Administer 30 minutes before study drug.

ⁿ Study drug administration: Day 1 (with a dosing window of up to +2 days) of each 21-day treatment cycle (with each treatment cycle being at least 21 days apart). Results of all clinical laboratory assessments must be known before study drug is administered.

^o Patient reported outcomes questionnaire should be completed on Day 1 of each treatment cycle and as part of the end-of-treatment evaluations before any other tests or procedures.

^p Perform disease assessments using the same radiographic technique (CT scans or MRI) every 6 weeks for the first 36 weeks on study and every 9 weeks, thereafter. The disease assessments should include radiographic imaging of the chest (with lung views), abdomen, and pelvis.

^q If disease progression has not occurred at the time of treatment discontinuation, continue radiographic assessments until there is evidence of disease progression or until the start of first subsequent anticancer therapy, whichever is earlier.

^r Survival follow-up should occur at least every 60 days for the first 2 years after the last dose of study drug and then every 90 days, thereafter, until the end of the study.

Source: adapted from Clinical Protocol

Dose Modifications

Dose reductions were to be made based on the worst drug-related toxicity that occurred since the previous dose (see Appendix for specific dose reduction criteria). Subjects who required more than 2 dose reductions were to discontinue study treatment. Dose escalations were not allowed following a dose reduction.

Tumor Assessments

Tumor response was to be assessed by investigators according to the RECIST (v1.1) response criteria. Tumor responses were to be evaluated separately by target lesions,

non-target lesions, and new lesions during each scheduled assessment. The combined results of the target, non-target and new lesions were to provide an overall tumor response.

Statistical Analysis Plan

The original efficacy objective was to evaluate overall survival in patients treated with trabectedin compared to patients treated with dacarbazine. Secondary objectives were to evaluate progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), symptom severity and safety.

Reviewer Comment:

Based on communications with FDA, the IDMC charter was modified to allow Janssen R&D to share the PFS and response rate data with FDA at the time of the planned interim analysis of OS. In order to assess for potential investigator assessment bias, FDA requested a blinded independent central review (BICR) radiographic assessment of disease (rPFS) by an independent radiologist. Janssen retrospectively prepared an audit plan using a statistically based approach that was reviewed and accepted by FDA. The audit plan included a review of radiological scans from approximately 60% of patients at the 19 sites with at least 9 patients randomized. For the BICR analysis, symptomatic progression, in the absence of radiographic evidence, was not to be considered a PFS event. No clinical data except information about prior radiation treatment was to be provided to the independent radiologist reviewer.

As discussed in the Risk-Benefit Analysis section of this review, although overall survival was initially defined as the efficacy endpoint, the clinical reviewers consider PFS, if substantial, clinically meaningful in this rare disease population with no therapeutic options that improve overall survival; this is supported by advice given to FDA by members of the sarcoma community (ODAC committee members as well as patient advocates) stating that a treatment effect that results in stabilizing the disease burden in patients rendering them to be free of progression is valuable in that patients can harbor very large, bulky disease that can impinge on vital structures. See Risk-Analysis section for further discussion (Section 1.2).

One analysis was to be conducted for PFS for this study, at the time of the OS interim analysis. It was anticipated that there would be approximately 331 PFS events and approximately 500 patients of the 570 planned patients would have been enrolled in the study at the time of the OS interim analysis. It was estimated that 331 PFS events would provide at least 90% power in detecting a HR of 0.667 (median PFS of 2.5 months for the dacarbazine groups versus 3.75 months for the trabectedin group) with a 2-sided significance level of 0.05. The analysis of OS compared the two treatment groups using the unstratified log-rank test and Kaplan-Meier method. The median times to event and estimate of hazard ratio (HR) with 2-sided 95% CIs were estimated. The effect of prognostic factors such as age, lines of prior therapy, ECOG Performance Status, and L-subtype were examined in the supplementary analysis of PFS and OS

using the Cox proportional hazards model. Secondary endpoints were evaluated using similar methods. Comparison of the ORR between the two treatment groups was made using the Fisher's exact test. For DOR, descriptive statistics were to be provided.

Planned interim analysis: The OS endpoint analysis incorporated group sequential design by including one interim analysis and one final analysis using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. This method was used to ensure that the type I error rate is not inflated. The interim analysis was planned at 50% of the required number of events. The cumulative alpha spent will be 0.003 and 0.050 for the 2 analyses, respectively.

Sample size: It was assumed that the hazards for the 2 treatment groups follow a proportional hazards model for OS. The test 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 (HR=0.74) at an overall 2-sided significance level of 0.05 with a power of 80% required 376 events. Assuming an enrollment rate of 25 patients per month over 23 months, a sample size of approximately 570 patients was planned for the study.

Table 6. Censoring rules for rPFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
PD that is >14 weeks (98 days) from randomization date and there is no scan prior to the PD	Date of randomization	Censored
No progression nor death	Date of last scan date prior to or on start of subsequent anti-cancer therapy if there is a subsequent anti-cancer therapy; Date of scan date before data cut-off date if there is no subsequent anti-cancer therapy; Date of randomization if there is no post baseline scan.	Censored
Death that is >14 weeks (98 days) from randomization date and there is no scan prior to death	Date of randomization	Censored
Missing 2 or more consecutive tumor assessments defined as above (14 weeks or 20 weeks interval) between the last no-PD assessment and	Date of the last non-PD scan date	Censored

Situation	Date of Progression or Censoring	Outcome
PD/death.		
With or without PD/Death after start of anti-cancer therapy.	Date of the last tumor assessment immediately prior to or on the start date of subsequent anti-cancer therapy.	Censored

Source: adapted from SAP

Protocol Amendments

There were 3 amendments to the protocol:

- Amendment #1 (December 9, 2010) included the following changes:
 - o Inclusion of 15 year of age or older
 - o The prohibition of subject crossover from the dacarbazine group to the trabectedin group
 - o Proactive reviews of the cases of sepsis
 - o Minor editorial changes and clarifications

Reviewer Comment: No patients had been enrolled at the time of the first amendment

- Amendment #2 (June 24, 2011) included the following changes:
 - o Clarification that assessments for disease status were to be conducted consistently and on schedule
 - o Additional dosing instructions for patients with abnormal liver function tests
 - o Treatment windows for the placement of central venous catheter and dosing
 - o Clarification to allow administration of colony stimulating factors (CSFs) during Cycle 1
 - o Specification that alkaline phosphatase (ALP) liver fraction of 5' nucleotidase was to be measured when ALP was >2.5 ULN
 - o The option to use echocardiograms if MUGA was not available
 - o Minor editorial changes and clarifications

Reviewer Comment: One patient was enrolled at the time of the second amendment; however, both the first and second amendments were adopted before any study-related procedures had begun.

- Amendment #3 (January 12, 2012) included the following changes:
 - o A change to allow anthracycline and ifosfamide containing regimens or an anthracycline containing regimen and 1 additional cytotoxic chemotherapy (in any order)
 - o The provision for de-bulking surgery and the criteria to be met for such surgery
 - o An update to the definition of PFS based on RECIST (version 1.1)
 - o An update to the most recent version of MDASI questionnaire

- Minor editorial changes and clarifications

Reviewer Comment: There were 58 patients enrolled at the time of the third amendment.

Summaries of additional supportive trials

ET743-STS-201 (Trial 201)

Trial 201 was an open-label, randomized (1:1), multicenter trial designed to compare trabectedin in 2 different treatment regimens (0.58 mg/m² given as a 3-hour infusion every week versus 1.5 mg/m² given as a 24-hour infusion every 3 weeks) in patients with relapsed or refractory locally advanced or metastatic L-type sarcoma who had been previously treated with an anthracycline and ifosfamide containing regimen. A total of 270 patients were randomized, 136 to the q3wk 24-hr infusion group and 134 in the qwk 3-hr infusion group. Patients were stratified by baseline ECOG PS (0 versus 1). The primary endpoint was initially a point estimate of clinical benefit (a composite rate of confirmed CR or PR or SSD lasting for at least 24 weeks) but it was changed to time-to-progression (TTP) after early descriptive data in 80 patients led to extension of the study to expand the sample size. TTP was independently reviewed by radiologists blinded to treatment group.

ET-B-005-98

Trial ET-B-005-098 was a single-arm, open-label, multicenter, activity-finding study that included patients with unselected STS who previously treated with a single agent (Group A, n=44) or more than one agent (Group C, n=55). Patients were treated with trabectedin (1.5 mg/m²) as an i.v. infusion over 24 hours once every 3 weeks.

ET-B-008-98

Trial ET-B-008-98 was a single-arm, open-label, multicenter, activity-finding study that included patients with unselected STS who previously treated with one or two single agents or one combination (Group 1, n=26), or 3 prior single agents or 2 combinations (Group 2, n=28). Patients were treated with trabectedin (1.5 mg/m²) as an i.v. infusion over 24 hours once every 3 weeks.

ET-B-017-99

Trial ET-B-017-99 was a single-arm, open-label, multicenter, activity-finding study that included patients with unselected STS who previously treated with at least one but no more than two chemotherapy regimens (n=36). Patients were treated with trabectedin (1.5 mg/m²) as an i.v. infusion over 24 hours once every 3 weeks.

ET-B-016-99

Trial ET-B-016-99 is a single-arm, open-label, multicenter, activity-finding study that included patients with untreated advanced and or metastatic STS (n=36). Patients were administered trabectedin 1.5 mg/m² as a 24 hour infusion every 3 weeks. [

ET-B-028

Trial ET-B-028-06 is a single-arm, open-label, multicenter, activity-finding study that included patients with untreated, localized, myxoid/round cell liposarcoma in the neoadjuvant setting (n=29). Patients were administered trabectedin 1.5 mg/m² as a 24 hour infusion every 3 weeks.

6 Review of Efficacy

Efficacy Summary

This **NDA submission** for trabectedin **contains data from** Trial ET743-SAR-3007, a randomized (2:1), open-label, active-controlled multicenter study of trabectedin compared to dacarbazine in patients with unresectable or metastatic L-type sarcoma who had received prior systemic therapy that included anthracyclines. Randomization was stratified by type of sarcoma, ECOG performance status (0 vs. 1), and number of prior chemotherapy regimens (1 vs. ≥2). The efficacy outcome measures were investigator-assessed progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), overall survival (OS), objective response rate (ORR), and duration of response (DOR). Patients in the dacarbazine arm were not offered trabectedin at the time of disease progression. At the time of the final PFS analysis, a total of 518 patients were randomized, 345 to the trabectedin arm and 173 patients to the dacarbazine arm.

Treatment with trabectedin resulted in a statistically significant 45% reduction in the risk of progressive disease or death compared with dacarbazine treatment (HR= 0.550; 95%: 0.43 ,0.696; p<0.0001). The median PFS by the unstratified analysis as determined by the investigator was 4.21 months for the patients treated with trabectedin compared to 1.54 months for patients treated with dacarbazine. An analysis of PFS as assessed by a blinded independent central review (BICR) per RECIST v1.1 was conducted on a retrospective audit plan of 60% of patients at 19 sites with at least 9 patients randomized. The BIRC analysis was conducted to evaluate for the introduction of bias in the investigator-assessed PFS analysis; the results of this BICR-assessed PFS analysis were consistent with investigator determination. The magnitude of the treatment effect on PFS was consistent across multiple subgroups. ***The final OS analysis was submitted at the time of the 120-Day Safety Update. There were a total of 381 death events. The final analysis of OS demonstrated a nominal decrease (estimated 7.3%) in the risk of death in patients treated with trabectedin compared to patients treated with dacarbazine (HR=0.927; 95% CI 0.748, 1.150; p=0.4920). The median OS was 13.7 months (95% CI; 12.2, 16.0) for the trabectedin arm and 13.1 months (95% CI: 9.1, 16.2) for the dacarbazine arm. Similar overall response rate and duration of response were observed between patients treated with trabectedin compared to patients treated with dacarbazine.***

6.1 Indication

The proposed indication statement is:

YONDELIS is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma, who have received (b) (4) prior anthracycline-containing regimen

6.1.1 Methods

This FDA review of efficacy primarily focuses on trial ET743-SAR-3007 (Trial 3007). Efficacy evidence from the trials ET743-STS-201, ET-B005-98, ET-B-008-98, and ET-B017-99 were also reviewed to examine consistency (summarized in Section 5.3). The reviewer evaluated the original protocol and follow-up amendments in relation to the FDA recommendations. Efficacy endpoints were evaluated by verifying the accuracy of the documented tumor lesions between case report forms (CRFs) and relevant datasets and by examining the completeness of the datasets based on the independent review. With the statistical reviewers' help, discrepancies in evaluation of tumor lesions between the independent review and investigator were also verified. Factors that might affect efficacy analysis such as withdrawal from study, intolerable toxicity, treatment after progression of disease, and missing or imbalanced efficacy assessments were evaluated. Statistical analyses were performed by the statistical reviewers and were compared to the applicant's study reports. Multiple subgroup and sensitivity analyses were conducted to assess the reliability of the results and conclusions in this patient population.

6.1.2 Demographics

Baseline Characteristics

At the time of the pre-specified analysis of PFS based on a data cutoff date of December 13, 2013, Trial 3007 had enrolled 518 subjects who were randomized, 345 to the trabectedin group and 173 to the dacarbazine group. The trial was conducted in 4 countries (Australia, Brazil, New Zealand, and the United States of America [US]) at 85 sites. Ninety-four percent of the patients were enrolled in US sites. Demographic characteristics were balanced between treatment groups with the exception of race and body mass index (BMI) of patients. There were more white patients (78.0%) in the trabectedin group compared with the dacarbazine group (72.3%) and there were more patients with a BMI ≥ 30 in the trabectedin treatment group compared to the dacarbazine group (41.2% vs. 35.3%). The final analysis of overall survival (OS) was completed in November 2013 after 577 patients were randomized at 90 sites: 384 to the trabectedin arm and 193 to the dacarbazine arm. The demographic characteristics of the patients in the final analysis were consistent with the 518 patients who were randomized at the time of the PFS analysis.

Table 7. Patient Population (ITT)

	Dacarbazine (N=173)	Trabectedin (N=345)
ITT	173	345
Not treated	18 (10%)	5 (1%)
Withdraw consent	14 (8%)	2 (<1%)
TRT after clinical cut off	2 (1%)	2 (<0.1)
AE	2 (1%)	1 (<1%)
Ongoing treatment	23 (15%)	96 (28%)
Audit Subset	100 (58%)	204 (59%)
Site >=9 Patients	102 (59%)	205 (59%)

Source: Adapted from statistical review

Table 8. Baseline Demographics in Trial 3007 at the Time of PFS Analysis

	Dacarbazine (n=173)	Trabectedin (n=345)
Age, years		
Category		
<18	1 (0.6%)	0
18-<65	138 (79.8%)	264 (76.5%)
65-<75	31 (17.9%)	67 (19.4%)
>75	3 (1.7%)	14 (4.1%)
Mean, Median	54.5, 56	56.19, 57
Range	17.0-79	18.0-81
Sex		
Male	47 (27.2%)	107 (31.0%)
Female	126 (72.8%)	238 (69.0%)
Race		
American Indian or Alaska native	4 (2.3%)	1 (0.3%)
Asian	10 (5.8%)	9 (2.6%)
Black or African American	19 (11.0%)	44 (12.8%)
White	125 (72.3%)	269 (78.0%)
Other	2 (1.2%)	3 (0.9%)
Unknown	6 (3.5%)	8 (2.3%)
Not reported	7 (4.0%)	11 (3.2%)
Ethnicity		
Hispanic or Latino	20 (11.6%)	26 (7.5%)
Not Hispanic or Latino	135 (78.5%)	304 (88.1%)
Unknown	12 (6.9%)	5 (1.4%)
Not reported	6 (3.5%)	10 (2.9%)
Baseline BMI, kg/m²		
Category		
<20	20 (11.6%)	16 (4.6%)
20-<25	50 (28.9%)	90 (26.1%)
25-<30	42 (24.3%)	97 (28.1%)
≥30	61 (35.3%)	142 (41.2%)
Mean (SD)	28.11 (7.392)	29.55 (7.760)
Median	27.05	28.11
Range	(13.3;66.7)	(14.5;78.1)

	Dacarbazine (n=173)	Trabectedin (n=345)
US enrollment	166 (96%)	323 (94%)

Source: ADSL.xpt and statistical review

Baseline Disease Characteristics

Table 10 summarizes the disease characteristics for all subjects randomized into the Trial 3007 at the time of the PFS analysis. The type of sarcoma, baseline ECOG status and number of prior lines of chemotherapy were stratification factors for this trial and were well balanced between treatment groups. Uterine leiomyosarcoma, which may have more favorable outcomes than non-uterine leiomyosarcoma, were more frequent in the dacarbazine group (45.1%) compared to the trabectedin group (38.8%). The updated final analysis was completed in November 2013 after 577 patients were randomized at 90 sites: 384 to the trabectedin group and 193 to the dacarbazine group. The disease characteristics of the patients in the final analysis were consistent with the 518 patients who were randomized at the time of the PFS analysis.

Table 9. Disease Characteristics in Trial 3007 at the Time of the PFS Analysis

Subgroup	Dacarbazine (n=173)	Trabectedin (n=345)
Histology		
Leiomyosarcoma	126 (72.8%)	252 (73.0%)
Uterine	78 (45.1%)	134 (38.8%)
Non-uterine	48 (27.7%)	118 (34.2%)
Liposarcoma	47 (27.2%)	93 (27.0%)
Myxoid +/- Round Cell	19 (11.0%)	38 (11.0%)
Pleomorphic	3 (1.7%)	10 (2.9%)
Dedifferentiated	25 (14.5%)	45 (13.0%)
Previous Lines of Chemotherapy		
1	19 (11.0%)	39 (11.3%)
≥2	154 (89.0%)	306 (88.7%)
Baseline ECOG performance status, score n(%)		
0	86 (49.7%)	169 (49.0%)
1	87 (50.3%)	176 (51.0%)
Time from last disease progression to randomization, months		
Mean (SD)	1.29 (1.400)	1.26 (1.416)
Median	0.82	0.85

Subgroup	Dacarbazine (n=173)	Trabectedin (n=345)
Range	(0.1; 9.8)	(0.0, 13.7)
Progressive Disease in last line of chemotherapy	103 (59.5%)	198 (57.4%)
ORR (CR/PR) in last line of chemotherapy	17 (9.8%)	32 (8.5%)

Source: ADSL.xpt and ADDIAG.xpt and statistical review

Note: Minor discrepancies noted between reviewer generated and application ECOG-PS. The discrepancies do not impact the efficacy analysis and the number of disease progression events was the same.

6.1.3 Subject Disposition

Of the 518 subjects randomized in Trial 3007, 495 received at least one dose of study drug (340 patients in the trabectedin group and 155 patients in the dacarbazine group). Reasons for study discontinuation at the time of the PFS analysis are shown in the Table 9 below. At the time of the final analysis, 10 patients were receiving ongoing treatment, two in the dacarbazine arm (1.2%) and eight in the trabectedin arm (2.1%).

Table 10. Primary Reason for Treatment Discontinuation at the Time of PFS Analysis

Treatment Discontinued	Trabectedin (N=345)	Dacarbazine (N=173)
PD	244 (72%)	130 (85%)
AE	186 (55%)	106 (68%)
Death	34 (10%)	11 (7%)
patient withdraws consent	9 (3%)	1 (0.6%)
Physician decision	11 (3%)	11 (3%)
Other	1 (<1%)	1 (<1%)
	3 (1%)	2 (1%)

Source: ADDS.xpt and statistical review

Note: Minor discrepancies noted between reviewer generated table and application. The discrepancies do not impact the efficacy analysis and the number of disease progression events were the same.

Prior Cancer Therapy

All but one patient received at least one prior chemotherapy regimen which contained an anthracycline plus ifosfamide or an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen (see Table 10 below). The one patient who did not receive prior anthracycline treatment was randomized to the trabectedin group and is considered a major protocol violation. There was no meaningful difference between the treatment groups in the proportions of subjects treated with various prior chemotherapies. Doxorubicin was the most frequently utilized anthracycline (89% of patients in the trabectedin group and 90.8% of patients in the dacarbazine group). The majority of patients received treatment with gemcitabine, docetaxel, and ifosfamide. No

patient had received previous dacarbazine. In addition, 93.5% of patients had previous surgery for their malignancy and 49.4% had previous radiotherapy.

Table 11. Previous Chemotherapy in at least 5% of Subjects in Either Treatment Group

	Dacarbazine (n=173)	Trabectedin (n=345)
Doxorubicin	157 (90.8%)	307 (89.0%)
Gemcitabine	138 (79.8%)	279 (80.9%)
Docetaxel	126 (72.8%)	256 (74.2%)
Ifosfamide	104 (60.1%)	202 (58.6%)
Mesna	25 (14.5%)	64 (18.6%)
Investigational drug	35 (20.2%)	50 (14.5%)
Pazopanib	13 (7.5%)	38 (11.0%)
Pegylated Liposomal Doxorubicin Hydrochloride	11 (6.4%)	28 (8.1%)
Temozolomide	9 (5.2%)	19 (5.5%)
Bevacizumab	9 (5.2%)	11 (3.2%)

Source: ADCM.xpt

Concomitant and Subsequent Therapy

The most common classes of concomitant medications were antiemetics and antinauseants (74.3%), psycholeptics (51.2%) and analgesics (51%). Antibacterials, immunostimulants and antithrombotic agents were more commonly used in the trabectedin group (43.2% vs. 31.8%; 42.0% vs. 30.6%; and 25.7% vs. 12.7% respectively). Corticosteroids were more commonly used in the dacarbazine group (52.0% vs. 32.8%). Use of blood products was similar between treatment groups (24.9% vs. 20.8%).

At the time of the PFS analysis, a lower proportion of patients in the trabectedin group received subsequent anti-cancer therapy (162 patients; 47%) compared to the dacarbazine group (97 patients; 56.1%). The most common systemic subsequent therapy in both treatment group was pazopanib. Both subsequent radiation and surgery were less frequently reported in the trabectedin-treated patients compared to the dacarbazine treated patients (10.1% vs. 14.5% and 6.7% vs. 9.8%, respectively).

Table 12. Subsequent Anti-Cancer Therapy in 5% of patients (trabectedin included regardless of frequency)

	Dacarbazine (n=173)	Trabectedin (n=345)
Chemotherapy		
Pazopanib	48 (27.7%)	63 (18.3%)
Dacarbazine	11 (6.4%)	60 (17.4%)
Gemcitabine	25 (14.5%)	30 (8.7%)
Docetaxel	21 (12.1%)	19 (5.5%)
Ifosfamide	10 (5.8%)	7 (2.0%)
Doxorubicin	5 (2.9%)	9 (2.6%)

	Dacarbazine (n=173)	Trabectedin (n=345)
Eribulin	1 (0.6%)	9 (2.6%)
Trabectedin	4 (2.3%)	1 (0.3%)
Radiation	25 (14.5%)	35 (10.1%)
Surgery	17 (9.8%)	23 (6.7%)

Source: ADCM.xpt

Major Protocol Deviations

Eight patients in the trabectedin group (2.3%) and five patients in the dacarbazine group (2.9%) were reported to have a major protocol deviation. Four of the eight trabectedin patients who entered the study did not meet the following entry criteria (n=1): ALP liver fraction < ULN, serum creatinine < 1.5x ULN, one patient did not received prior treatment with an anthracycline and one did not have measurable disease per RECIST 1.1 criteria. In the trabectedin group, five patients did not receive protocol mandated dexamethasone prior to administration of study drug and one patient had an ECG performed for the study before patient consent was signed. In the dacarbazine group, patients who entered the study did not meet the following entry criteria (n=1): ALP liver fraction < ULN, serum creatinine < 1.5x ULN, a patient did not meet the 3-week washout period, one patient had an echocardiogram and CT prior to signing consent (this was classified as “other”).

One patient was randomized in error and treated with dacarbazine; this patient had previously been randomized to the trabectedin group but did not meet entry criteria based on CPK laboratory values and was discontinued prior to being treated with dacarbazine. Another patient was randomized to the dacarbazine group, withdrew consent and then went to another site and was randomized to the trabectedin group; this patient was not treated.

Table 13. Major Protocol Deviations (adapted from CSR)

Major Protocol deviation	Dacarbazine (n=173)	Trabectedin (n=345)	Total (n=518)
Entered study but entry criteria not met	5 (2.9%)	8 (2.3%)	13 (2.5%)
Other	1 (0.6%)	6 (1.7%)	7 (1.4%)
Randomization Error	1 (0.6%)	0	1 (0.2%)

Exposure

Three hundred and forty of the 345 patients randomized to the trabectedin group were treated with trabectedin. At the time of the PFS, the median number of cycles of treatment received by patients in the trabectedin group was 4.0 cycles; 34.4% of these patients received 6 or more cycles. Of the 173 patients randomized to receive dacarbazine, only 155 patients were treated with dacarbazine. The median number of cycles of treatment receive by patients in the dacarbazine group was 2.0 cycles; 17.4% of these patients received more than 6 cycles. The median dose intensity of trabectedin

was 1.37 mg/m² per cycle, 91% of the target dose. The median dose intensity of dacarbazine was 0.98 g/m² per cycle, 98% of the target dose.

Table 14. Study Medication Administration

	Dacarbazine (n=155)	Trabectedin (n=340)
Total treatment duration, weeks		
Mean	10.99 (9.13)	16.75 (15.44)
Median	7.00	12.00
Range	3.0; 57.1	0.6; 89.0
Total treatment cycles		
Category, n(%)		
1 cycle	30 (19.4%)	42 (12.4%)
2 cycles	58 (37.4%)	104 (30.6%)
3 cycles	14 (9.0%)	23 (6.8%)
4 cycles	21 (13.5%)	39 (11.5%)
5 cycles	5 (3.2%)	15 (4.4%)
6 cycles	7 (4.5%)	34 (10.0%)
7 cycles	6 (3.9%)	11 (3.2%)
8 cycles	6 (3.9%)	13 (3.8%)
9 cycles	3 (1.9%)	8 (2.4%)
10 cycles	2 (1.3)	13 (3.8%)
11 cycles	0	3 (0.9%)
12 cycles	1 (0.6%)	8 (2.4%)
≥13 cycles	2	27 (7.9%)
Mean (SD)	3.3	5.0 (4.48%)
Median	2	4.0
Range	1;18	1;28
Dose Intensity, mg/m ² /cycle		
Mean (SD)	0.92 (0.118)	1.32 (0.193)
Median	0.98	1.37
Range	(0.4; 1.0)	(0.7, 1.6)
Relative dose intensity, %		
Mean (SD)	0.92 (0.118)	0.88 (0.129)
Median	0.98	0.91
Range	(0.4; 1.0)	(0.5; 1.1)

Source: ADEXS.xpt, ADEXCYC.xpt

Cycle Delays and Dose Modifications

More patients in the trabectedin group reported a treatment cycle delay (56.8% vs. 40%) or a dose reduction (35.0% vs. 9.7%) compared with the dacarbazine group. Most dose reductions in the trabectedin group occurred in earlier cycles. The most frequently reported TEAEs leading to dose reductions were ALT and AST increase. Temporary infusion interruptions were reported for 17 patients in the trabectedin group and 10 patients in the dacarbazine group. None of these interruptions were due to TEAEs in the trabectedin group; all of these interruptions were due to TEAEs in the dacarbazine group.

Table 15. Treatment Cycle Delays and Dose Reductions for Patients Who Received at Least 2 Cycles of Treatment

	Dacarbazine (n=155)	Trabectedin (n=340)
Cycle Delay		
Yes	62 (40.0%)	193 (56.8%)
No	63 (40.6%)	105 (30.9%)
Number of Cycle Delays		
1	35 (22.6%)	96 (28.2%)
2	13 (8.4%)	37 (10.9%)
3	8 (5.2%)	27 (7.9%)
4	1 (0.6%)	12 (3.5%)
>5	5 (3.2%)	21 (6.2%)
Dose Reduction		
Yes	15 (9.7%)	119 (35.0%)
No	110 (71.0%)	179 (52.6%)
Number of Dose Reductions		
1	13 (8.4%)	83 (24.4%)
2	2 (1.3%)	36 (10.6%)

Source: ADEXS.xpt, ADEXCYC.xpt

6.1.4 Analysis of Primary Endpoint(s)

Although the protocol specified primary endpoint of Trial 3007 was overall survival (OS), the major efficacy endpoint from a regulatory standpoint for this application is progression-free survival (PFS). A substantial improvement in PFS in the sarcoma population of a large magnitude is generally accepted as clinically meaningful by the clinical community and by regulatory standards. This review will first focus on the significant improvement in PFS for the basis of approval of this application.

Progression Free Survival

Treatment with trabectedin resulted in a statistically significant 45% reduction in the risk of progressive disease or death compared with dacarbazine treatment (HR= 0.550; 95%: 0.43 ,0.696; p<0.0001). The median PFS by the unstratified analysis as determined by the investigator was 4.21 months for the patients treated with trabectedin compared to 1.54 months for patients treated with dacarbazine. At the time of the interim analysis for OS, the Independent Data Monitoring Committee (IDMC) recommended to the sponsor Committee that the level of clinical benefit observed in PFS was of a magnitude that should support a reevaluation of the study conduct recommended that the Sponsor Committee share the un-blinded data with FDA. On January 9, 2014, the sponsor shared the data with FDA along with a proposed audit

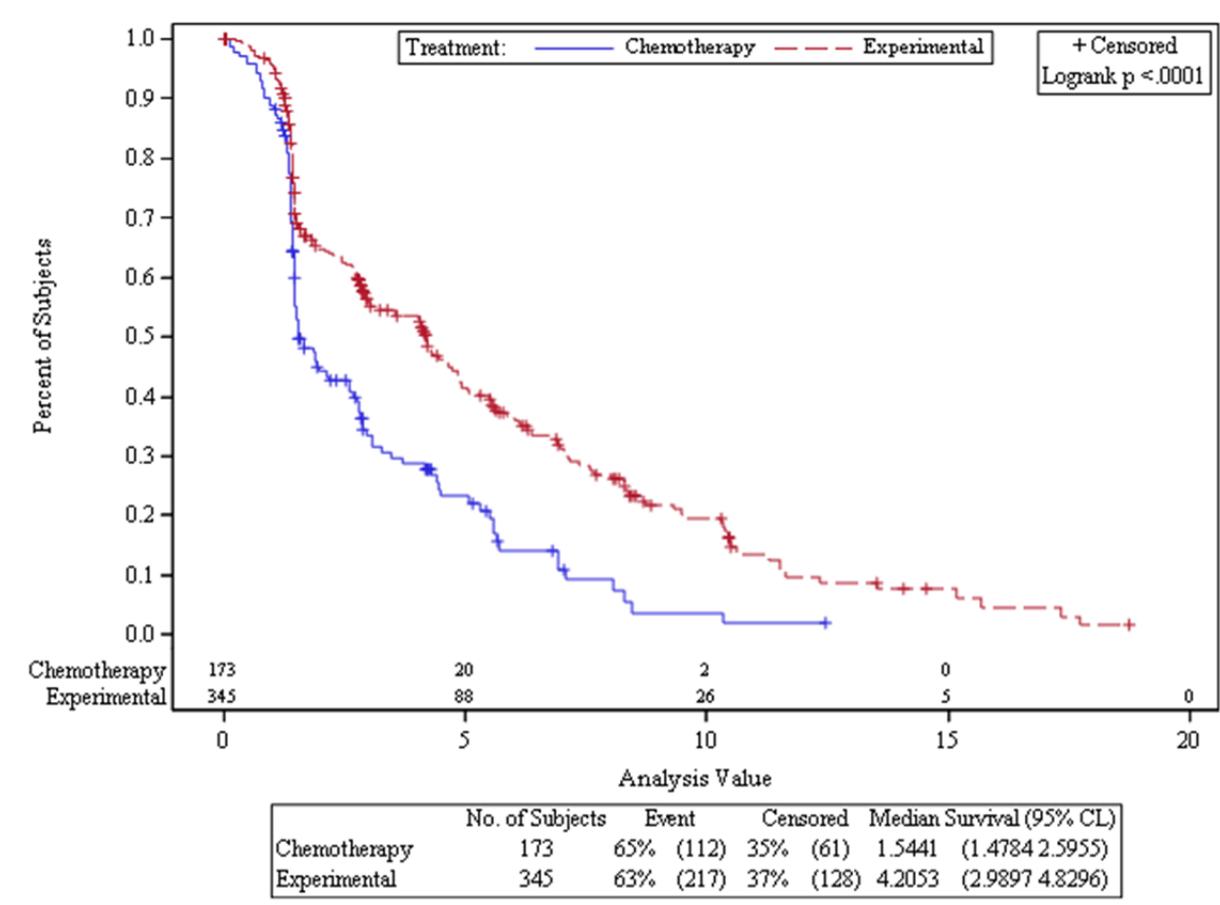
plan for independent review of PFS. The timing of assessments for both treatment groups is consistent with the schedule specified in the protocol.

Table 16. FDA PFS Analysis per INV Assessment (ITT)

	Trabectedin (N=345)	Dacarbazine (N=173)
Number of PFS Events, n (%)	217 (62.9%)	112 (64.7%)
PD, n (%)	204 (59.1%)	109 (63.0%)
Radiographic PD only	170 (49.3%)	82 (47.4%)
Clinical PD only	21 (6.1%)	16 (9.2%)
Both Radiographic and Clinical PD	13 (3.8%)	11 (6.4%)
Death, n (%)	13 (3.8%)	3 (1.7%)
Number of Censored	128 (37.1%)	61 (35.3%)
2 consecutive missing	4 (1.2%)	1 (0.6%)
Anti-cancer therapy	19 (5.5%)	14 (8.1%)
No tumor assessment	0	1 (1.6%)
No post baseline tumor assessment	7 (2.0%)	17 (9.8%)
Withdrew follow up Consent	0	2 (1.2%)
Clinical Cut off	98 (28.4%)	26 (15.0%)
Median PFS in months (95% CI)	4.21 (2.99, 4.83)	1.54 (1.48, 2.60)
Unstratified Cox HR (95% CI)	0.550 (0.436, 0.696)	
Unstratified Log-Rank Test P-value	<0.001	

Source: statistical review

Figure 4. FDA's analysis of Investigator PFS, radiographic and clinical progression (where chemotherapy =dacarbazine and experimental =trabectedin)



Reviewer Comment: The PFS effect in Trial 3007 was similar in magnitude to the PFS effect seen in the trial that supported the approval of pazopanib, the only FDA-approved drug indicated for the treatment of recurrent or refractory soft tissue sarcoma who have received prior chemotherapy*. An important distinction to make regarding Trial 3007 compared to the primary trial supporting FDA approval of pazopanib for STS is that the PFS effect seen with trabectedin was compared to an active control versus pazopanib which was compared to placebo. See Benefit-Risk Analysis (Section 1.2) for further discussion.

*Limitation of use: The efficacy for pazopanib for the treatment of patients with adipocytic soft tissue sarcoma or gastrointestinal stromal tumors was not demonstrated.

To minimize the potential for investigator bias affecting the PFS endpoint in this open-label trial, a retrospective audit strategy was implemented. The audit included the determination of the date of progression and quantitative tumor assessments of radiographic images by independent radiologist blinded to treatment assignments. The

independent review was carried out using all available scans from investigative sites with 9 or more subjects randomized onto the trial at the time of the interim analysis for OS. Nineteen sites met this criterion representing approximately 60% (307 patients) of the total patients (518) randomized on the study at the time of the clinical cut-off for the interim analysis (see Statistical Review for full detail of the amended auditing plan). These data were then transferred to [REDACTED] (b) (4) which used the data in conjunction with limited clinical data (start of subsequent therapy, date of randomization, and date of death) to calculate the PFS. Radiographic progression-free survival (rPFS) was defined as the time between randomization and disease progression or death regardless of the cause of death, whichever occurred first. Symptomatic deterioration in the absence of radiographic evidence of progression was not considered to be a progression event. Tumor assessments were mandated every 6 weeks for the first 36 weeks and every 9 weeks after until disease progression (See Section 5.3 for censoring rules for rPFS).

Within the audited subset, treatment with trabectedin resulted in a 45% reduction in the risk of radiographic disease progression or death compared with dacarbazine treatment (HR 0.549, 95% CI: 0.399, 0.754; p=0.0001) by independent radiologist assessment. The median rPFS was 4.3 months in the trabectedin group and 1.94 months in the dacarbazine group. The HR for the audited subset of patients by investigator assessments was 0.582 (95% CI 0.427, 0.793; p=0.0004).

The magnitude of PFS as evaluated by FDA was consistent across multiple sensitivity analysis analyses (See Table 15)

Table 17. FDA PFS Sensitivity Analyses of ITT population by Investigator and BRIC assessments

Method	HR (95% CI)	P-Value
PFS (INV) ITT (unstratified)	0.550 (0.436, 0.696)	<0.0001
PFS (INV) ITT (stratified)	0.551 (0.435, 0.699)	<0.0001
PFS (INV) ITT (unstratified) adjust by factors in Tables 5 and 6	0.564 (0.445, 0.715)	<0.0001
PFS (INV)Site WITH >=9 PAT	0.546 (0.374, 0.798)	0.0014
PFS (INV)Site WITH< 9 PAT	0.554 (0.411, 0.746)	0.0001
rPFS (INV) ITT	0.569 (0.446, 0.724)	<0.0001
rPFS (IRC) audit subgroup	0.549 (0.399, 0.754)	0.0001
rPFS (INV) audit subgroup	0.582 (0.427, 0.793)	0.0004
rPFS (INV) unaudit subgroup	0.543 (0.367, 0.803)	0.0018

Method	HR (95% CI)	P-Value
Overall rPFS (BRIC) – 1st stage of Dott et. al	0.536 (0.407, 0.705)	

Source: Statistical review
 INV: Investigator reviewed
 IRC:

Reviewer Comment: PFS results remains significant across multiple sensitivity analyses and are similar to the results of the primary analysis of PFS.

Table 18. Reasons for Event/Censored in the rPFS Analysis by Independent Radiologist Assessment; Audited Subset (Source: adapted from applicant response to FDA request)

	Dacarbazine (N = 100)		Trabectedin (N = 204)	
Event	63	(63.0%)	105	(51.5%)
Progression	58	(58.0%)	95	(46.6%)
Radiographic progression	58	(58.0%)	95	(46.6%)
Death	5	(5.0%)	10	(4.9%)
Censored	37	(37.0%)	99	(48.5%)
Permanently censored	26	(26.0%)	47	(23.0%)
No baseline and post baseline assessments	0		0	
With baseline but no post baseline assessments	8	(8.0%)	6	(2.9%)
Initiation of subsequent anti-cancer therapy	17	(17.0%)	35	(17.2%)
2 consecutive missing scans	0		6	(2.9%)
Withdraw consent for follow-up	1	(1.0%)	0	
Lost to follow-up	0		0	
Still at risk	11	(11.0%)	52	(25.5%)
Still on treatment by cutoff	10	(10.0%)	46	(22.5%)
Discontinued treatment and in follow-up by cutoff	1	(1.0%)	6	(2.9%)

Table 19. Reasons for Event/Censored in the rPFS Analysis by Investigator Assessment; Audited Subset (source: adapted from applicant response to FDA request)

Event	Dacarbazine (N = 100)		Trabectedin (N = 204)	
	n	(%)	n	(%)
Event	64	(64.0%)	121	(59.3%)
Progression	59	(59.0%)	109	(53.4%)
Radiographic progression	59	(59.0%)	109	(53.4%)
Death	5	(5.0%)	12	(5.9%)
Censored	36	(36.0%)	83	(40.7%)
Permanently censored	23	(23.0%)	30	(14.7%)
No baseline and post baseline assessments	0		0	
With baseline but no post baseline assessments	9	(9.0%)	6	(2.9%)
Initiation of subsequent anti-cancer therapy	12	(12.0%)	20	(9.8%)
2 consecutive missing scans	0		4	(2.0%)
Withdraw consent for follow-up	2	(2.0%)	0	
Lost to follow-up	0		0	
Still at risk	13	(13.0%)	53	(26.0%)
Still on treatment by cutoff	13	(13.0%)	50	(24.5%)
Discontinued treatment and in follow-up by cutoff	0		3	(1.5%)

Reviewer Comment: More patients in the Independent Radiologist Assessment were censored for initiation of subsequent anti-cancer therapy compared to the Investigator Assessment (35 vs 20 patients). This did not impact the magnitude of benefit of rPFS.

The PFS HR for patients randomized at sites not selected for the audited subset was consistent with the audited subset (HR 0.543, 95% CI 0.367, 0.803; p=0.0018) suggesting that the audited sites were representative of the entire population of sites.

Overall Survival

The unstratified interim analysis was highly censored and showed a median OS of 12.39 months (95% CI: 11.17, 14.55) for patients treated with trabectedin compared to 12.91 months (95% CI: 0.64, 1.18) for patients treated with dacarbazine. The HR was 0.872 (95% CI: 0.644, 1.18). There were a total of 189 (50%) death events.

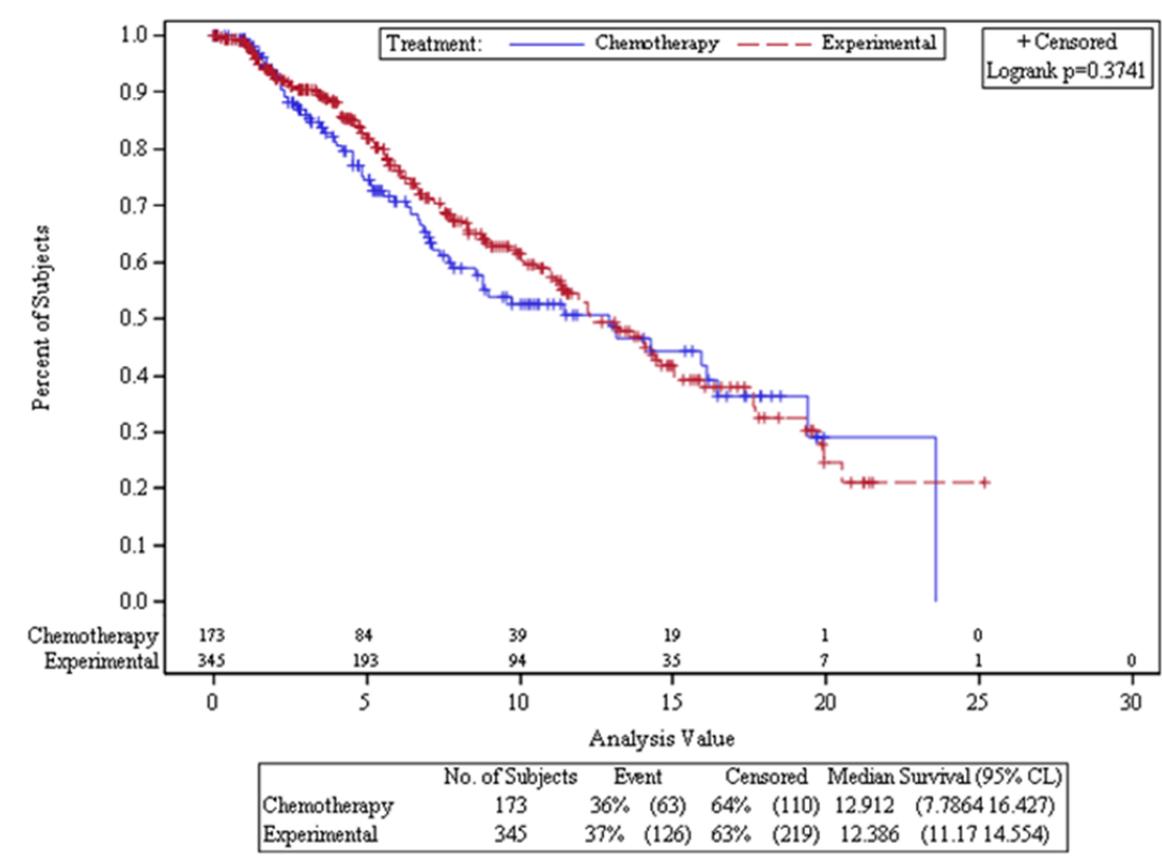
Table 20. OS Interim Analysis (ITT)

	Trabectedin (N=345)	Dacarbazine (N=173)
Number of deaths, n (%)	126 (36.5%)	63 (36.4%)
Median OS in months (95% CI)	12.39 (11.17, 14.55)	12.91 (7.79, 16.43)
Unstratified Cox HR (95% CI)	0.872 (0.644, 1.181)	

	Trabectedin (N=345)	Dacarbazine (N=173)
Unstratified Log-Rank Test P-value	0.3471	

Source: statistical review

Figure 5. FDA's Kaplan-Meier Curve for Interim OS Analysis (ITT)



Source: statistical review

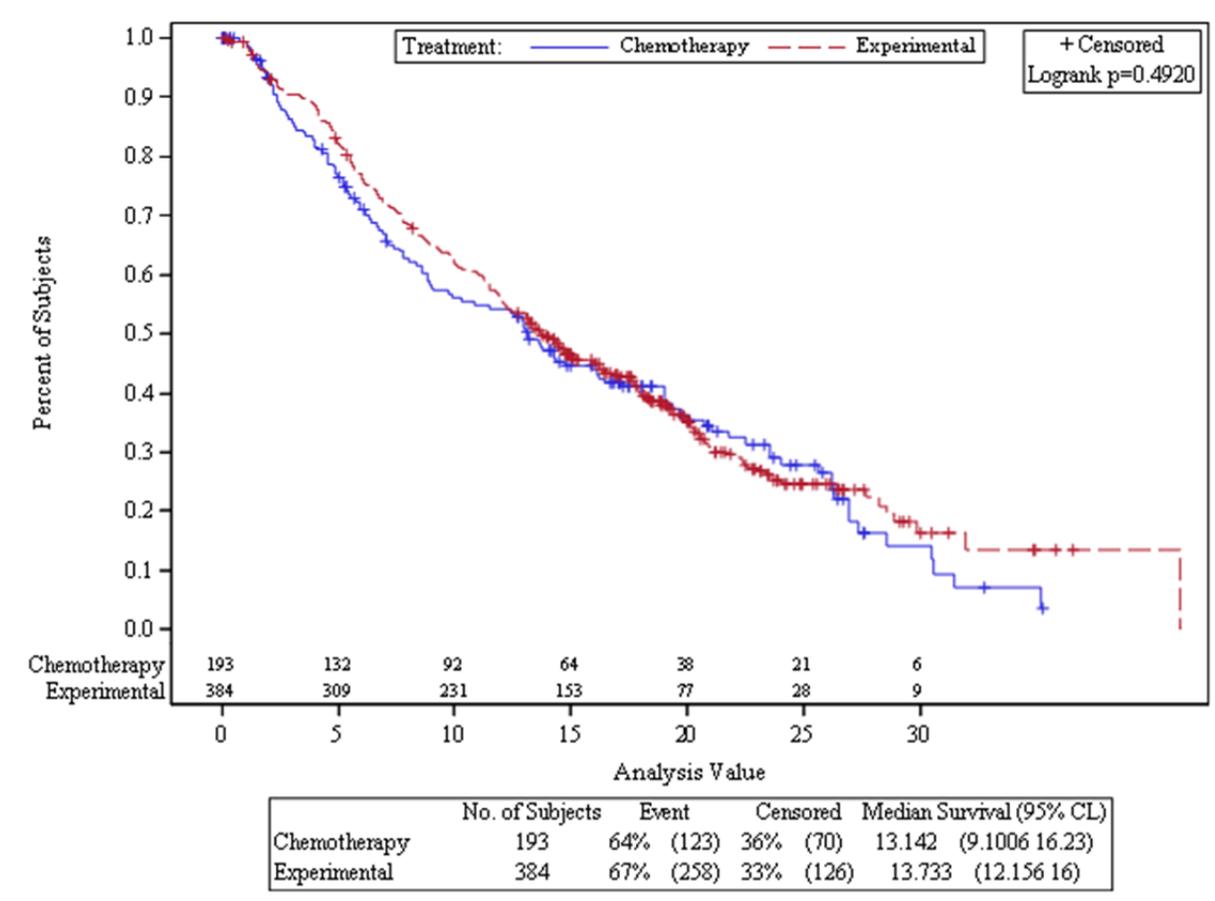
The final OS analysis was submitted at the time of the 120-Day Safety Update. There were a total of 381 death events. The final analysis of OS demonstrated a nominal decrease (estimated 7.3%) in the risk of death in patients treated with trabectedin compared to patients treated with dacarbazine (HR=0.927; 95% CI 0.748, 1.150; p=0.4920). The median OS was 13.7 months (95% CI; 12.2, 16.0) for the trabectedin arm and 13.1 months (95% CI: 9.1, 16.2) for the dacarbazine arm. A pre-specified stratification analysis by ECOG performance status score, subtype of L-sarcoma, and number of prior lines of chemotherapy was consistent with the unstratified analysis of OS (HR=0.939,; 95% CI: 0.756, 1.167; p=0.5721).

Table 21. OS Final Analysis Results (ITT)

	Trabectedin (N=345)	Dacarbazine (N=173)
Number of deaths, n (%)	258 (67.2%)	123 (63.7%)
Median OS in months (95% CI)	13.73 (12.16, 16.00)	13.14 (9.10, 16.23)
Unstratified Cox HR (95% CI)	0.927 (0.748, 1.150)	
Unstratified Log-Rank Test P-value	0.4920	

Source: statistical review

Figure 6. FDA's Kaplan-Meier Curve for Final OS Analysis (ITT)



Source: statistical review

6.1.5 Analysis of Secondary Endpoints(s)

Objective Response Rate

The objective response rate (ORR) was defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) as the best response. The FDA determined the confirmed ORR prior to the clinical cutoff for the Interim Analysis was 6.7% for the trabectedin group and 5.8% for the dacarbazine group. The odds ratio was 1.16 (95% CI: 0.52, 2.81; p=0.33) using the Fisher exact method. Among the 12 responders in the dacarbazine arm and 34 responders in the trabectedin arm, 2 and 11 patients, respectively, did not have scans confirming response prior to the clinical data cut-off (CCO) date for the NDA submission. Therefore these thirteen responders were not considered as responders in Sensitivity Analysis 1. There were no CRs in either treatment group.

Table 22. Confirmed ORR Results in Sensitivity Analysis 1

	Trabectedin (N=345)	Dacarbazine (N=173)
Overall Response	23 (6.7%)	10 (5.8%)
Fisher Exact 95% CI	(4.3%, 9.8%)	(2.8%, 10.4%)
Fisher Exact Odds Ratio (95% CI)	1.16 (0.52 – 2.81)	
Fisher Exact P-value	0.33	

Source: statistical review addendum

Five additional patients' (4 in the trabectedin and 1 in the dacarbazine) confirmatory scans were performed after the Clinical Cut-off for Interim Analysis. Therefore, eight responders were not considered as responders in Sensitivity Analysis 2.

Table 23. Confirmed ORR Results for Sensitivity Analysis 2

	Trabectedin (N=345)	Dacarbazine (N=173)
Overall Response	27 (7.8%)	11 (6.4%)
Fisher Exact 95% CI	(5.2%, 11.2%)	(3.2%, 11.1%)
Fisher Exact Odds Ratio (95% CI)	1.25 (0.58 – 2.86)	
Fisher Exact P-value	0.60	

Source: statistical review addendum

Duration of Response

Duration response was defined as the time from first documentation of a CR/PR to the date of disease progression or death due to disease progression. Patients treated with trabectedin showed a trend towards increased duration of response compared to patients treated with dacarbazine, however, this is considered exploratory.

Table 24. DOR Analysis based on Sensitivity Analysis 1 (described in ORR section)

	Trabectedin	Dacarbazine
Number of responder, n	23	10
Median DoR in months (95% CI)	6.93 (4.47, 7.62)	4.17 (2.92, NE)

Source: statistical review addendum

Table 25. DOR Analysis based on Sensitivity Analysis 2 (described in ORR section)

	Trabectedin	Dacarbazine
Number of responder, n	23	10
Median DoR in months (95% CI)	6.93 (4.47, 7.62)	4.17 (2.92, NE)

Source: statistical review addendum

Time to Response

Time to response was defined as the time from randomization until the first date of documented CR or PR. The median time to response was 3.07 months (range 1.2 to 10.4 months) for the trabectedin group and 2.35 months (range 1.3 to 8.3 months) for the dacarbazine group.

Duration of Stable Disease

Duration response was defined as the time from randomization to the date of disease progression or death due to disease progression. A higher percentage of patients treated with trabectedin achieved SD as best response compared to dacarbazine (51.3% vs. 34.7%, respectively). The median duration of SD was 6.01 months for the trabectedin treatment group and 4.17 months for the dacarbazine group (HR=0.449; 95% CI : 0.300, 0.673; p=0.0001). No patients in the dacarbazine group experienced stable disease for more than 9 months compared to 31.3% of those in the trabectedin group; 16.5 percent of patient in the trabectedin in group achieved SD for 12 months.

Reviewer Comment: Endpoints such as duration of response and duration of stable disease are reviewed in the context of the entire application and are not predefined to make regulatory claims. Improvement in either duration of response or duration of stable disease is supportive of the overall improvement in PFS.

6.1.6 Other Endpoints

Patient Reported Outcome

Patients were asked to completed MDASI (M.D. Anderson Symptom Inventory[7]) questionnaires reflecting their experience across 13 measure of symptoms (Symptom

Severity) and 6 measures of physical and mental function (Symptom Inference). At baseline, 96.8% of patients completed the questionnaires in both treatment groups. By Cycle 8, 71 patients in the trabectedin group and 14 patients in the dacarbazine group completed questionnaires, corresponding to 98.6% and 100% of patients being treated at that time, respectively. Baseline MDASI scores were reported to be low for all symptoms (severity and inference) in both the trabectedin and dacarbazine groups. Mean baseline scores were similar between both groups. No meaningful changes from baseline were observed through 8 cycles for either treatment group, aside from nausea in Cycle 2. At Cycle 2, patient in the 9.4% of patients in the trabectedin group reported nausea, verses 3.3% of patients in the dacarbazine group (p=0.0396). These data are consistent with a study population experiencing a relatively low baseline symptom burden who maintained low levels of symptoms for the duration of therapy.

Time to First Opiate or Other Analgesic

Time to first opiate analysis was conducted as an exploratory analysis. The analysis was highly censored, but showed a longer time to first opiate or other analgesic use for the trabectedin group compared to the dacarbazine group (11.5 months verses 6.08 months, respectively; HR- 0.651, 95% CI: 0.473, 0.895; p=0.0076).

Time to Initiation of Subsequent Therapy

Time to initiation of subsequent therapy was defined as the period of time between the date of randomization and the date of initiation of subsequent therapy. The median time to initiation of subsequent therapy was 6.87 month for the trabectedin group and 3.71 months for the dacarbazine group (HR-0.466, 95% CI: 0.358, 0.607; p<0.0001). Subsequent anti-cancer therapies included radiation, surgery and systemic treatments (See Table 13).

Reviewer Comment; Endpoints such as “Patient Reported Outcomes (PRO),” “Time to First Opiate,” and “Time to Initiation of Subsequent Therapy” are exploratory and are not interpretable due issues with data collection, missing data, and highly censored data. There are no validated instruments for assessing PROs in soft tissue sarcoma.

6.1.7 Subpopulations

A planned subgroup analysis cross 19 demographic and baseline characteristics was performed as part of the final overall survival analysis. The estimated HRs across most subgroups were consistent with HR for the overall study population.

FDA subgroup analysis across multiple demographic and baseline characteristics was performed (Table 17). The estimated HRs for PFS across most subgroups were consistent with the HR for the overall study population. See Statistics review for more detail.

Table 26. FDA PFS Subgroup Analysis by Baseline Demographics

Subgroup	Trabectedin (N=345)	Dacarbazine (N=173)	Hazard Ratio (95% CI)
Age			
>65	81 (23%)	34 (20%)	0.40 (0.23, 0.69)
<65	264 (77%)	139 (80%)	0.60 (0.46, 0.79)
Race			
White	238 (78%)	125 (72%)	0.52 (0.39, 0.68)
Black	9 (3%)	10 (6%)	0.54 (0.25, 1.19)
Asian	44 (13%)	19 (11%)	1.05 (0.21, 5.29)
Sex			
Female	238 (69%)	126 (73%)	0.57 (0.43, 0.76)
Male	107 (31%)	47 (27%)	0.55 (0.34, 0.87)
Country			
USA	323 (94%)	166 (96%)	0.55 (0.43, 0.70)
Non-USA	22 (6%)	7 (4%)	1.29 (0.30, 5.60)

Source: statistical review

Table 27. FDA Subgroup Analysis by Disease Characteristics

Subgroup	Trabectedin (N=345)	Dacarbazine (N=173)	Hazard Ratio (95% CI)
ECOG PS			
0	169 (49%)	86 (50%)	0.50(0.43, 0.70)
1	176 (51%)	87 (50%)	1.29 (0.30, 5.60)
BMI			
≥30	142 (41%)	61 (35%)	0.54 (0.36, 0.81)
Histology			
Leiomyosarcoma			
Uterine	134 (38.8%)	78 (45.1%)	0.55 (0.39, 0.79)
Non-uterine	118 (34.2%)	48 (27.7%)	0.59 (0.38, 0.93)
Liposarcoma			
Myxoid +/-	38 (11%)	19 (11.0%)	0.55 (0.23, 1.31)
Round Cell			
Dedifferentiated	45 (13.0%)	25 (14.5%)	0.66 (0.35, 1.24)
Previous Lines of Chemotherapy			
1	39 (11%)	19 (11%)	0.40 (0.18, 0.90)
≥2	306 (89%)	154 (89%)	0.56 (0.444, 0.72)
Prior Surgery			
No	327 (94.8%)	158 (91.3%)	0.11 (0.02, 0.55)
Prior Radiotherapy			
No	176 (51%)	80 (46.2%)	0.67 (0.48, 0.95)

Source: statistical review

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing regimen for trabectedin for study ET743-3007 (1.5 mg/m² i.v. as a 24-hour continuous infusion given every 3 weeks) was based on study ET743-STS-201. ET743-STS-201 was an open-label, randomized (1:1), multicenter trial designed to compare trabectedin in 2 different treatment regimens (0.58 mg/m² given as a 3-hour infusion every week versus 1.5 mg/m² given as a 24-hour infusion every 3 weeks) in patients with relapsed or refractory locally advanced or metastatic L-type sarcoma who had been previously treated with an anthracycline and ifosfamide containing regimen. The median TTP was 2.3 months (95% CI 2.0-3.5 month) in the qwk 3-h group and 3.7 months (95% CI, 2.1-5.4 months) in the q3w 24-h group (HR=0.734; 95% CI: 0.55, 1.974, p=0.0302).

Relationships were identified between trabectedin exposure and toxicity (neutropenia, elevation in serum transaminases, and hyperbilirubinemia). According to the modeling and simulation results, the sponsor's proposed dose adjustments for toxicity from 1.1 mg/ m² appear reasonable as it moderately decreases the toxicities. FDA suggested revised labeling to clarify further reduction in dose when used in combination with CYP3A inhibitors. See Clinical Pharmacology Review for further detail.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

n/a

6.1.10 Additional Efficacy Issues/Analyses

n/a

7 Review of Safety

Safety Summary

The review of safety primarily focuses on analyses of data submitted for the ET743-SAR-3007 trial because it is the only randomized, comparative trial submitted by the Applicant to support the safety of trabectedin. The size of the ISS database and duration of trabectedin exposure are sufficient to characterize the safety of trabectedin for the treatment of a serious and life-threatening condition, i.e., recurrent, metastatic leiomyosarcoma and liposarcoma. The level of detail of the data collected in Trial ET743-3007, however, is not sufficient to characterize the risk of cardiomyopathy and its sequelae as a result of exposure to trabectedin. As a result, a postmarketing requirement (PMR) was issued to the Applicant. Across seven clinical trials (ET743-SAR-3007, ET743-STS-201, ET-B-005, ET-B-008S, ET-B-016, ET-B-017, and ET-B-

028), 755 patients with metastatic soft tissue sarcoma received a median dose of 1.4 mg/m² (94%) of trabectedin with a median number of cycles of 6 (range 1-59 cycles). Thirty percent of patients were on study treatment longer than 6 months. In the ISS database, the most common adverse reaction (≥20%) for trabectedin are nausea, vomiting, constipation, diarrhea, fatigue, edema peripheral, pyrexia, alanine aminotransferase increased, aspartate aminotransferase increased, anemia, neutropenia, decreased appetite, dyspnea, cough, and headache.

The ET743-SAR-3007 trial is an ongoing, open-label, multicenter, international, randomized (2:1), active-controlled trial with 550 patients treated (as of the date of the 120-Day Safety Update, dated 7/10/2014) with metastatic leiomyosarcoma or liposarcoma, previously treated with an anthracycline-containing regimen who were allocated to receive trabectedin 1.5 mg/m² intravenously every 3 weeks as a 24 hour infusion (n=378) or dacarbazine 1000 mg/m² intravenously every 3 weeks (n=172), administered until disease progression or intolerable toxicity. The median duration on treatment is 13 months in the trabectedin group versus 8 months in the dacarbazine group. The mean dose intensity is 94% for trabectedin versus 97% for dacarbazine. One hundred fifty-eight (42%) patients in the trabectedin required at least one dose reduction, and 98 (26%) required treatment discontinuation for an adverse event.

Overall, the most common (≥ 20%) AE in the trabectedin group are nausea, fatigue, vomiting, diarrhea, constipation, decreased appetite, dyspnea, headache, fever, and cough. The most common laboratory abnormalities (≥20%) are increases in AST or ALT, neutropenia, and anemia.

Serious adverse events (SAE) occurred in 148 (39%) in the trabectedin group and 50 (29%) in the dacarbazine group. The most frequent (≤2% difference between groups) non-fatal SAEs in the trabectedin group compared to the dacarbazine group were nausea, vomiting, dyspnea, febrile neutropenia, pyrexia, dehydration, and acute renal failure.

Additional clinically significant adverse reactions of trabectedin are neutropenia, rhabdomyolysis, cardiomyopathy, and hepatotoxicity.

The incidence of AE leading to study treatment discontinuation is 26% (98/378) in the trabectedin group. The most common (greater than 1%) AEs are elevated liver function tests (LFT), defined as elevations in ALT/AST, total bilirubin, alkaline phosphatase, thrombocytopenia, fatigue, elevated creatine phosphokinase, and decreased ejection fraction. The incidence of AE leading to dose reductions is 42% (158/378) in the trabectedin group. The most common (greater than 1%) AEs are elevated LFT, neutropenia (including febrile neutropenia), thrombocytopenia, elevated creatine phosphokinase, nausea, vomiting, and fatigue. The incidence of AE leading to dose interruptions is 53% (200/378) in the trabectedin group. The most common (greater

than 1%) AEs are neutropenia, thrombocytopenia, elevated LFT, fatigue, anemia, blood creatinine increased, and nausea.

The reviewer recommends a postmarketing requirement to characterize the risk of cardiomyopathy and its sequelae in the patients exposed to trabectedin.

7.1 Methods

The ISS database comprises safety data from 755 patients with soft tissue sarcoma who were exposed to trabectedin at a dose of 1.5 mg/m² as a 24 hour infusion every 3 weeks. These patients were enrolled in seven studies listed in Table 28.

Table 28. Trials included in the Integrated Safety Summary (ISS) Database

Study Number Geography	Study Design Indication	Trabectedin Regimen	Patients Exposed to Trabectedin Status of Study
ET743-SAR-3007 (IND 050286) USA; multicenter	randomized (2:1), active- controlled,	1.5 mg/m ² as 24 hour infusion every 3-weeks	Planned: patients Ongoing:
ET743-ST5-201 (IND 050286) USA; multicenter	Randomized (1:1), open label Locally advanced or metastatic liposarcoma or leiomyosarcoma following treatment with an anthracycline and ifosfamide	Arm 1: 1.5 mg/m ² as 24 hour infusion every 3-weeks Arm 2: 0.58 mg/m ² as 3 hour infusion weekly	260 patients completed: 5/31/2006
ET-B-005-98 (non-IND study) France: multicenter	Non-randomized, open-label Advanced STS, including GIST with one prior treatment versus multiple prior treatments	1.5 mg/m ² as 24 hour infusion every 3-weeks	208 patients completed 2/18/2003
ET-B-008S-98 (non-IND study) France: multicenter	Non-randomized, open-label STS with prior therapy using 1-2 single agents or 1 combination versus ≥3 single agents or ≥2 combinations	1.5 mg/m ² as 24 hour infusion every 3-weeks	53 patients completed: 3/10/2003
ET-B-016 (IND 050286) USA: multicenter	Non-randomized, open-label Advanced and/or metastatic STS, untreated	1.5 mg/m ² as 24 hour infusion every 3-weeks	36 patients completed: 5/31/2001
ET-B-017-99	Non-randomized, open-label	1.5 mg/m ² as 24 hour	36 patients

Study Number Geography	Study Design Indication	Trabectedin Regimen	Patients Exposed to Trabectedin Status of Study
(IND 050286 USA: multicenter	advanced and/or metastatic STS with 1 or 2 prior therapies	infusion every 3-weeks	completed 3/18/2003
ET-B-028 (IND 050286) Italy: multicenter	Non-randomized, open-label localized liposarcoma, untreated, in neoadjuvant setting	1.5 mg/m ² as 24 hour infusion every 3-weeks	29 patients completed: 1/12/2010

Source: NDA 207953, Module 5.2; Annual Report for IND (b) (4)

The review of safety is primarily based on the ET743-SAR-3007 trial based on the following:

- ET743-SAR-3007 is the only randomized, active-controlled trial submitted by the Applicant to support the safety of trabectedin
- ET743-SAR-3007 accounts for approximately 49% of the trabectedin-exposed patients in the ISS database.

For the ET743-SAR-3007 trial, during the Screening Phase, safety assessments included documentation of medical history, including commitment medications; oncologic history including prior therapy, organs involved with metastatic disease; physical examination; vital signs assessment; laboratory assessment (including hematology, chemistry, and liver panels); documentation of ECOG Performance Status; ECG testing; LVEF assessment; serum pregnancy testing (if applicable); and documentation of AEs. During the Treatment Phase, safety assessments conducted on D1, D8, and D15 of each treatment cycle included documentation of adverse events, concomitant medications, laboratory assessment for hematology, chemistry, and liver panels. During the Follow-Up Phase, End-Of-Treatment safety assessments included laboratory assessment (including hematology, chemistry, and liver panels); documentation of ECOG Performance Status; ECG testing; LVEF assessment; and documentation of AEs, concomitant medications. Drug-related Grade 3 or Grade 4 toxicities will be monitored until Grade 2 or less, or for a maximum of 6 months after the last dose of study drug, whichever, occurs first. Grade 2 to 4 liver or cardiac toxicities will be monitored until the toxicity is Grade 1 or less, or for a maximum of 6 months after the last dose of study drug, whichever, occurs first.

Reviewer Comment

No scheduled cardiac monitoring during the Treatment Phase was specified in the protocol for ET743-SAR-3007. Incidence of cardiac toxicity dependent on Investigator-reported adverse events database. The incidence of decreased LVEF cannot be reliably inferred from the adverse events reporting. Furthermore, characterization of the sequelae of cardiomyopathy (duration of toxicity, time to recovery, rates of sequelae

and complications) cannot be assessed based on the provided safety assessments in the NDA. Therefore, a PMR was issued to the Applicant.

Furthermore, during the Treatment Phase of the Study, ECOG PS, physical examination, vital signs were not captured in the datasets at each treatment cycle.

FDA review includes a comparison of the datasets from the initial submission (NDA 207953, SDN 1, 11/24/2014) with a data cut-off date of 9/16/2013 and datasets from the 120-Day Safety Update (120DSU) (NDA207953, SDN 22, 4/17/2015) with a data cut-off date of 12/10/2014. This reviewer applied a data cut-off date of 9/16/2013 to the 120DSU datasets to replicate the initial datasets for comparison. This comparison identified several discrepancies in data that led to a Data Re-Verification Process performed by the Applicant to verify the integrity of the datasets. Section 3.1 provides further details surrounding findings of the comparison of the datasets by the FDA and the results of the Data Re-Verification Process. Similarly, the reviewer constructed a new ISS database by replacing the data related to the ET743-SAR-3007 Trial submitted under the initial submission (340 patients in the trabectedin group) with data from ET743-SAR-3007 Trial submitted under the 120DSU (378 patients in the trabectedin group), generating a new ISS comprising 755 patients (ISS120DSU). Note that all analyses involving ISS uses this newly constructed dataset, referred to as ISS120DSU

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review of safety included analysis of ISS database comprising 755 patients with a diagnosis STS and exposed to at least one cycle of trabectedin at a dose of 1.5 mg/m² as a 24 hour infusion every 3 weeks from seven clinical studies, including one randomized, active-controlled clinical trial, ET743-SAR-3007 (n=550) (Table 28). The review of safety, primarily focused on the safety data from ET743-SAR-3007 trial that was submitted as part of the 120-Day Safety Update (NDA 207953 SDN 0017, 3/24/2015) with safety data cut-off date of 7/10/2014.

The Applicant submitted a list of 75 studies comprising the Trabectedin Clinical Development Program (NDA 207953, SDN 1, 11/24/2015, Module 5.2) which represents 9,799 patients who have been exposed to at least one dose of trabectedin in completed or ongoing clinical studies, worldwide. The Applicant excluded 51 studies from pooled safety datasets for the following reasons (Table 29).

- Trabectedin is being evaluated in ongoing studies (21 studies)
- Trabectedin was evaluated in Phase 1 study (16 studies)
- Trabectedin was evaluated in combination with other cytotoxic regimens (11 studies)
- Trabectedin was evaluated in the first-line setting for STS patients (2 studies): ET-C-002-07 and ET-D-006-09

- Trabectedin was evaluated in a pediatric STS patient population (1 study):
 ET743-SAR-2005 (IIS)

Table 29. Selected Studies Excluded from Safety Datasets

Study Number Geography	Study Design Indication	Trabectedin Regimen	Patients Exposed to Trabectedin Status of Study
ET-C-002-07 (non-IND study) Spain; multicenter	Randomized (1:1), active-comparator First-line therapy in patients with translocation-related sarcomas (TRS)	Arm 1: Trabectedin 1.5 mg/m ² , as a 24 hour infusion every 3 weeks Arm 2: Doxorubicin 75 mg/m ² IV q3 weeks; or doxorubicin 60 mg/m ² IV followed by ifosfamide (range 6 to 9 g/m ²) IV q3 weeks	121 patients Completed 8/20/2012
ET-D-006-09 / EORTC 62091 (IND (b) (4)) France; multicenter	Randomized, active-comparator First-line therapy in patients with advanced or metastatic untreated soft-tissue sarcoma	Phase 2a: Arm 1: Doxorubicin 75 mg/m ² IV q3 weeks Arm 2: Trabectedin 1.3 mg/m ² , as a 3 hour infusion every 3 weeks Arm 3: Trabectedin 1.5 mg/m ² , as a 24 hour infusion every 3 weeks Phase 3: Arm 1: Doxorubicin 75 mg/m ² IV once every 3 weeks Arm 2: Trabectedin at a dose and regimen determined at the end of Phase 2a	133 patients Completed 8/24/2012
ET743-SAR-2005 (non-IND study) Canada; multicenter	Phase 2 Recurrent, pediatric rhabdomyosarcoma, Ewing sarcoma, or non-rhabdomyosarcomatous soft tissue sarcomas	Trabectedin 1.3 or 1.5 mg/m ² , as a 24 hour infusion every 3 weeks	50 patients Completed 2/25/2010

Source: NDA 207953, Module 5.2; Annual Report for IND (b) (4)

In order to verify the completeness of the list of clinical studies, this review compared the provided list in Module 5.2 in NDA 207953 to the list of phase 2 and 3 clinical studies provided in the Investigator's Brochure for Yondelis, Edition 9, dated 10 December 2013 (IND 050286, SDN 1981). This comparison revealed three additional phase 2 or phase 3 studies that were not included in the Module 5.2 Phase 1 and phase 4 studies were not included in this comparison of lists (Table 30).

Table 30. Additional Trials Identified from Investigator's Brochure

Study Number Geography	Study Design Indication	Trabectedin Regimen	Patients Exposed to Trabectedin Status of Study
ET-B-011-00 n/a	Open-label, single-arm Uterine carcinoma	Trabectedin 1.5 mg/m ² , as a 3 hour infusion every 3 weeks	1 patient Study closed due to low enrollment
ET-B-020-99 n/a	Open-label, single-arm Malignant pleural mesothelioma	Trabectedin 1.5 mg/m ² , as a 3 hour infusion every 3 weeks	4 patients n/a
ET743-SAR-3006 (EAP) China, multicenter	Phase 3, open-label (bridging study) Locally advanced or metastatic liposarcoma or leiomyosarcoma	Trabectedin 1.5 mg/m ² , as a 24 hour infusion every 3 weeks Dacarbazine, 1 g/m ² q3 weeks	171 patients (planned) Ongoing study

Source: Investigator's Brochure for Yondelis, Edition 9, dated 10 December 2013 (IND 050286, SDN 1981)

Reviewer Comment

These additional trials identified have low enrollment (5 patients) or are ongoing. Their omission in the ISS should have minimal impact on the interpretation of the safety data submitted in this NDA.

In addition, the ISS24 database submitted by the Applicant comprises pooled safety data from 23 completed Phase 2 trials and one Phase 3 clinical trial, ET743-SAR-3007, consisting of a total of 1736 patients (Table 31) to evaluate the safety of trabectedin. The safety data submitted by the Applicant includes information from 1736 patients with diagnosis of soft-tissue sarcoma or other solid malignancy and exposure to at least 1 cycle of trabectedin, administered as monotherapy in the following dosing regimens:

- 1.5 mg/m², as a 24 hour infusion once every 3 weeks
- 1.3 mg/m², as a 3 hour infusion once every 3 weeks
- 0.58 mg/m², as 3 hour infusion once every week

Table 31. Enumeration of Patients for Safety Datasets 1, 2, and 3 by Treatment Regimen

	1.5 mg/m ²	1.3 mg/m ²	0.58 mg/m ²	Dacarbazine
Safety Dataset 1 (n=550)	378			172
Safety Dataset 2 (n=920)	755	18	130	
Safety Dataset 3 (n=1736)	982	400	337	

Source: adsl.xpt and Module 2.7.4

The FDA clinical review of safety primarily depended on review of the data from ET743-SAR-3007 because it was the only trial submitted to the NDA which would allow a comparison of AEs to a control group. The review also evaluated major safety findings (deaths, SAEs) and AEs of interest using pooled data (ISS database) from the 755 patients from seven trials who had a diagnosis of STS and were exposed to at least one cycle of trabectedin 1.5 mg/m², as a 24 hour infusion once every 3 weeks, as a single agent (Table 31).

(b) (4)

7.1.2 Categorization of Adverse Events

The Applicant mapped and coded verbatim AE terms for the ET743-SAR-3007 trial using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. The Applicant graded the severity of AE toxicities encountered on the ET743-SAR-3007 trial using NCI CTCAE version 4.

The FDA clinical review of safety assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA PTs for 100% of the ET743-SAR-3007 SDTM AE dataset (ae.xpt). Of the 12,678 AE line listings in the ae.xpt dataset (ET743-SAR-3007, 120-Day Safety Update, cutoff date July 10, 2014), the review used manual evaluation of the 2926 verbatim terms to assess the acceptability of the Applicant's mapping from the verbatim term to 736 MedDRA Preferred Terms (PT). The MedDRA PTs contained in the datasets adequately represented the investigator recorded term (i.e., verbatim term) in nearly all cases. Minor differences did not alter the reliability and interpretation of the safety data.

The Applicant has provided 258 Case Report Forms (CRF) with Case Narratives, representing 47% of the treatment population (trabectedin 194/378 (51%) and dacarbazine 64/172 (37%). The selection criteria for patients were:

- Death for reasons other than disease progression that occurred within 30 days of the last dose of study medication (n=12)
- Treatment-emergent serious adverse events (n=206)
- Treatment-emergent adverse events that led to discontinuation of study medication (n=135)

The FDA clinical review of safety also included an audit of AE case report forms (CRFs) as well as an assessment of the coding of AE verbatim terms to MedDRA preferred terms (PT) to assess the completeness and verify the accuracy of the raw AE datasets. In an audit of 5% of trial population, few minor differences between the information captured on the CRFs and that included in the AE datasets submitted for the 120 Day Safety Update with a data cutoff date of July 10, 2014.

Case Report Forms (CRF) were selected for review based on death within 30 days of last dose of study medication (n=29) or treatment emergent SAE (n=53). An additional 20 CRFs from randomly selected patients were also reviewed. A review consisted of verification of properly coded variables in the dataset, AE appropriately classified and coded, outcomes appropriately classified and coded. This audit suggests that the quality of data in the integrated safety datasets is adequate.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The ISS database included AE data from seven trials (see Section 7.1.1 and Table 28). The review of safety included an analysis of the rates of the most common (>10% of patients) treatment-emergent adverse events (TEAE)s in trabectedin-exposed patients on ET743-SAR-3007 compared to event rates in the entire ISS database. The incidence of TEAEs by severity of toxicity grade was not analyzed in the ISS database because different versions of the NCI CTCAE were used to grade AEs for trials in the ISS. Overall, the incidences of the most common TEAEs occurring on the primary trial, ET743-SAR-3007, were similar to the incidences in the ISS database. Anemia, alanine

aminotransferase increased, white blood cell count decreased, neutrophil count decreased, and aspartate aminotransferase increased occurred at a higher incidence (>10% difference) in ET743-SAR-3007 than in the ISS database. This analysis is summarized in Table 32.

Table 32. Incidence of Common (≥10%) Treatment-Emergent Adverse Events in Trabectedin-Treated Patients. ET743-SAR-3007 – Safety Population and ISS Database

	ET743-SAR-3007 Trabectedin Group (n=378) n(%)	ISS (n=755) n(%)
Gastrointestinal disorders	341 (90)	673 (89)
Nausea	285 (75)	562 (74)
Vomiting	173 (46)	340 (45)
Constipation	140 (37)	284 (38)
Diarrhea	132 (35)	201 (27)
Abdominal pain	68 (18)	129 (17)
General disorders and administration site conditions	324 (86)	650 (86)
Fatigue	261 (69)	505 (67)
Edema peripheral	107 (28)	155 (21)
Pyrexia	71 (19)	156 (21)
Investigations	281 (74)	447 (59)
Alanine aminotransferase increased	186 (49)	265 (35)
Aspartate aminotransferase increased	142 (38)	206 (27)
White blood cell count decreased	97 (26)	108 (14)
Neutrophil count decreased	96 (25)	113 (15)
Blood alkaline phosphatase increased	85 (22)	125 (17)
Platelet count decreased	62 (16)	69 (9)
Blood creatine phosphokinase increased	56 (15)	71 (9)
Blood creatinine increased	48 (13)	60 (8)
Blood and lymphatic system disorders	230 (61)	340 (45)
Anemia	157 (42)	204 (27)
Neutropenia	119 (31)	205 (27)
Thrombocytopenia	74 (20)	103 (14)
Leukopenia	45 (12)	62 (8)
Metabolism and nutrition disorders	221 (58)	347 (46)
Decreased appetite	139 (37)	243 (32)
Dehydration	57 (15)	70 (9)
Hypokalemia	53 (14)	67 (9)

	ET743-SAR-3007 Trabectedin Group (n=378) n(%)	ISS (n=755) n(%)
Musculoskeletal and connective tissue disorders	202 (53)	337 (45)
Back pain	65 (17)	106 (14)
Arthralgia	56 (15)	96 (13)
Myalgia	47 (12)	79 (10)
Pain in extremity	47 (12)	71 (9)
Respiratory, thoracic and mediastinal disorders	201 (53)	368 (49)
Dyspnea	94 (25)	194 (26)
Cough	85 (22)	155 (21)
Nervous system disorders	198 (52)	344 (46)
Headache	93 (25)	167 (22)
Dizziness	46 (12)	68 (9)
Psychiatric disorders	113 (30)	199 (26)
Insomnia	55 (15)	83 (11)
Anxiety	40 (11)	68 (9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (3.2)	93 (12)
Tumor pain	6 (1.6)	80 (11)

Source: adae.xpt (120DSU); adae.xpt (ISS120DSU)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.

In the ET743-SAR-3007 trial, 378 patients received trabectedin and 172 patients received dacarbazine. Patients in the trabectedin group remained on treatment longer than in the dacarbazine group (median of 21 vs. 13 months). The mean relative dose intensity for trabectedin was 1.4 mg/m² (94%) compared to 973 mg/m² (97%) in the dacarbazine group. The median number of cycles of trabectedin administered to patients was 4 cycles in the trabectedin group compared to 2 cycles in the dacarbazine group. Within the ISS database of 755 patients, the mean relative dose intensity was 1.4 mg/m² (94%). The median number of cycles of trabectedin administered to patients was 6 cycles. Table 33 summarizes the exposure for each the ET743-SAR-3007 trial and the ISS.

Table 33. Exposure to Study Drug. ET743-SAR-3007 – Safety Population and ISS

	Trial ET743-SAR-3007	ISS
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Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

	Trabectedin (n=378)	Dacarbazine (n=172)	(n=755)
Time on study, months 1			
Mean	21	13	5
Standard Deviation	20	14	5
Median	13	8	3
Minimum	1	3	0
Maximum	127	100	55
Number of Patients, n(%)			
≤2 months	2 (0.5)	0 (0)	340 (45)
>2 to ≤4 months	32 (8)	32 (19)	138 (18)
>4 to ≤6 months	70 (19)	46 (27)	95 (13)
≥7 months	274 (72)	94 (55)	182 (24)
Dose Intensity, mg/m²/cycle 2			
Mean	1.4	973	1.4
Standard Deviation	0.1	69	0.1
Median	1.5	1000	1.5
Minimum	1.0	579	1.0
Maximum	1.6	1100	1.8
Number of Cycles			
Minimum	1	1	1
1 st Quartile	2	2	2
Median	4	2	6
3 rd Quartile	9	4	8
Max	36	29	59
Number of Patients, n(%)			
1-2 Cycles	140 (37)	92 (53)	294 (39)
3-4 Cycles	66 (17)	39 (23)	129 (17)
5-6 Cycles	44 (12)	12 (7)	112 (15)
≥7 Cycles	128 (34)	29 (17)	220 (29)

Source: adexs.xpt (120DSU) and adexs.xpt (ISS120DSU)

¹ Time on study treatment is the time from the first dose date to the last dose date including interruptions. Months = Number of Days / 30.

² Dose Intensity calculated by the summation of the cumulative exposure per patient and dividing by number of cycles per patient and then dividing by initial target dose.

As summarized in Table, demographics and baseline characteristics within each treatment group were well matched and comparable to the ISS. Of note, the demographics and baseline characteristics of the ET743-SAR-3007 trial safety population were similar to those of the ITT population (Table 8 and Table 9).

Table 34. Demographics and Baseline Characteristics. ET743-SAR-3007 – Safety Population and ISS

	Trial ET743-SAR-3007	ISS
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	Trabectedin (n=378)	Dacarbazine (n=172)	(n=755)
Age, years			
Median	57	56	54
Minimum	18	17	18
Maximum	81	79	81
Age >65, n(%)	93 (25)	35 (20)	143 (19)
Gender, n(%)			
Female	257 (68)	124 (72)	477 (63)
Male	121 (32)	48 (28)	278 (37)
Race/Ethnicity, n(%)			
White	295 (78)	128 (74)	439 (58)
Black	47 (12)	19 (11)	55 (7)
Asian	11 (2.9)	9 (5)	14 (1.9)
American Indian	1 (0.3)	4 (2.3)	1 (0.1)
Multiple	1 (0.3)	2 (1.2)	1 (0.1)
Other ¹	23 (6)	10 (6)	245 (32)
ECOG PS, n(%)²			
0	183 (48)	80 (47)	372 (49)
1	195 (52)	92 (53)	381 (50)
≥2	0 (0)	0 (0)	1 (0.1)
Tumor Subtype n(%)			
Leiomyosarcoma	276 (73)	127 (74)	n/a
Uterine	140 (37)	81 (47)	n/a
Non-Uterine	136 (36)	46 (27)	n/a
Liposarcoma	102 (27)	45 (26)	n/a
Dedifferentiated	49 (13)	27 (16)	n/a
Myxoid +/- Round Cell	42 (11)	14 (8)	n/a
Pleomorphic	11 (2.9)	4 (2.3)	n/a

Source: dm.xpt (120DSU), suppdm.xpt (120DSU), mh.xpt (120DSU), adddiag.xpt (120DSU), and addm.xpt (ISS120DSU)

¹ "Other" includes: "Not Reported," "Not Collected," "Other," and "Unknown."

² ECOG Status was missing for one patient in the ISS with Subject ID: ET-B-005-147-00500104.

Reviewer Comment

ECOG Status was missing for one patient in the ISS with Subject ID: ET-B-005-147-00500104. This is not expected to have an impact on the interpretation and generalizability of the findings in the safety analyses.

While the percentage of patients with leiomyosarcoma versus liposarcoma were well balanced in ET743-SAR-3007 based on stratification by L-type sarcoma subtype at randomization, there is an imbalance in the histologies for leiomyosarcoma (uterine versus non-uterine). The clinical significance of this imbalance is uncertain because of the variability of criteria between investigators and the absence of a central pathology

review of the pathology specimens. Further, the imbalance may not have a significant impact on the review of clinical safety.

7.2.2 Explorations for Dose Response

The trabectedin development program did not include dose-response trials. See Section 7.5.1 for explorations of exposure-response relationships for AEs.

7.2.3 Special Animal and/or In Vitro Testing

See the summary of pharmacology/toxicology in Section 4.3.

7.2.4 Routine Clinical Testing

Please refer to sections 7.4.2-7.4.4.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of clinical pharmacology in Section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Trabectedin represents the first agent in this class of novel alkylators and mechanism of action is not well understood. As such no information is available for other agents in this class.

7.3 Major Safety Results

7.3.1 Deaths

Table 35 summarizes the primary causes of death for patients in the ET743-SAR-3007 Trial – Safety Population and in the ISS database. Overall, 220 (58%) patients in the trabectedin group and 102 (59%) patients in the dacarbazine group died during the Treatment and Follow-Up Phases of the trial. Progressive disease as reported by the Investigator is the most commonly reported primary cause of death for the trabectedin group and the dacarbazine group for all deaths (196 (58%) versus 99 (58%)). Overall, the Applicant reports treatment-emergent deaths (within 30 days of last investigational dosing) in 7% of patients in the trabectedin group and 2% in dacarbazine group. Of these treatment-emergent deaths, the Applicant attributed 13 (3%) deaths in the trabectedin group to progressive disease and 12 (3%) to an adverse event; in the dacarbazine group, four (2%) deaths are attributed to the progressive disease and none

were attributed to an adverse event. Table 36 summarizes the case narratives for the 29 patients (25 trabectedin group, 4 dacarbazine group) who died within 30 days of last investigational dosing.

ISS Database Analysis

In the ISS database, the Applicant reports 515 (68%) patients died; 467 (62%) patients were reported to have died from progressive disease. Fifty-three (7%) deaths occurred within 30 days of last trabectedin dosing.

Reviewer Comment

FDA clinical review of the deaths identified 12 (3.2%) of patients with a cause of death listed as "Other" in the ET743-SAR-3007 Trial – Safety Population and 1.6% in the ISS database. One death (Subject ID ET743-ST5-201-201-12345004) that occurred within 30 days of last trabectedin dosing (C1D25) and whose cause of death is reported as "Other." A review of the adverse events (adae.xpt - ISS) for this patient did not reveal any AE assessed as an SAE or resulting in change in the study treatment. The toxicities ranged from G2 to G3. The impact of these missing data are unlikely to have a significant impact on the serious adverse event profile for trabectedin.

Table 35. Primary Causes of Death by Treatment Group. ET-743-SAR-3007 – Safety Population

	Trial ET743-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Total number of deaths	220 (58)	102 (59)	515 (68)
Death within 60 days of initiation of study drug	27 (7)	12 (7)	62 (8)
Death within 30 days from last dose	25 (7)	4 (2.3)	53 (7)
Death due to TEAE	12 (3.2)	0	33 (4.4)
Drug related	8 (2.1)	0	16 (2.1)
Death due to progressive disease	13 (3.4)	4 (2.3)	27 (3.6)
Death due to other	0	0	1 (0.1)
Death more than 30 days after last dose	195 (52)	98 (57)	462 (61)
Death due to progressive disease	183 (48)	95 (55)	440 (58)
Death due to other	12 (3.2)	3 (1.7)	12 (1.6)

Source: dm.xpt (120DSU), ds.xpt (120DSU), addm.xpt (ISS120DSU), and adds.xpt (ISS120DSU).

Table 36. Summary of Case Narratives of Deaths within 30 Days of Last Dose– ET743-SAR-3007 – Safety Population

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
Trabectedin Group (25 deaths occurring within 30 days from last dose) Death due to TEAE, related to drug (8)		
000073 64 M Liposarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	<p>On (b) (6), the patient experienced a G5 septic shock that was attributed to the study drug by the investigator. On (b) (6), the patient was hospitalized for G4 neutropenia and G3 thrombocytopenia. Blood culture positive for <i>Pseudomonas aeruginosa</i>. The patient received filgrastim, platelet transfusions, and piperacillin/tazobactam. Patient was also found to have renal failure and abnormal liver function tests. On (b) (6) the patient died. Other relevant past medical history included deep vein thrombosis (resolved), right ventricular heart dysfunction (LVEF 43%, ongoing).</p>	<p>Reviewer agrees with the attribution of septic shock with associated neutropenia as the cause of death. Occurrence of other adverse events renal failure and abnormal LFTs laboratory abnormalities associated with renal failure and hepatotoxicity are likely secondary to shock.</p>
000096 56 M Liposarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	<p>On (b) (6), patient experienced a G5 cardiac arrest and G5 acute renal failure (creatinine 9.1). On (b) (6) patient was hospitalized for G4 neutropenia, G3 hyperkalemia, and G2 hyperbilirubinemia. Patient was being evaluated for dialysis for acute renal failure with oliguria. On (b) (6) patient developed atrial fibrillation, ventricular tachycardia, followed by asystole. Cardiopulmonary Resuscitation was attempted without response.</p> <p>Other relevant past medical history include hypertension. LVEF at screening was 32%. ECG was reported as “abnormal, clinically insignificant. On (b) (6) creatinine value was 1.07.</p>	<p>Reviewer notes that patient’s pre-existing cardiomyopathy is a confounding factor in attributing cardiac event to the trabectedin. Per protocol for ET743-SAR-3007, this patient should have been excluded from the study based on unresolved cardiomyopathy. The Applicant was not able to respond adequately to an IR on 8/25/2015 for additional LVEF assessments because the Applicant reports that the data was not captured. A PMR will be issued to characterize the risk of cardiomyopathy and its sequelae.</p> <p>Reviewer agrees with attribution of acute renal failure to trabectedin, but the attribution to the cause of death is less certain given confounding factors.</p>
000232	<p>On (b) (6), patient experienced G5 sepsis with</p>	<p>Reviewer agrees with the</p>

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
54 F Liposarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	G4 neutropenia, after completion of a course of antibiotics for community acquired pneumonia and urinary tract infection. The patient received broad spectrum antibiotics as well as filgrastim. The neutropenia recovered, but sepsis persisted and on (b) (6) the patient died shortly after family decided to withdraw aggressive treatment.	attribution of septic shock with associated neutropenia as the cause of death. The Applicant did not provide microbiology evaluation or infection work up for etiology of patient's sepsis.
000332 49 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel	On (b) (6), patient experienced G5 acute renal failure, G4 neutropenia, and G4 thrombocytopenia. On (b) (6) patient also had abnormal LFTs. On (b) (6), patient developed G2 elevation of CPK that worsened to G4 on (b) (6) (CPK 3,223). On (b) (6) patient was transferred to hospice and died on (b) (6) Other relevant medical history include diabetes, hypothyroidism, high cholesterol treated with simvastatin.	Reviewer does not agree with cause of death as acute renal failure because of many confounding factors, such as rhabdomyolysis, although rhabdomyolysis was not recorded as an AE. Confounding factors include concurrent medication of simvastatin. Abnormal LFT's was consistent with hepatotoxicity, but attribution to trabectedin is confounded by several other active medical issues at time of presentation.
000357 53 M Leiomyosarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	On (b) (6) patient experienced G5 rhabdomyolysis with a G4 CPK elevation and G3 renal failure, and G5 sepsis. On (b) (6), patient was hospitalized for G3 anemia, G4 thrombocytopenia, and G4 neutropenia. Patient was transfused and received filgrastim. Patient developed anuria and sepsis and was started on hemodialysis, broad spectrum antibiotics and vasopressors. On (b) (6) patient died. Other relevant medical history includes atrial fibrillation, diabetes.	Reviewer agrees with attribution of G5 rhabdomyolysis and G5 sepsis as cause of death.
000371 60 F Leiomyosarcoma doxorubicin, docetaxel, gemcitabine,	On (b) (6) patient experienced G5 multi-organ failure, with peripheral pulmonary opacities, soft tissue mass in R kidney, new mass adjacent to R kidney, ascites, and LVEF of 20%. Patient also developed biventricular heart failure, renal failure, and shock liver. On (b) (6) patient abnormal LFTs. On (b) (6), patient died.	Reviewer does not agree with G5 multi-organ failure as the only cause of death. The patient also presented with G5 heart failure which is not reported as an SAE. Although patient had baseline LVEF of 50%, it was below institutional

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
palifosfamide-tris versus placebo (clinical trial; randomization remains censored)	At baseline, patient had LVEF of 50% (institutional limit of normal is 55%). Other relevant medical history includes atrial fibrillation on anticoagulation, papillary thyroid carcinoma.	limit of normal. Attribution to trabectedin is confounded by patient's prior cardiac conditions, including atrial fibrillation.
000516 47 M Liposarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	On (b) (6), patient experienced G5 Clostridium difficile sepsis with G4 neutropenia. On (b) (6), patient was hospitalized for G4 neutropenia, G4 thrombocytopenia, and pneumonia. Patient was treated with broad spectrum antibiotics, epoetin alfa, filgrastim, and transfusion. Patient also has had recurring neutropenia and febrile neutropenia that had resolved prior to hospitalization. On (b) (6) patient also experienced G3 CVA, but did not receive tissue plasminogen activator, given recent MRI finding of small cerebral hemorrhage. Patient was not responding to treatment including broad spectrum antibiotics, vasopressors, levetiracetam. On (b) (6) patient died.	Reviewed agrees with attribution of cause of death to neutropenic sepsis.
000685 77 F Leiomyosarcoma Doxorubicin, gemcitabine	On (b) (6) patient experienced a G3 elevation in CPK that worsened to G4 and G3 muscle weakness. Patient also developed G2 elevated creatinine, G4 thrombocytopenia, and G3 transaminitis, CPK worsened to grade 4 rhabdomyolysis. Patient developed atrial fibrillation with RVR. Patient then decided to become comfort care. In (b) (6) patient died. Other relevant medical history includes cardiomyopathy. At baseline, patient had a G1 elevation in creatinine. CPK was normal.	Reviewer agrees with attribution of G5 rhabdomyolysis as cause of death.
Death due to TEAE, unrelated to drug (4)		
000110 63 F Leiomyosarcoma Doxorubicin, ifosfamide	On (b) (6) patient was hospitalized with fever and shortness of breath. CT showed multipole pulmonary metastases and evidence of lymphangitis carcinomatosa. Patient was treated with broad spectrum antibiotics and prophylactic pegfilgrastim. On (b) (6), the patient died. The investigator attributed the cause of death due to G5 respiratory tract	Reviewer is unable to assess the attribution of G5 respiratory tract infection as the cause of death because of lack of sufficient information. Microbiology lab results, neutrophil count, and presence of fever during the presentation

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
	infection.	of dyspnea were not provided in the Narrative Summaries or the datasets. The CT did not show evidence of pneumonia, but is consistent with progressive disease.
000456 79 M Leiomyosarcoma Liposomal doxorubicin, gemcitabine, docetaxel	On (b) (6), patient experienced G3 lower GI bleed with G3 anemia, G4 thrombocytopenia, and G4 neutropenia and was hospitalized. On (b) (6) patient developed abnormal LFT's and increased troponin, assessed by the investigator to be related to demand ischemia from anemia. Patient received transfusion of pRBC, and platelets, filgrastim, and phytomenadione. On (b) (6), patient experienced a G5 cardiac arrest. Other relevant history: CAD, chronic renal failure, DVT on warfarin, lymphoma. LVEF at baseline was 50%.	Reviewer agrees with attribution of cardiac arrest as cause of death. The ability to attribute the adverse event to trabectedin is confounded by patient's previous cardiac history and demand ischemia secondary to anemia. No LVEF assessment was provided at time of acute event.
000482 55 F Leiomyosarcoma Doxorubicin, ifosfamide	On (b) (6) patient experienced G5 hypotension and G5 respiratory distress and was hospitalized. Patient was received vasopressors and mechanical ventilation. On (b) (6) patient died. On (b) (6), the Applicant reports that patient developed G3 pulmonary embolism. VQ scan was reported negative, and patient was given enoxaparin 40mg SC and then fondaparinux 2.5mg. CT scan or other supporting evidence of PE is not provided in narrative summaries.	Reviewer is unable to assess the cause of the death because of lack of sufficient information. The Investigator-assessed cause of death as respiratory distress, may be secondary to PE. The data reviewed from the case narrative and conmed.xpt indicates that patient was only given prophylactic doses of anticoagulation for a possible diagnosis of PE. This dose is insufficient to treat the condition and may have contributed to patient's respiratory distress.
000606 63 M Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel	On (b) (6), patient experienced G5 cardiac arrest and G5 respiratory arrest. Patient was treated with vasopressors and crystalloid volume expansion. Patient died on same day of presentation. Other relevant medical history: obesity, Obstructive sleep apnea, warfarin (indication not specified). At baseline, patient had a LVEF	Reviewer is unable to assess the attribution of the cause of death to trabectedin because of a lack of sufficient information provided in the case narrative and datasets.

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
	of 65% and ECG was reported to have clinically insignificant abnormalities.	
Death due to Progressive Disease (13)		
000006 62 F Leiomyosarcoma Doxorubicin, ifosfamide, gemcitabine, vinorelbine, docetaxel, liposomal doxorubicin, topotecan.	On (b) (6), patient was hospitalized for G3 asthenia and G1 pyrexia. On (b) (6), during the hospitalization, patient experienced a G5 GI hemorrhage was received transfusion of pRBC. On (b) (6), patient died. The investigator attributed the G5 hemorrhage to tumor burden.	Reviewer agrees with assessment of the G5 hemorrhage to Progressive Disease in the absence of alternate etiologies. Review of platelet count in lb.xpt did not reveal any evidence of associated thrombocytopenia with PLT count nadir was 94 on C3D15. Results of CT to document progression of disease was not provided, however.
000026 47 F Leiomyosarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel, pegylated liposomal doxorubicin, carboplatin, temozolomide	On (b) (6), patient experience G3 tumor pain and missed her appointment for C2 of trabectedin. On (b) (6), the investigator reported an SAE of "unknown death." No additional details were provided by the Applicant or the Investigator.	Reviewer is unable to assess the cause of the death because of lack of sufficient information on the events preceding the patient's death.
000040 46 M Liposarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel, pegylated liposomal	On (b) (6) patient experienced G3 pancreatitis and was hospitalized. CT showed pancreatitis and metastatic disease in the abdomen, lung, and pericardium. On (b) (6), the patient experienced G5 respiratory failure. Patient was transferred to hospice, and on (b) (6), patient died. Other relevant history: G3 pancreatitis that was resolved was reported on screening evaluation (b) (6)	Reviewer agrees with attribution of pancreatitis as unrelated to trabectedin based on past medical history of pancreatitis that was resolved at time of enrollment. Respiratory distress is a known complication of pancreatitis, but it insufficient information is provided to apply Ranson's criteria to this case.

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
doxorubicin		
000223 37 F Leiomyosarcoma doxorubicin, carboplatin, gemcitabine, cisplatin, docetaxel	On (b) (6), patient experienced G4 acute renal failure, anemia, neutropenia, thrombocytopenia, all G3. Target lesions on CT scan met criteria for progression of disease. On (b) (6) patient experienced hydronephrosis and on (b) (6) underwent cystoscopy with ureteral stents. Post operatively, patient experienced acute respiratory failure G5, acidosis G3, and sepsis G3. Patient was intubated for mechanical ventilation. On (b) (6), the patient died.	Reviewer identified confounding factors to attributing progressive disease as the cause of death, including post-operative complications such as acute respiratory failure. These may be unrelated to the drug.
000320 55 F Leiomyosarcoma doxorubicin, ifosfamide, gemcitabine, docetaxel	On (b) (6) patient experienced G3 tachycardia. CT scan showed multiple large heterogeneous and necrotic masses in abdomen. On (b) (6) patient experienced G5 respiratory failure and died on the same day.	Reviewer is unable to assess the cause of the death or attribution to trabectedin because of lack of sufficient information.
000380 70 M Leiomyosarcoma Doxorubicin ifosfamide	On (b) (6) patient experienced persistent and worsening G5 obstruction at the gastro-esophageal junction. Endoscopy showed tight external compression of lower 4-5cm of esophagus and a large fungating mass in stomach. Biopsy demonstrated gastric cardia leiomyosarcoma. On (b) (6) patient died.	Reviewer agrees with attribution of cause of death as related to malignancy.
000386 64 F Leiomyosarcoma Doxorubicin, ifosfamide, pazopanib, gemcitabine, docetaxel	On (b) (6) patient experienced G5 hyperkalemia (K 7.2), ongoing G3 fatigue and G3 abdominal distension. Patient was hospitalized and treated with IV fluids for hyperkalemia and referred to hospice. On (b) (6) patient died.	Reviewer is unable to assess the cause of the death or attribution to trabectedin because of lack of sufficient information. It is a reasonable that worsening malignant ascites led to volume depletion, and G5 event of hyperkalemia, but cannot be confirmed without further information.
000407 40 F Liposarcoma	On (b) (6), patient experienced G5 respiratory failure and G4 pleural effusion. Patient underwent thoracentesis for pleural effusion, and mechanical ventilation for respiratory	Reviewer agrees with attribution of cause of death as related to malignancy.

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
Doxorubicin, ifosfamide, pazopanib, gemcitabine, docetaxel	failure. On (b) (6), patient died. Relevant history: post-treatment Echocardiogram (b) (6) had LVEF 60%.	
000458 62 M Liposarcoma Doxorubicin, ifosfamide, pazopanib, gemcitabine, docetaxel, eribulin	On (b) (6) patient experienced G5 respiratory failure and died on the same day. No further details provided regarding patient death.	Reviewer is unable to assess the cause of the death or attribution to trabectedin because of lack of sufficient information.
000534 42 F Leiomyosarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	On (b) (6), patient experienced persistent G2 increased creatinine. On (b) (6) patient percutaneous nephrostomy tubes and Foley catheter places for G2 acute renal failure. A subsequent CT scan showed progression of disease. Patient was transferred to hospice. On (b) (6), patient died.	Reviewer agrees with attribution of cause of death as related to malignancy.
000535 64 M Leiomyosarcoma, Doxorubicin, gemcitabine, docetaxel	On (b) (6), patient developed worsening G3 exertional dyspnea and SVC syndrome. CT scan showed mass invading innominate vein and extending into SVC. On (b) (6), patient died.	Reviewer agrees with attribution of cause of death as related to malignancy.
000576 58 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel, bevacizumab, Ly3023414	On (b) (6), the patient experienced death, as reported by Investigator. Circumstances surrounding death were uncertain as patient died "in her sleep." Case summary reports that prior to (b) (6) patient had progression of disease, but continued on treatment.	Reviewer agrees with attribution of cause of death as related to malignancy.

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
(investigational drug)		
000694 74 M Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel	On (b) (6), patient experienced G3 intestinal obstruction. The investigator attributed the AE to be not related to study drug. Patient elected for hospice care and on (b) (6) patient died.	Reviewer agrees with attribution of cause of death as related to malignancy.
Dacarbazine Group (4) Death due to Progressive Disease (4)		
000303 70 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel, pazopanib	On (b) (6), patient experienced worsening G4 decreased appetite and G4 fatigue. Patient also developed, decreased G3 neutrophil count treated with filgrastim, and G3 anemia and G3 thrombocytopenia treated with transfusions. Patient was transferred to hospice, and on (b) (6), patient died.	Reviewer agrees with attribution of cause of death as related to malignancy.
000392 55 M Leiomyosarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	On (b) (6) patient had CT showing progression of disease with mild mass effect on SVC and large right pleural effusion. Patient elected to change treatment regimen to pazopanib. On (b) (6), patient experienced G5 respiratory failure and died on that day.	Reviewer agrees with attribution of cause of death as related to malignancy.
000599 70 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel, ixabelpilone,	On (b) (6), patient experienced G3 cancer pain and was hospitalized. Patient underwent CT scan that showed increased tumor size and hemorrhage that was proposed as the cause of her pain. Patient was treated with opiates. On (b) (6), patient experience G5 circulatory collapse and died. LVEF at baseline was 55%.	Reviewer is unable to assess the cause of the death or attribution to trabectedin because of lack of sufficient information.

Subject ID Age/Gender Sarcoma Subtype Prior chemotherapy	Case Description	Reviewer Comment
pegylated liposomal doxorubicin		
000700 44 M Liposarcoma Doxorubicin, ifosfamide	On (b) (6), patient experienced G3 dyspnea, secondary to worsening right pleural effusion. Patient was treated with Pleurex catheter and transferred to hospice. On (b) (6), patient died. LVEF at baseline was 60%.	Reviewer agrees with attribution of cause of death as related to malignancy.

Source: Case Narratives provided in Clinical Study Report ET743-SAR-3007: 120-Day Safety Update.

Grade 5 Adverse Events

Overall, there were 34 Grade 5 Adverse Events (AE) reported for 30 patients in Study ET743-SAR-3007 (25 in the trabectedin and five in the dacarbazine groups). Table 37 summarizes the incidence of Grade 5 AEs that were attributed to a patient's death by the Investigator in Study ET743-SAR-3007 and in the Integrated Safety Database.

In the ISS database, the Grade 5 AEs reported mostly consist of adverse events reported in the ET743-SAR-3007 trial, and as a result, the safety profiles are similar. Six additional Grade 5 AEs were identified as: death, injection site infection, sepsis, cerebrovascular accident, renal failure, and rhabdomyolysis.

Table 37. Incidence of Grade 5 Adverse Events by Preferred Term. ET743-SAR-3007 – Safety Population and ISS Database

System Organ Class Preferred Term	ET743-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Cardiac disorders			
Cardiac arrest	3 (0.8)	0 (0)	3 (0.4)
Gastrointestinal disorders			
Gastrointestinal hemorrhage	1 (0.3)	0 (0)	1 (0.1)
Obstruction gastric	1 (0.3)	0 (0)	1 (0.1)
General disorders and administration site conditions			
Death	5 (1.3)	3 (1.7)	6 (0.8)
Multi-organ failure	1 (0.3)	0 (0)	1 (0.1)
Infections and infestations			
Sepsis	2 (0.5)	0 (0)	3 (0.4)
Clostridium difficile sepsis	1 (0.3)	0 (0)	1 (0.1)

System Organ Class Preferred Term	ET734-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Respiratory tract infection	1 (0.3)	0 (0)	1 (0.1)
Septic shock	1 (0.3)	0 (0)	1 (0.1)
Injection site infection	0 (0)	1 (0.6)	0 (0)
Metabolism and nutrition disorders			
Hyperkalemia	1 (0.3)	0 (0)	1 (0.1)
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis	2 (0.5)	0 (0)	3 (0.4)
Nervous system disorders			
Cerebrovascular accident	0 (0)	0 (0)	1 (0.1)
Renal and urinary disorders			
Renal failure acute	2 (0.5)	0 (0)	2 (0.3)
Renal failure	0 (0)	0 (0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders			
Respiratory failure	4 (1.1)	1 (0.6)	4 (0.5)
Acute respiratory failure	1 (0.3)	0 (0)	1 (0.1)
Respiratory arrest	1 (0.3)	0 (0)	1 (0.1)
Respiratory distress	1 (0.3)	0 (0)	1 (0.1)
Vascular disorders			
Hypotension	1 (0.3)	0 (0)	1 (0.1)
Circulatory collapse	0 (0)	1 (0.6)	1 (0.1)

Source: ae.xpt (120DSU), dm.xpt (120DSU), adae.xpt (ISS120DSU), and adsl.xpt (ISS120DSU)

Reviewer Comment

Comparison of list of patients in Trial ET743-SAR-3007 who died within 30 days of last treatment (Table 35) to the list of patients who experienced a G5 TEAE revealed one additional patient 000059 in the G5 listing who died on C1D32.

Six patients (3 in the trabectedin and 3 in the dacarbazine groups) had the cause of death listed as "Other" (DSDECOD=Other) (Patients 070, 334, 434, 543, 554, and 557) Review of the reported term for disposition event (DSTERM) were:

- *alternative anti-cancer therapy (1)*
- *lost to follow up (4)*
- *disease progression (1)*

In the ISS, an additional eight patients with causes of death listed as "Other".

The review of patient deaths included further analyses of the following SAEs to characterize the risks of adverse events due to trabectedin:

- Cardiac Events Related to Ventricular Dysfunction
- Neutropenia
- Rhabdomyolysis

Cardiac Disorders

In the ET-743-SAR-3007, 98 cardiac events of any grade, as defined by the Applicant based on a composite of MedDRA High Level Group Terms (see Appendix 9.5, Table 66), occurred in 57 (15%) patients in the trabectedin group. In the dacarbazine group, 29 adverse events occurred in 25 (15%) patients. Of the 57 patients in the trabectedin group with cardiac-related events, 20 (5%) patients experienced a total of 28 SAEs. (Table 38)

Table 38. Summary of Case Narratives of Cardiac-Related SAE. ET743-SAR-3007 – Safety Population

Subject ID Age/Gender Malignancy Prior chemotherapy	Case Description	Reviewer Comment
000074 48 F Leiomyosarcoma doxorubicin, ifosfamide, gemcitabine, pemetrexed, etoposide	<p>On (b) (6) patient experienced G3 cardiac failure congestive, with G2 pulmonary edema, and G4 respiratory failure. Patient was hospitalized and treated with carvedilol and furosemide. The AE resolved on (b) (6). The AE led to a dose reduction to 1 mg/m². After C8, patient discontinued treatment due to progressive disease.</p> <p>Baseline LVEF: 37% End of Treatment LVEF: not available.</p>	<p>Reviewer notes that patient's abnormal LVEF at screening is a confounding factor in attributing cardiac event to the trabectedin. Per protocol for ET743-SAR-3007, this patient should have been excluded from the study based on unresolved cardiomyopathy. The Applicant was not able to respond adequately to an IR on 8/25/2015 for additional LVEF assessments because the Applicant reports that the data was not captured. A PMR will be issued to characterize the risk of cardiomyopathy and its sequelae.</p>
000096	Reviewed under Patient Deaths (Table 36).	
000131 76 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel	<p>On (b) (6), patient experienced G3 pulmonary edema and fluid retention. Patient was treated with diuretics and AE improved.</p> <p>On (b) (6) patient experience G2 fluid retention. The investigator assessed that patient had recurring congestive heart failure that improved with diuresis. The AE led to a dose reduction from 1.5 1 mg/m² to 1.21 mg/m².</p> <p>On (b) (6), patient experienced G3 congestive cardiac failure and atrial fibrillation. On (b) (6) the patient also developed G4 pulmonary embolism. LVEF was <10%. Study drug discontinued.</p>	<p>Reviewer notes that this patient was rechallenged with trabectedin and developed recurrent heart failure that improved with diuresis.</p>

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
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Subject ID Age/Gender Malignancy Prior chemotherapy	Case Description	Reviewer Comment
	Baseline LVEF 54% Unscheduled LVEF: <10% End-of-Treatment: LVEF 20%	
000143 53 F Leiomyosarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	On (b) (6), patient experienced G3 cardiac disorder (chest tightness) and G3 dyspnea. Work up for myocardial infarction was negative. The AE led to dose interruption and dose reduction to 1.2 mg/m ² for C2. After C2, patient discontinued treatment due to progressive disease. Baseline LVEF: 50% End of Treatment LVEF: 44%	
000178 66 M Leiomyosarcoma Doxorubicin, PCI-24781, gemcitabine, docetaxel	On (b) (6), patient experienced neutropenia, thrombocytopenia, and anemia. Patient was transfused, treated with filgrastim, and antibiotics. On (b) (6) patient experienced G3 UTI and was treated with broad-spectrum antibiotics. UCx grew Staphylococcus. On (b) (6), patient experienced G3 cardiac failure congestive, renal failure. Patient was treated with hemodialysis. Investigator reported that patient was also developed G4 decrease in ejection fraction. The narrative states that ejection fraction decreased “was resolved in 40 days.” Baseline LVEF 59%	The Applicant was not able to respond adequately to an IR on 8/25/2015 for additional LVEF assessments because the Applicant reports that the data was not captured. A PMR will be issued to characterize the risk of cardiomyopathy and its sequelae.
000186 52 M Liposarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	On (b) (6), patient experienced G4 decreased ejection fraction (LVEF 27%) and G3 atrial fibrillation. On (b) (6) the case narrative states that cardiac failure G3 resolve, but decreased EF only improved to G3. Patient was taken off the study because of persistence of decreased ejection fraction. Baseline LVEF: 47% End of Treatment LVEF: 27%	Reviewer notes that no further data regarding AE decreased EF was provided in the Follow-up Phase of the trial. The Applicant was not able to respond adequately to an IR on 8/25/2015 for additional LVEF assessments because the Applicant reports that the data was not captured. A PMR will be issued to characterize the risk of cardiomyopathy and its sequelae.
000295	On (b) (6) the patient experienced G3 cardiac failure congestive and G2 atrial flutter.	

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
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Subject ID Age/Gender Malignancy Prior chemotherapy	Case Description	Reviewer Comment
59 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel, bevacizumab, valproic acid	Echocardiogram showed LVEF 45-50%. Patient was treated with diuretics and AE resolved on (b) (6). The AE led to treatment discontinuation. PMH: QT prolongation, intermittent tachycardia Baseline LVEF: 50% End of Treatment LVEF: 45%	
000296 65 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel, pegylated liposomal doxorubicin	On (b) (6) patient experienced dyspnea on exertion and G3 decreased ejection fraction (LVEF 25%). Patient was hospitalized and repeat echocardiogram showed 25-30%. Interventions to treat decreased ejection fraction was not provided. The AE led to treatment discontinuation. Baseline LVEF: 55% End of Treatment LVEF: 25%	
000308 79 M Liposarcoma Doxorubicin, ifosfamide, gemcitabine, docetaxel	On (b) (6), patient experienced G2 atrial flutter and G1 hypotension. Atrial flutter resolved with metoprolol. On (b) (6), patient experienced PE G3, CVA G2. On (b) (6), transthoracic echocardiogram suggested paradoxical emboli as possible cause for CVA. The case narrative did not mention ejection fraction. Baseline LVEF 55% End of Treatment LVEF 45%	
000313 55 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel	On (b) (6), patient experienced G3 dyspnea and G4 cardiac failure (LVEF of 15%). Patient was treated with diuretics and AE was resolving. The AE led to treatment discontinuation. baseline LVEF: 45% post LVEF: 15%	Reviewer is not able to assess the recovery course of cardiomyopathy because no additional follow up information was provided.
000320	Reviewed under Patient Deaths (Table 36).	
000365 56 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel, anastrozole	On (b) (6), patient experience G2 cardiomyopathy (LVEF 36%) and G3 pulmonary hypertension. On (b) (6) patient experienced recurrence of G3 cardiac failure congestive (LVEF 34%). Patient was treated with diuretics. The AE led to treatment discontinuation. Baseline LVEF: 60%	Reviewer is not able to assess the recovery course of cardiomyopathy because no additional follow up information was provided.

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Malignancy Prior chemotherapy	Case Description	Reviewer Comment
	End of Treatment LVEF: 34%	
000456	Reviewed under Patient Deaths (Table 36).	
000522 67 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel	On (b) (6), patient experienced G3 cardiac failure congestive (LVEF 50%). Patient was treated with diuretics, AE is recovering, but persistent upon study discontinuation. The AE led to treatment discontinuation. Baseline LVEF:60% End of Treatment LVEF: 50%	Reviewer is not able to assess the recovery course of cardiomyopathy because no additional follow up information was provided.
000540 61 F Leiomyosarcoma Doxorubicin, ifosfamide	On (b) (6), patient experienced G3 ejection fraction decreased (LVEF 35-40%). AE was reported as improving, but not resolved. The AE led to treatment discontinuation. Baseline LVEF: 55% End of Treatment LVEF 35%	
000565 54 F Leiomyosarcoma, non-uterine Gemcitabine, docetaxel, doxorubicin	On (b) (6), patient experienced G3 atrial fibrillation. Patient was treated with diltiazem and AE resolved (b) (6). No action on study drug was reported. Baseline LVEF: 60% End of Treatment LVEF: 60%	
000593 65 F Leiomyosarcoma Doxorubicin gemcitabine	On (b) (6) patient experienced G3 cardiac failure congestive. Patient was treated with diuretics. AE led to dose reduction from 1.2 to 1mg/m ² . On (b) (6) the patient experienced recurrent G4 cardiac failure acute. The AE lead to treatment discontinuation. Baseline LVEF: 40%	Reviewer notes that patient's abnormal LVEF at screening is a confounding factor in attributing cardiac event to the trabectedin. Per protocol for ET743-SAR-3007, this patient should have been excluded from the study based on unresolved cardiomyopathy. The Applicant was not able to respond adequately to an IR on 8/25/2015 for additional LVEF assessments because the Applicant reports that the data was not captured. A PMR will be issued to characterize the risk of cardiomyopathy and its sequelae.

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Malignancy Prior chemotherapy	Case Description	Reviewer Comment
000606	Reviewed under Patient Deaths (Table 36)..	
000623 71 F Leiomyosarcoma Doxorubicin, gemcitabine, docetaxel, vinorelbine, pegylated liposomal doxorubicin	On (b) (6) the patient experienced G3 cardiac failure congestive, G2 acute renal failure. Echocardiogram was reported to be normal by Investigator. Patient was treated with diuretics. Patient also experienced G1 elevation in bilirubin which led to a treatment discontinuation. Baseline LVEF: 57%	The Applicant was not able to respond adequately to an IR on 8/25/2015 for additional LVEF assessments because the Applicant reports that the data was not captured. A PMR will be issued to characterize the risk of cardiomyopathy and its sequelae.
000676 74 M Leiomyosarcoma gemcitabine, docetaxel, paclitaxel, pegylated liposomal doxorubicin	On (b) (6), patient experienced G2 right ventricular dysfunction. On C4D15, patient had a repeat echocardiogram that demonstrated dilated L ventricle, and concentric LVH. Patient was treated with diuretics. Treatment is ongoing Relevant past medical history: coronary artery disease. Baseline LVEF: 60%	Reviewer notes that attribution of AE of right ventricular dysfunction is confounded by patients pre-existing coronary artery disease and hypertension.

Source: Case Narratives provided in Clinical Study Report ET743-SAR-3007: 120-Day Safety Update.

Of all 98 cardiac-related adverse events in 57 patients in the trabectedin group, investigational product withdrawal was the most common treatment modification (n=12), followed by dose interruption (n=8), and dose reduced (n=3). Investigators reported that 59 of the AE resulted in no action taken on the investigational drug. Among the cardiac-related SAEs, there were 3 recurrences of cardiomyopathy following rechallenge with trabectedin.

Reviewer Comment:

The incidence of recurrent cardiomyopathy after rechallenge with trabectedin cannot be accurately assessed because the protocol for ET743-SAR-3007 did not adequately capture unscheduled LVEF data.

Thirty-seven of 57 patients (65%) had cardiac-related AE reported as Recovered/Resolved. Seven of 57 patients (11%) had cardiac-related AE reported as

Recovering/Resolving. Twenty of 57 patients (35%) had cardiac-related AE reported as Not Recovered/Not Resolved, at the time of the data cut-off.

The protocol for ETS-743-SAR-3007 scheduled assessments of cardiac function once during the Screening Phase of the trial and once at the end of the Treatment Phase of the trial. Routine assessments of cardiac function were not scheduled during the Treatment Phase of the Trial. An Information Request was issued to the Applicant on 8/21/2015 for additional LVEF assessment data, including missing End of Treatment LVEF data and any unscheduled cardiac assessments for acute cardiac events, for 23 patients identified as having a cardiomyopathy-related adverse event by Preferred Term. In the response on 8/25/2015, the Applicant stated that reasons for missing end-of-treatment LVEF assessments were due to withdrawal of consent, refusal for LVEF or study related procedures, decline in medical condition resulting in prolonged hospitalization, hospice admission, or early death, as well as patients still on active treatment. For 13 out of 23 patients The Applicant was able to retrieve additional, unscheduled LVEF assessments that were reported as a comment in the CRF of within the CIOMS reports.

Of the patients in the trabectedin group with a baseline LVEF assessment (n=377), 240 patients had an End-of-Treatment LVEF assessment (Table 39).

Table 39. Change from Baseline for LVEF. ET743-SAR-3007 – Safety Population

Baseline	Baseline n(%)	Grade 0 ¹ n(%)	Grade 2 n(%)	Grade 3 n(%)	Grade 4 n(%)
Trabectedin					
Grade 0	359 (95)	210 (97)	14 (93)	6 (75)	0 (0)
2	14 (4)	6 (3)	1 (7)	2 (25)	1 (100)
3	4 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal	377	216	15	8	1
Dacarbazine					
0	164 (95)	84 (28)	5 (100)	2 (40)	0 (0)
2	8 (5)	2 (1)	0 (0)	3 (60)	0 (0)
Subtotal	172	86	5	5	0
Total	549	302	20	13	1

Source: adeg.xpt (120DSU).

¹ Assessment of severity of decreased ejection fraction based on CTCAE v4.03.

The review of safety included analyses of the ETS-743-;SAR-3007 trial to evaluate potential complications of left ventricular dysfunction including arrhythmias, syncope, and sudden death. The incidence of cardiac arrhythmias was 15% in the trabectedin group and 14% in the dacarbazine group in a search of narrow-based standardized MedDRA query (SMQ) for cardiac arrhythmias (Table 35). Eight patients in the trabectedin group experienced a cardiac arrhythmia SAE, compared to 1 patient in the dacarbazine group. Five patients in the trabectedin group experienced a Grade 4 or 5 AE compared to no patients in the dacarbazine group.

Table 35: Incidence of Cardiac Arrhythmias (Narrow Based Standardized MedDRA Query) by Treatment Group. ET743-SAR-3007 – Safety Population

	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)
Any Cardiac Arrhythmia	45 (12)	22 (13)
Tachycardia	17 (4.5)	7 (4.1)
Sinus tachycardia	10 (2.6)	5 (2.9)
Palpitations	8 (2.1)	8 (4.7)
Atrial fibrillation	4 (1.1)	1 (0.6)
Syncope	4 (1.1)	2 (1.2)
Atrial flutter	3 (0.8)	0 (0)
Cardiac arrest	3 (0.8)	0 (0)
Arrhythmia	2 (0.5)	0 (0)
Heart rate increased	2 (0.5)	1 (0.6)
Electrocardiogram QT prolonged	2 (0.5)	0 (0)
Bradycardia	1 (0.3)	0 (0)
Extrasystoles	1 (0.3)	0 (0)

Source: ae.xpt (120DSU), dm.xpt (120DSU)

Reviewer Comment

Adequate characterization of the risk of cardiac-related events associated with trabectedin exposure could not be performed because of the lack of regular LVEF assessments in ET743-SAR-3007 trial. An Information Request was issued to the Applicant on 8/21/2015 requesting additional data on unscheduled left ventricular assessments, patient narrative summaries. The Applicant was not able to respond adequately to an IR on 8/25/2015 for additional LVEF assessments because the Applicant reports that the data was not captured. Without this data, it is difficult to characterize the cardiac toxicity profile for trabectedin to inform recommendations in the labeling for trabectedin. The reviewers recommend a PMR to characterize the risk of cardiomyopathy and its sequelae. See Section 1.4 of this review.

Neutropenia and Neutropenia-related complications

In the ET-743-SAR-3007, the incidence of neutropenic-related adverse events, as defined by the Applicant based on a composite of MedDRA High Level Group Terms (see Appendix 9.5, Table 67) and concurrent neutropenia of any grade, occurred in 22

(6%) patients in the trabectedin group and in 3 (1.7%) in the dacarbazine group. Table 40 summarizes the incidence of neutropenia-related adverse events.

Table 40. Incidence of Neutropenia-Related Adverse Events. ET743-SAR-3007 – Safety Population

	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)
Any Neutropenia-Related AE	22 (6)	3 (1.7)
Clostridium difficile sepsis	1 (0.3)	0 (0)
Febrile neutropenia	18 (4.8)	3 (1.7)
Sepsis	6 (1.6)	0 (0)
Septic shock	2 (0.5)	0 (0)

Source: ae.xpt (120DSU), dm.xpt (120DSU)

Of the 27 neutropenia-related adverse events in the trabectedin group, dose reduction was the most common treatment modification (n=8), followed by dose interruption (n=4), and investigational product withdrawal (n=1). Investigators reported that 12 of the AE resulted in no action taken on the investigational drug. Four neutropenia-related adverse events were reported as fatal. Twenty-two AEs were reported as Recovered/Resolved, and one AE was reported as Not Recovered/Not Resolved at the time of the data cutoff. Concomitant Medication of colony-stimulating factors (i.e., filgrastim or pegfilgrastim) was reported in 17 patients in the trabectedin group and no patients in the dacarbazine group.

Analysis of the laboratory data provided for ET743-SAR-3007 shows that the incidence of neutropenia defined as neutrophil count below the institutional lower limit of normal was 252 (67%) for the trabectedin group and 83 (48%) dacarbazine group. Grade 3-4 laboratory abnormalities in neutrophil count occurred in 162 (43%) patients in the trabectedin group and 44 (26%) patients in the dacarbazine group. These incidences compare to the investigator-reported AE of neutropenia or neutrophil count decreased of 192 (51%) in the trabectedin group and 54 (31%) in the dacarbazine group. In the trabectedin group, the median time to the first occurrence of Grade 3 or 4 neutropenia was 16 days (range 8-294 days). The median time to complete resolution of neutropenia was 22 days (range 7-152 days).

Reviewer Comment

The review of incidence of neutropenia-related adverse events is based on Investigator-reported events. An Information Request issued on 3 August 2015 for clarification on the definition of neutropenia-related adverse events, such as febrile neutropenia. Applicant responded that adverse event of febrile neutropenia was reported by the Investigator and that diagnoses were reported in place of signs and symptoms. Vital signs (i.e., body temperature and blood pressure) were not captured in the eCRF during

the Treatment Phase of ET743-SAR-3007 in order to support the diagnosis of febrile neutropenia or sepsis or to identify additional cases that may have not been reported by the Investigator.

Rhabdomyolysis

Overall, in the ET743-SAR-3007 trial, four patients experienced rhabdomyolysis as reported by the Investigator, all of whom were in the trabectedin group. Two cases were Grade 5 in severity, and two were Grade 4. The median time to onset is 40 days after first exposure to trabectedin (range: 34-63 days). In two of the non-fatal cases, the outcome of the rhabdomyolysis was reported as recovered/resolved and recovered/resolved with sequelae. Both patients were treated with hemodialysis. One patient (Subject ID 000106) had trabectedin discontinued as a result of rhabdomyolysis, and the other (Subject ID 000513) died during the same hospitalization from respiratory failure.

In the ET743-SAR-3007 trial, 193 patients experienced a rhabdomyolysis-related event, as defined by the Applicant based on a composite of preferred terms (see Appendix 9.5, Table 68), 160 (42%) in the trabectedin group and 33 (19%) in the dacarbazine group. Of these, 22 patients experienced a rhabdomyolysis-related SAE; 21 in the trabectedin group and 1 in the dacarbazine group. Table 39 summarizes the case narratives provided for these patients.

Table 41. Summary of Selected Case Narratives of Rhabdomyolysis-Related SAE. ET743-SAR-3007 – Safety Population

Subject ID Age/Gender Malignancy Prior chemotherapy	Case Description	Reviewer Comment
000036 54 M Leiomyosarcoma Doxorubicin, ifosfamide gemcitabine, docetaxel, liposomal docetaxel	On (b) (6), patient experienced recurrent CPK increases with resolution. Renal function was not consistent elevated at the same time as CPK. On (b) (6) patient experienced recurrent G3 CPK increased G3, G2 myositis, G1 myoglobinuria. Increased CPK resolved on (b) (6) AE led to withdrawal of trabectedin was withdrawn.	
000096	Reviewed under Patient Deaths (Table 36).	
000106 42 F Leiomyosarcoma	On (b) (6) patient experienced CPK increase G4, acute renal failure G4, rhabdomyolysis G4. Patient was treated with dialysis. CPK increase and rhabdomyolysis	

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Subject ID Age/Gender Malignancy Prior chemotherapy	Case Description	Reviewer Comment
Doxorubicin, ifosfamide, gemcitabine, docetaxel	resolved on (b) (6). AE of acute renal failure was not resolved. Treatment was discontinued.	
000177 57 F Leiomyosarcoma Doxorubicin, palifosfamide, gemcitabine, docetaxel	On (b) (6) patient experienced CPK increase G4 (CK 3134) and musculoskeletal pain (G1). Trabectedin was discontinued. AE resolved on (b) (6)	
000223	Reviewed under Patient Deaths (Table 36).	
000332	Reviewed under Patient Deaths (Table 36).	
000357	Reviewed under Patient Deaths (Table 36).	
000513 69 M Liposarcoma Doxorubicin, ifosfamide	On (b) (6) patient developed rhabdomyolysis G4 (CK 4155) in the setting of progressively worsening respiratory failure. On (b) (6), subject died from G5 respiratory failure.	
000623	Reviewed under Cardiac-Related SAEs (Table 38).	
000676	Reviewed under Cardiac-Related SAEs (Table 38).	
000685 77F Leiomyosarcoma Doxorubicin, gemcitabine	On (b) (6) patient experience elevated CPK G3, muscle weakness G3. On (b) (6), CPK level increased to 13,210 G4. Patient underwent dialysis. On (b) (6), patient developed atrial fibrillation with RVR and treated with metoprolol. Patient was transitioned to hospice care and on died on (b) (6) due to rhabdomyolysis. PMH: hyperlipidemia on pravastatin	Attribution o rhabdomyolysis to trabectedin is confounded by concurrent use of pravastatin.

Source: Case Narratives provided in Clinical Study Report ET743-SAR-3007: 120-Day Safety Update.

<i>Reviewer Comment</i>

The review of rhabdomyolysis as an adverse event of trabectedin was confounded by several factors, including use of concomitant medications at baseline which are associated with rhabdomyolysis and other concurrent SAEs. Causality of elevated CPK to trabectedin is supported by positive rechallenges cases and the higher incidence of rhabdomyolysis-related AE and elevation CPK in the trabectedin group compared to the dacarbazine.

7.3.2 Nonfatal Serious Adverse Events

In the ET743-SAR-3007 trial, non-fatal SAEs occurred in 148 (39%) of trabectedin-treated patients and 50 (29%) of dacarbazine-treated patients. The most frequent ($\geq 2\%$) non-fatal SAEs in the trabectedin group were nausea, vomiting, dyspnea, febrile neutropenia, pyrexia, dehydration, and acute renal failure. In the ISS, non-fatal SAE's occurred in 248 (33%) of patients. The most common ($\geq 2\%$) non-fatal SAEs were nausea, vomiting, abdominal pain, dyspnea, pyrexia, anemia, and dehydration. Table 42 summarizes the non-fatal SAEs that occurred in two or more patients in the trabectedin group. Corresponding incidences of non-fatal SAEs in the dacarbazine group of ET743-SAR-3007 trial and the ISS database are summarized as well.

Table 42. Incidence of Non-Fatal Serious Adverse Event (Occurring in ≥ 2 Trabectedin-Treated Patient) by Preferred Term. ET743-SAR-3007 – Safety Population and ISS Population

System Organ Class Preferred Term	ET734-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Gastrointestinal disorders	58 (15)	19 (11)	85 (11)
Nausea	16 (4.2)	3 (1.7)	23 (3)
Vomiting	16 (4.2)	3 (1.7)	25 (3.3)
Abdominal pain	14 (3.7)	8 (4.7)	23 (3)
Small intestinal obstruction	10 (2.6)	4 (2.3)	15 (2)
Diarrhea	4 (1.1)	0 (0)	6 (0.8)
Intestinal obstruction	3 (0.8)	0 (0)	7 (0.9)
Pancreatitis	3 (0.8)	0 (0)	3 (0.4)
Abdominal pain lower	2 (0.5)	1 (0.6)	2 (0.3)
Ascites	2 (0.5)	0 (0)	3 (0.4)
Colitis	2 (0.5)	0 (0)	2 (0.3)
Constipation	2 (0.5)	1 (0.6)	6 (0.8)
Dysphagia	2 (0.5)	0 (0)	2 (0.3)
Gastrointestinal hemorrhage	2 (0.5)	0 (0)	3 (0.4)
Infections and infestations	38 (10)	8 (4.7)	55 (7)
Catheter site infection	8 (2.1)	1 (0.6)	8 (1.1)
Urinary tract infection	7 (1.9)	2 (1.2)	7 (0.9)
Pneumonia	6 (1.6)	0 (0)	12 (1.6)
Sepsis	6 (1.6)	0 (0)	7 (0.9)

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

System Organ Class Preferred Term	ET734-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Bacteremia	3 (0.8)	0 (0)	4 (0.5)
Cellulitis	2 (0.5)	0 (0)	2 (0.3)
Lung infection	2 (0.5)	0 (0)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	35 (9)	7 (4.1)	54 (7)
Dyspnea	13 (3.4)	2 (1.2)	21 (2.8)
Pulmonary embolism	7 (1.9)	1 (0.6)	10 (1.3)
Pleural effusion	4 (1.1)	3 (1.7)	6 (0.8)
Pulmonary edema	3 (0.8)	0 (0)	4 (0.5)
Cough	2 (0.5)	0 (0)	2 (0.3)
Hemoptysis	2 (0.5)	0 (0)	2 (0.3)
Hypoxia	2 (0.5)	0 (0)	4 (0.5)
Pulmonary hypertension	2 (0.5)	0 (0)	4 (0.5)
Respiratory failure	2 (0.5)	0 (0)	4 (0.5)
Blood and lymphatic system disorders	34 (9)	8 (4.7)	44 (6)
Anemia	16 (4.2)	4 (2.3)	18 (2.4)
Febrile neutropenia	12 (3.2)	2 (1.2)	12 (1.6)
Neutropenia	9 (2.4)	1 (0.6)	14 (1.8)
Thrombocytopenia	7 (1.9)	3 (1.7)	10 (1.3)
Leukopenia	4 (1.1)	3 (1.7)	4 (0.5)
Leukocytosis	3 (0.8)	0 (0)	3 (0.4)
General disorders and administration site conditions	32 (8)	6 (3.5)	53 (7)
Pyrexia	12 (3.2)	2 (1.2)	23 (3)
Asthenia	5 (1.3)	0 (0)	5 (0.7)
Fatigue	4 (1.1)	1 (0.6)	5 (0.7)
Infusion site extravasation	2 (0.5)	0 (0)	2 (0.3)
Edema peripheral	2 (0.5)	1 (0.6)	3 (0.4)
Pain	2 (0.5)	1 (0.6)	5 (0.7)
Metabolism and nutrition disorders	24 (6)	6 (3.5)	28 (3.7)
Dehydration	15 (4)	3 (1.7)	17 (2.2)
Decreased appetite	3 (0.8)	1 (0.6)	3 (0.4)
Failure to thrive	2 (0.5)	0 (0)	2 (0.3)
Investigations	23 (6)	4 (2.3)	29 (3.8)
Ejection fraction decreased	5 (1.3)	0 (0)	5 (0.7)
Blood creatine phosphokinase increased	4 (1.1)	0 (0)	4 (0.5)
Blood creatinine increased	4 (1.1)	0 (0)	6 (0.8)
Neutrophil count decreased	4 (1.1)	1 (0.6)	4 (0.5)
Platelet count decreased	4 (1.1)	2 (1.2)	4 (0.5)
Aspartate aminotransferase increased	3 (0.8)	0 (0)	5 (0.7)
Alanine aminotransferase increased	2 (0.5)	0 (0)	4 (0.5)
International normalized ratio increased	2 (0.5)	0 (0)	2 (0.3)

System Organ Class Preferred Term	ET734-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Liver function test abnormal	2 (0.5)	0 (0)	3 (0.4)
Transaminases increased	2 (0.5)	0 (0)	2 (0.3)
Troponin I increased	2 (0.5)	0 (0)	2 (0.3)
White blood cell count decreased	2 (0.5)	0 (0)	2 (0.3)
Renal and urinary disorders	20 (5)	2 (1.2)	27 (3.6)
Renal failure acute	11 (2.9)	1 (0.6)	14 (1.8)
Hydronephrosis	2 (0.5)	1 (0.6)	2 (0.3)
Obstructive uropathy	2 (0.5)	0 (0)	2 (0.3)
Urinary retention	2 (0.5)	0 (0)	2 (0.3)
Cardiac disorders	16 (4.2)	1 (0.6)	23 (3)
Cardiac failure congestive	7 (1.9)	0 (0)	8 (1.1)
Atrial fibrillation	2 (0.5)	1 (0.6)	4 (0.5)
Cardiac failure	2 (0.5)	0 (0)	3 (0.4)
Cardiomyopathy	2 (0.5)	0 (0)	3 (0.4)
Musculoskeletal and connective tissue disorders	13 (3.4)	5 (2.9)	21 (2.8)
Back pain	3 (0.8)	2 (1.2)	6 (0.8)
Rhabdomyolysis	3 (0.8)	0 (0)	6 (0.8)
Pain in extremity	2 (0.5)	2 (1.2)	3 (0.4)
Nervous system disorders	10 (2.6)	6 (3.5)	13 (1.7)
Syncope	3 (0.8)	2 (1.2)	4 (0.5)
Cerebrovascular accident	2 (0.5)	0 (0)	2 (0.3)
Vascular disorders	9 (2.4)	3 (1.7)	22 (2.9)
Deep vein thrombosis	3 (0.8)	1 (0.6)	10 (1.3)
Hypotension	3 (0.8)	1 (0.6)	4 (0.5)
Injury, poisoning and procedural complications	6 (1.6)	0 (0)	7 (0.9)
Fall	2 (0.5)	0 (0)	2 (0.3)
Psychiatric disorders	4 (1.1)	0 (0)	5 (0.7)
Confusional state	3 (0.8)	0 (0)	3 (0.4)
Reproductive system and breast disorders	3 (0.8)	1 (0.6)	3 (0.4)
Pelvic pain	2 (0.5)	0 (0)	2 (0.3)

Source: adae.xpt (120DSU), adae.xpt (ISS120DSU).

The review of safety included further analyses of the following SAEs to identify adverse reactions of trabectedin:

- Dyspnea
- Renal failure
- Thrombocytopenia
- Multi-organ failure

Dyspnea and Respiratory-related complications

Dyspnea and related AEs, including preferred terms: dyspnea, dyspnea exertional, respiratory arrest, respiratory distress, acute respiratory failure, and respiratory failure, occurred in 122 patients (32%) in the trabectedin group and 37 patients (22%) in the dacarbazine group. Grade 3-5 dyspnea-related AE, occurred in 28 (7%) patients in the trabectedin group and 4 (2.3%) patients in the dacarbazine group (Table 43). In the trabectedin group, four AE's lead to investigational product withdrawal, two AEs led to dose interruption, and one AE led to dose reduction.

Table 43. Incidence of Dyspnea and Dyspnea-Related Adverse Events. ET743-SAR-3007 – Safety Population

	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grade 3-5 n(%)	All Grades n(%)	Grade 3-5 n(%)
Any Dyspnea	122 (32)	27 (7)	37 (22)	4 (1.7)
Dyspnea	94 (25)	16 (4.2)	35 (20)	2 (1.2)
Dyspnea exertional	27 (7)	2 (0.5)	4 (2.3)	0 (0)
Respiratory failure	6 (1.6)	6 (1.6)	2 (1.2)	2 (1.2)
Acute respiratory failure	2 (0.5)	2 (0.5)	0 (0)	0 (0)
Respiratory arrest	1 (0.3)	1 (0.3)	0 (0)	0 (0)
Respiratory distress	1 (0.3)	1 (0.3)	0 (0)	0 (0)

Source: ae.xpt (120DSU), dm.xpt (120DSU)

All SAE occurred in the trabectedin group (22 patients). Review of the case narratives for these patients, showed that dyspnea and related AE had concurrent conditions that provided alternate explanation:

- Progressive disease (7)
- Infection (3)
- Heart failure (3)
- PE (2)
- Pancreatitis (1)
- Post-operative complication (1)
- Anemia (1)
- Unexplained, but resolved in 1 day with supportive care

Reviewer Comment

FDA Clinical Review or respiratory-related events could not establish causality with trabectedin. However, the higher incidence of SAE and serious AE related to dyspnea and other related adverse events is higher in the trabectedin group. Review of case

narratives provided alternative explanations for all AE's except for one case of G3 dyspnea which resolved in 1 day with only supportive care.

Renal Failure

In the ET-743-SAR-3007 trial, the incidence of renal failure and renal-related adverse events, as defined by the Applicant based on a composite of MedDRA Preferred Terms (see Appendix 9.5, Table 70), occurred in 69 (18%) patients in the trabectedin group and in 9 (5%) in the dacarbazine group. Table 44 summarizes the incidence of renal-related adverse events.

Table 44. Incidence of Renal Failure and Renal-Related Adverse Events. ET743-SAR-3007 – Safety Population

	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grade 3-5 n(%)	All Grades n(%)	Grade 3-5 n(%)
Any Renal-Related AE	57 (15)	15 (4)	8 (4.7)	1 (0.6)
Blood creatinine increased	48 (13)	8 (2.1)	3 (1.7)	0 (0)
Renal failure acute	15 (4)	10 (2.6)	4 (2.3)	1 (0.6)
Blood urea increased	2 (0.5)	(0)	0 (0)	(0)
Renal failure	2 (0.5)	2 (0.5)	2 (1.2)	0 (0)
Creatinine urine increased	1 (0.3)	(0)	0 (0)	(0)
Renal tubular necrosis	1 (0.3)	1 (0.3)	0 (0)	0 (0)

Source: ae.xpt (120DSU), dm.xpt (120DSU)

Thrombocytopenia and Bleeding-Related Adverse Events

In the ET-743-SAR-3007, the incidence of bleeding-related adverse events, as defined by the Applicant based on a composite of MedDRA Preferred Terms (see Appendix 9.5, Table 71), occurred in 11 (2.9%) patients in the trabectedin group and in 9 (4.1%) in the dacarbazine group. All three cases of bleeding-related SAE occurred in the trabectedin group: One case led to discontinuation, and two cases did not result in dose modification..

The incidence of thrombocytopenia, including preferred terms thrombocytopenia and platelet count decreased, occurred in 124 (33%) patients in the trabectedin group and 60 (35%) patients in the dacarbazine group. Grade 3-4 thrombocytopenia occurred in 78 (21%) patients in the trabectedin group and 34 (20%) in the dacarbazine group.

Reviewer Comment

Review of thrombocytopenia and bleeding-related AE showed comparable incidences in both groups.

Multi-Organ Failure

In the ET-743-SAR-3007 trial, the incidence of multi-organ failure related-AE, as defined by the Applicant based on a composite of MedDRA Preferred Terms (see Appendix 9.5, Table 72), occurred in 32 (8%) patients in the trabectedin group and in 8 (4.6%) in the dacarbazine group. Multi-organ Failure-related SAE occurred in 27 (7%) patients the trabectedin group and 3 (1.7%) patients in the dacarbazine group. Fatal AE occurred in 9 (2.3%) patients in the trabectedin group and 2 (1.2%) patients in the dacarbazine group (Table 45). The most common fatal AE were respiratory failure.

Table 45. Incidence of Multi-Organ Failure-Related Adverse Events. ET743-SAR-3007 – Safety Population

	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grade 3-5 n(%)	All Grades n(%)	Grade 3-5 n(%)
Any Multi-Organ Related AE	32 (8)	29 (8)	8 (4.7)	4 (2.3)
Renal failure acute	15 (4)	10 (2.6)	4 (2.3)	1 (0.6)
Cardiac failure congestive	8 (2.1)	8 (2.1)	1 (0.6)	0 (0)
Respiratory failure	6 (1.6)	6 (1.6)	2 (1.2)	2 (1.2)
Acute respiratory failure	2 (0.5)	2 (0.5)	0 (0)	0 (0)
Cardiac failure	2 (0.5)	2 (0.5)	0 (0)	0 (0)
Multi-organ failure	2 (0.5)	2 (0.5)	0 (0)	0 (0)
Renal failure	2 (0.5)	2 (0.5)	2 (1.2)	0 (0)
Cardiac failure acute	1 (0.3)	1 (0.3)	0 (0)	0 (0)
Diastolic dysfunction	1 (0.3)	1 (0.3)	0 (0)	0 (0)
Respiratory distress	1 (0.3)	1 (0.3)	0 (0)	0 (0)
Circulatory collapse	0 (0)	0 (0)	1 (0.6)	1 (0.6)

Source: ae.xpt (120DSU), dm.xpt (120DSU)

7.3.3 Dropouts and/or Discontinuations

In the ET743-SAR-3007 trial, 359 (95%) patients in the trabectedin group and 166 (97%) patients in the dacarbazine group discontinued investigational drug product at the time of data cutoff for the 120-Day Safety Update as summarized in Table 46. The most common reason for discontinuing treatment was progressive disease which occurred in 262 (69%) patients in the trabectedin group and 136 (79%) in the dacarbazine group. The incidence of treatment discontinuation for an adverse event was 17% (64 patients) in the trabectedin group and 7% (12 patients) in the dacarbazine group.

Table 46. Reason for Treatment Discontinuations. ET743-SAR-3007 – Safety Population

Reason for Treatment Discontinuation	Trabectedin (n=378) n(%)	Dacarbazine (N=172) n(%)
Adverse Event	64 (17)	12 (7)
Death	10 (2.6)	1 (0.6)
Other	3 (0.8)	3 (1.7)
Physician Decision	1 (0.3)	2 (1.2)
Subject Has Disease Progression	262 (69)	136 (79)
Subsequent Anticancer Therapy	1 (0.3)	0 (0)
The Subject Withdraws Consent	18 (4.8)	12 (7)

Source: adds.xpt (120DSU)

Table 47 summarizes the rate of treatment modifications (i.e., discontinuations, delays, and dose reductions) because of AEs in the ET743-SAR-3007 trial. Treatment modifications as a result of AEs occurred more frequently in the trabectedin group than in the dacarbazine group, 73% (276 patients) vs. 55% (95 patients), respectively.

Table 47. Frequency of Adverse Events Leading to Treatment Modification. ET743-SAR-3007 – Safety Population

Treatment Modification	Trabectedin (n=378) n(%)	Dacarbazine (N=172) n(%)
Any Treatment Modification	276 (73%)	95(55%)
Dose Reduced	158 (42)	21 (12)
Drug Interrupted	198 (52)	66 (38)
Drug Withdrawn	98 (26)	37 (22)

Source: adae.xpt (120DSU)

Treatment discontinuation due to AEs occurred in 98 patients (26%) in the trabectedin group, compared to 37 patients (22%) in the dacarbazine group (Table 48).

Table 48. Incidence of Adverse Events Leading to Treatment Discontinuation (Occurring in ≥2 Trabectedin-Treated Patient) by Preferred Term. ET743-SAR-3007 – Safety Population and ISS

System Organ Class Preferred Term	ET743-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Investigations	35 (9)	2 (1.2)	42 (6)
Blood alkaline phosphatase increased	11 (2.9)	0 (0)	14 (1.8)
Alanine aminotransferase increased	6 (1.6)	0 (0)	10 (1.3)
Blood bilirubin increased	4 (1.1)	1 (0.6)	4 (0.5)
Blood creatine phosphokinase increased	4 (1.1)	0 (0)	4 (0.5)
Ejection fraction decreased	4 (1.1)	0 (0)	4 (0.5)
Neutrophil count decreased	3 (0.8)	0 (0)	4 (0.5)
Platelet count decreased	3 (0.8)	0 (0)	3 (0.4)
Gastrointestinal disorders	15 (4)	10 (6)	18 (2.4)
Small intestinal obstruction	4 (1.1)	1 (0.6)	5 (0.7)
Abdominal pain	2 (0.5)	3 (1.7)	3 (0.4)
Nausea	2 (0.5)	0 (0)	2 (0.3)
Blood and lymphatic system disorders	13 (3.4)	6 (3.5)	20 (2.6)
Thrombocytopenia	10 (2.6)	3 (1.7)	14 (1.8)
Neutropenia	2 (0.5)	3 (1.7)	9 (1.2)
General disorders and administration site conditions	10 (2.6)	5 (2.9)	15 (2)
Fatigue	6 (1.6)	2 (1.2)	7 (0.9)
Musculoskeletal and connective tissue disorders	10 (2.6)	4 (2.3)	13 (1.7)
Arthralgia	2 (0.5)	1 (0.6)	2 (0.3)
Rhabdomyolysis	2 (0.5)	0 (0)	4 (0.5)
Cardiac disorders	7 (1.9)	1 (0.6)	11 (1.5)
Cardiac failure	2 (0.5)	0 (0)	2 (0.3)
Cardiac failure congestive	2 (0.5)	0 (0)	2 (0.3)
Renal and urinary disorders	5 (1.3)	4 (2.3)	8 (1.1)
Renal failure acute	2 (0.5)	2 (1.2)	4 (0.5)
Respiratory, thoracic and mediastinal disorders	5 (1.3)	4 (2.3)	8 (1.1)
Respiratory failure	2 (0.5)	1 (0.6)	3 (0.4)
Metabolism and nutrition disorders	4 (1.1)	1 (0.6)	5 (0.7)
Failure to thrive	3 (0.8)	0 (0)	3 (0.4)

Source: adae.xpt (120DSU), adae.xpt (ISS120DSU)

Reviewer Comment

In the review of the ISS database (N=755 patients), there were 18,976 adverse events. The action taken with study drug data was missing for 1697 AE or classified as not applicable for 350 events. Taken together, these 2047 AEs represent 222 patients

from 4 studies, ETSAR3007, ET-B-005, ET-B-008S, and ET-B-028. These missing data will make interpreting AE leading to treatment modification difficult. Therefore, the review will focus on ET743-SAR-3007 trial.

The review of AE's leading to discontinuation of trabectedin included further analyses of the following:

- Hepatotoxicity

Hepatotoxicity

In ET743-SAR-3007, the incidence of liver-injury-related adverse events, as defined by the Applicant based on a composite of preferred terms (Appendix 9.5, see Table 69), in the trabectedin group was 60% (225 patients) compared to the dacarbazine group 20% (34 patients). The most frequent liver injury-related AEs in the trabectedin group were increased ALT (49%) and increased AST (38%) as summarized in Table 49. The incidence of Grade 3-4 liver injury-related adverse events in the trabectedin group was 30% (113 patients), compared to the dacarbazine group 3.5% (6 patients). There were no Grade 5 AEs in either group. Liver injury-related SAEs occurred in eight patients in the trabectedin group and one patient in the dacarbazine group.

Table 49. Incidence of Liver Injury-Related Adverse Events. ET743-SAR-3007 – Safety Population

	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grade 3-4 n(%)	All Grades n(%)	Grade 3-4 n(%)
Any Liver Injury Related AE	225 (60)	113 (30)	34 (20)	6 (3.5)
Alanine aminotransferase increased	186 (49)	111 (29)	12 (7)	1 (0.6)
Aspartate aminotransferase increased	142 (38)	57 (15)	10 (6)	0 (0)
Blood alkaline phosphatase increased	85 (22)	6 (1.6)	15 (9)	1 (0.6)
Blood bilirubin increased	34 (9)	5 (1.3)	5 (2.9)	1 (0.6)
Hypoalbuminemia	31 (8)	7 (1.9)	7 (4.1)	2 (1.2)
Gamma-glutamyltransferase increased	8 (2.1)	6 (1.6)	1 (0.6)	1 (0.6)
Ascites	6 (1.6)	4 (1.1)	4 (2.3)	1 (0.6)

	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grade 3-4 n(%)	All Grades n(%)	Grade 3-4 n(%)
Blood cholesterol increased	4 (1.1)	(0)	0 (0)	(0)
Transaminases increased	4 (1.1)	3 (0.8)	0 (0)	0 (0)
Alanine aminotransferase decreased	1 (0.3)	(0)	0 (0)	(0)
Aspartate aminotransferase decreased	1 (0.3)	(0)	0 (0)	(0)
Hepatic pain	1 (0.3)	(0)	0 (0)	(0)
Hepatotoxicity	1 (0.3)	1 (0.3)	0 (0)	0 (0)
5'nucleotidase increased	0 (0)	(0)	1 (0.6)	(0)
Hyperbilirubinemia	0 (0)	0 (0)	1 (0.6)	1 (0.6)

Source: ae.xpt (120DSU), dm.xpt (120DSU)

The median time to onset of first liver injury-related adverse event in the trabectedin group was 8 days (range 1-351 days) and in the dacarbazine group was 22.5 days (range 1-206 days). The median duration of all hepatic AEs that recovered was 8 days (range 1-183 days) in trabectedin group and 10 days (range 2-56 days) in the dacarbazine group.

Table 50 summarizes the frequency of liver injury-related adverse events that led to a treatment modification. Laboratory abnormalities related to liver enzyme elevations occurred more frequently in the trabectedin group than in the dacarbazine group as summarized in Table 52. Review of the laboratory data in the trabectedin group identified five potential Hy's Law cases. Further review of case narratives, found alternative explanations for laboratory abnormalities (Table 51).

Table 50. Frequency of Liver Injury-Related Adverse Events Leading to Treatment Modification. ET743-SAR-3007 – Safety Population

Treatment Modification	Trabectedin (n=378) n(%)	Dacarbazine (N=172) n(%)
No Modification	190 (50)	25 (15)
Dose Reduced	93 (25)	3 (1.7)
Drug Interrupted	22 (6)	5 (2.9)
Drug Withdrawn	21 (6)	4 (2.3)

Source: adae.xpt (120DSU)

Table 51. Summary of Case Narratives of that Met Hy's Law. ET743-SAR-3007 – Safety Population

Subject ID Age/Gender Malignancy Prior chemotherapy	Case Description	Reviewer Comment
000073	Reviewed under Patient Deaths (Table 36).	
000332	Reviewed under Patient Deaths (Table 36).	
000371	Reviewed under Patient Deaths (Table 36).	
000456	Reviewed under Patient Deaths (Table 36).	
000602 65M liposarcoma, pleomorphic gemcitabine, docetaxel, doxorubicin	On (b) (6) patient experience renal failure acute G3, hypotension G3. Patient was hospitalized and treated with crystalloid volume expansion. AE resolved on (b) (6) On (b) (6) patient also developed laboratory abnormalities consistent with drug-induced liver injury. Patient withdrew consent from study on C2D2. Baseline LVEF: 39%	Attribution of elevated liver function tests to possible drug-induced liver injury is confounded by other acute medical problems including renal failure, hypotension. In addition the quick resolution of LFT abnormalities is inconsistent with liver injury.

Source: Case Narratives provided in Clinical Study Report ET743-SAR-3007: 120-Day Safety Update.

Table 52. Incidence of Liver Enzyme Elevations (All Grades and Grade 3-4). ET743-SAR-3007 – Safety Population.

Elevation in Laboratory Value	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grade 3-4 n(%)	All Grades n(%)	Grade 3-4 n(%)
Alkaline Phosphatase	265 (70)	6 (1.6)	101 (59)	1 (0.6)
Alanine Aminotransferase	341 (90)	119 (31)	55 (32)	1 (0.6)
Aspartate Aminotransferase	318 (84)	63 (17)	54 (31)	2 (1.2)
Total Bilirubin	49 (13)	7 (1.9)	8 (4.7)	1 (0.6)

Source: adlb.xpt (120DSU)

Reviewer Comment

The Applicant identified 5 potential Hy's Law cases by laboratory abnormalities in patients on the trabectedin group. Analysis of laboratory data identified four additional patients in the trabectedin group whose LFT elevations met the criteria for drug-induced liver injury based on peak values of ALT, AST, bilirubin and alkaline phosphatase at any time during the Treatment Phase of the trial.

Review of these cases did not present a clinical picture of drug-induced liver injury. Many of the cases had multiple acute medical issues that may confound attribution. Other cases resolved with supportive care which is also not consistent clinically.

7.3.4 Significant Adverse Events

Grade 3 and 4 Adverse Events

Overall, in ET743-SAR-3007, treatment-emergent adverse events (TEAE) occurred in 377 (100%) patients in the trabectedin group and in 170 (99%) patients in the dacarbazine group. Grade 3 or 4 TEAE occurred in 305 (81%) patients in the trabectedin group and 95 (55%) patients in the dacarbazine group (Table 53). The most common Grade 3 or 4 TEAEs ($\geq 10\%$) in the trabectedin group were elevated liver function tests, neutropenia, and anemia. In general, most TEAEs occurring in the trabectedin treatment group were Grade 3 in severity.

Table 53. Incidence of Grade 3 & 4 AE in ≥ 3 Patients. ET743-SAR-3007 – Safety Population

System Organ Class Preferred Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	Grade 3 n(%)	Grades 4 n(%)	Grade 3 n(%)	Grade 4 n(%)
Investigations	199 (52.6)	58 (15.3)	34 (19.8)	12 (7)
Alanine aminotransferase increased	111 (29.4)	6 (1.6)	1 (0.6)	0 (0)
White blood cell count decreased	70 (18.5)	16 (4.2)	15 (8.7)	3 (1.7)
Neutrophil count decreased	65 (17.2)	32 (8.5)	15 (8.7)	8 (4.7)
Aspartate aminotransferase increased	56 (14.8)	4 (1.1)	0 (0)	0 (0)
Platelet count decreased	35 (9.3)	17 (4.5)	13 (7.6)	7 (4.1)
Blood creatine phosphokinase increased	16 (4.2)	12 (3.2)	1 (0.6)	0 (0)
Lymphocyte count decreased	9 (2.4)	1 (0.3)	1 (0.6)	0 (0)
Blood creatinine increased	8 (2.1)	3 (0.8)	0 (0)	0 (0)
Blood alkaline phosphatase increased	6 (1.6)	(0)	1 (0.6)	(0)
Ejection fraction decreased	6 (1.6)	3 (0.8)	2 (1.2)	0 (0)

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

System Organ Class Preferred Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	Grade 3 n(%)	Grades 4 n(%)	Grade 3 n(%)	Grade 4 n(%)
Gamma-glutamyl transferase increased	6 (1.6)	1 (0.3)	1 (0.6)	0 (0)
Blood bilirubin increased	5 (1.3)	(0)	1 (0.6)	(0)
Blood and lymphatic system disorders	134 (35.4)	55 (14.6)	43 (25)	17 (9.9)
Neutropenia	72 (19)	42 (11.1)	16 (9.3)	11 (6.4)
Anemia	66 (17.5)	1 (0.3)	20 (11.6)	1 (0.6)
Thrombocytopenia	35 (9.3)	25 (6.6)	13 (7.6)	10 (5.8)
Leukopenia	31 (8.2)	11 (2.9)	9 (5.2)	2 (1.2)
Febrile neutropenia	17 (4.5)	1 (0.3)	3 (1.7)	0 (0)
Lymphopenia	6 (1.6)	(0)	0 (0)	(0)
Gastrointestinal disorders	67 (17.7)	1 (0.3)	22 (12.8)	2 (1.2)
Nausea	26 (6.9)	(0)	3 (1.7)	(0)
Vomiting	22 (5.8)	(0)	2 (1.2)	(0)
Abdominal pain	16 (4.2)	(0)	10 (5.8)	(0)
Diarrhea	6 (1.6)	(0)	0 (0)	(0)
Small intestinal obstruction	6 (1.6)	1 (0.3)	2 (1.2)	1 (0.6)
Ascites	4 (1.1)	(0)	1 (0.6)	(0)
Metabolism and nutrition disorders	58 (15.3)	12 (3.2)	14 (8.1)	3 (1.7)
Dehydration	18 (4.8)	(0)	5 (2.9)	(0)
Hypokalemia	12 (3.2)	3 (0.8)	2 (1.2)	0 (0)
Hyponatremia	10 (2.6)	(0)	5 (2.9)	(0)
Hyperglycemia	8 (2.1)	3 (0.8)	1 (0.6)	0 (0)
Decreased appetite	7 (1.9)	0 (0)	1 (0.6)	1 (0.6)
Hypoalbuminemia	6 (1.6)	1 (0.3)	2 (1.2)	0 (0)
Hypophosphatemia	6 (1.6)	(0)	0 (0)	(0)
General disorders and administration site conditions	56 (14.8)	1 (0.3)	10 (5.8)	1 (0.6)
Fatigue	31 (8.2)	0 (0)	3 (1.7)	1 (0.6)
Asthenia	7 (1.9)	(0)	0 (0)	(0)
Infections and infestations	42 (11.1)	7 (1.9)	6 (3.5)	1 (0.6)
Catheter site infection	10 (2.6)	(0)	1 (0.6)	(0)
Urinary tract infection	8 (2.1)	(0)	2 (1.2)	(0)
Pneumonia	7 (1.9)	(0)	0 (0)	(0)
Cellulitis	4 (1.1)	(0)	0 (0)	(0)
Sepsis	2 (0.5)	6 (1.6)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders	34 (9)	6 (1.6)	7 (4.1)	2 (1.2)
Dyspnea	15 (4)	1 (0.3)	2 (1.2)	0 (0)
Pulmonary embolism	11 (2.9)	2 (0.5)	2 (1.2)	0 (0)
Vascular disorders	20 (5.3)	3 (0.8)	3 (1.7)	0 (0)

System Organ Class Preferred Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	Grade 3 n(%)	Grades 4 n(%)	Grade 3 n(%)	Grade 4 n(%)
Hypertension	10 (2.6)	(0)	0 (0)	(0)
Hypotension	5 (1.3)	3 (0.8)	2 (1.2)	0 (0)
Musculoskeletal and connective tissue disorders	19 (5)	3 (0.8)	12 (7)	0 (0)
Pain in extremity	5 (1.3)	(0)	4 (2.3)	(0)
Back pain	4 (1.1)	(0)	4 (2.3)	(0)
Soft tissue necrosis	4 (1.1)	(0)	0 (0)	(0)
Cardiac disorders	16 (4.2)	3 (0.8)	3 (1.7)	0 (0)
Cardiac failure congestive	8 (2.1)	(0)	0 (0)	(0)
Renal and urinary disorders	11 (2.9)	7 (1.9)	3 (1.7)	0 (0)
Renal failure acute	3 (0.8)	5 (1.3)	1 (0.6)	0 (0)
Nervous system disorders	9 (2.4)	1 (0.3)	6 (3.5)	0 (0)
Syncope	4 (1.1)	(0)	2 (1.2)	(0)

Source: ae.xpt (120DSU), dm.xpt (120DSU)

Adverse Events Leading to Dose Reductions

In the ET743-SAR-3007 trial, adverse events leading to dose reductions occurred in 158 (42%) patients in the trabectedin group and 21 (12%) patients in the dacarbazine group. The most common AEs (≥5%) leading to dose reductions of trabectedin are elevated liver function tests and neutropenia. In the ISS database, adverse events leading to dose reductions occurred in 239 (32%) patients. The most common AEs (≥5%) leading to dose reductions of trabectedin are elevated liver function tests. Table 54 summarizes the AEs leading to dose reduction in two or more patients in the trabectedin group for the ET743-SAR-3007 trial and the ISS.

Table 54. Incidence of Adverse Events Leading to Dose Reduction (Occurring in ≥2 Trabectedin-Treated Patient) by Preferred Term. Safety Population ET743-SAR-3007 and ISS Population

System Organ Class Preferred Term	ET734-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Investigations	105 (28)	10 (6)	162 (21)
Alanine aminotransferase increased	59 (16)	0 (0)	96 (13)
Aspartate aminotransferase increased	25 (7)	0 (0)	50 (7)
Blood alkaline phosphatase increased	20 (5)	3 (1.7)	40 (5)
Blood bilirubin increased	10 (2.6)	0 (0)	17 (2.2)
Blood creatine phosphokinase	9 (2.4)	0 (0)	12 (1.6)

System Organ Class Preferred Term	ET734-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
increased			
Platelet count decreased	4 (1.1)	5 (2.9)	5 (0.7)
Neutrophil count decreased	3 (0.8)	2 (1.2)	4 (0.5)
Transaminases increased	2 (0.5)	0 (0)	2 (0.3)
Blood and lymphatic system disorders	35 (9)	10 (6)	45 (6)
Neutropenia	19 (5)	5 (2.9)	28 (3.7)
Thrombocytopenia	12 (3.2)	5 (2.9)	13 (1.7)
Febrile neutropenia	8 (2.1)	0 (0)	9 (1.2)
General disorders and administration site conditions	17 (4.5)	3 (1.7)	26 (3.4)
Fatigue	14 (3.7)	2 (1.2)	20 (2.6)
Gastrointestinal disorders	10 (2.6)	0 (0)	16 (2.1)
Nausea	4 (1.1)	0 (0)	6 (0.8)
Vomiting	4 (1.1)	0 (0)	6 (0.8)
Diarrhea	2 (0.5)	0 (0)	4 (0.5)

Source: adae.xpt (120DSU), adae.xpt (ISS120DSU)

The review included a hierarchical analysis at the HLT and HLGTL level based on MedDRA HLTs for AEs leading to dose reductions, including those occurring in <2 patients. Analyses did not result in any additional imbalances in AE incidence.

Adverse Events Leading to Treatment Interruptions/Delays

In the ET743-SAR-3007 trial, adverse events leading to dose delay occurred in 198 (51%) patients in the trabectedin group and 66 (38%) patients in the dacarbazine group. The most common AEs (≥5%) leading to dose delay of trabectedin are neutropenia and thrombocytopenia. In the ISS database, adverse events leading to dose delay occurred in 305 (40%) patients. The most common AEs (≥5%) leading to dose delay of trabectedin are neutropenia and thrombocytopenia. Table 55 summarizes AEs leading to dose delays in ≥2 trabectedin-treated patients.

Table 55. Incidence of Adverse Events Leading to Treatment Interruption/Delay Reduction (Occurring in ≥2 Trabectedin-Treated Patient) by Preferred Term. ET743-SAR-3007 – Safety Population and ISS

System Organ Class Preferred Term	ET734-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Investigations	98 (26)	31 (18)	136 (18)
Neutrophil count decreased	61 (16)	16 (9)	72 (10)
Platelet count decreased	29 (8)	14 (8)	34 (4.5)
White blood cell count decreased	13 (3.4)	2 (1.2)	15 (2)

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
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System Organ Class Preferred Term	ET734-SAR-3007		ISS
	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	(n=755) n(%)
Alanine aminotransferase increased	12 (3.2)	0 (0)	28 (3.7)
Blood creatine phosphokinase increased	12 (3.2)	1 (0.6)	17 (2.2)
Blood alkaline phosphatase increased	6 (1.6)	3 (1.7)	12 (1.6)
Blood creatinine increased	4 (1.1)	0 (0)	4 (0.5)
Blood bilirubin increased	3 (0.8)	2 (1.2)	5 (0.7)
Blood and lymphatic system disorders	87 (23)	36 (21)	149 (20)
Neutropenia	65 (17)	23 (13)	125 (17)
Thrombocytopenia	30 (8)	19 (11)	42 (6)
Anemia	9 (2.4)	5 (2.9)	10 (1.3)
Leukopenia	6 (1.6)	1 (0.6)	9 (1.2)
General disorders and administration site conditions	26 (7)	3 (1.7)	36 (4.8)
Fatigue	11 (2.9)	1 (0.6)	14 (1.8)
Infusion site extravasation	3 (0.8)	0 (0)	3 (0.4)
Pyrexia	3 (0.8)	1 (0.6)	4 (0.5)
Device component issue	2 (0.5)	0 (0)	2 (0.3)
Edema peripheral	2 (0.5)	0 (0)	3 (0.4)
Infections and infestations	22 (6)	4 (2.3)	36 (4.8)
Upper respiratory tract infection	5 (1.3)	1 (0.6)	10 (1.3)
Catheter site infection	4 (1.1)	0 (0)	4 (0.5)
Urinary tract infection	3 (0.8)	0 (0)	4 (0.5)
Bacteremia	2 (0.5)	0 (0)	3 (0.4)
Cellulitis	2 (0.5)	0 (0)	2 (0.3)
Pneumonia	2 (0.5)	1 (0.6)	5 (0.7)
Sepsis	2 (0.5)	0 (0)	2 (0.3)
Respiratory, thoracic and mediastinal disorders	14 (3.7)	2 (1.2)	20 (2.6)
Dyspnea	3 (0.8)	1 (0.6)	6 (0.8)
Pulmonary embolism	3 (0.8)	0 (0)	4 (0.5)
Cough	2 (0.5)	0 (0)	5 (0.7)
Pleural effusion	2 (0.5)	0 (0)	2 (0.3)
Pulmonary edema	2 (0.5)	0 (0)	2 (0.3)
Gastrointestinal disorders	13 (3.4)	4 (2.3)	22 (2.9)
Nausea	4 (1.1)	0 (0)	8 (1.1)
Vomiting	2 (0.5)	0 (0)	4 (0.5)
Cardiac disorders	5 (1.3)	0 (0)	5 (0.7)
Atrial fibrillation	2 (0.5)	0 (0)	2 (0.3)
Cardiac failure congestive	2 (0.5)	0 (0)	2 (0.3)

Source: adae.xpt (120DSU), adae.xpt (ISS120DSU)

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the SAR-3007 trial, the most common AE ($\geq 10\%$) occurring more frequently ($>5\%$ all Grades) in the trabectedin group compared to the dacarbazine group were: nausea, fatigue, elevated liver function tests, vomiting, anemia, constipation, decreased appetite, diarrhea, neutropenia, peripheral edema, headache, musculoskeletal pain, and renal failure. Table 56 summarizes the treatment-emergent adverse events (TEAE) occurring within 30 days of last treatment dose whose incidence is $\geq 5\%$ at any grade in the trabectedin group.

Table 56. Incidence of TEAE ($\geq 5\%$ of Trabectedin-Treated Patients) by Treatment Group. ET743-SAR-3007 – Safety Population

System Organ Class Preferred Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
Gastrointestinal disorders	341 (90)	68 (18)	136 (79)	23 (13)
Nausea	285 (75)	26 (7)	86 (50)	3 (2)
Vomiting	173 (46)	22 (6)	37 (22)	2 (1)
Constipation	140 (37)	3 (1)	53 (31)	1 (1)
Diarrhea	132 (35)	6 (2)	40 (23)	0
Abdominal pain	68 (18)	16 (4)	36 (21)	10 (6)
Abdominal distension	30 (8)	1 (0)	16 (9)	2 (1)
Dyspepsia	30 (8)	0	12 (7)	0
Dry mouth	22 (6)	0	12 (7)	0
Stomatitis	21 (6)	0	6 (3)	0
Abdominal pain upper	19 (5)	2 (1)	8 (5)	1 (1)
General disorders and administration site conditions	324 (86)	57 (15)	121 (70)	10 (6)
Fatigue	261 (69)	31 (8)	89 (52)	3 (2)
Edema peripheral	107 (28)	3 (1)	22 (13)	1 (1)
Pyrexia	71 (19)	3 (1)	28 (16)	1 (1)
Chills	33 (9)	0	11 (6)	0
Chest pain	20 (5)	1 (0)	6 (3)	0
Catheter site pain	19 (5)	2 (1)	1 (1)	0
Investigations	281 (74)	202 (53)	80 (47)	38 (22)
Alanine	186 (49)	111 (29)	12 (7)	1 (1)

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

System Organ Class Preferred Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
aminotransferase increased				
Aspartate aminotransferase increased	142 (38)	57 (15)	10 (6)	0
White blood cell count decreased	97 (26)	75 (20)	20 (12)	15 (9)
Neutrophil count decreased	96 (25)	77 (20)	25 (15)	17 (10)
Blood alkaline phosphatase increased	85 (22)	6 (2)	15 (9)	1 (1)
Platelet count decreased	62 (16)	38 (10)	28 (16)	16 (9)
Blood creatine phosphokinase increased	56 (15)	22 (6)	2 (1)	1 (1)
Blood creatinine increased	48 (13)	8 (2)	3 (2)	0
Blood bilirubin increased	34 (9)	5 (1)	5 (3)	1 (1)
Weight decreased	27 (7)	0	5 (3)	1 (1)
Lymphocyte count decreased	20 (5)	9 (2)	3 (2)	1 (1)
Blood and lymphatic system disorders	230 (61)	140 (37)	77 (45)	44 (26)
Anemia	157 (42)	67 (18)	48 (28)	20 (12)
Neutropenia	119 (31)	91 (24)	31 (18)	22 (13)
Thrombocytopenia	74 (20)	40 (11)	34 (20)	18 (10)
Leukopenia	45 (12)	37 (10)	13 (8)	10 (6)
Metabolism and nutrition disorders	221 (58)	63 (17)	78 (45)	15 (9)
Decreased appetite	139 (37)	7 (2)	36 (21)	1 (1)
Dehydration	57 (15)	18 (5)	20 (12)	5 (3)
Hypokalemia	53 (14)	14 (4)	21 (12)	2 (1)
Hypoalbuminemia	31 (8)	7 (2)	7 (4)	2 (1)
Hyperglycemia	28 (7)	8 (2)	5 (3)	1 (1)
Hypocalcaemia	27 (7)	3 (1)	3 (2)	0
Hyponatremia	27 (7)	10 (3)	7 (4)	5 (3)
Musculoskeletal and connective tissue disorders	202 (53)	21 (6)	77 (45)	12 (7)
Back pain	65 (17)	4 (1)	30 (17)	4 (2)
Arthralgia	56 (15)	0	14 (8)	2 (1)
Myalgia	47 (12)	0	11 (6)	0
Pain in extremity	47 (12)	5 (1)	15 (9)	4 (2)
Musculoskeletal	29 (8)	0	13 (8)	1 (1)

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
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System Organ Class Preferred Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
pain				
Muscular weakness	25 (7)	3 (1)	4 (2)	1 (1)
Bone pain	20 (5)	0	12 (7)	0
Respiratory, thoracic and mediastinal disorders	201 (53)	37 (10)	76 (44)	8 (5)
Dyspnea	94 (25)	16 (4)	35 (20)	2 (1)
Cough	85 (22)	1 (0)	36 (21)	0
Dyspnea exertional	27 (7)	2 (1)	4 (2)	0
Nasal congestion	23 (6)	0	6 (3)	0
Oropharyngeal pain	19 (5)	0	4 (2)	0
Nervous system disorders	198 (52)	10 (3)	78 (45)	6 (3)
Headache	93 (25)	1 (0)	32 (19)	0
Dizziness	46 (12)	1 (0)	21 (12)	0
Dysgeusia	34 (9)	0	10 (6)	0
Hypoesthesia	22 (6)	0	3 (2)	0
Paresthesia	22 (6)	0	9 (5)	0
Infections and infestations	157 (42)	46 (12)	50 (29)	6 (3)
Urinary tract infection	36 (10)	8 (2)	10 (6)	2 (1)
Upper respiratory tract infection	24 (6)	0	10 (6)	0
Psychiatric disorders	113 (30)	4 (1)	37 (22)	0
Insomnia	55 (15)	1 (0)	16 (9)	0
Anxiety	40 (11)	0	13 (8)	0
Depression	30 (8)	0	7 (4)	0
Vascular disorders	84 (22)	23 (6)	33 (19)	3 (2)
Hypotension	23 (6)	8 (2)	7 (4)	2 (1)
Hypertension	22 (6)	10 (3)	2 (1)	0
Flushing	19 (5)	0	9 (5)	0

Source: ae.xpt (120DSU), dm.xpt (120DSU)

The review of safety evaluated additional potential toxicities of trabectedin through analyses of the incidence of AEs based on hierarchical composite of MedDRA high-level group terms (i.e., system organ classes), a hierarchical composite of MedDRA high-level terms (i.e., high-level group terms), and a hierarchical composite of MedDRA preferred terms (i.e., high level terms) in each treatment group as summarized in Table 57, Table 58, and Table 59, respectively. These analyses support the attribution of previously identified potential toxicities to trabectedin.

Table 57. Incidence of TEAE (≥10% of Trabectedin-Treated Patients or ≥5% Higher in Trabectedin Treatment Group by System Organ Class. ET743-SAR-3007 – Safety Population

System Organ Class	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
Gastrointestinal disorders	341 (90)	68 (18)	136 (79)	23 (13)
General disorders and administration site conditions	324 (86)	57 (15)	121 (70)	10 (6)
Investigations	281 (74)	202 (53)	80 (47)	38 (22)
Blood and lymphatic system disorders	230 (61)	140 (37)	77 (45)	44 (26)
Metabolism and nutrition disorders	221 (58)	63 (17)	78 (45)	15 (9)
Musculoskeletal and connective tissue disorders	202 (53)	21 (6)	77 (45)	12 (7)
Respiratory, thoracic and mediastinal disorders	201 (53)	37 (10)	76 (44)	8 (5)
Nervous system disorders	198 (52)	10 (3)	78 (45)	6 (3)
Infections and infestations	157 (42)	46 (12)	50 (29)	6 (3)
Psychiatric disorders	113 (30)	4 (1)	37 (22)	0
Skin and subcutaneous tissue disorders	93 (25)	0	44 (26)	0
Vascular disorders	84 (22)	23 (6)	33 (19)	3 (2)
Renal and urinary disorders	68 (18)	16 (4)	28 (16)	3 (2)
Injury, poisoning and procedural complications	57 (15)	6 (2)	17 (10)	0
Cardiac disorders	51 (13)	17 (4)	21 (12)	3 (2)

Source: ae.xpt(120DSU), dm.xpt (120DSU)

Table 58. Incidence of TEAE (≥10% of Trabectedin-Treated Patients or ≥5% Higher in Trabectedin Treatment Group by High Group Level Term. ET743-SAR-3007 – Safety Population

High Level Group Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
Gastrointestinal signs and symptoms	317 (84)	49 (13)	115 (67)	16 (9)
General system disorders NEC	314 (83)	46 (12)	110 (64)	9 (5)
Gastrointestinal motility	213 (56)	9 (2)	83 (48)	1 (1)

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
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High Level Group Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
and defecation conditions				
Hepatobiliary investigations	203 (54)	125 (33)	18 (10)	2 (1)
Respiratory disorders NEC	185 (49)	23 (6)	69 (40)	4 (2)
Anemias non-hemolytic and marrow depression	158 (42)	67 (18)	48 (28)	20 (12)
Hematology investigations (incl blood groups)	154 (41)	118 (31)	50 (29)	30 (17)
Appetite and general nutritional disorders	143 (38)	11 (3)	37 (22)	2 (1)
Musculoskeletal and connective tissue disorders NEC	139 (37)	15 (4)	58 (34)	10 (6)
White blood cell disorders	139 (37)	102 (27)	38 (22)	27 (16)
Infections - pathogen unspecified	128 (34)	38 (10)	40 (23)	6 (3)
Enzyme investigations NEC	127 (34)	27 (7)	17 (10)	2 (1)
Electrolyte and fluid balance conditions	123 (33)	43 (11)	41 (24)	11 (6)
Neurological disorders NEC	116 (31)	7 (2)	46 (27)	3 (2)
Headaches	97 (26)	1 (0)	34 (20)	0
Muscle disorders	86 (23)	6 (2)	20 (12)	2 (1)
Platelet disorders	76 (20)	40 (11)	34 (20)	18 (10)
Body temperature conditions	71 (19)	3 (1)	28 (16)	1 (1)
Joint disorders	59 (16)	1 (0)	15 (9)	2 (1)
Epidermal and dermal conditions	55 (15)	0	31 (18)	0
Sleep disorders and disturbances	55 (15)	1 (0)	16 (9)	0
Bone, calcium, magnesium and phosphorus metabolism disorders	51 (13)	9 (2)	10 (6)	0
Renal and urinary tract investigations and urinalyses	50 (13)	9 (2)	3 (2)	0
Urinary tract signs and symptoms	48 (13)	2 (1)	18 (10)	0
Anxiety disorders and symptoms	44 (12)	0	14 (8)	0
Administration site reactions	39 (10)	5 (1)	6 (3)	0

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
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High Level Group Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)

Source: ae.xpt(120DSU), dm.xpt (120DSU)

Table 59. Incidence of TEAE ($\geq 10\%$ of Trabectedin-Treated Patients or $\geq 5\%$ Higher in Trabectedin Treatment Group by High Level Term. ET743-SAR-3007 – Safety Population

High Level Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
Nausea and vomiting symptoms	296 (78)	32 (8)	92 (53)	3 (2)
Asthenic conditions	267 (71)	36 (10)	92 (53)	3 (2)
Liver function analyses	203 (54)	125 (33)	18 (10)	2 (1)
Anemias NEC	158 (42)	67 (18)	48 (28)	20 (12)
Gastrointestinal atonic and hypomotility disorders NEC	148 (39)	3 (1)	61 (35)	1 (1)
Appetite disorders	141 (37)	7 (2)	37 (22)	1 (1)
White blood cell analyses	139 (37)	107 (28)	36 (21)	24 (14)
Diarrhea (excl infective)	132 (35)	6 (2)	41 (24)	0
Musculoskeletal and connective tissue pain and discomfort	129 (34)	11 (3)	55 (32)	9 (5)
Neutropenia's	124 (33)	97 (26)	33 (19)	24 (14)
Breathing abnormalities	119 (31)	18 (5)	37 (22)	2 (1)
Edema NEC	116 (31)	6 (2)	25 (15)	2 (1)
Gastrointestinal and abdominal pains (excl oral and throat)	104 (28)	20 (5)	46 (27)	12 (7)
Headaches NEC	95 (25)	1 (0)	33 (19)	0
Coughing and associated symptoms	93 (25)	2 (1)	42 (24)	0
Tissue enzyme analyses NEC	85 (22)	6 (2)	15 (9)	1 (1)
Thrombocytopenia's	75 (20)	40 (11)	34 (20)	18 (10)
Febrile disorders	71 (19)	3 (1)	28 (16)	1 (1)
Potassium imbalance	68 (18)	16 (4)	23 (13)	2 (1)
Platelet analyses	63 (17)	38 (10)	28 (16)	16 (9)
Sensory abnormalities NEC	60 (16)	1 (0)	17 (10)	1 (1)
Skeletal and cardiac muscle analyses	60 (16)	22 (6)	2 (1)	1 (1)
Total fluid volume decreased	57 (15)	18 (5)	20 (12)	5 (3)
Joint related signs and symptoms	56 (15)	1 (0)	15 (9)	2 (1)
Disturbances in	55 (15)	1 (0)	16 (9)	0

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

High Level Term	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
initiating and maintaining sleep				
Pain and discomfort NEC	52 (14)	3 (1)	23 (13)	2 (1)
Leukopenia's NEC	51 (13)	40 (11)	14 (8)	10 (6)
Renal function analyses	50 (13)	8 (2)	3 (2)	0
Neurological signs and symptoms NEC	49 (13)	1 (0)	21 (12)	0
Muscle pains	47 (12)	0	11 (6)	0
Upper respiratory tract infections	46 (12)	0	18 (10)	0
Anxiety symptoms	43 (11)	0	14 (8)	0
Upper respiratory tract signs and symptoms	40 (11)	0	10 (6)	0
Feelings and sensations NEC	38 (10)	0	14 (8)	0
Flatulence, bloating and distension	37 (10)	1 (0)	19 (11)	2 (1)
Urinary tract infections	37 (10)	9 (2)	10 (6)	2 (1)
Physical examination procedures and organ system status	36 (10)	0	9 (5)	2 (1)
Implant and catheter site reactions	34 (9)	3 (1)	3 (2)	0

Source: ae.xpt(120DSU), dm.xpt (120DSU)

The clinical review also included safety analyses of the ET743-SAR-3007 trial using a narrow-based Standardized MedDRA Queries (SMQ). SMQs with a relative risk (RR) of 5 or greater in the trabectedin group compared to the dacarbazine group were rhabdomyolysis, hypertension, dyslipidemia, and cardiac arrhythmias. Table 60 summarizes the incidence of narrow based SMQ terms with a relative risk ≥ 2 .

Table 60. Analysis of Narrow-Based Standardized MedDRA Queries by Treatment Group. ET743-SAR-3007 – Safety Population

SMQ	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	RR
Rhabdomyolysis/myopathy	6 (2)	0	6.5
Hypertension	25 (7)	2 (1)	6.3
Dyslipidemia	5 (1)	0	5.5
Extravasation events (injections, infusions and implants)	5 (1)	0	5.5
Cardiac arrhythmias	11 (3)	1 (1)	5.5
Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) 1	11 (3)	1 (1)	5.5

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

SMQ	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	RR
Hepatic disorders	208 (55)	23 (13)	4.5
Hepatic disorders	208 (55)	23 (13)	4.5
Liver related investigations, signs and symptoms 2	208 (55)	23 (13)	4.5
Hemolytic disorders	4 (1)	0	4.5
Myocardial infarction 1	4 (1)	0	4.5
Cerebrovascular disorders	4 (1)	0	4.5
Central nervous system hemorrhages and cerebrovascular conditions 1	4 (1)	0	4.5
Lens disorders	4 (1)	0	4.5
Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) 2	8 (2)	1 (1)	4.0
Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous 1	16 (4)	2 (1)	4.0
Biliary disorders	38 (10)	5 (3)	3.8
Functional, inflammatory and gallstone related biliary disorders 1	37 (10)	5 (3)	3.7
Biliary system related investigations, signs and symptoms 2	36 (10)	5 (3)	3.6
Ischemic cerebrovascular conditions 2	3 (1)	0	3.5
Hemorrhagic cerebrovascular conditions 2	3 (1)	0	3.5
Pseudomembranous colitis	3 (1)	0	3.5
Psychosis and psychotic disorders	3 (1)	0	3.5
Pulmonary hypertension	3 (1)	0	3.5
Supraventricular tachyarrhythmias 3	7 (2)	1 (1)	3.5
Shock	7 (2)	1 (1)	3.5
Hearing impairment 1	7 (2)	1 (1)	3.5
Acute central respiratory depression	11 (3)	2 (1)	2.8
Cardiac failure	21 (6)	4 (2)	2.6
Embolic and thrombotic events	41 (11)	8 (5)	2.6
Torsade de pointes/QT prolongation	2 (1)	0	2.5
Bradyarrhythmias (incl conduction defects and disorders of sinus node function) 2	2 (1)	0	2.5
Conduction defects 3	2 (1)	0	2.5
Cardiac arrhythmia terms, nonspecific 2	2 (1)	0	2.5
Premalignant disorders	2 (1)	0	2.5
Extrapyramidal syndrome	2 (1)	0	2.5

SMQ	Trabectedin (n=378) n(%)	Dacarbazine (n=172) n(%)	RR
Akathisia 1	2 (1)	0	2.5
Ischemic colitis	2 (1)	0	2.5
Periorbital and eyelid disorders	2 (1)	0	2.5
Ocular infections	2 (1)	0	2.5
Liver-related coagulation and bleeding disturbances 2	5 (1)	1 (1)	2.5
Gastrointestinal hemorrhage 1	19 (5)	4 (2)	2.4
Hearing and vestibular disorders	14 (4)	3 (2)	2.3
Agranulocytosis	18 (5)	4 (2)	2.3
Embolic and thrombotic events, venous 1	26 (7)	6 (3)	2.2
Depression and suicide/self-injury	34 (9)	8 (5)	2.1
Depression (excl suicide and self-injury) 1	34 (9)	8 (5)	2.1
Hyperglycemia/new onset diabetes mellitus	34 (9)	8 (5)	2.1
Hemodynamic edema, effusions and fluid overload	138 (37)	33 (19)	2.1
Ischemic heart disease	4 (1)	1 (1)	2.0
Hyponatremia/SIADH	28 (7)	7 (4)	2.0
Cardiomyopathy	16 (4)	4 (2)	2.0
Retinal disorders	4 (1)	1 (1)	2.0

Source: ae.xpt(120DSU), dm.xpt (120DSU)

Abbreviation in Table: RR = relative risk

¹ Second SMQ level

² Third SMQ level

³ Fourth SMQ level

7.4.2 Laboratory Findings

In the ET743-SAR-3007 trial, laboratory testing of clinical chemistry parameters (creatinine, calcium, ALT, AST, alkaline phosphatase, total bilirubin, albumin, CPK) and hematology parameters (WBC with differential, hemoglobin, platelet count) was performed at baseline and on Day 1, D8, and 15 of each treatment cycle. Of note, sodium, potassium chloride, bicarbonate, blood urea nitrogen, glucose were not routinely entered in the eCFR and therefore not captured in the datasets from this submission. As summarized in Table 61, the most common (≥50%) laboratory abnormalities (all Grades) in the trabectedin group were elevated liver function tests, neutropenia, anemia, thrombocytopenia, hypoalbuminemia. Grade 3 or 4 elevation of ALT occurred in 31% of trabectedin group and 1% of dacarbazine group.

Table 61. Incidence of Treatment-Emergent Grade 1-4 Laboratory Abnormality (≥10% of YONDELIS-Treated Patients). ET743-SAR-3007 – Safety Population

Laboratory Abnormality	Trabectedin (n=378)		Dacarbazine (n=172)	
	All Grades n(%)	Grades 3-4 n(%)	All Grades n(%)	Grades 3-4 n(%)
ALT increase	336 (89)	119 (31)	47 (27)	1 (1)
AST increase	298 (79)	63 (17)	46 (27)	2 (1)
Leukopenia	290 (77)	146 (39)	93 (54)	31 (18)
Anemia	278 (74)	71 (19)	85 (49)	20 (12)
Neutropenia	248 (66)	161 (43)	78 (45)	43 (25)
Thrombocytopenia	210 (56)	78 (21)	87 (51)	33 (19)
Alkaline phosphatase increase	204 (54)	6 (2)	76 (44)	1 (1)
Hypoalbuminemia	189 (50)	14 (4)	52 (30)	4 (2)
Creatine increase	155 (41)	16 (4)	38 (22)	2 (1)
Creatine phosphokinase increase	117 (31)	24 (6)	14 (8)	1 (1)
Hyperbilirubinemia, conjugated	72 (19)	14 (4)	14 (8)	3 (2)
Hyperbilirubinemia	48 (13)	7 (2)	7 (4)	1 (1)

Source: ae.xpt(120DSU), dm.xpt (120DSU)

Reviewer Comment

Review of laboratory data notes that sodium, potassium chloride, bicarbonate, blood urea nitrogen, glucose were not routinely entered in the eCFR and therefore not captured in the datasets from this submission.

7.4.3 Vital Signs

In the ET743-SAR-3007 trial, vital signs (i.e., body temperature, pulse, blood pressure, respiratory rate, and pulse oximetry) were only captured in the eCRF during the Screening Phase. Any clinically significant change in vital signs during the Treatment Phase of the study were reported as an adverse event. Therefore no vital signs data are available before each cycle. In the vs.xpt dataset, only BMI is recorded for each cycle in the Treatment Phase.

Reviewer Comment

Review of vital signs data is not possible because of the missing data. Capturing adverse events that require vital signs (e.g., febrile neutropenia, hypertension, and hypoxia) for the safety profile of trabectedin is dependent upon Investigator reporting. There is no way to confirm the validity of certain adverse events and no way to determine whether more subtle adverse events are missed which may lead to under reporting of certain adverse events. The incidence of febrile neutropenia, sepsis,

dyspnea, tachycardia, hypertension, hypotension, were reviewed and discussed in Sections 7.3 and 7.4.1.

7.4.4 Electrocardiograms (ECGs)

In the ET743-SAR-3007 trial, electrocardiograms and LVEF assessments (echocardiogram or MUGA) are only scheduled during the Screening Phase of the trial and at the end of the Treatment Phase. These data point are the only ones captured in the datasets and summarized in Table 62. An IR was issued to the Applicant requesting additional unscheduled LVEF assessments. The Sponsor responded that this data was not captured in the eCFR and therefore could not be provided in datasets. A PMR is recommended by this reviewer to better characterize the AE of cardiomyopathy and its sequelae. See Section 7.3.1 for further details regarding LVEF assessments and cardiomyopathy.

Study ET743-OVC-1001, a single-blind study with open-label extension phase to evaluate the effect of trabectedin 1.3 mg/m² in a 3 hours infusion time on QT/QTc interval duration in 75 patients with advanced solid malignancies. The Phase 1/2a study designed to examine QT prolongation in trabectedin treated patients, ET743-OVC-1001, was finalized in September 2008. The study completed recruitment April 16, 2009. Overall, trabectedin did not prolong the QTc interval as measured by ECGs in patients with advanced solid tumor. No AE suggested of pro-arrhythmic potential were reported.

Table 62. Change from Baseline for ECG. ET743-SAR-3007 – Safety Population

	Baseline	Within Normal Limits n(%)	Abnormal, Clinically Insignificant ¹ n(%)	Abnormal, Clinically Significant ¹ n(%)	On Study n(%)
<u>Trabectedin</u>					
Within Normal Limits	213 (58)	105 (71)	43 (40)	3 (43)	62 (58)
Abnormal, Clinically Insignificant	155 (42)	43 (29)	64 (60)	4 (57)	44 (42)
Subtotal	368	148	107	7	106
<u>Dacarbazine</u>					
Within Normal Limits	102 (60)	52 (72)	14 (33)	0 (0)	36 (64)
Abnormal, Clinically Insignificant	69 (40)	20 (28)	29 (67)	0 (0)	20 (36)
Subtotal	171	72	43	0	56
Total	539	220	150	7	162

	Baseline	Within Normal Limits n(%)	Abnormal, Clinically Insignificant ¹ n(%)	Abnormal, Clinically Significant ¹ n(%)	On Study n(%)
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Source: adeg.xpt dataset (120DSU)

¹ The protocol for ET743-SAR-3007 state that computer-generated interpretations of ECGs were reviewed for data integrity and reasonableness by an appropriately trained investigator (e.g., a cardiologist or internist).

Reviewer Comment

Assessment of cardiac arrhythmia from ECG data is not able to be performed based on the absence of routine ECGs during the treatment phase of the study. The description of the ECG were generated by computer and only provided 3 interpretations: Within normal limits, abnormal clinically insignificant, and abnormal clinically significant. This level of detail is insufficient to conduct an adequate review of the primary data. As a result, the review of the effect of trabectedin on ECGs, specifically prolongation of the QT interval, is based on Study ET743-OVC-1001, which showed that trabectedin 1.3 mg/m² as a 3 hour infusion did not prolong QTc intervals on assessment collected up to 24 hours after the start of the infusion. See FDA Clinical Pharmacology Review of NDA 207953.

7.4.5 Special Safety Studies/Clinical Trials

See Section 7.4.4 for additional QT prolongation studies in Study ET743-OVC-1001.

7.4.6 Immunogenicity

There are no immunogenicity data provided in this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

According to the FDA Clinical Pharmacology NDA review, population pharmacokinetic f(PK) and exposure-response (E-R) analyses using PK data across clinical studies did not identify significant covariates influencing trametinib PK or evident E-R relationships for effectiveness and safety. Please see the FDA Clinical Pharmacology NDA review for additional details.

7.5.2 Time Dependency for Adverse Events

Please see sections 7.3.1 (cardiac events, neutropenia, and rhabdomyolysis), 7.3.2 (dyspnea, thrombocytopenia), 7.3.3 (hepatotoxicity), and 7.3.4 for analyses of time dependency for AEs.

7.5.3 Drug-Demographic Interactions

In the ET743-SAR-3007 trial, patients age 65 years or older represented 25% and 20% of the trabectedin and dacarbazine groups, respectively, whereas female patients represented 68% and 72% of the trabectedin and dacarbazine groups, respectively. The incidence of any AE (all grades) was similar across both these demographic subgroups and within each treatment group with almost every patient experiences an AE during the Treatment Phase. The incidence of Grade 3 or 4 AEs was similar in female and male patients in the trabectedin group, 81% and 79%, respectively. In addition, patients age 65 years or older in the trabectedin group experienced a lower incidence of Grade 3 or 4 AEs compared to those younger than 65 years. In contrast, the incidence of Grade 3 or 4 AEs in the dacarbazine group was higher in patients 65 years of age or older compared to younger than 65 years. The incidence of SAEs was higher in patients age 65 years or older compared to patients younger than 65 years. Table 63 summarizes the incidence of AEs by toxicity grade as well as serious AEs by age and gender subgroups.

Table 63. Summary of Safety Analyses by Age (< 65 vs. ≥65) and Gender Subgroups. ET743-SAR-3007 – Safety Population

	Age Subgroup				Gender Subgroup			
	Trabectedin		Dacarbazine		Trabectedin		Dacarbazine	
	<65 n=285 n(%)	≥65 n=93 n(%)	<65 n=137 n(%)	≥65 n=35 n(%)	Female n=257 n(%)	Male n=121 n(%)	Female n=124 n(%)	Male n=48 n(%)
All Grade AE	284 (100)	93 (100)	135 (99)	35 (100)	256 (100)	121 (100)	123 (99)	47 (98)
Grade 3-4	234 (82)	71 (76)	72 (53)	23 (66)	209 (81)	96 (79)	75 (60)	20 (42)
Grade 4	83 (29)	29 (31)	25 (18)	8 (23)	75 (29)	37 (31)	25 (20)	8 (17)
Any SAE	112 (39)	42 (45)	41 (30)	11 (31)	108 (42)	46 (38)	43 (35)	9 (19)
AE Leading to Withdrawal	63 (22)	35 (38)	30 (22)	7 (20)	67 (26)	31 (26)	32 (26)	5 (10)

Source: adae.xpt (120DSU), dm.xpt (120DSU)

Reviewer Comment

1. The safety review included analyses of Grade 3 or 4 AEs at the level of MedDRA preferred terms within age and gender subgroups. Several exploratory analysis methods, including analyses of attributable and relative risk, suggest that patients age ≥65 are at an increased risk for Grade 3 or 4 myelosuppression, nausea, vomiting,

fatigue, and dehydration with a >10% relative risk with trabectedin for each of the preferred terms when compared to patients younger than 65. In the dacarbazine group, the relative risk is <5% among all AEs. .

2. The safety population consisted of 77%% white patients which limited the utility of safety analyses based on racial subgroups.

7.5.4 Drug-Disease Interactions

Refer to the FDA clinical pharmacology NDA review for details.

7.5.5 Drug-Drug Interactions

Refer to the FDA Clinical Pharmacology NDA review for details.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were conducted. The following is excerpted from

(b) (4)

(b) (4)

No preclinical carcinogenicity studies were submitted as part of this NDA.

7.6.2 Human Reproduction and Pregnancy Data

There are no data available on the use of trabectedin in pregnant or lactating women. The FDA Pharmacology/Toxicology reviewers recommend classification of trabectedin as Pregnancy Category D based on the nonclinical reproductive toxicology data. See the FDA Pharmacology/Toxicology NDA Review for details.

(b) (4)

(b) (4)

(b) (4)



7.6.3 Pediatrics and Assessment of Effects on Growth

Trabectedin has not been studied in a pediatric population. The Applicant is requesting waiver of pediatric studies because trabectedin qualifies for an exemption from PREA requires (see Section 2.5).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant states that there is limited data on the effects of trabectedin overdose. In the ET743-SAR-3007 trial, the maximum dose that any patient received was 2.6 mg/m² per cycle, 3.96mg per cycle, or a cumulative dose 52.5mg of trabectedin. The major anticipated toxicities are gastrointestinal, bone marrow suppression, and hepatic toxicity. Two of 3 subjects in a Phase 1 study who received 1.8 mg/m² as a 24-hour infusion developed severe hematologic toxicity. In 2 other cases, accelerated delivery of a therapeutic dose was associated with minor repolarization changes and transient flushing. The Applicant states that there are no studies conducted to evaluate the abuse potential of trabectedin in animals or humans. The Applicant cites that preclinical testing on receptor binding did indicate any potential for drug abuse. The Applicant states that no withdrawal symptoms or medical complications from the interruption or discontinuation of trabectedin have been described.

7.7 Additional Submissions / Safety Issues

On April 17, 2015, the Applicant submitted updated safety datasets with a database cutoff date of July 10, 2014, as part of its 120-Day Safety Update (NDA 207953, SDN22) and an updated Clinical Study Report submitted on March 24, 2015 (NDA 207953, SDN17). Comparison of ae.xpt datasets from the Interim Analysis (11/24/2014, NDA 207953, SDN 01) and the 120-Day Safety Update revealed several modifications to historical adverse events entries. After further discussion with the Applicant, this submission was considered a Major Amendment. See Section 3.1 for further details.

8 Postmarket Experience

Based on NDA 207953, Module 5.3.6, the Applicant states that trabectedin is licensed in 75 countries for soft tissue sarcoma (STS). Cumulative exposure in Company Sponsored interventional clinical studies is 5,286 subjects, and cumulative post-marketing exposure is estimated at 103,424 treatments (cycles) or 34,475 patients, based on product distribution data. The Applicant provided an ad hoc report including a cumulative tabulation of serious adverse events that have occurred over the post-marketing period of trabectedin use.

Review of the most commonly reported serious adverse events from trabectedin postmarketing experience did not uncover any new adverse events that have not been adequately reflected in the proposed labeling.

9 Appendices

9.1 Labeling Recommendations

Based on the clinical and statistical reviews of the submission, numerous recommendations were made to improve the Applicant's proposed package insert. This included changes to the Highlights, Indications and Usage, Dosage and Administration, Warning and Precautions, Adverse Reactions, Use in Specific Populations, Clinical Studies, and Patient Counseling Information sections.

9.2 Advisory Committee Meeting

The Division did not obtain the advice of the Oncologic Drugs Advisory Committee (ODAC) for this application.

9.3 Financial Disclosure

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 640		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

9.4 Literature Review/References

1. National Cancer Institute: PDQ® Adult Soft Tissue Sarcoma Treatment. Bethesda, M.N.C.I.D.I.m.A.a.h.c.g.c.p.
2. Demitri, G.D.G., Suzanne, *UpToDate, Post TW (ed)*. Systemic treatment of metastatic soft tissue sarcoma, ed. R. Maki. July 28, 2014.
3. van der Graaf, W.T., et al., *Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial*. The Lancet, 2012. **379**(9829): p. 1879-1886.
4. Judson, I., et al., *Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial*. The lancet oncology, 2014. **15**(4): p. 415-423.
5. Maki, R.G., et al., *Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002*. Journal of Clinical Oncology, 2007. **25**(19): p. 2755-2763.
6. Schlemmer, M., et al., *Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group*. European Journal of Cancer, 2008. **44**(16): p. 2433-2436.
7. Cleeland, C.S., et al., *Assessing symptom distress in cancer patients*. Cancer, 2000. **89**(7): p. 1634-1646.

Appendix I: Dose Reduction Guidelines

Table 64. Dose Reduction Due to Hematologic Toxicity (adapted from CSR)

Nadir toxicity	Nadir Value	Dose modification
ANC	<1,000/ μ L with fever/infection or <500/ μ L lasting >5 days	Decrease 1 level ^{a, b}
Platelets	<25,000/ μ L	Decrease 1 level ^a

ANC=absolute neutrophil count

^a If toxicity reappears, decrease dose to Level -2.

^b Colony-stimulating factor support may be added to the next cycle.

Table 65. Dose Reduction Due to Non-Hematologic Toxicity (adapted from CSR)

Toxicity	Worst Grade	Dose modification	
Nausea or vomiting despite adequate treatment ^a	≥ 3	Decrease 1 dose level	
Transaminase elevation	Recovery to ≤ 2.5 x ULN by day of next dose or within 3 weeks after the day the next dose is due.	≥ 3	Decrease 1 dose level
	Not recovered after a 3-week delay	≥ 3	Off treatment unless clinical benefit, then decrease 1 dose level
ALP liver fraction or 5' nucleotidase elevation >ULN	First occurrence	≥ 1	Decrease 1 dose level.
	Worsening to or recurrence of ALP liver fraction or 5' nucleotidase >ULN despite 1 st dose reduction.	≥ 1	Decrease 1 dose level.
Total bilirubin > ULN at any time	≥ 1	Decrease 1 dose level	
Other	≥ 3	Decrease 1 dose level	

ALP=alkaline phosphatase; ULN=upper limit of normal

^a Before dose modification, use full antiemetic regimen to include anti-HT3+/ other/ dexamethasone.

9.5 Definitions of Adverse Events of Special Interest

Table 66. Cardiac Disorders as Defined by Applicant

Level	MedDRA Term
HLGT	Cardiac and vascular investigations (excl enzyme tests)
HLGT	Cardiac arrhythmias
HLGT	Cardiac disorder signs and symptoms
HLGT	Coronary artery disorders
HLGT	Endocardial disorders
HLGT	Heart failures
HLGT	Myocardial disorders
HLGT	Pericardial disorders

Source: NDA 207953. Module 5.3.5.3. Integrated Summary of Safety.

Table 67. Neutropenia – Selected Infections as Defined by Applicant.

Level	MedDRA Term
PT	Abdominal sepsis
PT	Bacterial sepsis
PT	Biliary sepsis
PT	Brucella sepsis
PT	Campylobacter sepsis
PT	Cerebral septic infarct
PT	Citrobacter sepsis
PT	Clostridium difficile sepsis
PT	Corynebacterium sepsis
PT	Device related sepsis
PT	Enterobacter sepsis
PT	Enterococcal sepsis
PT	Escherichia sepsis
PT	Febrile Neutropenia
PT	Haemophilus sepsis
PT	Helicobacter sepsis
PT	Klebsiella sepsis
PT	Listeria sepsis
PT	Meningococcal sepsis
PT	Micrococcal sepsis
PT	Myocarditis septic
PT	Neutropenic sepsis
PT	Nocardia sepsis
PT	Pelvic sepsis
PT	Pneumococcal sepsis
PT	Post procedural sepsis
PT	Pseudallescheria sepsis
PT	Pseudomonal sepsis
PT	Pulmonary sepsis
PT	Salmonella sepsis
PT	Sepsis
PT	Sepsis pasteurella
PT	Sepsis syndrome
PT	Septic embolus
PT	Septic encephalopathy
PT	Septic necrosis
PT	Septic phlebitis
PT	Septic rash
PT	Septic shock
PT	Septic vasculitis
PT	Serratia sepsis
PT	Staphylococcal sepsis
PT	Stenotrophomonas sepsis
PT	Streptococcal sepsis
PT	Thrombophlebitis septic
PT	Urosepsis

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Level	MedDRA Term
PT	Wound sepsis
PT	Yersinia sepsis

Source: NDA 207953. Module 5.3.5.3. Integrated Summary of Safety.

Table 68. CPK Elevations / Rhabdomyolysis as Defined by Applicant.

Level	MedDRA Term
PT	Blood creatine phosphokinase MM increased
PT	Blood creatine phosphokinase abnormal
PT	Blood creatine phosphokinase increased
PT	Chromaturia
PT	Electromyogram abnormal
PT	Muscle enzyme increased
PT	Muscular weakness
PT	Musculoskeletal pain
PT	Myalgia
PT	Myoglobin blood increased
PT	Myoglobin blood present
PT	Myoglobin urine
PT	Myoglobin urine present
PT	Myoglobinemia
PT	Myoglobinuria
PT	Myopathy
PT	Myopathy toxic
PT	Myositis
PT	Renal failure
PT	Renal failure acute
PT	Renal impairment
PT	Renal tubular necrosis
PT	Rhabdomyolysis
PT	Blood creatinine increased

Source: NDA 207953. Module 5.3.5.3. Integrated Summary of Safety.

Table 69. Liver Injury as Defined by Applicant.

Level	MedDRA Term
PT	5'nucleotidase increased
PT	Acute hepatic failure
PT	Alanine aminotransferase abnormal
PT	Alanine aminotransferase increased
PT	Ascites
PT	Aspartate aminotransferase abnormal
PT	Aspartate aminotransferase increased
PT	Asterixis
PT	Biliary cirrhosis
PT	Biliary cirrhosis primary
PT	Biliary sepsis
PT	Biliary tract infection
PT	Biliary tract infection bacterial

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Level	MedDRA Term
PT	Bilirubin conjugated abnormal
PT	Bilirubin conjugated increased
PT	Blood alkaline phosphatase abnormal
PT	Blood alkaline phosphatase increased
PT	Blood bilirubin abnormal
PT	Blood bilirubin increased
PT	Blood bilirubin unconjugated increased
PT	Cholaemia
PT	Cholangitis
PT	Cholangitis acute
PT	Cholangitis suppurative
PT	Cholecystitis
PT	Cholecystitis acute
PT	Cholecystitis infective
PT	Cholestasis
PT	Cholestatic liver injury
PT	Coma hepatic
PT	Drug-induced liver injury
PT	Gallbladder empyema
PT	Gallbladder pain
PT	Gamma-glutamyltransferase abnormal
PT	Gamma-glutamyltransferase increased
PT	Hepatic cirrhosis
PT	Hepatic encephalopathy
PT	Hepatic enzyme abnormal
PT	Hepatic enzyme increased
PT	Hepatic failure
PT	Hepatic fibrosis
PT	Hepatic function abnormal
PT	Hepatic infection
PT	Hepatic infection bacterial
PT	Hepatic ischemia
PT	Hepatic necrosis
PT	Hepatic pain
PT	Hepatitis
PT	Hepatitis acute
PT	Hepatitis cholestatic
PT	Hepatitis fulminant
PT	Hepatitis toxic
PT	Hepatobiliary infection
PT	Hepatocellular injury
PT	Hepatomegaly
PT	Hepatopulmonary syndrome
PT	Hepatorenal failure
PT	Hepatorenal syndrome
PT	Hepatotoxicity
PT	Hyperbilirubinemia
PT	Hypercholia
PT	Hypertransaminasaemia
PT	Hypoalbuminemia

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Level	MedDRA Term
PT	Ischemic hepatitis
PT	Jaundice
PT	Jaundice cholestatic
PT	Jaundice hepatocellular
PT	Liver disorder
PT	Liver function test abnormal
PT	Liver injury
PT	Liver tenderness
PT	Mixed liver injury
PT	Subacute hepatic failure
PT	Transaminases abnormal
PT	Transaminases increased
PT	Venoocclusive liver disease

Source: NDA 207953. Module 5.3.5.3. Integrated Summary of Safety.

Table 70. Renal Disorders as Defined by Applicant.

Level	MedDRA Term
HLT	Glomerulonephritis and nephrotic syndrome
HLT	Nephritis NEC
HLT	Nephropathies and tubular disorders NEC
HLT	Renal disorders NEC
HLT	Renal failure and impairment
HLT	Renal failure complications
HLT	Renal function analyses
HLT	Renal hypertension and related conditions
HLT	Renal vascular and ischemic conditions

Source: NDA 207953. Module 5.3.5.3. Integrated Summary of Safety.

Table 71. Thrombocytopenia-Bleeding as Defined by Applicant.

Level	MedDRA Term
PT	Abdominal wall hematoma
PT	Abdominal wall hemorrhage
PT	Acute hemorrhagic conjunctivitis
PT	Adrenal hematoma
PT	Adrenal hemorrhage
PT	Anal hemorrhage
PT	Anal ulcer hemorrhage
PT	Application site hematoma
PT	Application site hemorrhage
PT	Basal ganglia hemorrhage
PT	Bloody discharge
PT	Brain stem hematoma
PT	Brain stem hemorrhage
PT	Brain stem micro-hemorrhage
PT	Breast hematoma
PT	Breast hemorrhage
PT	Bronchial hemorrhage

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
 YONDELIS® (trabectedin)

Level	MedDRA Term
PT	Catheter site hematoma
PT	Catheter site hemorrhage
PT	Central nervous system hemorrhage
PT	Cerebellar hematoma
PT	Cerebellar hemorrhage
PT	Cerebellar micro-hemorrhage
PT	Cerebral hematoma
PT	Cerebral hemorrhage
PT	Cerebral micro-hemorrhage
PT	Cerebrovascular accident
PT	Cervix hematoma uterine
PT	Cervix hemorrhage uterine
PT	Choroidal hematoma
PT	Intracranial hematoma
PT	Intracranial tumor hemorrhage
PT	Intraocular hematoma
PT	Interventricular hemorrhage
PT	Iris hemorrhage
PT	Lacrimal hemorrhage
PT	Large intestinal hemorrhage
PT	Large intestinal ulcer hemorrhage
PT	Lower gastrointestinal hemorrhage
PT	Melena
PT	Meningorrhagia
PT	Menorrhagia
PT	Mesenteric hematoma
PT	Mesenteric hemorrhage
PT	Metrorrhagia
PT	Mouth hemorrhage
PT	Occult blood positive
PT	Ocular retrobulbar hemorrhage
PT	Oesophageal hemorrhage
PT	Oesophagitis hemorrhagic
PT	Optic disc hemorrhage
PT	Optic nerve sheath hemorrhage
PT	Ovarian hematoma
PT	Ovarian hemorrhage
PT	Pelvic hematoma
PT	Pelvic hematoma obstetric
PT	Pelvic hemorrhage
PT	Penile hematoma
PT	Penile hemorrhage
PT	Perineal hematoma
PT	Periorbital hematoma
PT	Periorbital hemorrhage
PT	Pituitary hemorrhage
PT	Pleural hemorrhage
PT	Post procedural hemorrhage
PT	Prostatic hemorrhage
PT	Putamen hemorrhage

Clinical Review
 Amy Barone, MD MSCI and Dow-Chung Chi, MD
 NDA 207953
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Level	MedDRA Term
PT	Rectal hemorrhage
PT	Renal hematoma
PT	Renal hemorrhage
PT	Retinal hemorrhage
PT	Retinopathy hemorrhagic
PT	Scleral hemorrhage
PT	Scrotal haematocoele
PT	Scrotal hematoma
PT	Spermatic cord hemorrhage
PT	Spinal cord hemorrhage
PT	Spinal epidural hemorrhage
PT	Spinal hematoma
PT	Subarachnoid hemorrhage
PT	Subdural hematoma
PT	Subdural hemorrhage
PT	Subretinal hematoma
PT	Testicular hemorrhage
PT	Thalamus hemorrhage
PT	Traumatic intracranial hemorrhage
PT	Tumor hemorrhage
PT	Upper gastrointestinal hemorrhage
PT	Ureteric hemorrhage
PT	Urethral hemorrhage
PT	Uterine hematoma
PT	Uterine hemorrhage
PT	Vaginal hematoma
PT	Vaginal hemorrhage
PT	Vessel puncture site hematoma
PT	Vitreous hematoma
PT	Vitreous hemorrhage
PT	Vulval hematoma
PT	Vulval hemorrhage
PT	Subdural hematoma
PT	Subdural hemorrhage
PT	Subretinal hematoma
PT	Testicular hemorrhage
PT	Thalamus hemorrhage
PT	Traumatic intracranial hemorrhage
PT	Tumor hemorrhage
PT	Upper gastrointestinal hemorrhage
PT	Ureteric hemorrhage
PT	Urethral hemorrhage
PT	Uterine hematoma
PT	Uterine hemorrhage
PT	Vaginal hematoma
PT	Vaginal hemorrhage
PT	Vessel puncture site hematoma
PT	Vitreous hematoma
PT	Vitreous hemorrhage
PT	Vulval hematoma

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Level	MedDRA Term
PT	Vulval hemorrhage

Source: NDA 207953. Module 5.3.5.3. Integrated Summary of Safety.

Table 72. Multi-Organ Failure as Defined by Applicant.

Level	MedDRA Term
PT	Acute left ventricular failure
PT	Acute prerenal failure
PT	Acute respiratory distress syndrome
PT	Acute respiratory failure
PT	Cardiac failure
PT	Cardiac failure Acute
PT	Cardiac failure congestive
PT	Circulatory collapse
PT	Diastolic dysfunction
PT	Hepatic failure
PT	Hepatorenal failure
PT	Left ventricular failure
PT	Multi-organ disorder
PT	Multi-organ failure
PT	Myocardial depression
PT	Organ failure
PT	Renal failure
PT	Renal failure acute
PT	Respiratory failure
PT	Right ventricular failure

Source: NDA 207953. Module 5.3.5.3. Integrated Summary of Safety.

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/s/

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The secondary reviewer agrees with the major conclusions and recommendations of the primary reviewers. Note that in Table 33 exposure is in weeks not months.