

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
207953Orig1s000

OFFICE DIRECTOR MEMO

Office Director Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur
Subject	Office Director Summary Review
NDA #	NDA 207953
Applicant Name	Janssen Pharmaceuticals, 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)
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Division Director Review	Patricia Keegan, MD
Regulatory Project Manager Review	Anuja Patel
CDTL Review	Marc Theoret, MD
Medical Review	Amy Barone MD, Dow-Chung Chi, MD
Statistical Review	Huanyu (Jade) Chen, PhD, Kun He, PhD
Pharmacology Toxicology Review	Dubravka Kufirin, PhD, Whitney Helms, PhD
Quality Team Review	Substance: Charles Jewell, PhD/Product: William Adams, PhD Process: Kumar Janoria Microbiology: Erica Pfeiler, PhD Facility: Robert Wittorf, PhD Biopharmaceutics: Okpo Eradiri, PhD Application Technical Lead: Olen Stephens, PhD
Clinical Pharmacology Review	Sriram Subramaniam, PharmD, Hong Zhao, PhD
OPDP Consult	Nazia Fatima, PharmD
OSI Consult	Lauren Iacono-Connor, PhD, Susan D. Thompson, MD
OSE/DMEPA Reviews	Tingting Gao (proprietary name) Otto Townsend, PharmD, Lubna Merchant, MS, PharmD (carton/container/USPI)
OSE/DRISK	Mona Patel, PharmD, Naomi Redd, PharmD
Patient Labeling Team (DMPP)	Sharon Mills, BSN, RN, CCRP/ Barbara Fuller RN, MSN, CWOCN
DPMH review	Carrie Ceresa
CDER DCRP QT IRT Review	Jiang Liu, PhD, Norman L Stockbridge, MD

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

1. Introduction & Background

On November 24, 2014, Janssen submitted an NDA for trabectedin

(b) (4)

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.

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 extraskelatal 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 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 (PFS) [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.

2. CMC/ Biopharmaceutics

There are no CMC issues that would preclude approval of this NDA. CMC reviewers have provided an overall acceptability recommendation 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.

Specific concerns identified during the CMC review (b) (4) 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.

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

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.

3. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from a nonclinical perspective. 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 µg/m².

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.

4. Clinical Pharmacology

There are no issues that preclude approval from a clinical pharmacology perspective. 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 transaminasitis (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 PFS.

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/m²/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.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

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/m² as a 24-hour continuous intravenous infusion once every 3 weeks to dacarbazine 1000 mg/m² 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 in the dacarbazine arm. 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).

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

Table 1: 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.

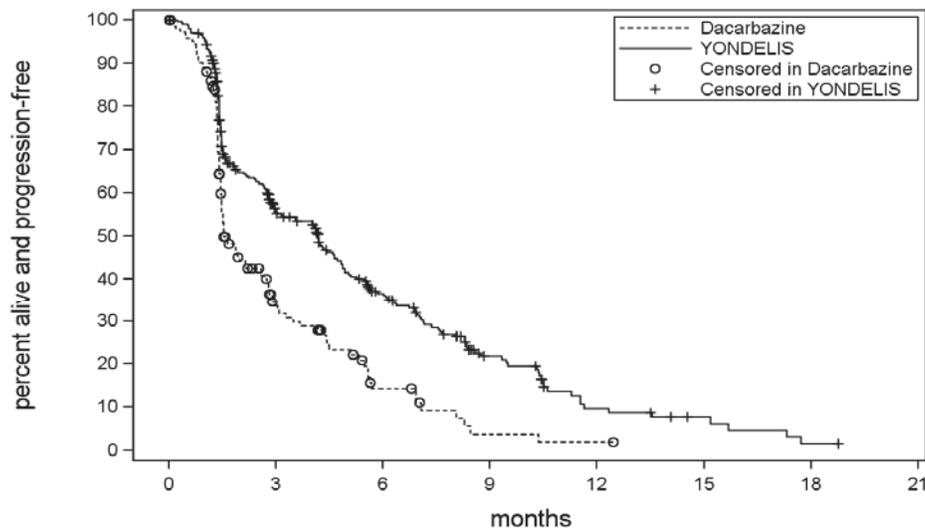
^b Unstratified log rank test.

^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

	0	3	6	9	12	15	18	21
Dacarbazine	173	35	10	2	1	0		
YONDELIS	345	133	71	29	10	5	1	0

7. Safety

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/m² 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. Additional information on serious adverse reactions were available through the Expanded Access Protocol (ET743-SAR-3002) and marketing experience outside the United States.

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.

Postmarketing data

Safety information was reviewed from the marketing experience outside the United States identified cases of severe allergic reactions following administration of trabectedin, and cases of tissue necrosis with extravasation.

8. 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.

9. Pediatrics

Trabectedin was granted Orphan Drug designation for the treatment of soft tissue sarcoma and is therefore 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)

10. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.
- Risk Benefit Assessment
Soft tissue is a serious and life-threatening disease, with leiomyosarcoma and liposarcomas accounting for approximately half of estimated 11,930 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 ($\geq 20\%$) 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 ($\geq 20\%$) were increases in AST or ALT, increased alkaline phosphatase, hypoalbuminemia, increased creatinine, increased creatine phosphokinase, anemia, neutropenia, and thrombocytopenia.

The risk:benefit assessment is 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.

- 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
See action letter.

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/s/

TAMY E KIM
10/23/2015

RICHARD PAZDUR
10/23/2015