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APPLICATION NUMBER:

207953Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	October 23, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 207953
Applicant Name	Janssen Products, L.P.
Date of Submission	November 24, 2014
Major Amendment Received	April 17 & 27, 2015
PDUFA Goal Date	October 24, 2015
Proprietary Name / Established (USAN) Name	Yondelis/ trabectedin
Dosage Forms / Strength	For injection/ 1 mg lyophilized powder per single use vial
Proposed Indication(s)	(b) (4) [redacted]
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Anuja Patel
Medical Review	Amy Barone & Dow-Chung Chi
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	Dubravka Kufrin
Quality Team Review	Olen Stevens (technical lead); Charles Jewell (drug substance); William Adams (drug product); Kumar Janoria (process); Okpo Eradiri (biopharm); Robert Wittorf (facility)
Microbiology Review	Erika Pfeiler
Clinical Pharmacology Review	Sriram Subramaniam
OPDP Consult	Nazia Fatima
OSI Consult	Lauren Iacono-Connors
OSE/DMEPA Reviews	Tingting Gao (proprietary name review) Otto Townsend (carton, container, and USPI review)
OSE/DRISK	Mona Patel
DPMH review	Carrie Ceresa
CDER DCRP QT IRT Review	Norman Stockbridge

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
DPMH=Division of Pediatric and Maternal Health
IRT=Interdisciplinary Review Team

Division Director Summary Review

1. Introduction

Trabectedin was originally isolated from the marine ascidian Ecteinascidia turbinate; the active pharmaceutical ingredient is chemically synthesized. 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. 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.

This NDA is supported primarily by a single trial, Study ET743-SAR-3007, a randomized (2:1), open-label, active-controlled trial conducted in patients with unresectable or metastatic leiomyosarcoma or liposarcoma, with progression following previous treatment with an anthracycline- and ifosfamide-containing regimen or an anthracycline-containing regimen and one additional cytotoxic chemotherapy regimen. Other key eligibility criteria include normal serum bilirubin, baseline left ventricular ejection fraction within the institutional limits of normal, and no prior history of New York Heart Association Class II to IV heart failure.

Patients were randomized to trabectedin 1.5 mg/m^2 as a 24-hour continuous intravenous infusion once every 3 weeks to dacarbazine 1000 mg/m^2 intravenous infusion (20 to 120 minutes) once every 3 weeks. All patients in the trabectedin arm received dexamethasone 20 mg intravenous bolus prior to each dose to mitigate the risks of serious hepatotoxicity. Patients in the dacarbazine arm were not offered YONDELIS at the time of disease progression. Randomization was stratified by subtype of soft tissue sarcoma (leiomyosarcoma vs. liposarcoma), ECOG performance status (0 vs. 1), and number of prior chemotherapy regimens (1 vs. ≥2). The primary efficacy endpoint was investigator-assessed progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1); key secondary efficacy endpoints were overall survival (OS), objective response rate (ORR), and duration of response (DOR). In addition, as agreed-upon with FDA prior to submission, a pre-specified audit for central radiologic review of imaging studies to assess PFS results was conducted for all clinical study sites enrolling 9 or more patients (approximately 60% of the study population).

There were 518 patients enrolled with 345 patients were randomized to trabectedin and 173 patients were randomized to dacarbazine. The median patient age was 56 years (range 17 to 81); 30% were male; 76% were White, 12% Black, and 4% Asian; 73% had leiomyosarcomas and 27% liposarcomas; 49% had an ECOG PS of 0; and 89% received ≥ 2 prior chemotherapy regimens. The most common (≥20%) pre-study chemotherapeutic agents administered were doxorubicin (90%), gemcitabine (81%), docetaxel (74%), and ifosfamide (59%). Approximately 10% of patients had received pazopanib.

The study demonstrated a statistically significant improvement in investigator-assessed PFS [HR 0.55 (95% CI: 0.44, 0.70); p<0.001], with a median PFS of 4.2 months in the trabectedin arm and 1.5 months. An exploratory analysis of independent radiology committee-determined PFS, in a subgroup consisting of approximately 60% of the total population, provided similar results to the investigator-determined PFS. There was no evidence of an improvement in overall survival [HR 0.93 (95% CI: 0.75, 1.15)], with median survival times of 13.7 and 13.1 months in the trabectedin and dacarbazine arms, respectively, and the overall response rates were similar in both arms (6.9% for trabectedin and 4.2% for dacarbazine).

Serious adverse reactions of trabectedin across clinical trials include anaphylaxis, neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy, and extravasation resulting in tissue necrosis. The most common adverse reactions (≥20%) of trabectedin observed in Protocol ET743-SAR-3007 were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common laboratory abnormalities (≥20%) were increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatine phosphokinase, anemia, neutropenia, and thrombocytopenia.

Issues to be discussed in greater detail in this review include:

- Change in primary endpoint from overall survival to progression-free survival in the major efficacy trial; its effects on demonstration of substantial evidence of effectiveness (Section 7 of this Summary Review)
- Steps to mitigate the potential for microbiological contamination during the 24-hour infusion period for the recommended dosage regimen (Section 3 of this Summary Review)
- Product labeling to reduce risks of hepatotoxicity (Section 4 of the Summary Review)
- Newly identified risk of cardiomyopathy (Section 8 of this Summary Review)

2. Background

Indicated Population and Available Therapy

According to statistics compiled by the American Cancer Society, 11,930 new cases and 4,870 deaths from malignancies arising in soft tissues are estimated to occur in the U.S. in 2015.[1] Soft tissue sarcomas constitute a heterogeneous group of malignancies arising in extraskeletal connective tissues (muscle, fat, fibrous tissue, blood vessels, or other mesenchymally-derived tissues). The most frequent histopathologic subtypes are leiomyosarcoma and liposarcoma, which account for approximately half of all soft-tissue sarcomas. Estimated median survivals have remained at approximately one-year for the past 2 to 3 decades.

Dactinomycin was approved on December 10, 1964 and, as part of a combination chemotherapy and/or multi-modality treatment regimen, is indicated for the treatment of childhood rhabdomyosarcoma, and Ewing's sarcoma. Based on the clinical studies section of product labeling, dactinomycin, as part of maintenance therapy in the United Kingdom Children's Cancer Study Group Ewing's Tumor Study (ET-1), led to a 41% 5-year disease-free survival rate and 44% 5-year survival rate.[2] In patients with previously

[1] http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf

untreated locally advanced and metastatic sarcoma, the overall response rate was 70% (31/44) following treatment with dactinomycin.[3]

Doxorubicin hydrochloride is indicated for the treatment of metastatic soft tissue sarcoma. The basis for this approval is not described in product labeling.

Pazopanib hydrochloride is indicated for the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy. The efficacy of pazopanib for the treatment of patients with adipocytic STS or gastrointestinal stromal tumors has not been demonstrated. Approval was based on demonstration of an improvement in progression-free survival [HR 0.35 (95% CI: 0.26, 0.48); p<0.001] in a randomized, placebo-controlled trial, with a median PFS of 4.6 months in the pazopanib arm and 1.6 months in the placebo arm.

Pre-submission Regulatory History

On April 7, 1996, PharmaMar USA, Inc. submitted IND 50286 for ecteinascidin 743 (trabectedin); the IND was received on April 10, 1996.

On October 18, 2000, an end-of-Phase 2 meeting was held with PharmaMar to discuss the development program for trabectedin for the (b) (4)

On December 4, 2000, FDA issued a Pediatric Written Request letter. The Written Request required the conduct of (b) (4)

[2] Craft, A.W.; et al: Long-Term Results from the First UKCCSG Ewing's Tumour Study (ET-1), Eur. J.Cancer, 33:1061-1069, 1997.

[3] Vietti, T.J.; et al: Multimodal Therapy in Metastatic Ewing's Sarcoma: An Intergroup Study, Nat. Cancer Inst. Monogr. 56:279-284, 1981.

[redacted]

March 5, 2002, meeting held to discuss the clinical development program for trabectedin for [redacted]

On June 3, 2003, FDA issued a letter acknowledging the transfer of sponsorship of IND 50286 to Johnson & Johnson from PharmaMar USA, Inc. effective October 1, 2002.

On May 19, 2004, a revised Pediatric Written Request letter was issued, modifying the December 4, 2000, letter to specify the [redacted] trials required under the Written [redacted]

May 21, 2004: meeting held to discuss the development program for trabectedin for the treatment of patients with locally advanced or metastatic liposarcoma or leiomyosarcoma, specifically Study ET743-STS-201. This study had been previously modified to increase the sample size from 90 patients (45 per arm) to 260 patients (130 per arm) with disease progression following prior anthracycline and ifosfamide treatment. Treatment arms remained unchanged: Arm A (0.58 mg/m^2 3-hour infusion weekly, Weeks 1-3 of each 28-day cycle) and Arm B (1.5 mg/m^2 24-hour infusion every 3 weeks). Overall response rate (ORR) in the 24-hour infusion regimen was 14%.

Johnson & Johnson proposed [redacted]

(b) (4)

FDA agreed that the design of the proposed confirmatory trial, demonstrating the superiority of trabectedin plus doxorubicin with doxorubicin alone in patients with soft tissue sarcoma in first-line treatment, was acceptable.

On September 7, 2004, Johnson & Johnson submitted a protocol amendment to IND 50286, containing revisions to Study ET743-STS-201. (b) (4) Comments on the trial design were conveyed to Johnson & Johnson on January 14, 2005 and March 10, 2005. FDA stated that whether a (b) (4) would support approval under 21 CFR 314.500, Subpart H would be a review issue. Concerns raised by FDA included the open-label nature of the trial and challenges in the accurate measurement of disease progression in this disease setting and confirmed that secondary endpoints should be ordered if they will be used to support labeling claims. FDA was informed that PharmaMar intended to utilize the data from ET743-STS-201 (estimated data cut-off as of September 2004) to support a marketing application in Europe.

On September 30, 2004, FDA granted orphan drug designation for trabectedin for the treatment of soft tissue sarcoma.

On December 14, 2004, FDA provided preliminary responses on the clinical pharmacology program to (b) (4)

On March 10, 2005, a preNDA meeting was held to discuss the content of a planned NDA based on the results of a single efficacy trial, Study ET743-STS-201, supported data obtained in patients with previously treated liposarcoma or leiomyosarcoma in Studies ET-B-005, ET-B-008, and ET-B-017. (b) (4)

On August 4, 2005, the first patient was enrolled the expanded access protocol, Protocol ET743-SAR-3002, titled "A Multicenter, Open-Label Single-Arm Study of YONDELIS® (trabectedin) for Subjects With Locally Advanced or Metastatic Soft Tissue Sarcoma Who Have Relapsed or Are Refractory to Standard of Care Treatment. A final study report was submitted for this trial, with a data cut-off date of October 1, 2010. The planned sample size was up to 3000 patients; a total of 1895 patients were actually enrolled.

On August 31, 2005, a meeting was scheduled to discuss an audit plan [redacted] the meeting was cancelled upon receipt of FDA's preliminary responses.

On November 4, 2005, FDA provided preliminary responses regarding a planned meeting to discuss the Independent Data Monitoring Committee's plan [redacted] for Study ET743-STS-201. [redacted] The NDA should not be submitted until the September analysis has been conducted.

The December 20, 2005, meeting was to discuss the results of Study ET743-STS-201 was cancelled upon receipt of FDA's preliminary responses. FDA stated that this trial was considered exploratory. [redacted] In addition, the proposal [redacted] was considered problematic [redacted]

The February 17, 2006 meeting was cancelled based on FDA's preliminary responses [redacted] In addition, FDA noted an unresolved issue with this study [redacted]

On April 16, 2006, a meeting was held to discuss Johnson & Johnson's proposal [redacted] FDA did not have any recommendation [redacted] noting that Study ET743-STS-201 was considered exploratory.

In 2007, trabectedin was granted marketing authorization (MA) under "exceptional circumstances" by the EMA 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, based primarily on results of Protocol ET743-STS-201.

On November 19, 2008, [redacted] L.P., seeking approval for trabectedin [redacted]. The NDA was referred to the Oncologic Drug Advisory Committee (ODAC) for discussion and advice. [redacted]

(b) (4)

On October 4, 2010, a new Pediatric Written Request was issued since the previous WR had expired.

On November 23, 2010, a meeting was held to discuss to the proposed clinical development plan of trabectedin for the treatment of locally advanced, unresectable, or metastatic L-sarcoma (liposarcoma and leiomyosarcoma) that has been previously treated with anthracyc1ines and ifosfamide, specifically the design of the proposed trial, Study ET743-SAR-3007. FDA agreed with the primary endpoint (overall survival), comparator arm (dacarbazine), randomization based on histopathologic diagnosis of liposarcoma or leiomyosarcoma per pathology report with central review of pathology at a later time. FDA did not agree (b) (4)

On March 30, 2011, Protocol ET743-SAR-3007, titled "A Randomized Controlled Study of YONDELIS® (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma Previously Treated With an Anthracycline and Ifosfamide," was submitted to IND 50286. On April 8, 2011, FDA sent comments by electronic mail, including a statement that the primary efficacy analysis in this study will be the unstratified log-rank test and that other testing procedures including Cox models with pre-specified covariates will be considered as exploratory.

On December 9, 2011, FDA issued a letter acknowledging the December 1, 2011 notification of transfer of sponsorship of IND 50286 from Johnson and Johnson Pharmaceutical Research and Development, LLC to Janssen Research & Development, LLC

On January 18, 2012, Janssen submitted an amendment to Protocol ET743-SAR-3007 to IND 50286, with the following revision: "If a decision is made to undertake de-bulking surgery during study treatment, then the principal investigator at the site should discuss the case with the medical monitor prior to the surgery. The subject must meet the following conditions in order to continue treatment with the study medication after surgery:

- The subject must have completed at least 4 cycles of study treatment and the 12- week post-baseline tumor assessment prior to the surgery;
- The surgery was not undertaken to treat new or worsening tumor-related signs or symptoms that could be considered evidence of progressive disease;
- There was no evidence of tumor progression at the most recent RECIST assessment, which should have been completed within 2 weeks prior to the surgery; and
- There was no evidence of progression of disease at the time of the surgery".

On February 1, 2012, FDA issued an advice letter stating that an imbalance of the number of patients receiving debulking surgery between the two arms of Protocol ET743-SAR-3007 may confound the final results.

On March 20, 2012, the Oncologic Drugs Advisory Committee was asked to provide advice on the efficacy supplement (NDA 22465/S-010) for pazopanib for the treatment of soft tissue sarcoma. The minutes of the meeting are quoted below.

This NDA supplement is based primarily on a single, randomized study in patients with metastatic STS who had received prior chemotherapy. The primary endpoint of this trial was progression-free survival (PFS) as assessed by independent radiology review (IRC). Overall survival (OS) and overall response rate (ORR) by IRC were secondary endpoints.

- The median PFS was 4.6 months in the pazopanib arm and 1.6 months in the placebo arm (HR 0.35; 95% CI: 0.26, 0.48).
- The difference in median PFS for patients classified in each of three pre-specified histological subgroups was 2.7 months (HR 0.37; 95% CI: 0.23, 0.60) in leiomyosarcoma, 3.1 months (HR 0.43; 95% CI: 0.19, 0.98) in synovial sarcoma and 3.6 months (HR 0.39; 95% CI 0.25, 0.60) in patients with "other" soft tissue sarcomas.
- No statistically significant improvement in OS was observed at the time of the final analysis (HR 0.87; 95% CI: 0.67, 1.12).
- The ORR was 4% (all partial responses) on the pazopanib arm with no responders on the placebo arm.
- The safety profile of pazopanib in STS is generally comparable to the safety profile in RCC with some differences. Unique adverse events seen more commonly in STS patients treated with pazopanib as compared to placebo include myocardial dysfunction (11% vs. 5%), pneumothorax (3% vs. 0%) and venous thromboembolism (5% vs. 2%).

In response to the question **[**Considering the observed improvement in PFS, the absence of an improvement in OS, and the adverse event profile of pazopanib, is the risk benefit assessment favorable for the use of pazopanib in the treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy?], 11 members of the ODAC voted yes and 2 members abstained.

On July 23, 2012, a preIND meeting was held under pIND (b) (4) Janssen states that during this meeting, 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. This discussion is not captured in FDA's official meeting minutes.

On June 7, 2013, FDA issued Written Responses Only to questions posed by Janssen. FDA stated that if Janssen sought approval based on an analysis of PFS and ORR in an open-label trial, then an independent analysis of tumor-based assessments to determine tumor response should be conducted by an independent radiologic review committee (IRC) blinded to treatment assignment. Alternatively, FDA stated that Janssen may propose a detailed auditing plan that includes a strategy to detect potential assessment bias and minimize selection bias; the auditing plan should include the percentage of patients to be audited, the method used to identify the subset of images to be audited, the method for comparing the PFS/ORR results obtained by local review with the PFS/ORR results of the audit, and the criteria for determining whether all images need to be audited. Janssen

proposed a mechanism by which the IDMC could recommend that clinically compelling PFS and ORR results, available at the time of the protocol-specified interim analysis for OS, be discussed with FDA. Janssen also proposed to crossover patients randomized to the dacarbazine arm if an NDA based on PFS is submitted. FDA stated that crossover might jeopardize the ability to demonstrate clinical benefit based on effect on overall survival in the event that the treatment effect on PFS is not of sufficient magnitude to be considered evidence of clinical benefit; however, FDA stated that the proposal may be reconsidered when summary results for the final analysis of PFS, ORR, and response duration are available.

On November 18, 2013, FDA issued Written Responses, in which FDA urged Janssen to submit their plan conducting an audit of the investigator-determined PFS results by central review of radiologic studies. FDA also stated that accelerated approval may be granted if the PFS improvement is large in magnitude and statistically robust. However, the proposed difference in median PFS times of 1.2 months (2.5 months in the control vs. 3.75 months in the trabectedin arm) was unlikely to predict a clinically relevant and statistically significant improvement in OS. FDA agreed with the analysis plan for control of Type I error and advised Janssen not to modify the ongoing protocol to allow "cross-over" from the control arm at disease progression, particularly in light of the apparently small treatment effect.

On January 9, 2014, Janssen submitted interim results for OS, PFS, and response rates from Study ET743-SAR-3007, accompanied by a proposed auditing plan for the PFS endpoint to assess for bias in this open-label trial. Janssen proposed to carry out an independent central review using all available scans from sites that enrolled nine or more subjects into the trial at the time of the interim analysis of OS. Janssen stated that 19 sites met this criterion, consisting of approximately 60% of the patients enrolled on the trial at the time of the interim analysis of OS. FDA notified Janssen on February 18, 2014, that the auditing plan was acceptable and stated that whether the proposal may introduce potential bias will be determined upon review of the NDA submission. FDA further requested that Janssen provide analyses of centers with < 9 patients (unaudited subset) versus ≥ 9 patients (audited subset) to show that the patients in the two groups are comparable. The proposed audit plan was limited to radiographic PFS (rPFS).

On February 18, 2014, FDA informed Janssen that the proposed audit plan submitted to IND 50286 on January 9, 2014, was acceptable.

On March 17, 2014, Janssen submitted an addendum to the original statistical analysis plan (SAP) dated October 22, 2013, to implement the audit plan and describe the analysis methods for comparisons between radiological PFS (rPFS) based on investigator's radiologic assessments and rPFS based on independent radiologic review using the audit methodology by Dodd et al[1]. The SAP and audit plan were modified to state that symptomatic deterioration, in the absence of radiographic evidence of progression, will not be considered a disease progression event.

On July 7, 2014, FDA held a Type C meeting with Janssen to discuss the audit results of the investigator-assessed PFS endpoint for Study ET743-SAR-3007 as assessed by independent radiologic review. FDA agreed that the results of the independent audit of investigator-assessed PFS appeared consistent with the results of the primary analysis of PFS; however, a determination that an independent audit sufficiently evaluates introduction of bias in an investigator-assessed PFS analysis would be made during review of an NDA submission. The FDA also stated that the PFS effect was similar in magnitude to a recent approval for treatment of STS and agreed that the result may support accelerated approval; however, whether a 2.7- month median improvement in PFS in the trabectedin arm over the dacarbazine arm will support a finding of effectiveness for trabectedin and demonstrate a positive benefit: risk assessment will be a review issue after the NDA submission. Furthermore, FDA stated that the acceptability of PFS to serve as direct evidence of clinical benefit or evidence that is reasonably likely to predict clinical benefit depends on whether FDA concludes that the improvement in PFS is clinically meaningful, statistically persuasive, free from bias, and supports an acceptable risk-benefit profile.

As of July 10, 2014, trabectedin was approved for the treatment of soft tissue sarcoma in 75 countries.

On October 17, 2014, a teleconference was held to discuss the proposed format and content of the planned NDA submission based primarily on Study ET743-SAR-3007. Key agreements were

- That the NDA should contain: (1) an integrated (side-by-side) analyses of the data from these studies according to dose and schedule, however, FDA stated individual CSRs is acceptable in lieu of inclusion of the integrated study report inclusive of these studies in the ISE, and (2) a thoughtful discussion of the results with the summaries of efficacy and safety to support the conclusion that the data from Study ET743-SAR-3007 represents substantial evidence of a trabectedin treatment effect that is reasonably likely to predict clinical benefit should be included.
- The proposal for presentation of safety data was acceptable, provided that there was an integration of the data in the narrative format in the ISS. A safety analysis for events of special interest consisting of sepsis, rhabdomyolysis, hepatitis, and other relevant adverse events identified by Janssen should be provided in the NDA.
- Janssen agreed to provide narratives for all treatment emergent serious adverse events and all treatment-emergent adverse events that led to discontinuation of study treatment.
- The final analysis of overall survival is expected to be conducted in December 2014, and should be included in the 120-day safety update.
- Microbial challenge studies should be repeated, using a lower inoculum and conducted at a laboratory that is experienced in performance of these studies. Studies should be conducted with a product that is reconstituted with a bacteriostatic diluent. FDA stated that these studies may be submitted during the NDA review and that an in-line filter may be required for product administration depending on results submitted in the original NDA.

NDA Submission History

On November 24, 2014, Janssen submitted the NDA for trabectedin for the treatment of [redacted] liposarcoma and leiomyosarcoma [redacted]

On February 9, 2015, FDA issued a Proprietary Name Request, Conditionally Acceptable letter for the proposed proprietary name, Yondelis.

On March 30, 2015, a teleconference was held between Janssen and staff from DOP2 and OSI to discuss concerns raised by the preliminary inspection observations and the potential impact on the integrity of the safety datasets for all study sites in the application. In response to subsequent information requests, Janssen submitted application amendments on April 17 and 27, 2015.

On May 1, 2015, FDA notified Janssen that the April 17 and 27, 2015, amendments to NDA 207953, together, constituted a major amendment and that the user fee goal date was extended to October 24, 2015.

3. CMC/ Biopharmaceutics

I concur with the conclusions reached by the chemistry review team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections for drug substance were acceptable; inspections of other sites were waived based on inspectional history. Stability testing supports an expiry of 36 months at 2-8° C. There are no outstanding issues.

Specific concerns identified during the CMC review [redacted] failure to pass sterility testing. This issue was addressed by review of infectious complications in the clinical trial, the absence of a safety signal for sepsis in the post-marketing experience outside the United States, and product labeling, which stipulates the use of a 0.2 micron in-line filter during infusion to mitigate potential risks. Based on this information and proposed labeling, the microbiology reviewer agreed that the application should be approved.

The agreed-upon product labeling (Dosage and Administration section) contain statements regarding biocompatible materials for preparation and infusion, as trabectedin adheres to certain materials, particularly at low doses.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/toxicology issues that preclude approval.

Review of nonclinical studies support the proposed mechanism of action. Toxicology studies were conducted in mice, rats, dogs, and monkeys which demonstrated findings consistent with the observed adverse reaction profile in clinical studies. Specifically, necrosis was demonstrated in the liver and injection site and hypocellularity in the bone marrow. Histopathologic changes and chemical evidence (elevated creatine phosphokinase and myoglobin) of skeletal and cardiac muscle damage were also demonstrated. Hemodynamic changes (decreased mean arterial pressure) were observed in monkeys following administration of a single dose of trabectedin 1080 $\mu g/m^2$.

In addition, toxicology studies identified testicular degeneration in rats and identified oligospermia and aspermia in monkeys, suggesting potential effects on male fertility. These findings support statements in product labeling regarding risks of male infertility; however, dedicated nonclinical fertility studies were not conducted.

Studies with radiolabeled trabectedin demonstrated placental transfer and fetal uptake of trabectedin. Dedicated nonclinical embryofetal development studies were not interpretable as exposures achievable with the recommended human dose could not be achieved in animals due to maternal toxicity. Therefore, the basis for labeling statements regarding the risk of embryofetal toxicity is the mechanism of action of trabectedin rather than animal data. Trabectedin was shown to be both mutagenic and clastogenic in nonclinical studies. As noted by the nonclinical pharmacology/toxicology reviewer, carcinogenicity studies were not required based on the short expected survival of the indicated patient population.

There was no evidence suggesting the potential for QT prolongation based on the hERG assay or in toxicology studies.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval."

The recommended dosage regimen proposed by Janssen is based on clinical experience. The trabectedin dosage regimen chosen for use in Protocol ET743-SAR-3007 was based on the evidence of greater anti-tumor activity for this 24-hour infusion regimen observed in Protocol ET743-STS-201, a randomized study conducted in patients with liposarcoma or leiomyosarcoma, comparing the safety and activity of a weekly 3-hr infusion (in 3 out of 4 weeks) to a 24-hr infusion every 3 weeks. No exploratory exposure-response analyses for efficacy endpoints or for adverse reactions could be conducted for Protocol ET743-SAR-3007 because no pharmacokinetic samples were collected in the registration trial. Exposure-toxicity relationships for neutropenia, for transaminitis (AST and ALT), and hyperbilirubinemia were identified based on data studies in patients with various cancers, soft tissue sarcoma, and ovarian cancer. No exposure-response relationship was identified in the randomized trial conducted in ovarian cancer, which may have been challenging in light of the small treatment effect on progression-free survival.

The clinical pharmacology reviewer confirmed the multi-phase kinetics (rapid initial decline at the end of the infusion with slower exponential phases) and population pharmacokinetic (popPK) analyses suggested dose-proportionality of the clinical dose range explored in the major efficacy trial. Trabectedin is extensively metabolized in liver by CYP3A4 and mainly excreted to feces. Drug interactions between trabectedin and strong CYP3A4, resulting in a 66% increase in trabectedin exposure, and between trabectedin and strong CYP3A4 inhibitors, resulting in a 31% decrease in trabectedin exposure, were identified in clinical pharmacology studies, which may be clinically important. However there was limited experience with this in the major efficacy trial and the limited data which was available did not identify differences in safety with concomitant administration of trabectedin and strong CYP3A4 inhibitors.

Based on early clinical studies, which confirmed the risks of hepatotoxicity predicted by nonclinical toxicology studies, patients with elevated bilirubin levels were excluded from the major efficacy trial and no dedicated studies have been conducted in patients with hepatic impairment. Therefore, product labeling states that there is no recommended dose for patients with elevated bilirubin or ≥ Grade 2 AST or ALT elevations. Based on evaluation of patients in the popPK analyses, no dose adjustment is necessary for patients with mild to moderate renal impairment.

A dedicated QT study was not performed, however assessment of effects on QT were evaluated based on ECG assessment obtained in a randomized (1:1), placebo-controlled, 150-patient trial using an alternative dose (trabectedin 1.3 mg/m^2/day) administered intravenously over 3 hours on days 1 and 2 of each treatment cycle. No patient receiving trabectedin had a QTc of >500 msec, no patient had an increase in QT of >60 msec over baseline, and no large changes (>20 msec) in the mean increase QTc interval was demonstrated, indicating a low risk for QTc prolongation.

6. Clinical Microbiology

Not applicable. See Section 3 of this Summary review with regard to sterility issues for drug manufacture/preparation.

7. Clinical/Statistical-Efficacy

This NDA is supported by a single major efficacy trial, Protocol ET743-SAR-3007, which enrolled 570 patients predominantly in the United States. Three clinical sites in the U.S. were inspected based on based on the high proportion of subjects enrolled at these sites. In addition, the study sponsor, Janssen, was inspected. Based on the inspectional findings at the clinical study sites, the conduct of the study and data submitted in the NDA are considered generally reliable; the deficiencies noted were considered unlikely to "importantly impact" the overall study outcome. However, inspection of the sponsor site raised concerns regarding oversight of clinical study sites to ensure timely reporting of adverse event. Based on this concern, FDA re-assessed the integrity and reliability of the safety database, particularly with regard to the 120-day safety update. Queries resulting from this re-assessment led to submission of a major

amendment to the NDA, extending the PDUFA goal date by 3 months. The major amendment addressed FDA's concerns regarding the completeness of safety reporting for the major efficacy trial.

An additional issue relating to the conduct of the trial was the change in the primary efficacy outcome measure, which occurred after the initiation of this open-label trial. This proposal was made in the pre-meeting package submitted April 9, 2013, and approximately one year after the March 20, 2012, the Oncologic Drugs Advisory Committee discussion of an efficacy supplement for pazopanib for a partially overlapping patient population with soft tissue sarcoma (included leiomyosarcoma but not liposarcoma) and following the April 26, 2012, approval for this indication.

Key amendments based on these discussions were

- January12, 2012: eligibility criterion for prior therapy was modified from "Treated with an anthracycline and ifosfamide administered either in combination or as sequential regimens" to "Treated in any order with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen."

- July 15, 2013: As requested by FDA to include a description of the assumptions for the proposed analysis of progression-free survival, including assumptions regarding estimated power, hazard ratio and median PFS in the control and experimental arms.

- January 9, 2014: the statistical analysis plan was amended (SAP addendum 1) to include the estimated power, assumed median for PFS in both arms, and assumed hazard ratio for PFS and proposed auditing plan for rPFS.

- On March 17, 2014, the statistical analysis plan was amended (SAP addendum 2) to include the agreed-upon plan for an independent radiologic audit of PFS based on review of scans (rPFS) from the subgroup of patients enrolled at clinical sites accruing 9 or more patients in the clinical trial.

Study Design
Protocol ET743-SAR-3007, titled "A Randomized Controlled Study of YONDELIS (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma Previously Treated With an Anthracycline and Ifosfamide"

Objectives
The primary study objective was to evaluate whether overall survival (OS) for the trabectedin group is superior to the dacarbazine group. Secondary objectives were to evaluate progression-free survival (PFS), time to progression (TTP), objective response rate (ORR), symptom severity, and safety in the trabectedin group and dacarbazine group.

Eligibility criteria

Key inclusion criteria were age 15 years or older; ECOG performance status 0-1; measurable disease per RECIST v1.1 as determined by the investigator; histologically documented liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic subtypes) or leiomyosarcoma; pathology specimens (eg, tumor blocks or unstained slides) for potential centralized pathology review and biomarker studies; with available tumor specimen; unresectable or metastatic disease; prior treatment with an anthracycline and ifosfamide containing regimen or an anthracycline-containing regimen and one additional cytotoxic chemotherapy; serum bilirubin within normal limits and AST, ALT, and alkaline phosphatase less than 2.5 times the upper limit of normal. Key exclusion criteria were prior exposure to trabectedin or dacarbazine; significant chronic liver disease; 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; or uncontrolled intercurrent illness. All patients were required to have a based left ventricular ejection fraction measurement however there was no eligibility requirement regarding the results of such testing. There was also no specification for maximum cumulative anthracycline exposure in the eligibility criteria.

Treatment plan:

Randomization followed a permuted-block randomization method using a 2:1 allocation, at a central site (IVRS), with stratification by the number of lines of prior chemotherapy (1 vs. ≥ 2), Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (0 vs.1), and sarcoma subtype (liposarcoma vs. leiomyosarcoma). Patients were allocated to:

- Trabectedin: 1.5 mg/m^2 as a 24 hour intravenous infusion on day 1 of each 21-day cycle administered until unacceptable toxicity or disease progression. All patients were to receive dexamethasone 20 mg intravenously 30 minutes prior to initiation of each trabectedin infusion.

- Dacarbazine: 1000 mg/m^2 as a 20-120 minute intravenous infusion on day 1 of each 21-day cycle until unacceptable toxicity or disease progression.

Baseline radiographic disease assessments (including radiographic imaging of the chest, abdomen and pelvis) were to be performed within 30 days before randomization, repeated every 6 weeks for the first 36 weeks on study and then every 9 weeks. Monitoring for drug-related Grade 3 or Grade 4 toxicities was to be conducted until improvement to ≤Grade 2 or for a maximum of 6 months after the last dose of study drug. Monitoring for Grade 2 to 4 liver or cardiac toxicities was to continue until ≤ Grade 1 or a maximum of 6 months after the last dose of study drug.

Analysis Plan:

The sample size of 570 patients was based on the planned final analysis of overall survival after 376 deaths in order to have 80% power to detect a hazard ratio (HR) of 0.74 with a two-sided alpha of 0.05 in a study with 2:1 randomization (experimental:control). Underlying assumptions were that the median overall survival would be 10.0 months for the dacarbazine

arm and 13.5 months for the trabectedin arm. An interim analysis of overall survival was to be conducted after 188 deaths (50% of the final analysis). The O'Brien-Fleming Lan-Demets alpha spending method was utilized with alpha allocation of 0.003 and 0.047 for interim and final analysis respectively.

A statistical method was not proposed to control the overall type I error rate at 0.05 (2-sided) for the analyses of the secondary endpoints in the original design. Sensitivity and subgroup analyses of the primary endpoint as well as the analyses of the other secondary endpoints were planned for non-confirmatory supportive analysis.

In the January 9, 2014, protocol amendment, Janssen submitted estimated sample size considerations for a single analysis of PFS by investigator assessment to be conducted at the time of the interim analysis of overall survival. As stated in the protocol, the analysis of PFS > 90% power to detect a hazard ratio (HR) of 0.667 with a two-sided alpha of 0.05, based on the assumption that 331 PFS events would be available at the time of the interim analysis of OS and that the median FDA would be 2.5 months for the dacarbazine arm and 3.75 months for the trabectedin arm.

Audit Plan for rPFS Subset

The protocol was amended to include an audit of investigator-determined PFS, based on central, blinded review of a subset of patients enrolled in Protocol ET743-SAR-3007, to evaluate for potential bias in determination of PFS and ORR, based on the open-label nature of the trial. The audit was limited to study sites which accrued 9 or more patients in the trial (constituting 19 study sites enrolled 307 patients) and required review of all available scans from the sites to determine rPFS and rORR. Details of the audit plan are provided in the Statistical Review.

Results

The study was initiated on May 27, 2011; the data cut-off date for the first interim analysis was September 16, 2013. A total of 570 patients were enrolled in the clinical trial prior to its termination across 85 clinical study sites in the United States of America (75 sites); Australia (4 sites), Brazil (4 sites), and New Zealand (2 sites). Of these 570, 518 were enrolled prior to the definitive efficacy analyses of investigator-determined PFS and OS; these 518 patients are considered the intent-to-treat population for all efficacy endpoints.

Among the ITT population of 518 patients, 345 patients were randomized to trabectedin and 173 patients were randomized to dacarbazine. There was an imbalance in the number of patients who were not treated due to withdrawal of consent after treatment assignment (0.6% in the trabectedin arm and 8% in the dacarbazine arm). The median patient age was 56 years (range: 17 to 81); 30% were male; 76% White, 12% Black, and 4% Asian; 73% had leiomyosarcomas and 27% liposarcomas; 49% had an ECOG PS of 0; and 89% received ≥2 prior chemotherapy regimens. The most common (≥20%) pre-study chemotherapeutic agents administered were doxorubicin (90%), gemcitabine (81%), docetaxel (74%), and ifosfamide (59%). Approximately 10% of patients had received pazopanib. The female predominance in this patient population reflect the substantial fraction of patients with uterine leiomyosarcoma (41% of the overall study population), while 32% had non-uterine leiomyosarcomas. Among

those with liposarcomas, approximately 50% had de-differentiated histology, 41% had mixed/round cell histology, and 9% had pleomorphic histology. There was inadequate information collected to determine the extent of prior exposure to anthracyclines.

The results of protocol E743-SAR-3007, abstracted from the agreed-upon package insert, are summarized below.

Efficacy Results for Protocol E743-SAR-3007

Efficacy endpoint	**YONDELIS N=345**	**Dacarbazine N=173**
Progression-free survival		
PFS Events, n (%)	217 (63%)	112 (65%)
Disease progression	204	109
Death	13	3
Median (95% CI) (months)	4.2 (3.0, 4.8)	1.5 (1.5, 2.6)
HR (95% CI)[a]	0.55 (0.44, 0.70)	
p-value[b]	<0.001	
Overall survival[c]		
Events, n (%)	258 (67%)	123 (64%)
Median (95% CI) (months)	13.7 (12.2, 16.0)	13.1 (9.1, 16.2)
HR (95% CI)[a]	0.93 (0.75, 1.15)	
p-value[b]	0.49	
Objective Response Rate (ORR: CR+PR)		
Number of patients (%)	23 (7%)	10 (6%)
95% CI[d]	(4.3, 9.8)	(2.8, 10.4)
Duration of Response (CR+ PR)		
Median (95% CI) (months)	6.9 (4.5, 7.6)	4.2 (2.9, NE)

[a] Cox proportional hazards model with treatment group as the only covariate.

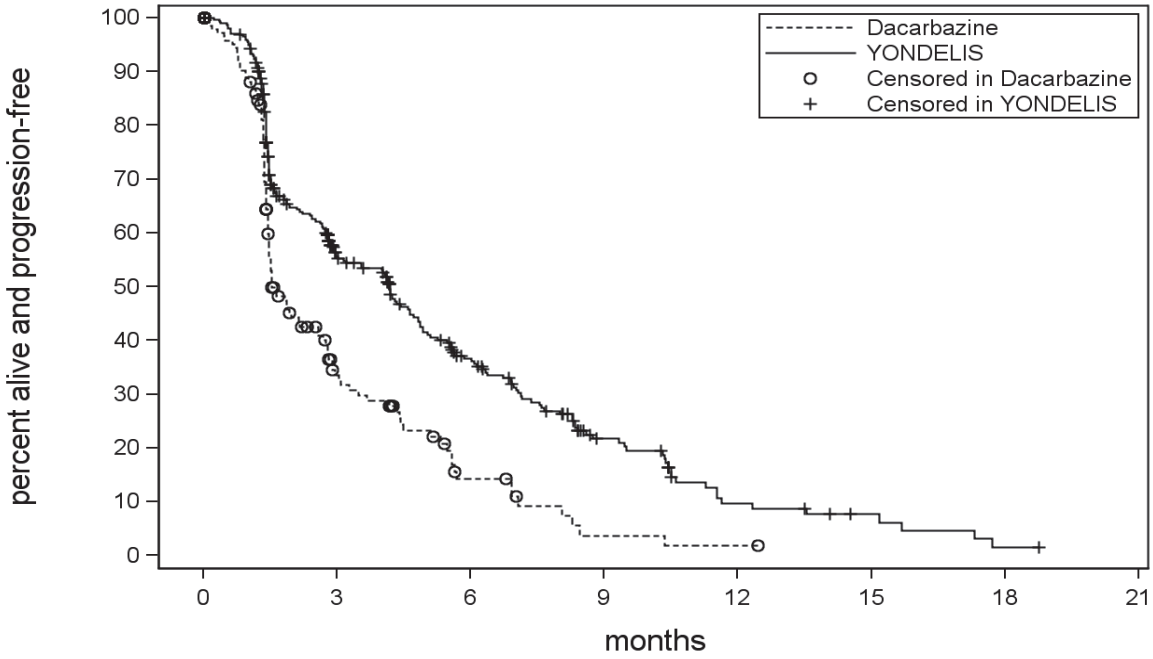
[b] Unstratified log rank test.

[c] Based on 384 patients randomized to YONDELIS arm and 193 patients randomized to dacarbazine.

[d] Fisher's exact CI.

CR=Complete Response; PR=Partial Response; CI=Confidence Interval, HR=hazard ratio, NE=not estimable.

Figure 1: Kaplan-Meier Curves of Progression-Free Survival in Protocol E743-SAR-3007



No. Subjects at Risk

Dacarbazine	173	35	10	2	1	0		
YONDELIS	345	133	71	29	10	5	1	0

In addition to the "primary" analysis of PFS, a series of sensitivity analyses were conducted to evaluate the robustness of the treatment effect as determined by the investigator and as determined by the independent radiologic review-audited subgroup. These results are displayed in the table below, abstracted from the statistical review, and show a consistent treatment effect.

Table 8 Sensitivity Analyses of PFS

Method	HR (95% CI)	P-Value
PFS (INV) ITT (unstratified)	0.55 (0.44, 0.70)	<0.0001
PFS (INV) ITT (stratified)	0.55 (0.44, 0.70)	<0.0001
PFS (INV) ITT (unstratified) adjust by factors in Tables 5	0.56 (0.45, 0.72)	<0.0001
PFS (INV)Site WITH >=9 PAT	0.55 (0.37, 0. 80)	0.0014
PFS (INV)Site WITH< 9 PAT	0.55 (0.41, 0.75)	0.0001
rPFS (INV) ITT	0.57 (0.47, 0.73)	<0.0001
rPFS (IRC) audit subgroup	0.55 (0.40, 0.75)	0.0001
rPFS (INV) audit subgroup	0.58 (0.43, 0.79)	0.0004
rPFS (INV) unaudit subgroup	0.54 (0.37, 0.80)	0.0018
Overall rPFS (BRIC) – 1st stage of Dott et. al	0.54 (0.41, 0.71)	

In addition, the treatment effect was consistent across subgroups based on demographic factors (see statistical review) with the exception of Asian race which was based on 13 patients and in subgroups defined by tumor characteristics and extent of prior treatment (abstracted from the statistical review).

Table 14 PFS Analysis by Baseline Disease Characteristics

Subgroup		Trabectedin (Censored/Event)	Dacarbazine (Censored/Event)	HR (95%)
ECOG PS	0	66/103	35/ 51	0.50 (0.35, 0.70)
	1	62/114	26/ 61	0.60 (0.43, 0.82)
Leiomyosarcoma		98/154	41/ 85	0.55 (0.42, 0.72)
Uterine		50/ 84	21/ 57	0.55 (0.39, 0.79)
Non-uterine		48/ 70	20/ 28	0.59 (0.38, 0.93)
Liposarcoma		30/ 63	20/ 27	0.54 (0.34, 0.88)
Myxoid with or without round		17/ 21	11/ 8	0.55 (0.23, 1.31)
Dedifferentiated		10/ 35	9/ 16	0.66 (0.35, 1.24)
Line of Chemo	1	15/ 24	8/ 11	0.40 (0.18, 0.90)
	≥2	113/193	53/101	0.56 (0.44, 0.72)
ORR w/ last line of chemo	No	112/201	52/104	0.55 (0.43, 0.71)
	Yes	16/ 16	28/ 42	0.45 (0.17, 1.24)
PD with last line of chemo	No	66/ 81	28/ 42	0.52 (0.34, 0.77)
	Yes	62/136	33/ 70	0.58 (0.43, 0.79)
Prior Surgery	No	10/ 8	5/ 10	0.11 (0.02, 0.55)
	Yes	118/209	56/102	0.57 (0.44, 0.72)
Prior Radiotherapy	No	60/109	33/ 60	0.67 (0.48, 0.95)
	Yes	68/108	28/ 52	0.47 (0.33, 0.67)

One of the major considerations during this review was acceptance of a clinical trial in which did not meet its primary efficacy endpoint. As early as 2005, FDA conveyed to the original developer of trabectedin, PharmaMar, that time-to-disease progression may be endpoint reasonably likely to predict clinical benefit. FDA did not accept the results from Protocol ET743-STS-201 primarily because of the numerous protocol modifications and concerns regarding integrity of such an analysis (e.g., whether informed by knowledge of the data). However, during the conduct of Protocol E743-SAR-3007, the Office of Hematology and Oncology Product's thinking regarding the acceptability of other measures of clinical benefit in advanced solid tumors with no satisfactory alternative therapy was evolving. In the context of soft tissue sarcoma, the Office of Oncology Drug Products further signaled their willingness to consider an improvement in progression-free survival that was clinically meaningful in magnitude as a direct measure of clinical benefit in the development program for pazopanib. FDA approved pazopanib based on similar magnitude of effect on PFS with pazopanib over a placebo-control as that demonstrated in Protocol E743-SAR-3007, for trabectedin over an active control (dacarbazine). Given this evolution in thinking, when approached by Janssen after the approval of pazopanib in the April 9, 2013, meeting package, in advance of the September 2013, data cut-off data for analysis of PFS, FDA agreed that the proposed

modification was reasonable provided that an acceptable proposal for auditing results of the PFS results through an independent radiologic review could be developed.

The results demonstrated in this trial are statistically robust, as demonstrated by the sensitivity analyses for both the investigator- and independent radiologic review-determined progression-free survival results, and clinically meaningful.

8. Safety

Size of the database,
The safety database was adequate to characterize the serious risks of trabectedin in the indicated patient population. The integrated safety database contained information on serious adverse reactions occurring in 755 patients with soft tissue sarcoma in six, open-label trials (n=377) and one randomized, open-label, active-controlled trials (n=378). All patients received trabectedin 1.5 mg/m^2 administered as an intravenous infusion over 24 hours once every 21-days, the median age was 54 years (range 18 to 81 years), 63% were female, and all patients had metastatic soft-tissue sarcoma. Across this safety database, 197 (26%) patients were exposed to trabectedin for at least 6 months and 57 (8%) patients exposed to YONDELIS for at least 1 year. This safety database is sufficient to detect serious adverse reactions at an incidence of 0.5%. Additional information on serious adverse reactions was available through the Expanded Access Protocol (ET743-SAR-3002) and marketing experience outside the United States.

In addition, all adverse reactions occurring in Protocol ET743-SAR-3007, both serious and non-serious, were provided in the NDA. In this trial, 378 patients received at least one dose of trabectedin and 172 patients received at least one dose of dacarbazine. Patients in the trabectedin-treated group experienced a delay in the initiation of the next treatment cycle delay (52%2) or a dose reduction (42%). Among trabectedin-treated patients who required dose reduction, most required one dose reduction by one dose level. The most frequently reported treatment-emergent adverse events leading to dose reductions of trabectedin were ALT and AST increase.

Major safety concerns related to labeling
The following serious safety concerns are included in product labeling

- Anaphylactic reaction has been identified as a Contraindication for use of trabectedin in product labeling. Serious allergic reactions have been identified in a limited number of patients across all clinical trials. The incidence of this serious risk appears to be less than 0.5% as it was not identified in the 755 patient safety database discussed above.

- Serious, including fatal, neutropenic sepsis has been listed as the first of the serious adverse reactions of Yondelis in the Warnings and Precautions section of labeling based on the observation that this was the most common fatal adverse reaction of Yondelis. Febrile neutropenia (fever ≥38.5°C with Grade 3 or 4 neutropenia) occurred in 5%, neutropenic sepsis occurred in 2.6%, and fatal febrile neutropenia occurred in 1.1% of patients receiving Yondelis for treatment of soft tissue sarcoma in Protocol ET743-SAR-3007. The

incidence of Grade 3 or 4 neutropenia, based on laboratory values, was 43%, with a median time to first occurrence of Grade 3 or 4 neutropenia of 16 days and median time to complete resolution of neutropenia of 22 days.

- Rhabdomyolysis occurred in 2.9% of the 378 trabectedin-treated patients in Protocol ET743-SAR-3007, was complicated by renal failure in 1.1% of patients and was fatal in 0.8% (3//378) of patients. Elevated creatine phosphokinase (CPK) levels of any severity were documented 32% of trabectedin-treated patients and 9% of dacarbazine-treated patients in Protocol ET743-SAR-3007. The incidence of Grade 3 or 4 CPK elevations was 6% and 0.6% for trabectedin- and dacarbazine-treated patients, respectively.

- Based on the risks of hepatotoxicity identified in early clinical trial development, patients with elevated serum bilirubin levels (above the upper institutional limit of normal) or with an AST or ALT level above 2.5 times the upper limit of normal were not eligible for enrollment in Protocol ET743-SAR-3007; in addition, all patients in the trabectedin arm were required to receive dexamethasone 20 mg intravenously 30 minutes prior to each dose of YONDELIS to mitigate the risks of Grade 3 and 4 toxicity, including hepatotoxicity. Despite these restrictions, the incidence of Grade 3-4 elevated liver function tests was 35% and the incidence of drug-induced liver injury (Hy's Law) was 1.3% in trabectedin-treated patients.

- Cardiomyopathy including cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction occurred in 6% of trabectedin-treated patients and 2.3% of dacarbazine-treated patients in Protocol ET743-SAR-3007, in which patients with a history of New York Heart Association Class II to IV heart failure. Grade 3 or 4 cardiomyopathy occurred in 4% of trabectedin-treated patients 1.2% of dacarbazine-treated patients, with one death (0.3%) due to cardiomyopathy in the YONDELIS arm and none in the dacarbazine arm. The median time to development of Grade 3 or 4 cardiomyopathy was 5.3 months in trabectedin-treated patients.

- Extravasation of YONDELIS, resulting in tissue necrosis requiring debridement, has been reported across clinical trial development but not in Protocol ET743-SAR-3007, where trabectedin was administered through a central venous line to mitigate this risk. In addition to describing this risk in the Warnings and Precautions section of labelling, the Dosage and Administration section directs prescribers to administer Yondelis through a central venous line.

Postmarketing data
Safety information was reviewed from the marketing experience outside the United States, which supported the proposed Contraindication, by identifying cases of severe allergic reactions following administration of trabectedin, and cases of tissue necrosis with extravasation.

REMS
I concur with the recommendations of the clinical review team and the DRISK reviewer that risk evaluation and mitigation strategies (REMS) are not required to ensure safe use of trabectedin, since these risks and steps to mitigate these risks are described in product labeling.

PMRs and PMCs
Two post-marketing requirement (PMR) trials have been identified by FDA under the provisions of the FDCA 505(o). The first PMR is required to obtain data necessary to further evaluate the serious risk of cardiomyopathy in patients exposed to trabectedin. The second PMR is required to evaluate the pharmacokinetics and determine the safe dose, if any, of trabectedin in patients with impaired hepatic function.

9. Advisory Committee Meeting

This new molecular entity was not referred for advice to the Oncologic Drugs Advisory Committee (ODAC) because the safety profile is acceptable for the proposed indication and the application did not raise significant safety or efficacy issues that were unexpected for this indication.

10. Pediatrics

On September 30, 2004, FDA granted orphan drug designation for trabectedin for the treatment of soft tissue sarcoma. Therefore, trabectedin is exempt from the requirements of the Pediatric Research Equity Act (PREA) for the proposed indication. However, there is a Pediatric Written Request for the conduct of studies in pediatric patients (b) (4)

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proposed proprietary name was reviewed for potential medication errors and misbranding by DMEPA. Both OPDP and the clinical review team concurred with DMEPA's conclusion that the proposed proprietary name was acceptable.

- Physician labeling
  - Indications and Usage: removed the phrase (b) (4) retaining only the reference to the two subtypes enrolled in the efficacy trial, to reflect the clinical trial and avoid confusion regarding the approved indication. Streamlined the detailed description of prior therapy by providing a reference to the Clinical Studies section for this information.
  - Dosage and Administration: Deleted statement administered (b) (4) in

accordance with FDA Guidance; revised recommended dose of Yondelis to state that this is limited to patients with normal serum bilirubin and to state that there is no recommended dose for patients with (b) (4) bilirubin levels; removed statements (b) (4) Edited directions for dose modifications for brevity and legibility and included directions for dose modification based on evidence of cardiomyopathy. Edited information on preparation for essential information, to include biocompatible materials and diluents, and to require use of an in-line filter and specify hold times/conditions from preparation to completion of infusion to mitigate potential risks of microbial contamination.

- Dosage Forms and Strengths: edited for brevity
- Contraindications: remove (b) (4) retained contraindications for patients with severe hypersensitivity reactions to trabectedin but removed (b) (4)
- Warnings and Precaution: Provided incidence data based on Protocol ET743-SAR-3007 for comparative incidence or the larger safety database for uncommon events. Added new subsection on cardiomyopathy based on identification of this serious risk in Protocol ET743-SAR-3007; removed subsection on Drug Interactions as the drugs of concern were co-administered in <3% of patients in Protocol ET743-SAR-3007 and no specific dose modification of trabectedin were undertaken or required in these patients; removed subsection on nausea and vomiting as was not likely to result in hospitalization or death nor does it occur at an unusually high rate/severity compared to other alkylating agents; removed (b) (4) statements added to the Dosage and Administration section (no recommended dose in patients with hepatic impairment) and risks of severe liver injury described in the subsection on hepatotoxicity in Warnings and Precautions; removed (b) (4) mild and moderate renal dysfunction does not result in clinically important effects on trabectedin pharmacokinetics and information on lack of data in patients with severe renal impairment is provided in Sections 8 and 12.
- Adverse Reactions: Revised to include description of the source of the safety database, demographic information on safety population, description of exposure and of adverse reactions resulting in termination or dose modification of trabectedin. Limited table on adverse reactions to clinical signs/symptoms occurring at a higher incidence in the

trabectedin arm (compared with dacarbazine) and provide a separate table for laboratory abnormalities occurring at higher incidence in trabectedin-treated patients in Protocol ET743-SAR-3007: removed (b) (4) .

- Drug Interactions: Edited for brevity and current labeling practices; grouping interactions based on CYP enzyme inducers and inhibitors; removed references to (b) (4)
- Use in Specific Populations: Revised for consistency with Pregnancy and Lactation Labeling Rule (PLLR) guidelines and format; modified duration of contraceptive use based on half-life of trabectedin (b) (4) edited geriatric use subsection for brevity and consistency with labeling policies in OHOP; removed (b) (4) noted that there is no recommended dose in patients with (b) (4) bilirubin levels.
- Overdosage: Edited for brevity to state only that there is no approved treatment for overdosage; added a statement that, due to the high level of protein binding, dialysis is unlikely to be effective in management of overdosage.
- Description: Removed statement (b) (4)
- Clinical Pharmacology: Under section 12.1, removed statement (b) (4) . Under section 12.2, edited subsection on cardiac electrophysiology for brevity and essential information; (b) (4) Under Section 12.3, extensive edits for brevity and essential information based on data obtained in clinical studies; included subsections describing effects of strong CYP3 inducers or inhibitors and effects on trabectedin on CYP enzymes.
- Nonclinical Pharmacology/Toxicology: Removed (b) (4) .
- Clinical Studies: Expanded description of the major efficacy trial but did not identify overall survival as primary endpoint, since FDA agreed to accept the NDA based on results of PFS. Expanded description of study population; removed (b) (4)

(b) (4) and added results of overall survival to the table as this was the primary study endpoint and the key secondary objective based on agreements with FDA in 2013; removed exploratory analyses of patient-reported outcomes (MDASI) which were reported to show no differences between arms.
  - References: removed references on (b) (4) added reference to OSHA website since trabectedin is genotoxic; sections 2 and 16 of labeling cross-reference section 15 (References) for this information.
  - How Supplied/Storage and Handling: Extensively edited for brevity and essential information.
  - Patient Counseling: edited to include information on cardiomyopathy; revised for conformance with current labeling guidances on this section of product labeling.

- Carton and immediate container labels: All recommendations by the DMEPA reviewer to increase legibility and prominence of important information, promote safe use, and clarify information were incorporated into final carton and container labeling.

- Patient labeling/Medication guide: Patient labeling was revised for consistency with the changes to the physician package insert and conformance with FDA policy and formatting.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of the review team and also recommend approval for this NDA, following agreement on product labeling.

- Risk Benefit Assessment
  Soft tissue is a serious and life-threatening disease, with leiomyosarcoma and liposarcomas accounting for approximately half of the estimated 11,930 new cases projected to occur in 2015. Survival for patients with unresectable or metastatic disease has remained unchanged under the past 2-3 decades at approximately one year, which is similar to the control arm in Protocol E743-SAR-3007.

  The study demonstrated a statistically significant improvement in investigator-assessed PFS [HR 0.55 (95% CI: 0.44, 0.70); $p<0.001$], with a median PFS of 4.2 months in the trabectedin arm and 1.5 months. An exploratory analysis of independent radiology committee-determined PFS, in a subgroup consisting of approximately 60% of the total population, provided similar results to the investigator-determined PFS. There was no evidence of an improvement in overall survival [HR 0.93 (95% CI: 0.75, 1.15)], with median survival times of 13.7 and 13.1 months in the trabectedin and dacarbazine arms, respectively, and the overall response rates was similar in both arms (6.9% for trabectedin and 4.2% for dacarbazine). These results are similar to those observed with pazopanib in a partially overlapping group of patients with soft tissue sarcoma.

  The safety profile of trabectedin is acceptable in light of the serious and life-threatening nature of the disease and is not qualitatively worse than the toxicity profile of other drugs

(dacarbazine, doxorubicin, pazopanib) which are approved for treatment of soft tissue sarcoma. Serious adverse reactions of trabectedin observed across clinical trials include anaphylaxis, neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy, and extravasation resulting in tissue necrosis. The most common adverse reactions (≥20%) of trabectedin observed in Protocol ET743-SAR-3007 were nausea, fatigue, vomiting, constipation, decreased appetite, diarrhea, peripheral edema, dyspnea, and headache. The most common laboratory abnormalities (≥20%) were increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatine phosphokinase, anemia, neutropenia, and thrombocytopenia.

I find the risk: benefit assessment to be favorable, given the statistically robust and clinically meaningful 45% reduction in the immediate risks of progression or death, corresponding to a 2.7 month improvement in median PFS, which is evidence of clinical benefit and the risks of trabectedin, which are acceptable in this serious and life-threatening disease and which do not impair survival

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the clinical review team and the DRISK reviewer that risk evaluation and mitigation strategies (REMS) are not required to ensure safe use of trabectedin, despite the serious risks of anaphylaxis, neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy and extravasation leading tissue necrosis and debridement. These serious adverse reactions are not unique to this product and are well-recognized by the medical oncology community. Description of the risks and steps to taken to mitigate these risks in product labeling is expected to suffice to mitigate these risks post-marketing.

- Recommendation for other Postmarketing Requirements and Commitments
  Two post-marketing trials have been required under the provisions of the FDCA 505(o) to further evaluate the serious risk of cardiomyopathy in patients exposed to trabectedin and to evaluate the pharmacokinetics and determine the safe dose, if any, of trabectedin in patients with impaired hepatic function, as follows:

  PMR 2964-1 Submit integrated safety analyses and supporting data from an adequate number of clinical trial(s) to characterize the risk of cardiomyopathy and its squeal in patients receiving trabectedin; to identify risk factors for development of these squeal; 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.

  PMR 2964-2 Submit the final report of the completed clinical pharmacokinetic trial to determine an appropriate dose of Yondelis (trabectedin) in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

  The rationale for these PMRs is discussed in Section 8 of the Summary Review.

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/s/

PATRICIA KEEGAN
10/23/2015