CLINICAL REVIEW

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Reviewer Name(s)	Amy Barone, MD
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(Proposed) Trade Name	YONDELIS®
Applicant	Janssen
Dosage Form(s)	n/a
Applicant Proposed Dosing Regimen(s)	n/a
Applicant Proposed Indication(s)/Population(s)	n/a
Recommendation on Regulatory Action	Approve label changes (Section 8.5)
Recommended Indication(s)/Population(s) (if applicable)	n/a

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Trabectedin, formerly known as ecteinascidin-743 (ET-743), is a natural marine tetrahydroisoquinoline compound with antitumor properties first isolated from the Caribbean tunicate *Ecteinascidia turbinata*, a colony-forming tunicate that grows in coastal temperate seas[1]. A synthetic process was implemented in 2002 for the manufacture of the trabectedin drug substance. Trabectedin is an alkylating drug that binds guanine residues in the minor groove of DNA, forming adducts and resulting in a bending of the DNA helix towards the major groove[2]. Adduct formation triggers a cascade of events that can affect the subsequent activity of DNA binding proteins, including some transcription factors, and DNA repair pathways, resulting in perturbation of the cell cycle and eventual cell death. In October 2015, trabectedin received marketing authorization in the US for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen. As of 23 July 2017, trabectedin is approved for the treatment of STS in 78 countries.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application does not support the use of trabectedin in the studied pediatric populations across five clinical trials. The adverse event profile of trabectedin in the pediatric population studied appears to be similar to that of the adult population; however, the pediatric studies failed to demonstrate that trabectedin is effective in the treatment of pediatric patients. Use of trabectedin in this population is not recommended.

The Division and Medical Policy Council recommend that Pediatric Exclusivity be granted for trabectedin and that relevant information obtained from pediatric studies of trabectedin be incorporated into the Yondelis® package insert. This recommendation is based on the review finding that the Application Holder fairly responded to all of the elements in the Pediatric Written Request (PWR).

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Safety and effectiveness in pediatric patients have not been established. Safety (n=99) and efficacy (n=91) were assessed but not established across five open-label studies in pediatric patients with pediatric histotypes of sarcoma (predominantly non-rhabdomyosarcoma soft tissue sarcoma, Ewing sarcoma, rhabdomyosarcoma, and osteosarcoma). No new safety signals were observed in pediatric patients across these studies. Pharmacokinetic parameters in pediatric patients were within the range of values previously observed in adults given the same dose per body surface area.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Malignant bone tumors of the osteosarcoma subgroup and Ewing related sarcomas subgroup occurring at incidence rates of 4.6 and 2.9, respectively, per 1,000,000 children (ages 0 to 19 years). Osteosarcoma accounts for approximately 3% of childhood cancers overall; Ewing sarcoma is the second most common bone cancer in children (~2.8% of childhood cancers). • Five-year survival rates for patients with metastatic osteosarcoma are reported to be approximately 15% to 30%. • Soft tissue sarcoma and other extraosseous sarcomas make up approximately 7% of all childhood cancers where rhabdomyosarcomas constitute almost half of all pediatric STS • Five-year survival rates for metastatic STS in the pediatric population are reported to be approximately 20%.	Bone and soft tissue sarcomas are rare in childhood cancers. Patients with metastatic or recurrent disease have low 5-year survival rates.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Treatment options for pediatric patients with osteosarcoma include surgery and combination chemotherapy. Doxorubicin, cisplatin, and high-dose methotrexate with leucovorin rescue has been the standard of care in the treatment of osteosarcoma. • Treatment options for pediatric patients with recurrent and metastatic STS include radiation, surgical resection, and combination chemotherapy (vincristine, actinomycin, cyclophosphamide with or without ifosfamide and etoposide [VAC-IE]; or combination therapy with doxorubicin). • Current approved therapies for STS include trabectedin, pazopanib, olaratumab, and eribulin mesylate. Of these approved therapies, only trabectedin has been tested in the clinical study setting for efficacy and safety in pediatric patients with sarcoma.	There are no approved treatment options for pediatric patients with relapsed or recurrent sarcoma. Given the poor outcomes for patients with relapsed and metastatic pediatric sarcoma, new treatments are needed to improve survival in this population.
Benefit	• Of the 91 pediatric patients assessed for efficacy across the 5 studies, 3 patients showed disease response (1 complete responder, 2 partial responders). • Duration of responses after trabectedin treatment for the 3 patients with either a CR or PR ranged from 3.6 months to 10.3 months. One patient had a minor responder, and 13 patients had stable disease.	The few instances of disease response and disease control observed in trabectedin-treated pediatric patients with pediatric histotypes of sarcoma (i.e., predominantly rhabdomyosarcoma, osteosarcoma, and Ewing sarcoma) do not meet the level of benefit required to provide a new treatment option for pediatric patients with pediatric histotypes of sarcoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The systemic exposure and safety data for trabectedin presented in NDA 207953 for the treatment of L-type sarcomas, the predominant histotypes of sarcoma observed in adults, are consistent with the exposure and safety results reported in this application.	No new safety signals were observed in pediatric patients across these studies.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
	☐ Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Soft tissue and bone sarcomas are a group of rare and heterogenous tumors consisting of more than 70 different histopathologic type. Soft tissue sarcomas (STS) comprise <1% of all solid tumors[3]. STS with characteristics of mesenchymal-derived structures include rhabdomyosarcoma, fibrosarcoma, liposarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumors (MPNSTs), angiosarcoma, and hemangiopericytoma. STS with characteristics comparable to mesenchymal stem cells include Ewing sarcoma and undifferentiated sarcoma. The most commonly occurring (40-50%) histopathologic types of STS in the adult population are leiomyosarcoma and liposarcoma (L-type sarcoma). These adult L-type sarcomas are also known to occur, though rarely, in adolescents.

Pediatric bone and soft tissue sarcomas are rare, with malignant bone tumors of the osteosarcoma subgroup and Ewing-related sarcomas subgroup occurring at incidence rates of 4.6 and 2.9, respectively, per 1,000,000 children (ages 0 to 19 years)[4, 5]. Osteosarcoma accounts for approximately 3% of childhood cancers overall; Ewing sarcoma is the second most common bone cancer in children (~2.8% of childhood cancers)[5]. Soft tissue sarcoma and other extraosseous sarcomas make up approximately 7% of all childhood cancers occurring at an incidence rate of 11.6 per 1,000,000 children, with rhabdomyosarcomas constituting almost half of all pediatric STS (4.5 per 1,000,000 children). The incidence of non-rhabdomyosarcoma STS (NRSTS) is 4% for all childhood cancers; however, they account for 77% of STS among patients 15 to 19 years old[6].

2.2. Analysis of Current Treatment Options

Treatment options for bone and soft tissue sarcomas are based on the histopathologic tumor type.

Treatment options for pediatric patients with osteosarcoma include surgery and combination chemotherapy. Doxorubicin, cisplatin, and high-dose methotrexate with leucovorin rescue has been the standard of care in the treatment of osteosarcoma, and the adjuvant chemotherapy treatment has not changed since the 1970's as multiple clinical studies have not shown any significant improvement (response rates ranging from 26 to 46%). Five-year survival rates for patients with metastatic osteosarcoma are reported to be approximately 15% to 30%[5].

Treatment options for pediatric patients with recurrent and metastatic STS include

radiation, surgical resection, and combination chemotherapy (vincristine, actinomycin, cyclophosphamide with or without ifosfamide and etoposide [VAC-IE]; or combination therapy with doxorubicin). Response rates, which vary by STS histotype and extent of disease, range from approximately 30% to 70%. Five-year survival rates for metastatic STS in the pediatric population are reported to be approximately 20%[4]. Current approved therapies for STS include trabectedin, pazopanib, olaratumab, and eribulin mesylate. Of these approved therapies, only trabectedin has been tested in the clinical study setting for efficacy and safety in pediatric patients with sarcoma.

There is no approved treatment for relapsed or refractory bone or soft tissue sarcoma in pediatric patients.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

In October 2015, trabectedin received marketing authorization in the U.S. for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

3.2. Summary of Presubmission/Submission Regulatory Activity

- **December 4, 2000: FDA issued a formal pediatric written request (PWR)** for trabectedin (known as ecteinascidin). The request was issued to the manufacturer, PharmaMar, requesting that information from Phase 1 and 2 studies be submitted in support of an indication for trabectedin in children for the treatment of refractory or relapsed pediatric malignancies, with at least 1 study specifically in pediatric patients with refractory brain tumors
- **July 2, 2002: Amended PWR issued**
- December 2003: Johnson & Johnson Pharmaceutical Research & Development (JNJ PRD) acquired exclusive US sales and marketing rights to trabectedin, JNJ PRD requested changes to the PWR to reflect completed, ongoing, and planned studies. **On May 19, 2004, the PWR was amended in response to JNJ PRD's request**.
- December 24, 2008: JNJ PRD requested that Study ET743-SAR-2004 be added to the PWR. The protocol for Study ET743-SAR-2004 was submitted to the FDA on April 16, 2010.
- **October 04, 2010: FDA issued a revised PWR**, as the previous PWR dated May 19, 2004 had expired. The PWR was issued to JNJ PRD requesting information from Phase 1and 2 studies in support of an indication to use trabectedin in children for the treatment of soft tissue sarcoma (STS).
- December 21, 2011: JRD proposed to extend the PWR reporting due date to March 31,

2017. **On March 15, 2012, the FDA reissued the PWR** for children for the treatment of STS and extended the reporting due date to March 31, 2017.

- October 23, 2015: The FDA approved JRD's NDA 207953 for trabectedin for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.
- August 01, 2016: JRD submitted a Type C pre-sNDA meeting request/briefing document to obtain the FDA's input on the proposed format and content of this supplement. Written Responses were received from FDA on October 15, 2016.
- February 09, 2017: JRD submitted a memorandum in response to the FDA's Type C pre-NDA Meeting Written Responses. The memo contained revised proposals in response to the Agency's written responses dated October 15, 2016, and requested advice on the suitability of the proposed sNDA for review and compliance with the requirements of the PWR.
- February 28, 2017: FDA Senior Regulatory Health Project Manager, Anuja Patel, instructed JRD, via e-mail, to submit specific questions that JRD would like the FDA to address.
- March 09, 2017: JRD submitted specific questions for the agency to address regarding JRD's revised proposals in response to the Agency's written responses dated October 15, 2016.
- March 24, 2017: FDA Senior Regulatory Health Project Manager, Anuja Patel, indicated via e-mail that JRD's submission "plan appears acceptable; however, a final determination will be made on review of the official submission to the NDA".
- March 30, 2017: JRD proposed an amendment to the PWR to extend the reporting due date from March 31, 2017 to March 31, 2018
- **On July 31, 2017, the FDA amended the PWR**, extending the reporting due date to March 31, 2018.
- November 07, 2017: The FDA issued a new original Written Request with a due date of March 31, 2018 replacing the March 15, 2012 Written Request. Due to the request for deadline extension submitted on March 30, 2017, there was insufficient time for the Agency to review and act on the amendment in a timely manner. Thus, the original Written Request (March 15, 2012) had expired because the July 31, 2017 Amended Written Request was not issued prior to the date of expiration (March 31, 2017). **A new Pediatric Written Request was issued November 07, 2017**

3.3. Foreign Regulatory Actions and Marketing History

In September 2007, trabectedin received marketing authorization in the EU for the treatment of patients with advanced STS, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. As of July 23, 2017, trabectedin is approved for the treatment of STS in 78 countries. In October 2009, the European Commission granted approval for trabectedin in combination with pegylated liposomal doxorubicin for the treatment of patients with relapsed platinum sensitive ovarian

cancer. As of July 23, 2017, trabectedin is approved for the treatment of patients with relapsed platinum sensitive ovarian cancer in 70 countries.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested for this supplemental application.

4.2. Product Quality

No new product quality issues were identified during the review of this supplemental application.

4.3. Clinical Microbiology

No new microbiology issues were identified during the review of this supplement application.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology issues were identified during the review of this supplement application

4.5. Clinical Pharmacology

No new clinical pharmacology issues were identified during the review of this supplement application

4.6. Devices and Companion Diagnostic Issues

No companion diagnostic issues were identified during the review of this supplement application

4.7. Consumer Study Reviews

No consumer study review issues were identified during the review of this supplement application

5. Sources of Clinical Data and Review Strategy

This supplement is supported by the results of 2 dose-finding studies (ET-A-008-00 and ET743-SAR-2004) and 3 activity-estimating studies (ET-B-019-99, ET-B-023-00, and ET743-SAR-2005). All 5 studies were non-randomized, open-label studies.

5.1. Table of Clinical Studies

Table 1 Clinical Studies Conducted in Pediatric Patients

Study	Design	Tumor Type (Enrolled)	Dosing Schedule	No. of Pediatric Subjects (Pediatric Subjects Evaluable for PK)
Phase 1 ET-A-008-00	Non-randomized, open-label, dose-escalation study in children with refractory solid tumors	Osteosarcoma Ewing's sarcoma Wilms Tumor Hepatoblastoma Rhabdomyosarcoma Synovial sarcoma	Trabectedin: q3wk; 3-h regimen Starting dose: 1.1 mg/m^2 Escalation dose: 1.3 mg/m^2	Total=12 (8 PK evaluable) 6 (4 PK evaluable) 6 (4 PK evaluable)
Phase 1 ET743-SAR-2004	Non-randomized, open-label, limited-escalation study in children and adolescents with relapsed or refractory solid tumors	Desmoplastic small round cell Sarcoma NOS Synovial sarcoma Neuroendocrine carcinoma Nasopharyngeal carcinoma Osteosarcoma Ewing's sarcoma Peripheral nerve sheath tumor Brain stem glioma Chondrosarcoma	Trabectedin: q3wk; 24-h regimen Starting dose: 1.1 mg/m^2 Escalation doses: 1.5 mg/m^2 1.7 mg/m^2	Total=12 (5 PK evaluable) 3 (1 PK evaluable) 6 (3 PK evaluable) 3 (1 PK evaluable)
Phase 2 ET-B-019-99	Non-randomized, open-label study to evaluate efficacy (ORR), PK, and safety of trabectedin in subjects with previously treated osteosarcoma	Osteosarcoma	Trabectedin: q3wk; 24-h, 1.5 mg/m^2	Total=13 (9 PK evaluable)
Phase 2 ET-B-023-00	Non-randomized, open-label study to evaluate the efficacy and safety of trabectedin in subjects with previously treated advanced or recurrent sarcoma	Soft tissue sarcoma Osteosarcoma Ewing's sarcoma Rhabdomyosarcoma	Trabectedin: q3wk; 3-h regimen Starting dose: 1.5 mg/m^2 Starting dose: 1.3 mg/m^2 for subjects with prior high dose methotrexate exposure or high dose therapy requiring blood progenitor therapy	Total=12 subjects (PK not part of study design)
Phase 2 ET743-SAR-2005	Non-randomized, open-label study to evaluate the efficacy, PK, and safety of trabectedin in children with recurrent or refractory rhabdomyosarcoma, Ewing's sarcoma/peripheral PNET, and NRSTS.	Rhabdomyosarcoma Ewing's sarcoma/peripheral PNET Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS)	Trabectedin: q3wk; 24-h regimen 1.3 mg/m^2 1.5 mg/m^2	Total=50 (10 PK evaluable)[a] 8 (0 PK evaluable) 42 (10 PK evaluable)[a]

No.=number; NOS=not otherwise specified; NRSTS=non-rhabdomyosarcoma soft tissue sarcoma; ORR=objective response rate; PK=pharmacokinetic; PNET=primitive neuroectodermal tumors; q3wk=once every 21 days

[a] N=8 in the reanalysis of PK.

5.2. Review Strategy

The objectives of this review were two-fold: 1) to determine if the Applicant fairly responded to the elements outlined in the Written Request (WR) and 2) to provide recommendations for incorporation of relevant pediatric information derived from the conduct of the studies outlined in the WR into the Yondelis® package insert. To accomplish these objectives, data from the clinical trials submitted with this supplement were comprehensively reviewed. Documentation from previous interactions with FDA regarding the pediatric development plan for trabectedin, the WR, and relevant published literature were also reviewed.

6. Review of Relevant Individual Trials Used to Support Efficacy

These studies do not support a claim for efficacy. In this section, the trial design and results will be briefly summarized for each study.

Compliance with Good Clinical Practices
Studies ET-B-019-99 and ET-B-023-00, and ET743-SAR-2004 were conducted in accordance with International Conference on Harmonization Good Clinical Practice (GCP) guidelines. Study ET-A-008-00 was conducted in accordance with GCP guidelines, except that the individual PK data were not accessible to ensure the integrity of the data flow; and Study ET743-SAR-2005 was conducted in accordance with the National Cancer Institute's Cooperative Group guidelines.

Financial Disclosure
Financial Disclosure information for investigators participating in Studies ET-B-019-99, ET-B-023-00 and ET743-SAR-2005 is provided (See Section 13.2). The clinical studies ET-A-008-00 and E743-SAR-2004 are not covered clinical studies, therefore financial disclosure information is not provided for those studies.

Data Quality and Integrity
This submission contained sufficient datasets and relevant case report forms. The quality and integrity of the submission were adequate to permit a comprehensive review to describe the trials where the sponsor does not seek a new indication claim.

6.1. ET-A-008-00

6.1.1. Study Design

Overview and Objective

The main objective of Study ET-A-008-00 was to determine the recommended dose of trabectedin administered at escalating doses starting from 1.1 mg/m^2 as a 3-h IV infusion every 21 days (q3wk; 3-h) in children with refractory or relapsed solid tumors. Two subsequent dose escalations to 1.3 mg/m^2 and 1.5 mg/m^2 were planned, until a MTD was defined. This study was conducted by the Children's Oncology Group (COG) Phase 1 Consortium and sponsored by Pharma Mar, S.A. (PharmaMar).

Trial Design

This was a pediatric 3+3 dose-finding, non-randomized, open-label study.

Study Endpoints

Efficacy was not the primary objective of this study; however, response data were to be documented in patients who were evaluable for response, to further support future studies. Evaluation Criteria in Solid Tumors (RECIST Version 1.0) was to be used to classify response for patients with measurable disease at study entry and at the end of each cycle.

Statistical Analysis Plan

Descriptive statistics were used to summarize the response data.

Protocol Amendments

The protocol was amended to include dexamethasone as a prophylactic treatment every 12 h for 4 days starting before the trabectedin infusion during each cycle. Ondansetron (every 4 hrs with a maximum of 3 doses in a 24 h period) or granisetron (12 hrs prior to trabectedin treatment) was administered.

6.1.2. Study Results

Demographic Characteristics

Twelve pediatric patients with refractory solid tumors were enrolled and treated on Study ET-A-008-00. The median age was 10.5 years (range: 2 to 17 years). Half the patients were male and the majority were white. See Section 8.2.2 for comparison of demographics across all 5 trials.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Three patients had osteosarcoma, 3 patients had Ewing sarcoma, 2 patients had Wilms tumor, and 1 patient each had hepatoblastoma and rhabdomyosarcoma at study entry. See Section 7 for comparison of baseline characteristics across all 5 trials. Tumor type was not reported for 2 patients, however, in the published manuscript, the reported tumor type in the remaining two patients was osteosarcoma and synovial sarcoma.

Concomitant medications commonly used included: analgesics, antibiotics, anticoagulants, antihistamines, antinauseants, antianxiolytics,bronchodilators, granulocyte colony-stimulating factors, and laxatives.

Efficacy Results – Primary Endpoint

Efficacy was not the primary endpoint of this study. See Section 8 for review of safety and MTD.

Efficacy Results – Secondary and other relevant endpoints (includes Dose/Dose Response)

Overall, 8 (66.7%) patients experienced progressive disease. One patient was not evaluable for response.

- At the 1.3 mg/m^2 dose level, 1 patient with Ewing sarcoma achieved a complete response (CR) as best response after 12 treatment cycles. This patient withdrew consent for further treatment after 16 treatment cycles. One additional patient with osteosarcoma had a best response of stable disease after Cycle one, however, the patient discontinues after Cycle 2 due to progressive pulmonary disease.
- At the 1.1 mg/m^2 dose level, one patient with Ewing sarcoma had stable disease lasting for 2 cycles and was subsequently discontinued from the study due to a reason of "Other;" described as insufficient pulmonary function.

6.2. ET743-SAR-2004

6.2.1. Study Design

Overview and Objective

The main objective of Study ET743-SAR-2004 was to determine the recommended dose of trabectedin administered as a 24-h continuous IV infusion every 21 days (q3wk; 24-h) in children and adolescents with relapsed or refractory solid tumors. Trabectedin was to be

administered at a starting dose of 1.1 mg/m^2 and, subsequently, escalated to 1.5 and 1.7 mg/m^2; until a MTD was defined. This study was conducted by the Pediatric Oncology Branch of the National Cancer Institute.

Trial Design

This was an open-label, non-randomized, limited dose escalation trial.

Study Endpoints

World Health Organization (WHO) criteria were used to quantify tumor response. Radiographic evaluations of measurable disease were to be performed at baseline, prior to Cycle 3, and then every 2 cycles thereafter. For each patient, the same radiographic study (computed tomography, magnetic resonance imaging) was to be performed for re-evaluation whenever possible. These evaluations were also to be performed prior at the end of study visit.

Statistical Analysis Plan

Descriptive statistics were used to summarize the response data.

6.2.2. Study Results

Demographic Characteristics

Twelve patients with relapsed or refractory solid tumors were enrolled and treated in Study ET743-SAR-2004. The median age was 15.0 years (range: 8 to 16 years). Half the patients were male, and most patients (41.7%) were white.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Three (25.0%) patients had osteosarcoma, and the remaining 9 patients each had a different type of cancer at the time of enrollment (brain stem glioma, chondrosarcoma recurrent, desmoplastic small round cell tumor, Ewing sarcoma NOS, Nasopharyngeal cancer NOS, Neuroendocrine cancer NOS, Peripheral nerve sheath tumor malignant, Sarcoma NOS, synovial sarcoma recurrent).

Efficacy Results – Primary Endpoint

Efficacy was not the primary endpoint of this study. See Section 8 for review of safety and MTD.

Efficacy Results – Secondary and other relevant endpoints (includes Dose/Dose Response)

Six (50.0%) patients were reported to have stable disease as best response:

- One of the 6 patients with stable disease was treated at the 1.1 mg/m^2 dose (6 cycles of treatment administered)
- Three of the 6 patients with stable disease were treated at the 1.5 mg/m^2 dose (3, 6, and 18 cycles of treatment administered, respectively)
- Two of the 6 patients with stable disease were treated at the 1.7 mg/m^2 dose (2 and 4 cycles of treatment administered, respectively)

One additional patient (1.5 mg/m^2 cohort) with a neuroendocrine tumor achieved a best response of minor response (MR) and continued therapy for 12 cycles of treatment. Five patients had progressive disease. No patient in this study experienced a CR or partial response (PR).

6.3. ET-B-019-99

6.3.1. Study Design

Overview and Objective

The main objective of Study ET-B-019-99 was to determine the overall response rate (ORR) achieved with trabectedin in previously treated patients with osteosarcoma. This study was conducted by PharmaMar.

Trial Design

This was an activity-estimating, non-randomized, open-label, salvage therapy study evaluating the efficacy, PK, and safety of trabectedin in adult and pediatric patients with previously treated metastatic osteosarcoma. Trabectedin was administered at a dose of 1.5 mg/m^2 as a 24-h IV infusion once every 3 weeks (q3wk; 24-h). A 2-stage study design was employed with 25 patients planned for the first stage. If at least 1 response was observed, 8 additional patients were to be entered in a second stage.

Study Endpoints

World Health Organization criteria were used to quantify tumor response. Tumor assessments for all lesions were performed at least every 2 cycles during the study and every 3 months until disease progression was observed. Any tumor response was to be confirmed 4 weeks later. These data were used to evaluate ORR, duration of response (DOR), progression free survival (PFS), and overall survival (OS).

Statistical Analysis Plan

Descriptive statistics were used to summarize the response data.

6.3.2. Study Results

Demographic Characteristics

Of the 25 patients enrolled and treated with trabectedin, 13 were pediatric patients (i.e., ≤ 18 years of age). The median age of the pediatric patients was 16.0 years (range: 12 to 18 years). Three quarters (76.9%) of the pediatric patients were male, and patient race and ethnicity were not reported.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All patients had osteosarcoma.

Efficacy Results – Primary Endpoint

There were no responders; all pediatric patients (i.e., ≤18 years of age) showed progression of Disease.

6.4. ET-B-023-00

6.4.1. Study Design

Overview and Objective

The main objective of Study ET-B-023-00 was to determine the anti-tumor activity, by objective response rate, of trabectedin as a 3-h IV infusion once every 3 weeks (q3wk; 3-h) in adult and pediatric patients with previously treated, advanced or recurrent STS, osteosarcoma, Ewing Family of Tumors, or rhabdomyosarcoma. This study was conducted by PharmaMar.

Trial Design

This was an activity-estimating, non-randomized, open-label, uncontrolled trial evaluating the efficacy and safety of trabectedin in adult and pediatric patients with previously treated, advanced or recurrent STS, osteosarcomas, Ewing sarcoma, or rhabdomyosarcoma.. Trabectedin was to be administered at a dose of 1.3 mg/m^2 for patients with prior exposure to high-dose methotrexate (>1.5 g/m^2/cycle) or prior exposure to high dose therapy that included rescue with blood progenitors. All other patients were to receive trabectedin at a starting dose of 1.5 mg/m^2. All doses were administered as a 3-h IV infusion once every 3 weeks (q3wk; 3-h).

Study Endpoints

Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used to quantify tumor response. Tumor assessments for all lesions were performed at least every 2 cycles during the study and every 3 months until disease progression was observed. Whenever the criteria for response were met, the response was confirmed 4 weeks later. These data were used to evaluate best response, time to progression (TTP), and PFS.

Statistical Analysis Plan

Descriptive statistics were used to summarize the efficacy endpoint response rates. Time-related response parameters were analyzed according to the Kaplan-Meier method compared to historical control.

6.4.2. Study Results

Demographic Characteristics

Of the 75 patients enrolled and treated with trabectedin, 12 were pediatric patients (i.e., <18 years of age). The median age of the pediatric patients was 17.0 years (range: 13 to 18 years). Fifty-eight percent of pediatric patients were male, and all the pediatric patients were white.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Of the 12 pediatric patients enrolled, four had osteosarcoma (33.3%), five had Ewing sarcoma (41.7%), two had rhabdomyosarcoma (16.7%) and one had soft tissue sarcoma (8.3%).

Efficacy Results – Primary Endpoint

One pediatric patient achieved PR, with a DOR of 3.6 months (a 17-year old female in the 1.5 mg/m2 dose group with Ewing sarcoma). Two patients (1 with Ewing sarcoma and 1 with osteosarcoma, both in the 1.3 mg/m^2 dose group) achieved stable disease. Of the remaining patients, 8 patients had progressive disease, and 1 patient was not evaluable.

6.5. ET743-SAR-2005

6.5.1. Study Design

Overview and Objective

The main objective of Study ET743-SAR-2005 was to evaluate both the efficacy and the safety of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma/peripheral primitive neuroectodermal tumor (PNET), or NRSTS. This study was conducted by the COG.

Trial Design

This was an activity-estimating, non-randomized, open-label study evaluating the efficacy, PK, and safety of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma/peripheral PNET, or NRSTS. The study was designed to confirm the tolerability of the 1.3 mg/m2 and 1.5 mg/m2 q3wk; 24-h trabectedin dose regimens in an initial cohort of patients. This was followed by a Phase 2 portion of the study in which trabectedin at the 1.5 mg/m2 dose was formally assessed for efficacy in patients with 3 histologically defined strata.

A 2-stage design was employed to evaluate efficacy in the Phase 2 portion of the study.

- Ten response-evaluable patients were enrolled in the first stage in each of the disease strata (NRSTS, Ewing sarcoma/PNET, and rhabdomyosarcoma). If none of the patients in the first stage demonstrated a CR or PR, as determined by RECIST (Version 1.0), enrollment to that stratum was closed with the conclusion that trabectedin did not demonstrate sufficient activity for further investigation.
- If 6 or more objective responses were observed in the first stage, the enrollment to that stratum was closed with the conclusion that trabectedin demonstrated sufficient activity for further investigation. Otherwise, enrollment was continued for 20 response-evaluable patients.
- If 3 or more of the 20 patients demonstrated an objective response, then trabectedin activity was deemed sufficient for further investigation; otherwise, it was concluded that trabectedin did not demonstrate sufficient activity for further investigation.

Study Endpoints

Response Evaluation Criteria in Solid Tumors (RECIST Version 1.0) criteria were used to quantify tumor response. Tumor assessments were performed at the end of Cycle 2 and Cycle 4 and then every 3rd Cycle until the end of therapy. These data were used to evaluate best overall response, ORR, and CBR.

Statistical Analysis Plan

Descriptive statistics were used to summarize the efficacy endpoint response rates.

6.5.2. Study Results

Demographic Characteristics

Of the 50 patients enrolled, the median age was 15.5 years (range: 4 to 24 years). Sixty-two percent of patients were male, and 76.0% of patients were white.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Of the 50 patients enrolled, 16 had Ewing sarcoma, 23 had rhabdomyosarcoma and 11 had NRSTS. Of the 42 patients treated at the 1.5 mg/m2 q3w 24-h dose, 11 had Ewing sarcoma, 21 had rhabdomyosarcoma and 10 had NRSTS.

Efficacy Results – Primary Endpoint

Of the 50 patients enrolled, 42 patients enrolled at the 1.5 mg/m^2 q3wk; 24-h dose; one was not treated. Of the 41 patients were treated with trabectedin at the 1.5 mg/m^2 dose, three (7.1%) patients had stable disease and 1 (2.4%) patient with rhabdomyosarcoma achieved PR. Thirty-six patients (85.7%) had progressive disease. Two patients were considered not evaluable: one patient due to withdrawal of consent and one patient due to non-compliance. The patients enrolled at the 1.3 mg/m^2 q3w were not included in the efficacy analysis, however, in this this group (n=8), one patient with Ewing sarcoma had a best response of unconfirmed PR (followed by progressive disease 3 weeks later), one had a best response of stable disease and the remaining six patients had progressive disease.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Table 2 provides a side-by-side comparison of the response rate across all studies. Of the 99 pediatric patients enrolled across all 5 studies, 91 pediatric patients were assessed for efficacy; the 8 patients in Study ET743-SAR-2005 at the 1.3 mg/m^2 dose were not evaluated for efficacy. Of the 91 pediatric patients assessed for efficacy across the 5 studies, 3 patients showed disease response (1 complete responder, 2 partial responders). Duration of responses after trabectedin treatment for the 3 patients with either a CR or PR ranged from 3.6 months to 10.3 months. One patient had a minor responder, and 13 patients had stable disease.

Table 2 Side-by-Side Comparison of Results Across studies (copied from Summary of Clinical Efficacy, verified by reviewer)

	ET-A-008-00		ET743-SAR-2004			ET-B-019-99	ET-B-023-00	ET743-SAR-2005	
Dosing Regimen	Trabectedin 1.1 mg/m^2 q 3 wk; 3-h	Trabectedin 1.3 mg/m^2 q 3 wk; 3-h	Trabectedin 1.1 mg/m^2 q 3 wk; 24-h	Trabectedin 1.5 mg/m^2 q 3 wk; 24-h	Trabectedin 1.7 mg/m^2 q wk; 24-h	Trabectedin 1.5 mg/m^2 q 3 wk; 24-h	Trabectedin 1.1, 1.3, or 1.5 mg/m^2 q 3 wk; 3-h	Trabectedin 1.3 mg/m^2 q 3 wk; 24-h	Trabectedin 1.5 mg/m^2 q 3 wk; 24-h
No. Subjects	6[a]	6	3	6	3	25	75	8	42
No. of Pediatric Subjects Treated	6	6	3	6	3	13	12	8	41
Treatment Information									
Median no. cycles (range)	1 (1 to 2)	5.5 (1 to 16)	2 (1 to 6)	4.5 (1 to 18)	2 (1 to 4)	2 (1 to 2)	2 (1 to 7)	2 (1 to 5)	2 (1 to 15)
Cycles administered (cycles/no. subjects)	1/5; 2/1	1/4; 2/1; 16/1	1/1; 2/1; 6/1	1/1; 2/1; 3/1; 6/1; 12/1; 18/1	1/1; 2/1; 4/1	1/3; 2/10	1/2; 2/7; 3/1; 4/1; 7/1	1/2; 2/4; 3/1; 5/1	1/20; 2/15; 3/2; 4/2; 7/1; 15/1
Efficacy									
Criteria used	RECIST		WHO-2 dimensional			WHO	RECIST	-	RECIST
Complete response	0	1 (16.7%)	0	0	0	0	0	-	0
Partial response	0	0	0	0	0	0	1 (8.3%)	-	1 (2.4%)
Minor response	0	0	0	1 (16.7%)	0	0	0	-	0
Stable disease	1 (16.7%)	1 (16.7%)	1 (33.3%)	3 (50.0)	2 (66.7%)	0	2 (16.7%)	-	3 (7.1%)
Progressive disease	5 (83.3%)	3 (50.0%)	2 (66.7%)	2 (33.3%)	1 (33.3%)	13 (100.0%)	8 (66.7%)	-	36 (85.7%)
Not evaluable	-	1 (16.7%)	-	-	-	-	1 (8.3%)	-	2 (4.8%)

Note: Data summarized from clinical study reports as noted in the cross references below. An analysis of pediatric subject data by dose was not available in the ET-B-023-00 clinical study report, but is provided in Appendix 3.

Key: q3wk=once every 21 days; RECIST = response evaluation criteria in solid tumors; WHO = World Health Organization

[a] One subject was excluded from study at the time of the first dose. (Mod5.3.3.3/ET-A-008-00/Sec4.1)

7.1.2. Subpopulations

A summary of best overall tumor response by tumor type is described below. Incidences of disease response (CR or PR) were observed in 3 pediatric patients; 1 patient with rhabdomyosarcoma and 2 with Ewing sarcoma (ORR 3%).

- Of the 20 patients with Ewing sarcoma who were evaluated for efficacy, 1 (5.0%) patient had a CR, 1 (5.0%) patient had a PR, and 3 (15.0%) patients had stable disease. The overall objective response rate for patients with Ewing sarcoma was 10% (2/20). One additional patient in study ET743-SAR-2005 had an unconfirmed PR.
- Of the 24 pediatric patients with rhabdomyosarcoma who were evaluated for efficacy, 1 (4.2%) patient had a PR and 1 (4.2%) patient had stable disease.
- Of the 23 pediatric patients with osteosarcoma who were evaluated for efficacy, 5 (21.7%) patients had stable disease.
- Stable disease was reported by 1 patient each with the following tumor types: brain stem glioma, desmoplastic small round cell tumor, nasopharyngeal cancer, and NRSTS.
- A MR was reported for 1 patient with neuroendocrine cancer.

7.1.3. Dose and Dose-Response

Of the 54 pediatric patients treated at the approved dose and regimen of trabectedin (1.5 mg/m^2, q3wk; 24-h), 1 patient had a PR, 1 patient had a MR, and 6 patients had stable disease.

- At the q 3wk; 3-h regimen, best overall responses included:
  - 1 patient with stable disease at 1.1 mg/m^2
  - 1 patient with a CR and 3 patients with stable disease at 1.3 mg/m^2
  - 1 patient with a PR at 1.5 mg/m^2
- At the q 3wk; 24-h regimen, best overall responses included
  - 1 patient with stable disease at 1.1 mg/m^2 1 patient with a PR
  - 1 patient with a MR, and 6 patients with stable disease at 1.5 mg/m^2
  - 2 patients with stable disease at 1.7 mg/m^2

7.2. Integrated Assessment of Effectiveness

Of the 91 pediatric patients with sarcoma assessed for efficacy across the 5 studies, 17 patients showed disease response (1 complete responder, 2 partial responders) or disease control (1 minor responder, 13 patients with stable disease). Duration of responses after trabectedin treatment for the 3 patients with either a CR or PR ranged from 3.6 months to 10.3 months. Based on these results, an indication for trabectedin in the treatment of pediatric patients with

sarcoma.

8. Review of Safety

8.1. Safety Review Approach

The data evaluating the safety of trabectedin for the treatment of pediatric patients with sarcoma are available from 2 dose-escalation (ET-A-0080, ET743-SAR-2004) and 3 activity-estimating studies (ET-B-019-99, ET-B-023-00, and ET743-SAR-2005) as described in Sections 5 and 6. Of the 99 pediatric patients enrolled across all 5 studies, 98 were evaluable for safety. Treatment-emergent adverse events (AEs) were reported in the clinical databases for Studies ET743-SAR-2004, ET-B-019-99, and ET-B-023-00. Additional source information was used to identify treatment-emergent AEs in Studies ET-A-008-00 and ET743-SAR-2005.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Across all five trials, trabectedin was administered as a monotherapy to pediatric patients with sarcoma at doses of 1.1 mg/m^2, 1.3 mg/m^2, 1.5 mg/m^2 and 1.7 mg/m^2. Descriptive statistics (mean, standard deviation, median, and range) for trabectedin in pediatric patients is based on an analysis of data from 5 clinical trials and are provided for the number of treatment cycles and cumulative dose of trabectedin (Table 3). Across the 5 studies, the median number of treatment cycles ranged from 1 to 2.5 cycles, with a maximum of 18 cycles. The median cumulative dose of trabectedin ranged from 1.30 to 3.55 mg/m^2, with a maximum cumulative dose of 27.0 mg/m^2.

In 3 of the 5 studies (ET743-SAR-2004, ET-B-019-99, and ET743-SAR-2005), a total of 60 pediatric patients received trabectedin in accordance with the approved dose and Schedule; similar exposure was observed as compared to the same dose regimen in adults. Please see the Clinical Pharmacology Review for more detail.

Table 3 Summary of Exposure to Trabectedin by Study (copied from Summary of Clinical Safety)

	ET-A-008-00	ET743-SAR-2004	ET-B-019-99	ET-B-023-00	ET743-SAR-2005
Treated Pediatric Subjects	12	12	13	12	49
Number of Cycles					
Mean (SD)	2.4 (4.29)	4.8 (5.22)	1.8 (0.44)	2.5 (1.62)	2.1 (2.21)
Median	1.0	2.5	2.0	2.0	2.0
Range	(1; 16)	(1; 18)	(1; 2)	(1; 7)	(1; 15)
Cumulative Dose of Trabectedin					
Mean (SD)	3.03 (5.618)	6.73 (7.562)	2.61 (0.641)	3.28 (2.318)	3.06 (3.258)
Median	1.30	3.55	3.00	2.60	2.60
Range	(1.1; 20.8)	(1.1; 27.0)	(1.5; 3.0)	(1.1; 9.9)	(1.3; 22.5)

8.2.2. Relevant characteristics of the safety population:

Demographic and baseline disease characteristics of the patient population are provided by study in Table 4. The majority of patients in the safety analysis set were white and male, with ages ranging from 2 years to 24 years of age. Across all studies, >10 patients had sarcoma histotypes of rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, or NRSTS. The median number of lines of prior chemotherapy ranged from 2 to 3.

- In the dose-escalation trials (ET-A-008-00 and ET743-SAR-2004), the majority of patients were white and 50% were male. Osteosarcoma, Ewing sarcoma, and Wilms tumor were the tumor types occurring in 2 or more patients per treatment group.

- In the activity-estimating trials (ET-B-019-99, ET-B-023-00, and ET743-SAR-2005), the majority of patients were white and male. Patient tumor types included osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, STS, and NRSTS.

Tumor type was not reported for 2 patients in ET-A-008-00, however, in the published manuscript, the reported tumor type in the remaining two patients was osteosarcoma and synovial sarcoma.

Table 4 Side-by-Side Comparison of Study Populations (copied from Summary of Clinical Efficacy, verified by reviewer)

	ET-A-008-00		ET743-SAR-2004			ET-B-019-99	ET-B-023-00	ET743-SAR-2005	
Dosing Regimen	Trabectedin 1.1 mg/m^2 q 3 wk; 3-h	Trabectedin 1.3 mg/m^2 q 3 wk; 3-h	Trabectedin 1.1 mg/m^2 q 3 wk; 24-h	Trabectedin 1.5 mg/m^2 q 3 wk; 24-h	Trabectedin 1.7 mg/m^2 q wk; 24-h	Trabectedin 1.5 mg/m^2 q 3 wk; 24-h	Trabectedin 1.1, 1.3, or 1.5 mg/m^2 q 3 wk; 3-h	Trabectedin 1.3 mg/m^2 q 3 wk; 24-h	Trabectedin 1.5 mg/m^2 q 3 wk; 24-h
No. Subjects	6[a]	6	3	6	3	25	75	8	42
No. of Pediatric Subjects Treated	6	6	3	6	3	13	12	8	41
Demographic Characteristics									
Gender, n (%)									
Male	3 (50.0%)	3 (50.0%)	2 (66.7%)	2 (33.3%)	2 (66.7%)	10 (76.9%)	7 (58.3%)	7 (87.5%)	24 (57.1%)
Female	3 (50.0%)	3 (50.0%)	1 (33.3%)	4 (66.7%)	1 (33.3%)	3 (23.1%)	5 (41.7%)	1 (12.5%)	18 (42.9%)
Median age (years)/range	11.0/3-17	9.0/2-16	15.0/11-15	15.0/13-16	11.0/8-15	16.0/12-18	17.0/13-18	18.5/9-24[b]	15.0/4-22[b]
Race, n (%)									
White/Caucasian	5 (83.3%)	3 (50.0%)	3 (100.0%)	2 (33.3%)	0	NA	12 (100%)	6 (75.0%)	32 (76.2%)
African American	1 (16.7%)	0	0	2 (33.3%)	1 (33.3%)	NA	0	1 (12.5%)	6 (14.3%)
Asian	0	1 (16.7%)	0	0	1 (33.3%)	NA	0	0	2 (4.8%)
Hispanic	0	0	0	1 (16.7%)	1 (33.3%)	NA	0	0	0
Other	0	2 (33.3%)	0	0	0	NA	0	1 (12.5%)	1 (2.4%)
Unknown	0	0	0	1 (16.7%)	0	NA	0	0	1 (2.4%)
Disease Characteristics									
Histology, n (%)									
Osteosarcoma	2 (40.0%)	1 (20.0%)	0	2 (33.3%)	1 (33.3%)	13 (100%)	4 (33.3%)	0	0
Ewing's sarcoma	1 (20.0%)	2 (40.0%)	0	1 (16.7%)	0	0	5 (41.7%)	5 (62.5%)	11 (26.2%)
Wilms tumor	2 (40.0%)	0	0	0	0	0	0	0	0
Hepatoblastoma	0	1 (20.0%)	0	0	0	0	0	0	0
Rhabdomyosarcoma	0	1 (20.0%)	0	0	0	0	2 (16.7%)	2 (25.0%)	21 (50.0%)
Synovial sarcoma	0	0[b]	1 (33.3%)	0	0	0	0	0	0
Desmoplastic small round cell	0	0	1 (33.3%)	0	0	0	0	0	0
Sarcoma NOS	0	0	1 (33.3%)	0	0	0	0	0	0
Neuroendocrine carcinoma	0	0	0	1 (16.7%)	0	0	0	0	0
Nasopharyngeal carcinoma	0	0	0	1 (16.7%)	0	0	0	0	0
Peripheral nerve sheath tumor	0	0	0	1 (16.7%)	0	0	0	0	0
Brain stem glioma	0	0	0	0	1 (33.3%)	0	0	0	0
Chondrosarcoma	0	0	0	0	1 (33.3%)	0	0	0	0
Soft tissue sarcoma	0	0	0	0	0	0	1 (8.3%)	0	0
NRSTS	0	0	0	0	0	0	0	1 (12.5%)	10 (23.8%)
Prior Chemotherapy									
Median no. of lines	3	2	1	1.5	4	3	2	NA	NA

Note: Data summarized from clinical study reports as noted in the cross references below. An analysis of pediatric subject data by dose was not available in the ET-B-023-00 clinical study report, but is provided in Appendix 3.

Key: NA=information not available; NOS=not otherwise specified; NRSTS=non-rhabdomyosarcoma soft tissue sarcoma; q3wk=once every 21 days

[a] One subject was excluded from study at the time of the first dose. (Mod5.3.3.3/ET-A-008-00/Sec4.1)

[b] Per protocol, the age at diagnosis was ≤21 years of age for all subjects.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

An assessment of the data collected in each of the 5 individual studies showed that differences in patient populations (i.e., sarcoma histotype), doses and dose regimens of trabectedin, and inconsistencies in data collection procedures and assessment criteria make the integration of safety data across studies uninformative. Database limitations that impacted data integration are summarized in Table 5. Sufficient clinical data from the individual studies are available to assess the safety of trabectedin in the pediatric population.

Table 5 Summary of Database Limitations (copied from Summary of Clinical Safety)

Category	Available	Not Available
Demographics	Completely reported for 4 studies	Partially reported for Study ET-B-019; where race is not reported.
AE terminology	MedDRA was used for 2 studies, but different versions were used (version 4.0 for ET-B-019; version 5.0 for ET-B-023).	Instead of MedDRA, AEs were reported using NCI-CTCAE terminology for 3 studies, but different versions (2.0 and 3.0) were used. In addition, the protocols for Studies ET-B-019 and ET-B-023 specified that laboratory abnormalities not be reported as AEs. This affects the incidence reporting of some of the most common AEs observed with trabectedin.
AE by toxicity grade	NCI-CTCAE used for 5 studies but different versions were used.	The use of different NCI-CTCAE versions prevents data integration as some of the trabectedin-related toxicities cannot be coded to same NCI-CTCAE version (ie, the toxicity grades are not comparable across the NCI-CTCAE versions and, therefore, across the studies).
AE seriousness	Classification of AEs as serious was reported for 3 studies.	Database classification of AEs as serious or not serious was not performed for Studies ET-A-008 and SAR-2005. Supplemental materials other than the database (eg, synoptic and progress reports, published peer reviewed literature, and the Global Safety Database) were used to partially address SAEs in the CSRs. However, this information is not available programmatically, precluding an integrated analysis of SAEs.
AEs leading to dose modifications	Reported for 2 studies	Not reported for ET-A-008, ET-B-023, and SAR-2005.
AEs leading to treatment discontinuation	Reported for 2 studies	Not reported for Studies ET-A-008, ET-B-023, and SAR-2005.
AE outcome	Reported for 4 studies	Not reported for Study ET-A-008.
Laboratory values	Reported for 3 studies.	Not reported for Studies ET-A-008 and SAR-2005. Abnormalities in laboratory values were reported as AEs.

AE=adverse event; CSR=clinical study report; MedDRA= Medical Dictionary for Regulatory Activities; NCI-CTCAE= National Cancer Institute–Common Terminology Criteria of Adverse Events; SAE=serious adverse event

Studies ET-A-008-00 and ET743-SAR-2005 had limitations in the databases regarding the reporting of SAEs and adverse event (AE) outcomes; therefore, additional sources of information were used to identify SAEs and treatment-emergent adverse events (TEAEs)

leading to treatment discontinuation.

- The ET-A-008-00 database provided to Janssen R&D did not include data reporting the seriousness of AEs; however, the study sponsor's synoptic report provided to Janssen R&D did report treatment-emergent SAEs in Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. The SAE assessment is aligned with the treatment emergent SAEs reported in the synoptic report and is correlated to the National Cancer Institute-Common Terminology Criteria of Adverse Events (NCI-CTCAE) reported terms from the database. In addition, TEAEs leading to discontinuation were not identified in the TEAE database. Patients with TEAEs leading to discontinuation were identified by the Sponsor through the patient disposition listing, with specific TEAEs leading to discontinuation being reported in the clinical comments. These AEs were then aligned with both the CTCAE reported terms in the database and the MedDRA preferred terms in the sponsor provided synoptic report.
- The ET743-SAR-2005 database provided to Janssen R&D did not identify the seriousness of AEs. Instead, expeditiously reported adverse events (AdEERS) were reported as treatment emergent SAEs in the clinical database and by the study sponsor (COG) in the Final Study Progress Report. In addition, TEAEs leading to discontinuation were not identified in the TEAE database. Patients with TEAEs leading to discontinuation were identified by the Sponsor through the patient disposition listing, with specific TEAEs leading to discontinuation being reported in the clinical comments.

Validation was undertaken by the Sponsor to confirm the safety findings reported in the clinical studies conducted by the Children's Oncology Group (COG) (ET-A-008-00 and ET743-SAR-2005), the National Institute of Health (ET743-SAR-2004), and Pharma Mar, S.A. (PharmaMar, ET-B-019-99 and ET-B-023-00). The validation exercise consisted of the re-creation of the summary safety tables in each clinical study, where the total safety population was evaluated and not just the pediatric population. All validation findings were minor and had no impact of the reporting of safety for the pediatric patients.

8.3.2. Categorization of Adverse Events

Treatment-emergent AEs were defined as any AEs aggravated in severity or frequency from baseline or that occurred on or after the first dose of the study drug, and within 30 days after the last treatment dose. A serious treatment emergent (TEAE) was defined as any event that was fatal or immediately life-threatening, resulted in or prolonged an existing hospitalization, was permanently or significantly disabling, was a congenital anomaly, or required medical or surgical intervention to prevent permanent sequelae or any of the previously mentioned outcomes. See Section 8.3.1. and Table 5 for limitations.

8.4. Safety Results

8.4.1. Deaths

There were no treatment emergent adverse events leading to death. All deaths were due to progressive disease.

8.4.2. Serious Adverse Events

Treatment-emergent serious adverse events (SAEs) reported across the five trials in pediatric patients were similar to the SAEs reported in adults who received trabectedin as monotherapy. Database classification of AEs as serious or not serious was not performed for Studies ET-A-008 and SAR-2005 (see Section 8.3). Supplemental materials other than the database (e.g., synoptic and progress reports, published peer reviewed literature, and the Global Safety Database) were used to partially address SAEs in the CSRs. However, this information is not available programmatically, precluding an integrated analysis of SAEs. Across Studies ET743-SAR-2004, ET-B-019-99, and ET-B-023-00, the incidence of treatment emergent SAEs was similar (16.7%, 23.1%, and 16.7%, respectively). Except for dyspnea (2 patients), all treatment-emergent SAEs occurred as single-incident events: elevations in liver function enzymes [ALT, AST, GGT], elevations in CPK, neutropenia, infection, pneumonia, febrile neutropenia, respiratory distress, dyspnea, pain, nausea, fatigue, pleural effusion, and general physical health deterioration (See Table 6).

Table 6 Serious Adverse Events by Study (copied from Summary of Clinical Safety)

	ET-A-008-00[c]	ET743-SAR-2004	ET-B-019-99[a]	ET-B-023-00[a]	ET743-SAR-2005[c]
Treated Pediatric Subjects	12	12	13	12	49
Number of subjects with at least one serious TEAE[b]	N/A	2 (16.7%)	3 (23.1%)	2 (16.7%)	N/A
System organ class/Preferred term[b]					
Blood and lymphatic system disorders	N/A	1 (8.3%)	0	0	N/A
Febrile neutropenia	N/A	1 (8.3%)	0	0	N/A
General disorders and administration site conditions	N/A	0	0	1 (8.3%)	N/A
General physical health deterioration	N/A	0	0	1 (8.3%)	N/A
Infections and infestations	N/A	2 (16.7%)	0	0	N/A
Infection	N/A	1 (8.3%)	0	0	N/A
Pneumonia	N/A	1 (8.3%)	0	0	N/A
Investigations	N/A	1 (8.3%)	0	0	N/A
Neutropenia	N/A	1 (8.3%)	N/A	N/A	N/A
Musculoskeletal and connective tissue disorders	N/A	0	2 (15.4%)	0	N/A
Back pain	N/A	0	1 (7.7%)	0	N/A
Pain in extremity	N/A	0	1 (7.7%)	0	N/A
Respiratory, thoracic and mediastinal disorders	N/A	0	2 (15.4%)	1 (8.3%)	N/A
Dyspnoea	N/A	0	2 (15.4%)	0	N/A
Pleural effusion	N/A	0	0	1 (8.3%)	N/A

Key: JRD=Janssen Research & Development, LLC, MedDRA=Medical Dictionary for Regulatory Activities, N/A= Not Applicable: information not available in data source.
TEAE=treatment-emergent adverse events.
Note: Percentages calculated with the number of treated pediatric subjects in each study as denominator.
[a] Protocols for Studies ET-B-019-99 and ET-B-023-00 specifically instructed investigators not to report laboratory abnormalities as adverse events in the case report form adverse event page but rather only in the case report form laboratory page.
[b] To allow for a side-by-side comparison of adverse events across studies, JRD mapped and up-versioned the datasets for all 5 studies to MedDRA version 16.0.
[c] Data for serious TEAE were not collected for Study ET-A-008-00 and ET743-SAR-2005.
Abdominal pain: pooled terms Abdominal pain, Abdominal pain upper and Abdominal pain lower.
Injection site reaction includes the following Preferred Terms: Catheter site pain, Catheter site inflammation, Injection site pain, Catheter site erythema, Catheter site pruritus, Catheter site swelling, Infusion site extravasation, Catheter site oedema, Catheter site related reaction, Infusion site pain, Injection site bruising, Injection site reaction, Catheter site bruise, Infusion site reaction, Phlebitis and Vascular access complication.
Leukopenia: pooled terms Leukopenia and White blood cell count decreased.
Anaemia: pooled terms Anaemia and Haemoglobin decreased.
Blood bilirubin increased: pooled terms Blood bilirubin increased and Hyperbilirubinaemia.
Renal failure: pooled terms Renal failure and Renal failure acute.

	ET-A-008-00[c]	ET743-SAR-2004	ET-B-019-99[a]	ET-B-023-00[a]	ET743-SAR-2005[c]
Thrombocytopenia: pooled terms Thrombocytopenia and Platelet count decreased.					
Neuropathy peripheral: pooled terms Neuropathy peripheral and Peripheral sensory neuropathy.					
Gamma-glutamyltransferase increased: pooled terms Gamma-glutamyltransfersase increased and Gamma-glutamyltransferase.					
Blood alkaline phosphatase increased: pooled terms Blood alkaline phosphatase increased and Blood alkaline phosphatase.					
Pneumonia: pooled terms Pneumonia, Lung infection, and Lobar pneumonia.					
Sepsis: pooled terms Sepsis and Clostridium difficile sepsis.					
Lymphopenia: pooled terms Lymphopenia and Lymphocyte count decreased.					
Neutropenia: pooled terms Neutropenia and Neutrophil count decreased.					
Blood albumin decreased: pooled terms Hypoalbuminaemia and Blood albumin decreased.					

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Treatment emergent AEs leading to treatment discontinuation in the pediatric population are consistent with the TEAEs leading to treatment discontinuation in adult patients with STS. In 2 of the 5 studies (ET743-SAR-2004 and ET-B-019-99), no TEAEs leading to treatment discontinuation were reported. In the other 3 studies, TEAEs leading to treatment discontinuation included increases in liver function enzymes (ALT, AST, GGT, or ALP), thrombocytopenia, and prolonged neutropenia.

The TEAEs leading to dose reductions and cycle delays in the pediatric population are consistent with the TEAEs leading to dose reductions and cycle delays in adult patients with STS. Treatment-emergent AEs leading to dose reductions in the pediatric patients treated with trabectedin included: fatigue, anorexia, dehydration, increases in GGT, thrombocytopenia, neutropenia, increases in CPK, and liver function test abnormalities. Treatment-emergent AEs leading to cycle delays included increases in CPK, prolonged myelosuppression, liver toxicity, hematologic toxicity, neutropenia, and thrombocytopenia.

8.4.4. Significant Adverse Events

The following events of clinical interest were identified because of their association with trabectedin treatment, association with other therapies used in the treatment of pediatric patients with sarcoma, or medical significance in the oncology pediatric population: hepatotoxicity, myelotoxicity, infections, rhabdomyolysis, respiratory failure, cardiotoxicity, and mucositis. There were no incidences of cardiotoxicity, rhabdomyolysis, mucositis, or drug-related respiratory failure reported in pediatric patients with sarcoma treated with trabectedin as a monotherapy.

Across the 5 studies, events of clinical interest that pediatric patients experienced included: hepatotoxicity, myelotoxicity, infection, and increases in CPK. Frequency and severity is consistent with current prescriber information.

Hepatotoxicity: The frequency of hepatotoxicity for Studies ET-A-008-00, ET743-SAR-2004, and ET743-SAR-2005 was 91.7%, 100.0%, and 59.2%, respectively. The most frequently reported TEAEs (≥20% for all 3 studies) were elevated ALT and AST levels. In addition, 83.3% of patients in Study ET743-SAR-2004 experienced elevated GGT levels and 58.3% of patients each experienced hypoalbuminemia and increases in blood ALP. In Study ET743-SAR-2005, 24.5% of patients also experienced increases in GGT levels. In Studies ET-B-019-99 and ET-B-023-00, the related laboratory tests with the highest proportions of patients having on-treatment abnormalities were increased ALT (92.3% and 100%, respectively), AST (100% in both

studies), and GGT (100% in both studies).

Myelotoxicity: The frequency of myelotoxicity for Studies ET-A-008-00, ET743-SAR-2004, and ET743-SAR-2005 was 50.0%, 100.0%, and 51.0%, respectively. The most frequently reported TEAEs (≤ 20% for all 3 studies) were neutrophil count decreased and white blood cell (WBC) count decreased. In addition, 100% and 20.4% of patients in Studies ET743-SAR-2004 and ET743-SAR-2005, respectively, experienced lymphopenia and 58.3% and 14.3% of patients in those respective studies experienced decreased platelets. In Studies ET-B-019-99 and ET-B-023-00, the related laboratory tests with the highest proportions of patients who had on-treatment abnormalities were decreased neutrophils (84.6% and 83.3%), decreased WBC count (84.6% and 83.3%), decreased lymphocytes (75.0% in Study ET-B-023-00 only; as lymphocytes were not systematically collected in Study ET-B-019-99), and decreased platelets (53.8% and 50.0%).

Infections: In Study ET743-SAR-2004, 2 patients (16.7%) experienced infections of pneumonia, lip infection, and upper respiratory tract infection; and in Study ET743-SAR-2005, 3 patients (6.1%) experienced events of mucosal infection and 1 patient experienced sepsis. All other TEAEs in this category were reported as single incidence events. The most frequently reported drug-related TEAE was mucosal infection (2 patients [4.1%]). All other drug-related TEAEs in this category were reported as single incidence events.

Rhabdomyolysis: While there were instances of increased CPK levels, there were no corresponding incidences of rhabdomyolysis. The frequency of blood CPK increased for Studies ET-A-008-00, ET743-SAR-2004, and ET743-SAR-2005 was 8.3%, 25.0%, and 2.0%, respectively. In Studies ET-B-019-99 and ET-B-023-00, the proportions of patients with laboratory CPK test abnormalities were 18.2% and 20%, respectively.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The safety profiles of pediatric patients receiving trabectedin as a monotherapy were consistent across the 5 studies with >80% of patients in each study experiencing a TEAE (see Table 7 below). The most common TEAEs (≥25%) among the 98 pediatric patients treated with trabectedin were elevated liver function enzymes (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma glutamyltransferase [GGT] and alkaline phosphatase [ALP]), decreases in albumin and circulating blood cells (i.e., lymphopenia, anemia, leukopenia, thrombocytopenia, and neutropenia), increases in creatine phosphokinase (CPK) and uric acid levels, nausea, vomiting, fatigue/asthenia, pain, headache, pyrexia/fever, decreased appetite, constipation, dehydration, hypotension, injection site reaction, prolonged thromboplastin time, and changes in electrolytes.

Across all 5 studies, Grade 3-4 TEAEs (≥10%) included hematologic (anemia, neutropenia,

thrombocytopenia, leukopenia, lymphopenia) and non-hematologic abnormalities (increased ALT, AST, and GGT), fatigue, pain, decreased appetite, pneumonia, headache, and dyspnea. These Grade 3-4 TEAEs are consistent with those observed in adults receiving trabectedin as a monotherapy and regardless of dose and regimen.

In Study ET743-SAR-2005, two patients that developed deep venous thrombosis despite the use of a central line and one patient required usage of anticoagulant and removal of the central line. One additional patient developed a 13 month after having completed protocol treatment and had received regimen containing other myelotoxic drugs such as temozolomide and etoposide.

Table 7 Treatment-Emergent Adverse Events ≥10% of Pediatric Patients Treated in any Study (copied from Summary of Clinical Safety and verified by reviewer)

	ET-A-008-00	ET743-SAR-2004	ET-B-019-99[a]	ET-B-023-00[a]	ET743-SAR-2005
Treated Pediatric Subjects	12	12	13	12	49
Number of subjects with at least one TEAE[b]	12 (100.0%)	12 (100.0%)	13 (100.0%)	10 (83.3%)	40 (81.6%)
System organ class/Preferred term[b]					
Investigations	12 (100.0%)	12 (100.0%)	0	1 (8.3%)	37 (75.5%)
Alanine aminotransferase increased	10 (83.3%)	12 (100.0%)	N/A	N/A	22 (44.9%)
Aspartate aminotransferase increased	4 (33.3%)	12 (100.0%)	N/A	N/A	20 (40.8%)
Neutropenia	3 (25.0%)	4 (33.3%)	N/A	N/A	20 (40.8%)
Leukopenia	3 (25.0%)	7 (58.3%)	N/A	N/A	17 (34.7%)
Anaemia	4 (33.3%)	8 (66.7%)	N/A	N/A	15 (30.6%)
Gamma-glutamyltransferase increased	7 (58.3%)	10 (83.3%)	N/A	N/A	12 (24.5%)
Thrombocytopenia	1 (8.3%)	7 (58.3%)	N/A	N/A	7 (14.3%)
Blood albumin decreased	0	7 (58.3%)	0	0	2 (4.1%)
Activated partial thromboplastin time prolonged	0	2 (16.7%)	N/A	N/A	1 (2.0%)
Blood alkaline phosphatase increased	1 (8.3%)	7 (58.3%)	N/A	N/A	1 (2.0%)
Blood bicarbonate decreased	0	6 (50.0%)	N/A	N/A	1 (2.0%)
Blood creatine phosphokinase increased	1 (8.3%)	3 (25.0%)	N/A	N/A	1 (2.0%)
Blood creatinine increased	0	2 (16.7%)	N/A	N/A	1 (2.0%)
Gastrointestinal disorders	5 (41.7%)	11 (91.7%)	9 (69.2%)	3 (25.0%)	15 (30.6%)
Vomiting	3 (25.0%)	8 (66.7%)	3 (23.1%)	1 (8.3%)	6 (12.2%)
Nausea	4 (33.3%)	10 (83.3%)	9 (69.2%)	2 (16.7%)	4 (8.2%)
Abdominal pain	1 (8.3%)	3 (25.0%)	0	0	2 (4.1%)
Constipation	1 (8.3%)	4 (33.3%)	1 (7.7%)	0	2 (4.1%)
Diarrhoea	0	2 (16.7%)	0	0	2 (4.1%)
Abdominal distension	0	2 (16.7%)	0	0	1 (2.0%)
Flatulence	0	2 (16.7%)	0	0	1 (2.0%)
General disorders and administration site conditions	5 (41.7%)	10 (83.3%)	8 (61.5%)	8 (66.7%)	13 (26.5%)
Fatigue	3 (25.0%)	9 (75.0%)	7 (53.8%)	2 (16.7%)	5 (10.2%)
Pain	1 (8.3%)	3 (25.0%)	1 (7.7%)	1 (8.3%)	3 (6.1%)
Pyrexia	1 (8.3%)	4 (33.3%)	1 (7.7%)	4 (33.3%)	3 (6.1%)
Injection site reaction	0	0	0	4 (33.3%)	2 (4.1%)
Asthenia	0	0	0	3 (25.0%)	0
Chills	0	2 (16.7%)	0	0	0
Metabolism and nutrition disorders	3 (25.0%)	11 (91.7%)	5 (38.5%)	0	11 (22.4%)
Hyperglycaemia	1 (8.3%)	0	0	0	5 (10.2%)
Decreased appetite	0	6 (50.0%)	5 (38.5%)	0	3 (6.1%)
Hypokalaemia	1 (8.3%)	6 (50.0%)	0	0	2 (4.1%)
Hypophosphataemia	0	7 (58.3%)	N/A	N/A	2 (4.1%)
Dehydration	0	3 (25.0%)	0	0	1 (2.0%)

	ET-A-008-00	ET743-SAR-2004	ET-B-019-99[a]	ET-B-023-00[a]	ET743-SAR-2005
Hypermagnesaemia	0	4 (33.3%)	N/A	N/A	1 (2.0%)
Hypocalcaemia	1 (8.3%)	6 (50.0%)	0	0	1 (2.0%)
Hyponatraemia	0	9 (75.0%)	0	0	1 (2.0%)
Hyperuricaemia	0	3 (25.0%)	N/A	N/A	0
Hypomagnesaemia	0	6 (50.0%)	N/A	N/A	0
Blood and lymphatic system disorders	1 (8.3%)	12 (100.0%)	0	1 (8.3%)	10 (20.4%)
Lymphopenia	0	12 (100.0%)	N/A	0	10 (20.4%)
Musculoskeletal and connective tissue disorders	1 (8.3%)	11 (91.7%)	4 (30.8%)	2 (16.7%)	9 (18.4%)
Pain in extremity	0	5 (41.7%)	2 (15.4%)	0	4 (8.2%)
Back pain	0	8 (66.7%)	1 (7.7%)	0	2 (4.1%)
Myalgia	1 (8.3%)	4 (33.3%)	0	0	2 (4.1%)
Muscular weakness	0	2 (16.7%)	0	0	1 (2.0%)
Arthralgia	0	4 (33.3%)	0	0	0
Bone pain	0	0	1 (7.7%)	2 (16.7%)	0
Infections and infestations	0	7 (58.3%)	0	0	7 (14.3%)
Pneumonia	0	2 (16.7%)	0	0	1 (2.0%)
Lip infection	0	2 (16.7%)	0	0	0
Upper respiratory tract infection	0	2 (16.7%)	0	0	0
Nervous system disorders	1 (8.3%)	7 (58.3%)	3 (23.1%)	3 (25.0%)	5 (10.2%)
Dizziness	0	2 (16.7%)	0	0	1 (2.0%)
Neuropathy peripheral	0	2 (16.7%)	1 (7.7%)	0	1 (2.0%)
Headache	1 (8.3%)	7 (58.3%)	2 (15.4%)	1 (8.3%)	0
Respiratory, thoracic and mediastinal disorders	2 (16.7%)	8 (66.7%)	2 (15.4%)	2 (16.7%)	3 (6.1%)
Dyspnoea	1 (8.3%)	1 (8.3%)	2 (15.4%)	0	2 (4.1%)
Cough	2 (16.7%)	1 (8.3%)	0	2 (16.7%)	1 (2.0%)
Epistaxis	0	2 (16.7%)	0	0	0
Rhinitis allergic	0	2 (16.7%)	0	0	0
Psychiatric disorders	0	3 (25.0%)	0	0	1 (2.0%)
Insomnia	0	2 (16.7%)	0	0	0
Vascular disorders	0	7 (58.3%)	4 (30.8%)	0	0
Flushing	0	0	3 (23.1%)	0	0
Hypotension	0	6 (50.0%)	0	0	0

Key: JRD=Janssen Research & Development, LLC, MedDRA=Medical Dictionary for Regulatory Activities, N/A= Not Applicable: information not available in data source, TEAE=treatment-emergent adverse events.
Note: Percentages calculated with the number of treated pediatric subjects in each study as denominator.
[a] Protocols for Studies ET-B-019-99 and ET-B-023-00 specifically instructed investigators not to report laboratory abnormalities as adverse events in the case report form adverse event page but rather only in the case report form laboratory page.
[b] To allow for a side-by-side comparison of adverse events across studies, JRD mapped and up-versioned the datasets for all 5 studies to MedDRA version 16.0.
Abdominal pain: pooled terms Abdominal pain, Abdominal pain upper and Abdominal pain lower.
Injection site reaction includes the following Preferred Terms: Catheter site pain, Catheter site inflammation, Injection site pain, Catheter site erythema, Catheter site pruritus, Catheter site swelling, Infusion site extravasation, Catheter site oedema, Catheter site related reaction, Infusion site pain, Injection site bruising, Injection site reaction, Catheter site bruise, Infusion site reaction, Phlebitis and Vascular access complication.
Leukopenia: pooled terms Leukopenia and White blood cell count decreased.
Anaemia: pooled terms Anaemia and Haemoglobin decreased.
Blood bilirubin increased: pooled terms Blood bilirubin increased and Hyperbilirubinaemia.
Renal failure: pooled terms Renal failure and Renal failure acute.
Thrombocytopenia: pooled terms Thrombocytopenia and Platelet count decreased.
Neuropathy peripheral: pooled terms Neuropathy peripheral and Peripheral sensory neuropathy.
Gamma-glutamyltransferase increased: pooled terms Gamma-glutamyltransfersase increased and Gamma-glutamyltransferase.
Blood alkaline phosphatase increased: pooled terms Blood alkaline phosphatase increased and Blood alkaline phosphatase.
Pneumonia: pooled terms Pneumonia, Lung infection, and Lobar pneumonia.
Sepsis: pooled terms Sepsis and Clostridium difficile sepsis.
Lymphopenia: pooled terms Lymphopenia and Lymphocyte count decreased.
Neutropenia: pooled terms Neutropenia and Neutrophil count decreased.
Blood albumin decreased: pooled terms Hypoalbuminaemia and Blood albumin decreased.

8.4.6. Laboratory Findings

Blood samples for serum chemistry and hematology evaluations were collected at specified times during the studies. Clinical laboratory values were reported for pediatric patients in Studies ET743-SAR-2004, ET-B-019-99, and ET-B-023-00. Laboratory abnormalities were reported as TEAEs only, per protocol, for Studies ETA-008-00 and ET743-SAR-2005. The on-treatment Grade 3-4 hematologic and clinical chemistry abnormalities observed in the pediatric patients (decreases in hemoglobin levels and lymphocytes, neutrophils, platelets and WBC counts; increases in ALP, ALT, AST, GGT, and CPK levels) were comparable to the findings observed in the trabectedin-treated adult population with STS.

8.4.7. Vital Signs

Vital signs data were reported for Study ET743-SAR-2004. For Study ET743-SAR-2004. There were no clinically relevant changes in physical examination abnormalities observed in Study ET743-SAR-2004.

8.4.8. Electrocardiograms (ECGs)

Across the five trials, ECGs were not routinely collected. During the Study ET743-SAR-2005, cardiac function was evaluated at the completion of Cycles 2 and 4, and every third treatment cycle thereafter by echocardiogram.

- At the 1.3 mg/m^2 dose, the 2 patients had an abnormal shortening fraction of 27% or less at the end of Cycle 2. Neither of the patients received further treatment as both the patients discontinued trabectedin treatment due to progressive disease.
- At the 1.5 mg/m^2 dose, 4 patients had an abnormal shortening fraction of 27% or less:
    - One patient had an abnormal shortening fraction at Cycles 1, 2, 4, 7 and 9. Per-protocol, trabectedin treatment for this patient should have discontinued at Cycle 1. At Cycles 12 and 14, the patient had normal shorting fraction values. The continued treatment of this patient after repeated cardiac tests that still revealed abnormal values was not reported as a protocol deviation.
    - One patient had an abnormal shortening fraction at Cycle 1 followed by a normal shortening fraction at the end of Cycle 2. This patient did not receive further treatment due to progressive disease.
    - One patient had an abnormal shortening fraction at Cycle 3. This patient did not receive further treatment due to study non-compliance.
    - One patient had an abnormal shortening fraction at Cycle 1 with no follow-up measurement at the end of Cycle 2. This patient did not receive further

treatment due to progressive disease.

8.4.9. Immunogenicity

Immunogenicity studies were not included in this application.

8.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified in this review.

8.6. Safety Analyses by Demographic Subgroups

There were no notable differences in the incidences of patients experiencing TEAEs when evaluated across age groups (≥1 month to <2 years; ≥2 years to <12 years; ≥12 years to ≤18 years; and >18 years), by sex (male vs female), weight (≥4 kg to <12 kg; ≥12 kg to <41 kg; ≥41 kg to <65 kg; and ≥65 kg), or BSA (<0.55 m2; ≥0.55 m2 to <1.30 m2; ≥1.30 m2 to <1.75 m2 and ≥1.75 m2).

8.7. Specific Safety Studies/Clinical Trials

No additional specific safety studies were included in this application.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Human carcinogenicity studies were not included in this application.

8.8.2. Human Reproduction and Pregnancy

In post-marketing data, 1 pregnancy has been reported in a patient who was receiving trabectedin. A 22-year-old woman with osteosarcoma was receiving trabectedin 1.3 mg/m^2 as a 24-hour infusion q3wk under compassionate use. Trabectedin was discontinued after 4 cycles of treatment, and the pregnancy was terminated at 20 weeks' gestation. Upon autopsy, the fetus' pathology was normal.

8.8.3. Pediatrics and Assessment of Effects on Growth

See pertinent sections of this review; all data reviewed as part of this application is based on pediatric patients.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose has not been reported in pediatric patients. In adult patients, two of 3 patients in a dose-escalation study who received 1.8 mg/m^2 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. Studies have not been conducted to evaluate the abuse potential, withdrawal or rebound of trabectedin in animals or humans; however, no potential for drug abuse is expected based on findings from routine preclinical testing on receptor binding or the cytotoxic mechanism of action.

8.9. Safety in the Postmarket Setting

Post-marketing experience and major compassionate safety of the use of trabectedin in the pediatric population (patients ≤18 years of age) was evaluated by the sponsor in a search of global medical safety database. The search retrieved 6,207 cases reported cumulatively through July 23, 2017. Of these 6,207 cases, 3,233 cases involved spontaneous and compassionate use programs reports. Of the 3,233 cases, 32 cases involved pediatric patients. Of the 32 pediatric cases, 18 were reported from clinical programs related to compassionate use experience, 7 were spontaneous and 7 were reported from literature. The 32 cases reported a total of 65 adverse events (AEs) of which 60 were serious. Among these, the most common AEs were disease progression (6/65; 9.2%), febrile neutropenia, hepatotoxicity (5/65; 7.7%), and anemia (4/65; 6.2%). All other AEs occurred at a reporting frequency of <5%.

The Empirica Signal data mining tool was used to identify potential safety signals not already described in the trabectedin prescribing information. A data mining run for safety was performed on May 30, 2018, by the clinical reviewer in an unrestricted patient population. No additional safety signals were uncovered through analysis of the Empirica Database. The most commonly reported events had limited narrative information and were often associated with the patients' underlying medical condition.

The surveillance of spontaneous cases of AEs reported with the use of trabectedin indicates that the safety profile of the drug in postmarketed use is consistent with what is known about the drug's overall established safety profile as a single agent from clinical studies.

8.10. Integrated Assessment of Safety

The adverse events observed in trabectedin-treated pediatric patients with pediatric sarcomas are consistent with the adverse events observed in trabectedin-treated adult patients with STS. Among the most common toxicities observed in the trabectedin treated pediatric patients were laboratory-related adverse events, reflecting the well-characterized toxicities of bone marrow

suppression and hepatotoxicity, which are known to be transient and non-cumulative in nature. In general, these toxicities are effectively managed by appropriate dose delays or reductions in accordance with treatment guidelines.

9. Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this application as a new indication is being reviewed.

10. Labeling Recommendations

Labeling review was ongoing at the time this clinical/statistical review was completed. Please see the package insert for trabectedin.

11. Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) was deemed not necessary as a new indication is being reviewed.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

13.1. References

1. D'Incalci, M. and C.M. Galmarini, *A review of trabectedin (ET-743): a unique mechanism of action.* Molecular cancer therapeutics, 2010. **9**(8): p. 2157-2163.
2. Information, Y.P., https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207953s003lbl.pdf.
3. National Cancer Institute: PDQ® Adult Soft Tissue Sarcoma Treatment. Bethesda, M.N.C.I.D.l.m.A.a.h.c.g.c.p.
4. PDQ® Pediatric Treatment Editorial Board. PDQ Childhood Soft Tissue Sarcoma Treatment. Bethesda, M.N.C.I.U.M.D.Y.A.a.h.w.c.g.
5. PDQ® Pediatric Treatment Editorial Board. PDQ Osteosarcoma and Malignant Fibrous Histiocytoma of Bone Treatment. Bethesda, M.N.C.I.U.M.D.Y.A.a.h.
6. National Cancer Institute: PDQ® Childhood Rhabdomyosarcoma Treatment. Bethesda, M.N.C.I.D.l.m.A.a.h.w.c.g.t.s.-t.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): ET-743-SAR-2005, "A Phase II Study of Trabectedin (ET-743, YONDELIS) in Children with Recurrent Rhabdomyosarcoma, Ewing Sarcoma, or Non-rhabdomyosaromatous Soft Tissue Sarcomas"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 142		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 6		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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A National Cancer Institute-supported member group of the National Clinical Trials Network

June 17, 2017

Janssen Pharmaceuticals

Re: Due Diligence Statement Regarding Sub Investigators on Children's Oncology Group (COG) Study, ADVL0221, A Phase II Study of Trabectedin (ET-743, Yondelis®) in Children with Recurrent Rhabdomyosarcoma, Ewing Sarcoma, or Non-rhabdomyosarcomatous Soft Tissue Sarcomas

The Children's Oncology Group (COG) is unable to provide the names of the individuals that were listed as sub-investigators on the 1572s submitted by six enrolling institutions for study ADVL0221, A Phase II Study of Trabectedin (ET-743, Yondelis®) in Children with Recurrent Rhabdomyosarcoma, Ewing Sarcoma, or Non-rhabdomyosarcomatous Soft Tissue Sarcomas. While COG maintains a list of all investigators at COG institutions that are involved in COG research, the only way to identify the investigators on a study-specific basis is the study-specific 1572. Unfortunately the central files were reviewed and 1572s for six enrolling institutions were missing. The electronic folders of many former employees who were involved in the study were reviewed in an attempt to locate 1572s that were not ultimately placed in the central files. This search was unsuccessful, but we were unable to access all former employee electronic folders. COG does not have access to electronic folders of staff that terminated their employment while COG was affiliated with the National Childhood Cancer Foundation (NCCF). COG disconnected from NCCF in late 2012.

Sincerely,

Elizabeth O'Connor

Elizabeth O'Connor, MPH
Chief Operating Officer
Children's Oncology Group

Covered Clinical Study (Name and/or Number): ET-B-023-00, "A Phase 2, multicenter, open label, uncontrolled, 2-stage study of ET-743(trabectedin) in pretreated adult and pediatric patients with advanced or recurrent sarcomas"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 12		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

NOTE TO FILE

Originator:	**To be filed with:**
Alain Rodriguez Corporate Regulatory Affairs Pharma Mar, S.A. Colmenar Viejo (Madrid), SPAIN.	ET-B-023-00 study archives

ET-B-023-00 / Investigators Financial Disclosure Forms (IFDFs)

Country	Study site	Investigational Staff Name
ITALY	Istitut Ortopedici Rizzoli, Bologna	Gaetano Bacci
	Instituto Nazionale dei Tumori, Milan	Monica Terenziani
	Policlinico A. Gemelli, Roma	Riccardo Riccardi

The electronic drives and the paper files have been thoroughly searched by the corporate Regulatory Affairs and Clinical Operations company staff at the Pharma Mar, S.A. headquarters located in Colmenar Viejo (Madrid). In parallel, additional paper files archived by Clinical Operations in Tres Cantos (Madrid) have also been searched by the company staff. Neither on the drives, nor in the paper files the Financial Disclosure Forms of Dr. Gaetano Bacci, Dr. Monica Terenzani and Dr Ricardo Riccadi could be found.

Dr. Monica Terenziani was contacted on 07-SEP-2016 and provided with IFD-Form and asked to provide the requested information for the trial mentioned above. On 09-SEP- 2016, she replied that she actually had not participated in the trial, even though her name was included in the Clinical Study Report section 16.1 "Study Information" in the list of investigators participating in the trial.
Dr Gaetano Bacci could not be contacted (he passed away).
Dr. Riccardo Riccardi was contacted on 07-SEP-2016 and provided with IFD-Form, and asked to send the requested information for the trial mentioned above. Until today, 05-OCT-2016, no feedback has been received.

Signature of originator:	**DATE (dd/mm/yyyy):**
	05/10/2016

Covered Clinical Study (Name and/or Number): ET-B-019-99, "A Phase 2, multicenter, open-label, study evaluating the efficacy and safety of trabectedin in osteosarcoma patients"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 25		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

NOTE TO FILE

Originator: Alain Rodriguez Corporate Regulatory Affairs Pharma Mar, S.A. Colmenar Viejo (Madrid), SPAIN.	**To be filed with:** ET-B-019-99 study archives

ET-B-019-99 / Investigators Financial Disclosure Forms (IFDFs)

Country	Study site	Investigational Staff Name
USA	Massachusetts General Hospital/Dana Farber Cancer Institute	Jeffrey Supko

The electronic drives and the paper files have been thoroughly searched by the corporate Regulatory Affairs and Clinical Operations company staff at the Pharma Mar, S.A. headquarters located in Colmenar Viejo (Madrid). In parallel, additional paper files archived by Clinical Operations in Tres Cantos (Madrid) have also been searched by the company staff. Neither on the drives, nor in the paper files the Financial Disclosure Forms of Dr. Jeffrey Supko could be found. Dr. Jeffrey Supko was contacted on 07-SEP-2016 and provided with IFD-Form, and asked to send the requested information for the trial mentioned above. Until today, 05-OCT-2016, no feedback has been received.

Signature of originator:	**DATE (dd/mm/yyyy):** 05/10/2016

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

/s/

AMY K BARONE
06/11/2018

SUZANNE G DEMKO
06/11/2018