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APPLICATION NUMBER:
207953Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

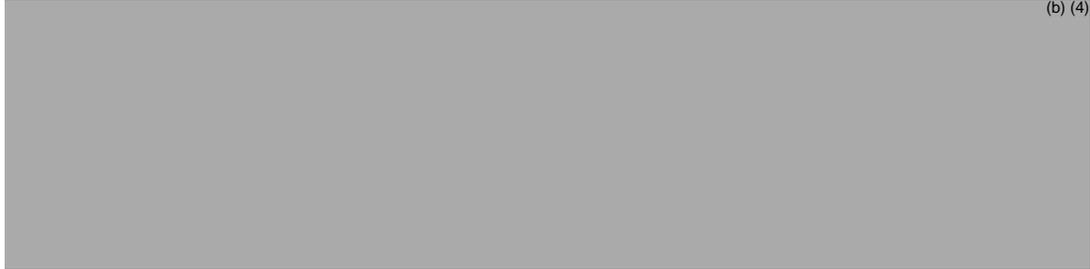
Cross-Discipline Team Leader Review

Date	October 22, 2015
From	Marc Theoret, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # / Supplement#	NDA 207953
Applicant	Janssen Products, L.P.
Date of Submission	November 24, 2014
PDUFA Goal Date	October 24, 2015
Proprietary Name / Established (USAN) names	Yondelis / Trabectedin
Dosage forms / Strength	For injection/1 mg sterile lyophilized powder single dose vial
Proposed Indication(s)	treatment of patients with unresectable or metastatic, liposarcoma or leiomyosarcoma, who have received (b) (4) prior anthracycline-containing regimen
Recommended:	Approval

Material Reviewed / Consultants	Primary/ Secondary Reviewer
Clinical Review	Amy Barone, M.D. and Dow-Chung Chi, M.D. / Marc Theoret, M.D.
Statistical Review	Huanyu Chen, Ph.D. / Kun He, Ph.D.
Regulatory Project Manager	Anuja Patel / Monica Hughes
Pharmacology Toxicology Review	Dubravka Kufirin, Ph.D. / Whitney Helms, Ph.D.
Product Reviews	Substance: Charles Jewell, Ph.D. Product: William Adams, Ph.D. Process: Kumar Janoria Microbiology: Erica Pfeiler, Ph.D. Facility: Robert Wittorf, Ph.D. Biopharmaceutics: Okpo Eradiri, Ph.D. Application Technical Lead: Olen Stephens, Ph.D.
Clinical Pharmacology Review	Clin Pharm: Sriram Subramaniam, Pharm, D./ Hong Zhao, Ph.D.
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OSI	Lauren Iacono-Connor, Ph.D./ Susan D. Thompson, M.D.
Patient Labeling Team (DMPP)	Sharon Mills, BSN, RN, CCRP/ Barbara Fuller RN, MSN, CWOCN
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Interdisciplinary Review Team for QT Studies	Jiang Liu, Ph.D. / Norman L Stockbridge

1. Introduction

On November 24, 2014, Janssen Products LP Submitted New Drug Application (NDA) 207953 for approval of trabectedin (Yondelis) for the following indication:



On January 24, 2015, FDA issued a Priority Review Designation letter notifying Janssen of the review designation of NDA 207953 as priority review. On February 5, 2015, FDA issued a Filing Communication – Filing Review Issues Identified letter. On May 1, 2015, FDA issued a review extension - major amendment letter informing Janssen that the April 17 and 27, 2015, submissions to the NDA constituted a major amendment and that the extended use fee goal date is October 24, 2015.

The Applicant relies on the results from Trial ET743-SAR-3007, a multicenter, international, open-label, randomized (2:1), active-controlled trial, to serve as the primary evidence in support of the safety and efficacy of trabectedin in patients with unresectable or metastatic, leiomyosarcoma or liposarcoma who received a prior anthracycline regimen. Patients were allocated in a 2:1 ratio to receive trabectedin 1.5 mg/m² administered as an intravenous infusion over 24 hours through a central venous catheter once every 3 weeks or dacarbazine 1000 mg/m² administered as an intravenous infusion over 20 to 120 minutes once every 3 weeks. All patients receiving trabectedin were required to receive dexamethasone 20 mg intravenously prior to each dose of trabectedin.

The trial demonstrated an improvement in investigator-assessed, progression-free survival (PFS) with a median PFS of 4.2 months (95% confidence interval (CI): 3.0, 4.8 months) on the trabectedin arm and 1.5 months (95% CI: 1.5, 2.6 months) on the dacarbazine arm, a median improvement of 2.7 months with a HR of 0.55 (95% CI: 0.44, 0.70; p < 0.001). Multiple sensitivity analyses of PFS, including a blinded independent committee review of an audit of available scans from 19 study sites with 9 or more patients (consisting of 59% of the intent-to-treat population) demonstrated results consistent with the results of the primary analysis of PFS. The final analysis results of overall survival (OS) did not demonstrate superiority of the trabectedin arm compared to the dacarbazine arm with a HR of 0.93 (95% CI: 0.75, 1.15; p value = 0.49). The confirmed, investigator-assessed overall response rate (ORR) per RECIST version 1.1 was 6.9% (95% CI: 4.5, 7.6) on the trabectedin arm and was 4.2% (95% CI: 2.9, not estimable) on the dacarbazine arm.

Key issues with this application considered by reviewers were

- Use of progression-free survival as the major efficacy outcome measure to serve as substantial evidence of efficacy in support of an approval as OS was the pre-specified, primary objective of the trial. This is considered further in Section 7.
- Mitigation of risk of microbial contamination of Yondelis following dissolution and dilution based on the 24-hour infusion schedule. This is considered further in Section 3.

2. Background

- Indicated Population

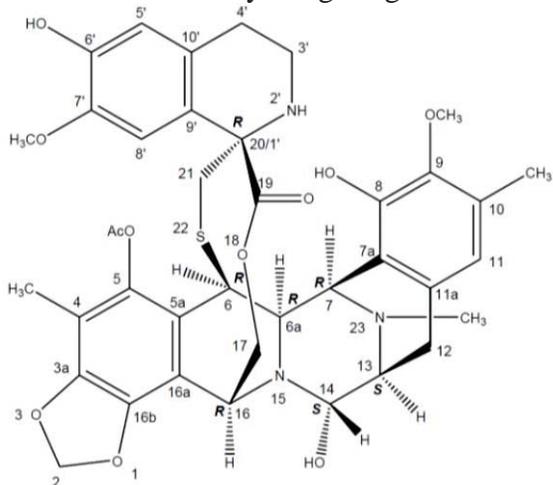
Soft tissue sarcoma (STS) is a heterogeneous group of malignancies arising from mesodermal tissue, accounting for approximately 1% of adult solid tumor malignancies.

In 2015, it is estimated that there will be 11,930 new STS cases and 4,870 deaths from STS in the U.S.¹ Approximately 40-50% of these patients will present with unresectable or metastatic disease. The median survival from time of diagnosis is approximately 1 year.

Leiomyosarcoma and liposarcoma account for approximately 40% of STS. Available (FDA-approved) therapies are doxorubicin (metastatic soft tissue sarcoma) and pazopanib (advanced STS after prior chemotherapy). However, pazopanib is not indicated for patients with liposarcoma, which is noted in a limitation of use in pazopanib labeling as it has not demonstrated efficacy in this population. Refer to the FDA Clinical Review of NDA 207953 for further details.

- Mechanism of Action/Pharmacology

Trabectedin is an alkylating drug with the following chemical structure:



¹ Siegel, RL, KD Miller, and A Jemal, 2015, Cancer Statistics, 2015, CA Cancer J Clin, 65:5-29.

As summarized in the FDA Nonclinical Pharmacology and Toxicology Review, trabectedin demonstrated cytotoxicity in in vitro cell line experiments and in vivo xenograft studies, including experiments with cell lines from sarcomas. The proposed mechanisms of cytotoxicity include DNA single strand breaks via the transcription-coupled nucleotide excision repair (TC-NER) system, formation of trabectedin DNA adducts with DNA double strand breaks during DNA replication, inhibitor of activated gene transcription, microtubule destabilization, and reductions in tumor induced angiogenesis.

- Regulatory History

Development Program in STS

Refer to Section 7 of this review.

NDA (b) (4) Complete Response Letter - Deficiencies



3. CMC/Device

The primary reviewers of the product quality sections of the NDA were Charles Jewell, Ph.D. (Drug Substance), William Adams, Ph.D. (Drug Product), Kumar Janoria, Ph.D. (Process), Erika Pfeiler, Ph.D. (Microbiology) from the Office of Pharmaceutical Quality. The product quality reviewers recommended approval of Yondelis (trabectedin) for human use under conditions specified in the package insert. Olen Stephens, Ph.D., OPQ, the FDA application technical lead, summarized the recommendation and conclusion on approvability as follows:

This application is recommended for approval from a CMC perspective pursuant the overall “approval” recommendation from the facilities reviewer. Sufficient stability data has been submitted to grant a 36 month shelf-life with storage conditions of 2-8 °C.

- General product quality considerations

Trabectedin, (1'R,6R,6aR,7R,13S,14S,16R)-5-(acetyloxy)-3',4',6,6a,7,13,14,16-octahydro-6',8,14-trihydroxy-7',9-dimethoxy-4,10,23-trimethylspiro[6,16-(epithiopropoxymethano)-7-13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one, has a molecular formula of $C_{39}H_{43}N_3O_{11}S$ and a molecular weight of 761.84.

The initial trabectedin drug substance (DS) manufacturing process, which is initiated with (b) (4)

Drug Product is manufactured at Baxter Oncology GmbH, Halle, Germany, and subsequently packaged at Janssen Pharmaceutica, NV, Beerse, Belgium. The DP, Yondelis (trabectedin) for injection, 1 mg, is a sterile, lyophilized white to off-white powder/cake in a single-dose glass vial consisting of trabectedin, potassium dihydrogen phosphate, and potassium hydroxide (for pH adjustment to 3.6 to 4.2). Finished drug product is packaged in a type I USP glass vial, (b) (4) grey (b) (4) stopper (b) (4), and an aluminum crimp seal.

Yondelis for injection is intended to be reconstituted with Water for Injection, USP to 50 ug/mL, then admixed with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a concentration of (b) (4) ug/mL for IV infusion over 24 hours, with completion of infusion within 30 hours of initial reconstitution.

Two key issues with Yondelis DP are:

- Incompatibility between the admixture solutions and (b) (4) polyethersulfone (PES) filters
- Microbial growth supported in microbial challenge studies

The FDA technical lead for NDA 207953 summarizes these two issues, as follows:

Compatibility studies have addressed interactions between the reconstituted solution in its packaging system, and the admixture solution in the containers and components for IV administration. Because the reconstituted solution is intended to be admixed with 5% Dextrose for Injection and the infusion will occur over 24 hours, microbial growth is a concern. Microbial challenge studies have demonstrated that this admixed drug product will support microbial growth. These concerns were discussed with the clinical division as well as potential risk mitigation approaches. Because of the way the clinical studies were conducted, (b) (4) was not a feasible risk mitigation option; (b) (4) were deemed unlikely to be successful due to developmental studies that did not yield sufficient control over microbial growth. In conjunction with the clinical division, the package insert was edited to direct the health care provider to use of an in-line filter during administration of the drug product to mitigate the risk of microbial growth. Compatibility studies have established material incompatibilities between the admixture solutions and (b) (4) polyethersulfone (PES) filters. The time from (b) (4) to end of infusion should be limited to 30 hours.

- Facilities review/inspection

Drug Substance Facilities

(b) (4) are the two active pharmaceutical ingredient manufacturers for DS. FDA waived the inspection of the (b) (4) facility, which performs (b) (4) based, in part, on the recent inspection (b) (4) and compliance history. FDA conducted an inspection of trabectedin DS at (b) (4) facility from (b) (4) FDA identified one Form-483 observation at the (b) (4) facility stating that no written validation protocols or reports were available to verify the (b) (4) software. As stated by the FDA DS reviewer:

No issues with data integrity was found or concerns with the raw data reviewed that correlates to the (b) (4) DIA spoke with the investigators and based on their findings and the promised corrective actions the investigators felt the (b) (4) site is acceptable with respect to NDA 207953. A review of the firm's response was also conducted and the corrective actions are acceptable. OPF/DIA considers the facility is acceptable with respect to NDA 207953.

Drug Product Facilities

FDA waived inspections of the drug product manufacturing facility, Baxter Oncology GmbH, and the packaging facility, Janssen Pharmaceutica. As summarized by the FDA Drug Product Reviewer for NDA 207953, the rationale for waiving inspection is as follows:

Despite the risk based model assessment, the decision was to waive the inspection for both facilities. For the Baxter Oncology facility, SVL is not a new dosage form, and their previous inspections were classified NAI (most recent in July 2014). The drug product manufacturing process is straightforward and the facility has experience in manufacturing of this product (drug is approved in other markets). The reason for the high overall risk assessment is due to the NME designation. The risk assessment focused on the lyophilization and microbial control. This product is a (b) (4)

The control strategy reviewed includes development work, and (b) (4) capabilities within NDA 207953 which appear adequate. A review of the firm's inspectional history demonstrates an understanding of the capabilities of the lyophilization process and (b) (4) manufacturing. The review team agreed with waiving the inspection based on the evaluation. Finally, the international district also conducted a review of the facility and there were no concerns with waiving the inspection. As this product is a sterile, lyophilized product, it is recommended for post-approval inspection (PoAI) evaluation.

Janssen facility inspection was waived due to the minimal risk of secondary packaging and labeling operations. The facility was inspected in May 2014. Although a form 483 was issued to the firm, the observations were not related to the packaging and labeling operations that pertain to this product. The review team had no concerns with the waiving of this inspection.

4. Nonclinical Pharmacology/Toxicology

Dubravka Kufrin, Ph.D., the primary nonclinical reviewer, Whitney Helms, Ph.D., the secondary reviewer, and John Leighton, Ph.D., the tertiary reviewer, concluded that the nonclinical pharmacology and toxicology data in the NDA support the approval of trabectedin, for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma, given as a 24-hour intravenous infusion at a dose of every 3 weeks. The nonclinical studies required to support use of trabectedin in the proposed indication were reviewed under NDA (b) (4) by Drs. Hans Rosenfeldt and Brenda Gehrke; relevant portions of the FDA Nonclinical Pharmacology and Toxicology review of NDA (b) (4) was appended to the FDA Nonclinical Pharmacology and Toxicology review of NDA 207953. One new relevant nonclinical study was submitted under NDA 207953 and was reviewed by Dr. Kufrin.

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The following information concerning general pharmacologic properties of trabectedin was excerpted from the FDA Pharmacology and Toxicology Review of NDA (b) (4) [references provided in the review]:

(b) (4)

(b) (4)

(b) (4)

The FDA Pharmacology and Toxicology Review of NDA 207953 noted that necrosis was the predominant toxicity—often accompanied by inflammation in immunocompetent animals—in toxicology studies in mice, rats, dogs, and monkeys; the major organs of toxicity were liver, injection site reactions, bone marrow, muscle (cardiac and skeletal), spleen, kidney, lung, pancreas, and gastrointestinal tract.

The FDA Pharmacology and Toxicology Review of NDA 207953 also noted that trabectedin is both mutagenic and clastogenic based on positive results in an in vitro Ames assay, an in vitro chromosome aberration assay, and an in vivo mouse micronucleus assay.

- Carcinogenicity

The Applicant did not conduct carcinogenicity studies with trabectedin based on its intended use in patients with advanced cancer, which is in accordance with the International Conference on Harmonization Guideline S9 (Nonclinical Evaluation of Anticancer Pharmaceuticals).

- Reproductive toxicology

Dedicated fertility studies were not conducted with trabectedin; however, toxicology studies in rats and monkeys suggest potential reduction in male fertility following exposure to trabectedin. As summarized by Dr. Kufirin, findings from dedicated embryofetal development studies conducted with trabectedin in rats and rabbits are of limited utility for assessing the reproductive risk of the drug based on the highest doses of trabectedin used in these studies that were significantly below the recommended human dose. Furthermore, toxicokinetic analysis was not conducted in the embryofetal development studies and the actual doses delivered to the animals may have been lower due to adsorption to the tubing. Based on the mechanism of action of trabectedin as a genotoxic agent, the FDA Pharmacology and Toxicology Review of NDA 207953 recommends that trabectedin labeling contain a Warning for embryofetal toxicity.

- Other notable issues (resolved or outstanding)

Adsorption of trabectedin to infusion materials

The FDA Nonclinical Review of NDA 207953 notes that the animal studies were adequate to demonstrate the toxicity of the drug but comparisons of trabectedin doses used in nonclinical studies to human doses is problematic due to adsorption of trabectedin that occurred to some infusion set materials used in the nonclinical pharmacology and toxicology studies.

Unqualified impurity

The FDA Pharmacology and Toxicology Review of NDA [REDACTED] (b) (4) [REDACTED]. The applicant resolved this issue in NDA 207953 with [REDACTED] (b) (4) [REDACTED] specification for [REDACTED] (b) (4) [REDACTED] to an acceptable level based on ICH Q3B. The FDA Pharmacology and Toxicology Reviewer concludes that at “this level, no further toxicological qualification is required.”

5. Clinical Pharmacology/Biopharmaceutics

The FDA Clinical Pharmacology Review Team recommended approval of the NDA from the clinical pharmacology perspective. The Office of Clinical Pharmacology recommended one postmarketing requirement, a hepatic impairment trial, as follows:

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.”

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The clinical dosing regimen for the primary trial (ET743-SAR-3007) submitted in the NDA to support the safety and efficacy of trabectedin was trabectedin 1.5 mg/m² administered as an intravenous infusion over 24-hours every 3 weeks. The following summary of the clinical dose selection is excerpted from the FDA Clinical Pharmacology Review of NDA 207953:

The dose-escalation study using a 24-hr q3wk dosing regimen identified a maximum tolerated dose of 1.8 mg/m² with a recommended Phase 2 dose of 1.5 mg/m². The dosing regimen for the registration trial (ET743-SAR-3007) is 1.5 mg/m² trabectedin administered as a 24-hour intravenous (IV) infusion once every 3 weeks (q3wk). Per the applicant, the dosing regimen in the registration trial was based on efficacy and safety outcome of three Phase 2 studies in advanced pretreated STS patients, and another Phase 2 study comparing a 24-hour IV q3wk infusion regimen to an alternative regimen [3-hour IV infusion once a week (qwk) for 3 weeks every 4 weeks] in patients with liposarcoma or leiomyosarcoma subtypes.

The following summary of the pharmacokinetics of trabectedin is excerpted from the FDA Clinical Pharmacology Review of NDA 207953:

The T_{max} of trabectedin typically occurs at the end of infusion, followed by a rapid decline phase and an additional slower exponential phase. The terminal half-life is approximately 175 hours (7.3 day). The trabectedin concentration at the terminal phase is orders of magnitude lower than the C_{max}; therefore, little or no accumulation is observed following multiple dosing at 3 week intervals. The pharmacokinetics of trabectedin is dose proportional and cycle independent. The trabectedin plasma clearance is approximately 31 L/hr with an intersubject variability of 51% and intra-patient variability of 28%. After administration of radio-labeled trabectedin, 58% of the

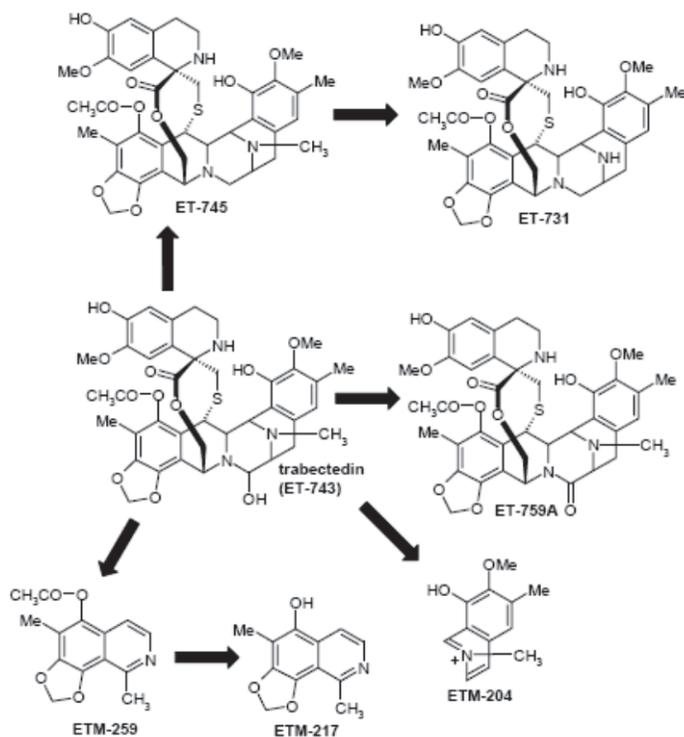
total radioactivity was eliminated in the feces and 6% recovered in the urine. Trabectedin is extensively metabolized in liver by CYP3A4. Co-administration with strong CYP3A4 inhibitors and strong CYP3A4 inducers changed the PK of trabectedin. In addition, trabectedin is a P-gp substrate. In-vitro, trabectedin is not an inhibitor or inducer of major CYP enzymes.

- Drug-drug interactions

The FDA Clinical Pharmacology reviewer describes CYP3A4 as the major CYP450 isozyme involved in the metabolism of trabectedin but the contribution of other CYP isozymes in the metabolism of trabectedin cannot be ruled out based on observation of metabolism with these isozymes at supratherapeutic concentrations of trabectedin. The FDA Clinical Pharmacology Review of NDA 207953 notes that “in-vitro studies suggested that trabectedin has limited potential to induce major CYPs and is not an inhibitor of CYP450 isozymes at clinically relevant concentrations.”

- Pathway of elimination

The following figure excerpted from the FDA Clinical Pharmacology Review of NDA 207953 illustrates the proposed route of metabolism of trabectedin:



Source: Appendix 23 of the clinical study report for ET-A-013-01

The following information on drug metabolism is excerpted from the FDA Clinical Pharmacology Review of NDA 207953:

Most trabectedin-derived metabolites have not been identified because the low concentrations of metabolites, low fecal extraction recoveries, and complex metabolite profile of trabectedin. Radio-chromatograms of feces showed that trabectedin was extensively metabolized to several radiolabeled metabolites including ET-745 (carbonyl metabolite), ET-731, and ETM-217. Metabolites ET-729, ET-759A, and ETM-259 were recovered in feces only under acidic conditions. Metabolites recovered in urine included ET-745, ET-759A, ETM-259, and ETM-204. There was no evidence that unchanged trabectedin undergoes direct glucuronidation. However, at least 1 oxidative metabolite appears to be glucuronidated prior to urinary excretion.

The concentrations of active metabolite ET-729 in plasma were below the limit of quantification of 0.1 ng/mL in samples collected from 14 subjects administered trabectedin as a 3-h or 24-h infusion during 6 Phase 1 and 2 studies. The glucuronide conjugates of trabectedin could not be measured in plasma samples of trabectedin-treated subjects.

The following information on drug excretion is excerpted from the FDA Clinical Pharmacology Review of NDA 207953:

The human mass balance study (Study ET-A-013-01) suggests that trabectedin and its related metabolites is excreted mainly by biliary routes into the feces (57.6% of the dose) compared to renal excretion (5.8% of the dose). The excretion of unchanged trabectedin in feces and urine is negligible (<1% of the dose), confirming the extensive metabolism of trabectedin in vivo.

- Demographic interactions/special populations

The FDA Clinical Pharmacology review did not identify any impact of age, sex, body weight, and BSA on the clearance of trabectedin based on population PK analyses. In addition, there was no significant correlation between renal function (range 30.3 to 150 mL/min) on clearance of trabectedin. The FDA Clinical Pharmacology review notes that hepatic dysfunction is expected to affect the PK of trabectedin based on the extensive metabolism of trabectedin in the liver and the biliary route as the main route of excretion.

- Thorough QT study or other QT assessment

A QT study, ET743-OVC-1001, provided in NDA 207953 demonstrated a mean difference in QTcF of trabectedin compared with placebo of less than 10 milliseconds (upper bound of the 2-sided 90% confidence interval for the mean difference), which is considered to have ruled out an effect of approximately 20 milliseconds based on the lack of demonstrated assay sensitivity. The following summary of the QT study is excerpted from the FDA Clinical Pharmacology Review of NDA 207953:

No significant QTc prolongation effect was detected in a dedicated non-randomized, single-blind, placebo controlled, sequential design QT study (ET743-OVC-1001) in 75 patients with locally advanced metastatic tumor (33% sarcoma, 31% ovarian cancer). The patients were administered placebo (saline solution) and trabectedin (1.3 mg/m²) as a 3-hr IV infusion on days 1 and 2, respectively. The 12-lead ECG was collected in

triplicate (three 10-second digital ECGs in close succession) at each of the following time points: predose (30 min prior to dose), 1, 2, 2.75, 4, 6, 8, and 24 hour. PK samples were time-matched to the ECG measurements and collected within 5 min of when the last ECG tracing was recorded. QTcF (Fredericia's correction method) was identified as the best correction method for the primary statistical analysis. Linear regression model to analyze the $\Delta\Delta\text{QTcF}$ (the difference in individual QTc changes from predose between trabectedin and placebo) effect showed that the largest upper bound of the 2-sided 90% CI for the mean difference between trabectedin and placebo was < 10 ms. Because of the lack of demonstrated assay sensitivity, the results should be interpreted as having ruled out an effect of about 20 ms. Exposure-response analysis did not indicate a relationship between $\Delta\Delta\text{QTcF}$ and trabectedin plasma concentrations (FIGURE 5). Categorical analysis indicated that no subjects' QTcF were >500 ms and no subjects' change from baseline were > 60 ms.

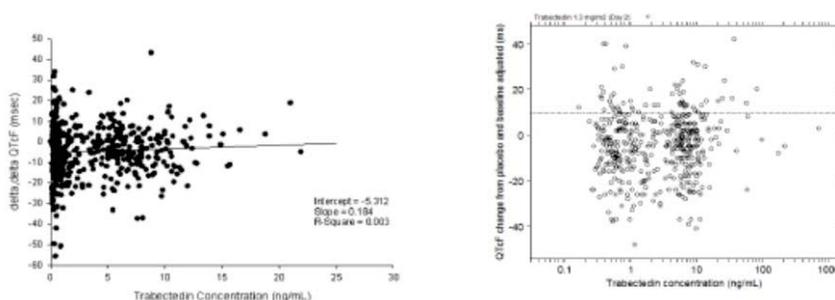


FIGURE 5: Relationship between $\Delta\Delta\text{QTcF}$ and trabectedin plasma concentrations. Applicant's analysis using a linear mixed effects modeling approach (left). The random intercept model was selected as the best fit model and the predicted value of $\Delta\Delta\text{QTc}$ (along with 90% confidence intervals) was estimated at the mean trabectedin Cmax values based on this model. FDA's plot of $\Delta\Delta\text{QTc}$ vs. log trabectedin concentrations (right).

The tested dose of 1.3 mg/m^2 as a 3-hr infusion resulted in higher trabectedin Cmax concentrations compared to the dose of 1.5 mg/m^2 as a 24-hr infusion used in the registration study. Also, the 21% increase (based Study ET743-OVC-1002, refer to Section 2.4.2.7) in trabectedin Cmax concentrations expected with a strong CYP3A4 inhibitor following a trabectedin dose of 1.5 mg/m^2 as a 24-hr infusion are lower than those of trabectedin alone at a dose of 1.3 mg/m^2 as a 3-hr infusion.

- Other notable issues (resolved or outstanding)

Exposure-Response Analyses

The FDA Clinical Pharmacology reviewer of NDA 207953 could not perform exploratory exposure-response analyses for efficacy endpoints and toxicities because no PK samples were collected in the registration trial. However, the FDA Clinical Pharmacology reviewer notes that "exposure-response relationships were identified for neutropenia, elevation in serum transaminases, and hyperbilirubinemia using trabectedin data from early trials."

6. Clinical Microbiology

The section is not applicable to the review.

7. Clinical/Statistical- Efficacy

I agree with the overall conclusions of the primary FDA Clinical Reviewer for efficacy, Dr. Amy Barone, and of the primary FDA Statistical Reviewer, Dr. Huanyu (Jade) Chen, pertaining to the efficacy data submitted in the NDA to support an indication for trabectedin for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

- **Background of Clinical Program** (b) (4)

The regulatory history regarding development of trabectedin for the (b) (4) indication under IND 50286 is summarized, as follows:

On October 18, 2000, FDA held a Type B, End-of-Phase 2 (EOP2) meeting with the sponsor (PharmaMar) to discuss the development program of trabectedin (b) (4)

(b) (4)

On March 5, 2002, FDA held an EOP2 meeting with PharmaMar to discuss a proposed trial, (b) (4)

(b) (4)

[REDACTED] (b) (4)

On May 21, 2004, FDA held an EOP2 meeting with the new sponsor (Johnson & Johnson) to discuss development of trabectedin for the indication treatment of patients with locally advanced or metastatic liposarcoma or leiomyosarcoma. Specifically, the proposal to submit the ORR results from Trial ET743-ST5-201, an activity-estimating trial investigating two dosage regimens of trabectedin (0.58 mg/m² administered as a 3-hour infusion every week for 3 out of 4 weeks and 1.5 mg/m² administered as a 24-hour infusion every 3 weeks) [REDACTED] (b) (4)

[REDACTED]

On March 10, 2005, FDA held a pre-NDA meeting with Johnson & Johnson to discuss the organization, content, and format of an NDA for the proposed indication [REDACTED] (b) (4)

[REDACTED] A separate pre-NDA meeting was held on March 15, 2005, to discuss CMC and Nonclinical sections of an NDA.

On November 4, 2005, FDA held a Type A meeting with Johnson & Johnson to discuss a proposal to perform [REDACTED] (b) (4) analysis of Trial ET743-ST5-201, which was recommended by an independent data monitoring committee (IDMC), and to discuss and reach agreement on the proposed NDA strategy including statistical analysis and submission of the ET743-ST5-201 trial data. FDA did not agree to a modification [REDACTED] (b) (4)

[REDACTED]

On December 15, 2005, FDA issued a Special Protocol Assessment – No Agreement letter for a protocol [REDACTED] (b) (4) titled [REDACTED] (b) (4)

[REDACTED]

(b) (4)
[Redacted]
[Redacted] FDA did not agree
that the proposed (b) (4) was acceptable for full approval (b) (4)
[Redacted]
[Redacted]

On April 14, 2006, FDA held a Type A meeting with Johnson & Johnson to reach agreement on a revision to the data acquisition process for the final analysis of the primary endpoint (b) (4) for Trial ET743-STS-201. FDA did not agree (b) (4)

[Redacted] FDA stated that a confirmatory study would likely be required given the problems identified.

On October 5, 2006, Johnson & Johnson submitted a meeting request to discuss their development program for trabectedin (b) (4). FDA granted a Type A meeting on October 19, 2006. Johnson & Johnson cancelled the meeting on November 6, 2006.

On November 23, 2010, FDA held a Type C meeting with Johnson & Johnson to discuss clinical development plan for treatment of locally advanced, unresectable, or metastatic L-sarcoma (liposarcoma and leiomyosarcoma), specifically to address the design of the proposed Phase 3 study ET743-SAR-3007, a randomized, open-label, active-controlled, parallel-group, multicenter study comparing the safety and efficacy of trabectedin with dacarbazine in adults with unresectable, locally advanced or metastatic L-sarcoma who were previously treated with anthracyclines and ifosfamide. The proposed primary endpoint of the trial was OS. Key agreements and comments at this meeting were as follows:

- FDA agreed with the proposed superiority design with OS as the primary endpoint.
- Johnson & Johnson clarified that patients with refractory disease on previous regimens would be eligible for the proposed trial. The Sponsor stated that patients will not be allowed to cross over to the trabectedin arm.
- FDA agreed with DTIC as an acceptable comparator arm.
- FDA agreed with Johnson & Johnson's plan to collect pathology samples from all randomized subjects and that a pathology report indicating a diagnosis of leiomyosarcoma or liposarcoma was acceptable for randomization. However, FDA stated that Johnson & Johnson must demonstrate an improvement in OS in the intent-to-treat (ITT) population.
- FDA agreed with Johnson & Johnson's proposal to limit enrollment of an expanded access protocol (ET743-SAR-3002; submitted to IND 50286 on August 1, 2005) to patients with non-L-type sarcoma in order to not impede the clinical development of

trabectedin for the proposed indication; however, FDA recommended that Johnson & Johnson consider continuing the EAP for patients ineligible for the proposed clinical trial.

- FDA did not agree that the studies supported the proposed (b) (4) information would be reviewed during the trial and at the time of the submission of the NDA.
- FDA recommended revising the proposed eligibility criterion for age (b) (4) to greater than 15 years of age.

On July 23, 2012, FDA held a pre-IND/EOP2 meeting with Janssen (b) (4). According to the October 17, 2014, pre-NDA meeting briefing document submitted by Janssen, FDA proposed that Janssen R&D share the mature PFS and response rate (RR) results from the ET743-SAR-3007 study with FDA as a basis for possible accelerated approval.

On April 9, 2013, Janssen submitted a Type C Meeting request to discuss use of progression-free survival (PFS) and response rate (RR) data from Trial ET743-SAR-3007 as a basis for possible accelerated approval. In the Written Responses Only, meeting minutes memorandum dated June 7, 2013, FDA recommended that if Janssen (formerly Johnson & Johnson) 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 RR 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 OS 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 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 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.² 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.

On October 17, 2014, FDA held a Type B, pre-NDA meeting with Janssen (by teleconference) to discuss the proposed format and content of the planned NDA submission based primarily on Study ET743-SAR-3007. Key agreements and discussion items included: submission of integrated analyses of efficacy data based on dose and schedule, inclusion of all adequate and well-controlled trials (positive and negative) in the integrated summary of efficacy, inclusion of a safety analysis for all patients treated at the proposed dosing regimen, inclusion of the proposed safety narratives for treatment-emergent adverse events regardless of attribution, inclusion of the final OS results from Trial ET743-SAR-3007 in the 120-Day safety update, and agreement on the proposed dates for inclusion in the analysis of the cumulative integrated postmarketing safety data.

² Dodd LE, Korn EL, Freidlin B, Gray R, Bhattacharya S. An audit strategy for progression-free survival. *Biometrics* 2011;67:1092-9.

- **Efficacy Summary**

ET743-SAR-3007 Design

The Applicant submitted data and results of Trial ET743-SAR-3007 titled “A Randomized Controlled Study of YONDELIS® (Trabectedin) or Dacarbazine for the Treatment of Advanced Liposarcoma or Leiomyosarcoma”, an open-label, multicenter, international, parallel group, randomized, active-controlled trial in patients with unresectable or metastatic, leiomyosarcoma or liposarcoma.

The primary objective of the trial is to evaluate whether overall survival (OS) for the trabectedin group is superior to the dacarbazine group for subjects with advanced L-sarcoma (liposarcoma or leiomyosarcoma) who were previously treated (in any order) with at least: a) an anthracycline and ifosfamide containing regimen, or b) an anthracycline containing regimen and one additional cytotoxic chemotherapy regimen. Secondary objectives are to evaluate PFS, time-to-progression (TTP), objective response rate (ORR), symptom severity, and safety in the trabectedin group and dacarbazine group.

The Applicant required the following additional key eligibility criteria for patients to enroll in the trial:

- Age 15 years or older
- Histologically proven, unresectable, locally advanced or metastatic liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) or leiomyosarcoma (pathology report indicating the diagnosis of liposarcoma or leiomyosarcoma that has been reviewed by the sponsor before randomization)
- Measurable disease at baseline (RECIST v1.1)
- ECOG performance status of 0 or 1,
- Recovery of all side effects from prior therapy (except alopecia) to Grade 1 or less according to NCI-CTCAE v 4.0
- Total bilirubin \leq upper limit of normal (ULN) and AST, ALT, and alkaline phosphatase \leq 2.5 ULN
- No prior exposure to trabectedin or dacarbazine
- No central nervous system metastasis
- No history of myocardial infarct within 6 months before enrollment, New York Heart Association Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmia, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities

Patients were randomized (2:1) to receive trabectedin 1.5 mg/m² via a central venous catheter as a 24-hour infusion on Day 1 of each 21-day treatment cycle or dacarbazine 1000 mg/m² as a 20-120 minute infusion on Day 1 of each 21-day treatment cycle until disease progression or unacceptable toxicity. In the original protocol design, patients on the dacarbazine arm were not offered trabectedin at the time of disease progression. Randomization stratification factors were number of lines of prior chemotherapy (1 vs. \geq 2), ECOG PS (0 vs. 1), and L-sarcoma subtype (liposarcoma vs. leiomyosarcoma). Note that on November 18, 2014, the protocol was

amended to permit patients on the dacarbazine arm to receive trabectedin in an optional extension phase of the trial.

This sample size of 570 patients with a final analysis at the time of 376 OS events provided 80% power to detect a hazard ratio (HR) of 0.74 with a two-sided alpha of 0.05 in a 2:1 randomization ratio, assuming a median OS of 10.0 months for the dacarbazine arm and 13.5 months for the trabectedin arm. An interim efficacy analysis of OS at 188 deaths (50%) was planned. 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. Following agreement with FDA on use of the final PFS analysis in trial ET743-SAR-3007 to support a marketing application, in an amendment to the analysis plan dated July 15, 2013, the applicant submitted estimate sample size considerations on PFS per investigator assessment at the interim OS analysis (50% information). Based on designed sample size of 570, this study would have more than 90% power to detect a hazard ratio (HR) of 0.667 with a two-sided alpha of 0.05, assuming a median PFS of 2.5 months for the dacarbazine arm and 3.75 months for the trabectedin arm. It was estimated that 331 PFS events were needed for the PFS analysis.

The statistical analysis method planned would provide median OS with corresponding 95% confidence interval (CI) and survival curve using the Kaplan-Meier (KM) method for each treatment arm. The Cox proportional HR with 95% CI of the trabectedin arm over the placebo arm was planned to be estimated. An un-stratified log-rank test was planned as supportive analysis. The statistical analysis method for PFS was identical to that planned for OS.

The statistical analysis plan for a blinded, independent committee review of PFS based on the audit of PFS to evaluate investigator bias is summarized by the FDA Biometrics Reviewer of NDA 207953, as follows:

This study did not include a prospectively planned BIRC assessment. In order to evaluate potential investigator assessment bias, FDA requested an independent radiologic assessment of disease status by a BIRC and a detailed auditing plan that includes a strategy to detect potential assessment bias and minimize selection bias. In the absence of a prospectively designed audit plan, the applicant retrospectively prepared an audit plan which was designed as the basis for confirmation of investigator assessment of rPFS and ORR. BIRC audit was limited to all available scans from 19 investigative sites with 9 or more patients in 307 patients (59% of ITT) at the time of OS interim analysis. The proposed audit plan was essentially the first stage of the Dodd two-stage plan. Comparisons between rPFS based on BIRC vs. INV assessment and unaudited subset vs. audited subset were planned.

ET743-SAR-3007 Results

On March 27, 2011, Trial ET743-SAR-3007 was initiated. The trial completed enrollment in November 2013. The data cutoff date for the interim analysis of OS (and final analysis of PFS)

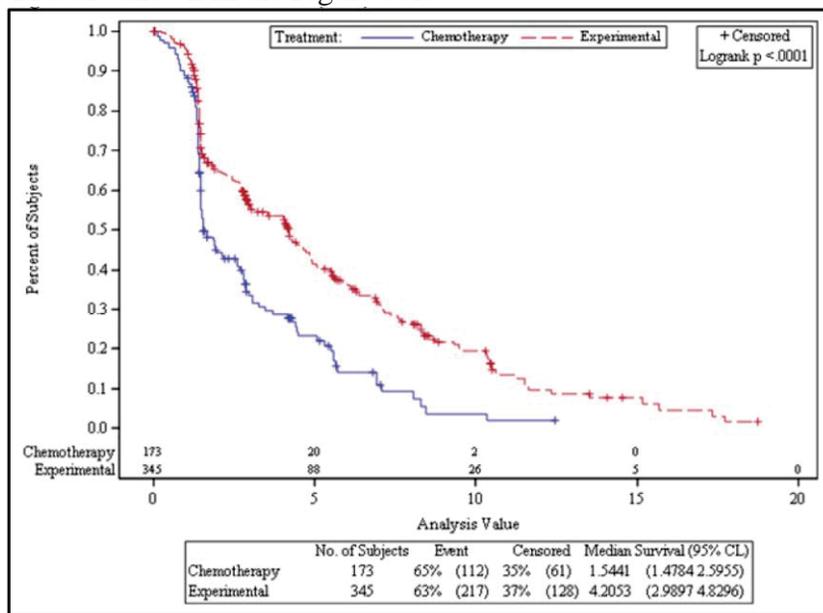
was September 16, 2013. The data cutoff date for the final analysis of OS was January 5, 2015.

At the time of the data cutoff date for the final PFS analysis, a total of 518 patients were randomized, 345 to the trabectedin arm and 173 patients to the dacarbazine arm. At this time 189 death events and 329 PFS events were observed. The median duration of follow-up was 8.6 months for all randomized subjects (ET743-SAR-3007 Interim CSR).

The trial was conducted in 4 countries (Australia, Brazil, New Zealand, and the United States of America [US]) at 85 sites. The median patient age was 56 years (range: 17 to 81 years); 94% were enrolled in the U.S., 30% were male; 76% White, 12% Black, and 4% Asian; 73% had leiomyosarcoma and 27% liposarcoma; 49% had an ECOG PS of 0; and 89% received ≥ 2 prior chemotherapy regimens. The most common ($\geq 20\%$) pre-study chemotherapeutic agents administered were doxorubicin (90%), gemcitabine (81%), docetaxel (74%), and ifosfamide (59%). Ten percent of patients had received pazopanib.

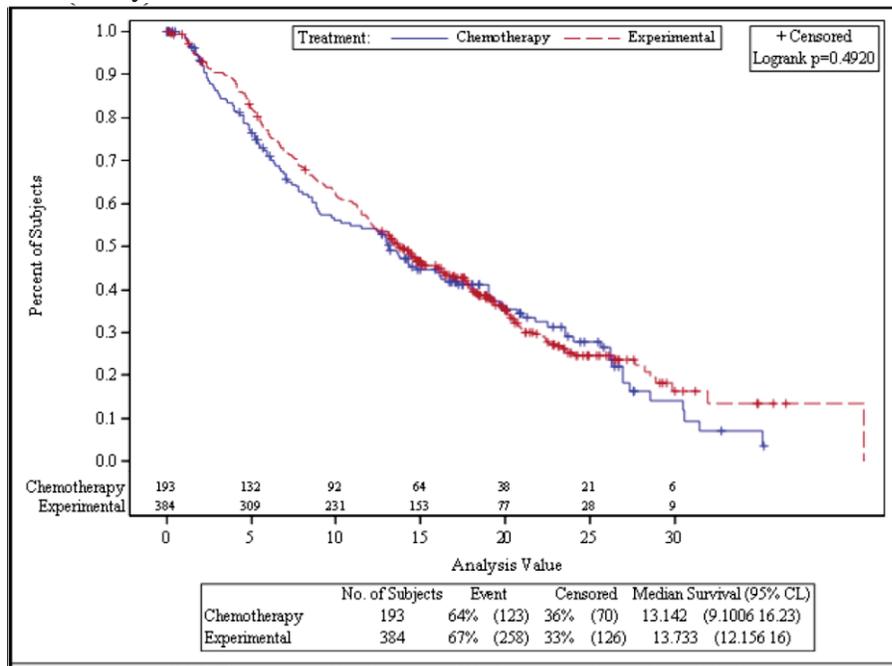
Of the 518 randomized patients, 495 patients (96%) received at least one dose of the study regimen: 340 patients on the trabectedin arm and 155 patients on the dacarbazine arm. Two (0.6% of the ITT population) of the 5 patients on the trabectedin arm and 14 (8% of the ITT population) of the 18 patients on the dacarbazine arm did not initiate the study regimen due to withdrawal of consent. Of the patients who received at least one dose of the study regimen, the most frequent reason for discontinuation of the study regimen was progression of disease in both trial arms: 186 (55%) of 340 patients on the trabectedin arm vs. 106 (68%) of 155 patients on the dacarbazine arm.

The trial demonstrated an improvement in investigator-assessed, progression-free survival (PFS) with a median PFS of 4.2 months (95% confidence interval (CI): 3.0, 4.8 months) on the trabectedin arm and 1.5 months (95% CI: 1.5, 2.6 months) on the dacarbazine arm, a median improvement of 2.7 months with a HR of 0.55 (95% CI: 0.44, 0.70; $p < 0.001$). The Kaplan Meier plots for PFS are shown in the Figure below:



The FDA Biometrics Review of NDA 207953 presents multiple sensitivity analyses of PFS, including a blinded independent central committee review of an audit of available scans from 19 study sites with 9 or more patients (consisting of 59% of the intent-to-treat population), all demonstrating similar PFS results (i.e., HR estimate ranging from 0.54 to 0.58 with upper bounds of the 95% CI ranging from 0.7 to 0.8) compared with those of the primary analysis of PFS. Exploratory subgroup analyses of PFS based on demographics and baseline disease characteristics demonstrated HR estimates that were less than 1 and consistent with the results of the primary PFS analysis (with the exception of Asian subgroup, which consisted of a total of 19 patients), including subgroup analyses based on subtype of sarcoma (refer to FDA Biostatistics Review of NDA 207953 for details).

The final analysis of overall survival based on a data cutoff date of January 5, 2015, with 381 total deaths, did not demonstrate superiority of the trabectedin arm compared with the dacarbazine arm with a HR of 0.93 (95% CI: 0.75, 1.15; p value = 0.49). The median OS was 13.7 months (95% CI: 12.2, 16.0 months) on the trabectedin arm and was 13.1 months (95% CI: 9.1, 16.2 months) on the dacarbazine arm. The Figure below presents the Kaplan-Meier plots for the final analysis of OS.



Janssen amended the protocol on November 18, 2014, to permit crossover of patients on the dacarbazine arm to receive trabectedin. As stated by the FDA Biometrics Reviewer of NDA 207953, the “lack of treatment effect was not confounded by patients (no more than 6 patients) in the dacarbazine arm crossing over to receive trabectedin.”

The objective response rates (ORR) in the ET743-SAR-3007 Interim CSR (September 16, 2013, data cutoff date) are based on investigator assessment per RECIST v1.1, inclusive of unconfirmed and confirmed objective responses. During the review of NDA 207953, FDA requested Janssen provide analyses of objective responses rates and duration of response based

on confirmed objective responses, i.e., complete responses (CR) and partial responses (CR) that have been confirmed on a repeat tumor response evaluation performed at least 4 weeks after the initial tumor response assessment demonstrating a CR or PR. Demonstration of a minimal durability of the tumor response (CR or PR) in the definition of ORR is consistent with FDA Guidance for Industry “Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.” The investigator-assessed, confirmed overall response rate (ORR) per RECIST version 1.1 in the trabectedin arm was 6.9% (95% CI: 4.5, 7.6) and in the dacarbazine arm was 4.2% (95% CI: 2.9, NE). The median duration of confirmed responses was 6.9 months (95% CI: 4.5, 7.6 months) with trabectedin and was 4.2 months (95% CI: 2.9, not evaluable) with dacarbazine.

8. Safety

I agree with the overall conclusions of the primary FDA Clinical Reviewer for safety, Dr. Dow-Chung Chi, regarding the safety data submitted in the NDA. I agree that a REMS is not required for this application and that a postmarketing requirement is necessary to further evaluate and characterize a risk of cardiomyopathy (see recommended PMRs in Section 13).

The safety profile of trabectedin was primarily evaluated in Trial ET743-SAR-3007, an open-label, multicenter, international, randomized, active-controlled trial in which 550 patients with unresectable or metastatic, leiomyosarcoma or liposarcoma received trabectedin 1.5 mg/m² administered by intravenous infusion over 24 hours through a central venous line once every three weeks or dacarbazine 1000 mg/m² administered as an intravenous infusion over 20 to 120 minutes once every 3 weeks. A pooled safety analysis was also performed in the 755 patients with soft tissue sarcoma who received trabectedin at the recommended dose across seven clinical trials (ISS) to evaluate and describe less common adverse events. The 120-day safety update data cutoff date was July 10, 2014, which was the data cutoff date used for the primary safety analysis of Trial ET743-SAR-3007, including the analyses performed on the pooled safety analyses, based on the concerns with data integrity of the safety datasets related Trial ET743-SAR-3007 (see FDA Clinical Review of NDA 207953 for details). Additional information from the expanded safety database, including postmarketing information, was used to evaluate allergic reactions and to identify potentially rare adverse reactions of trabectedin.

The median duration of exposure to trabectedin was 13 weeks (range 1 week to 127 weeks) among the 378 patients who received trabectedin and was 8 weeks (range: 3 to 100 weeks) among the 172 patients who received dacarbazine on Trial ET743-SAR-3007. In this trial, the demographics and baseline characteristics of the safety population was similar to those described for the efficacy population.

The key safety findings of trabectedin are as follows (Trial ET743-SAR-3007 unless otherwise noted):

- Twenty-five patients (6.6%) receiving trabectedin and five patients (2.9%) receiving dacarbazine with fatal adverse events. Grade 5 adverse events occurring in ≥ 2 patients

- receiving trabectedin were death (n=5), respiratory failure (n=4), cardiac arrest (n=3), sepsis (n=2), rhabdomyolysis (n=2), and acute renal failure (n=2).
- Serious adverse events occurred in 39% of patients receiving trabectedin and 29% of the patients receiving dacarbazine. The most frequent ($\geq 2\%$) non-fatal serious adverse events in patients receiving trabectedin compared with dacarbazine were nausea (4.2% vs. 1.7%), vomiting (4.2% vs. 1.7%), anemia (4.2% vs. 2.3%), dehydration (4% vs. 1.7%), abdominal pain (3.7% vs. 4.7%), dyspnea (3.4% vs. 1.2%), febrile neutropenia (3.2% vs. 1.2%), pyrexia (3.2% vs. 1.2%), acute renal failure (2.9% vs. 0.6%), neutropenia (2.4% vs. 0.6%), and catheter site infection (2.1% vs. 0.6%),
 - Discontinuations due to adverse events occurred in 26% of patients receiving trabectedin and 22% of patients receiving dacarbazine. AEs leading to treatment discontinuation occurring in $\geq 2\%$ patients receiving trabectedin and compared with dacarbazine were liver test abnormalities (defined as increased ALT, increased AST, increased alkaline phosphatase, increased bilirubin) (6% vs. 0.6%) and thrombocytopenia (3.4% vs. 1.7%).
 - Adverse events leading to dose reduction occurred in 42% of patients receiving trabectedin and 12% of patients receiving dacarbazine. The most frequent ($\geq 2\%$) adverse events leading to dose reduction of trabectedin and compared with dacarbazine were liver test abnormalities (24% vs. 1.7%), neutropenia (including febrile neutropenia) (8% vs. 4%), increased alkaline phosphatase (5% vs. 1.7%), thrombocytopenia (4.2% vs. 5.8%), fatigue (3.7% vs. 1.2%), increased bilirubin (2.6% vs. 0), and creatine phosphokinase (2.4% vs. 0).
 - Adverse events leading to dose delays occurred in 51% of patients receiving trabectedin and 38% of patients receiving dacarbazine. The most frequent ($\geq 2\%$) adverse events leading to dose delays of trabectedin and compared with dacarbazine were neutropenia (31% vs. 22%), thrombocytopenia (15% vs. 19%), leukopenia (3.4% vs. 1.2%), liver test abnormalities (6% vs. 2.3%), increased creatine phosphokinase (3.2% vs. 0.6%), fatigue (2.9% vs. 0.6%), anemia (2.6% vs. 2.9%).
 - Grade 3-4 treatment-emergent adverse events (TEAE) occurred in 81% of patients receiving trabectedin and 55% of patients receiving dacarbazine. Common ($\geq 5\%$) Grade 3-4 TEAEs were increased ALT (29% vs. 0.6%), neutropenia (40% vs. 23%), thrombocytopenia (20% vs. 19%), anemia (18% vs. 12%), increased AST (15% vs. 0), fatigue (8% vs. 1.7%), increased creatine phosphokinase (6% vs. 0.6%), vomiting (6% vs. 1.2%), and vomiting (6% vs. 1.2%).
 - Common TEAEs ($\geq 20\%$) in patients receiving trabectedin compared with dacarbazine were nausea (75% vs. 50%), fatigue (69% vs. 52%), neutropenia (51% vs. 32%), increased ALT (49% vs. 7%), vomiting (46% vs. 22%), anemia (42% vs. 28%), increased AST (38% vs. 6%), constipation (37% vs. 31%), decreased appetite (37% vs. 21%), diarrhea (35% vs. 23%), thrombocytopenia (33% vs. 35%), peripheral edema (28% vs. 13%), dyspnea (25% vs. 20%), headache (25% vs. 19%), and cough (22% vs. 21%).
 - Common laboratory abnormalities representing an increase in Grade from baseline ($\geq 20\%$) in patients receiving trabectedin compared with dacarbazine were increased anemia (95% vs. 79%), ALT (90% vs. 33%), increased AST (84% vs. 32%), increased alkaline phosphatase (70% vs. 60%), neutropenia (66% vs. 47%), hypoalbuminemia

(63% vs. 51%), thrombocytopenia (59% vs. 57%), increased creatinine (46% vs. 29%), and increased creatine phosphokinase (33% vs. 9%).

Note that the incidence of neutropenia, thrombocytopenia, and anemia leading to dose modifications as listed above and for labeling were based on analyses of the NDA 207953 120-Day Safety update datasets using a composite of preferred terms indicative of these adverse reactions, as follows: neutropenia (neutropenia, neutrophil count decrease, febrile neutropenia), thrombocytopenia (thrombocytopenia, platelet count decrease), and anemia (anemia, hemoglobin decrease, hematocrit decrease). Analyses of dose modifications based on liver test abnormalities as a composite term (increased ALT, increased AST, increased alkaline phosphatase, increased bilirubin) is also included above.

The following major safety risks of trabectedin identified in the clinical program were included in the Warnings and Precautions section: neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy, and extravasation reactions and tissue necrosis. The following is a summary of these safety risks:

- Neutropenic Sepsis: febrile neutropenia (defined as fever $\geq 38.5^{\circ}\text{C}$ with Grade 3 or 4 neutropenia) occurred in 5% of patients receiving trabectedin in Trial ET743-SAR-3007. Neutropenic sepsis occurred in 2.6% of the patients receiving trabectedin, including 5 patients with febrile neutropenia, which was fatal in 4 patients (1.1%). The incidence of Grade 3 or 4 neutropenia (identified by laboratory testing) was 43% with a median time to the first occurrence of Grade 3 or 4 neutropenia of 16 days (range: 8 days to 9.7 months); the median time to complete resolution of neutropenia was 13 days (range: 3 days to 2.3 months).
- Rhabdomyolysis: rhabdomyolysis leading to death occurred in 0.8% of patients receiving trabectedin in Trial ET743-SAR-3007. Elevations in creatine phosphokinase (CPK) occurred in 32% of patients receiving trabectedin in Trial ET743-SAR-3007, including Grade 3 or 4 CPK elevation in 6%. The median time to first occurrence of Grade 3 or 4 CPK elevations was 2 months (range: 1 to 11.5 months); the median time to complete resolution was 14 days (range: 5 days to 1 month).
- Hepatotoxicity: patients with serum bilirubin levels above the upper limit of normal or AST or ALT levels >2.5 times ULN were not enrolled in the ET743-SAR-3007 Trial. The incidence of Grade 3 to 4 elevated liver function tests (defined as elevations in ALT, AST, total bilirubin, or alkaline phosphatase) was 35% in patients receiving trabectedin in the ET743-SAR-3007 Trial. The median time to development of Grade 3 to 4 elevation in ALT or AST was 29 days (range: 3 days to 11.5 months). Of the 134 patients with Grade 3-4 elevations in LFTs, 114 (85%) experienced complete resolution with the median time to complete resolution of 13 days (range: 4 days to 4.4 months). The incidence of drug induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) was 1.3% in patients receiving trabectedin in Trial ET743-SAR-3007. The protocol required all patients to receive dexamethasone 20 mg administered intravenously 30 minutes prior to each dose of trabectedin. The

information submitted in NDA 207953 did not support a specific claim for hepatoprotective effects of dexamethasone premedication.

- **Cardiomyopathy:** cardiomyopathy (cardiac failure, congestive heart failure, ejection fraction decreased, diastolic dysfunction, or right ventricular dysfunction) occurred in 6% of patients receiving trabectedin and in 2.3% of patients receiving dacarbazine in Trial ET743-SAR-3007. Cardiomyopathy leading to death occurred in 1 patient receiving trabectedin in Trial ET743-SAR-3007. The median time to development of Grade 3 or 4 cardiomyopathy in patients receiving trabectedin was 5.3 months (range: 26 days to 15.3 months). The risk of cardiomyopathy with trabectedin requires further characterization (see Section 13, postmarketing requirements).
- **Extravasation:** extravasation of trabectedin with resulting tissue necrosis was identified in the development program of trabectedin. The dosage and administration section of the label instructs healthcare providers to administer trabectedin through a central venous line.

An additional major safety risk identified in the extended safety database was a case of anaphylaxis and death, which led to a contraindication in patients with prior allergic reactions with Yondelis.

9. Advisory Committee Meeting

The application was not referred to an Oncologic Drug Advisory Committee (ODAC) as this drug is not the first in its class; the clinical trial design is acceptable; the safety profile is acceptable for the treatment of patients with unresectable or metastatic liposarcoma and leiomyosarcoma who have received a prior anthracycline containing regimen; and the application did not raise significant public health questions on the role of Yondelis for this indication and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

A Special Government Employee, Dr. Angela Meyers, a patient advocate, was consulted for general advice concerning the application, including any general comments regarding labeling. Dr. Myers noted that the side effects with trabectedin appeared to be greater than with dacarbazine, but stated that overall benefit outweighed the risks for trabectedin. With regards to the draft labeling:

- Dr. Myers asked whether LVEF risk would be included in the label. Dr. Myers expressed the concern that the rate of cardiomyopathy observed with trabectedin is reflective of the patient population (underlying cardiac risk factors and prior anthracycline exposure) under study rather than a treatment effect. This concern was based, in part, upon the lack of information regarding the control arm in the draft labeling.
- Dr. Myers expressed concern in regards to the clinical significance of anemia given that the between group difference in the incidence of Grade 3-4 anemia was not as large as was the difference in all grades anemia.

- Dr. Myers requested clarification on Efficacy Results for Trial 1, regarding the PFS events. FDA clarified that the components (disease progression and death) of the composite endpoint, PFS, were not available at the time that the labeling (dated September 17, 2015) was provided to her for review. FDA confirmed that this information would be included in the final label.

10. Pediatrics

Trabectedin is exempt from the pediatric study requirements of the Pediatric Research Equity Act (PREA), i.e., to assess the safety and effectiveness of the product for the claimed indication(s) in pediatric patients, because FDA granted this product orphan designation (b) (4) on September 30, 2004.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Financial Disclosures:**

No issues. As summarized in the FDA Clinical Review of NDA 207953, three instances of disclosable financial information were identified, all which were self-disclosures pertained to equity interest greater than \$50,000. Two instances were investigators from Trial ET743-SAR-3007. However, bias was minimized in this randomized study performed at multiple investigators at multiple sites, monitoring, and blinded independent central review of radiology images for PFS to evaluate for investigator bias. Both investigators provided minimal contributions to the overall study, i.e., enrolling a total of 6 patients from the two sites.

- **Other GCP Issues:** None

Office of Scientific Investigation (OSI) Audits:

Three clinical sites were inspected: Site 001033 (Dr. Scott Schuetze, Ann Arbor, Michigan), Site 001028 (Dr. Shreyaskumar Patel, Houston, Texas) and Site 001001 (Dr. George Demetri, Boston, Massachusetts) based on enrollment of large numbers of study subjects. OSI also inspected Janssen. In general, the information submitted to the Agency in the NDA appeared reliable based on inspection of the three sites. A Form FDA 483 Inspectional Observations was issued citing inspection observations to two of the three sites. Inspection of Janssen revealed evidence of under-reporting of AEs/SAEs in the original application. Noted in the OSI clinical inspection summary was that for one of the five sites included in the inspection,

“that there was a significant lag between the times a study AE occurred and the time that the AE data were entered into the eCRF by study site staff. The monitor found and recorded in their monitoring visit reports that the site was falling behind on data entry and as such eCRFs were not “current”. This [] deficiency was noted during numerous monitoring interim visits.”

FDA queries concerning data integrity of the safety datasets and review of Janssen’s responses led to a determination that completeness and integrity of the datasets submitted to support the 120-Day safety update were acceptable. On May 1, 2015, FDA issued a

review extension - major amendment letter informing Janssen that the April 17 and 27, 2015, submissions to the NDA constituted a major amendment and that the extended use fee goal date is October 24, 2015.

12. Labeling

- **Proprietary name:** In the FDA Proprietary Name Memorandum dated February 4, 2015, Tingting Gao, PharmD, DMEPA, concluded that the proposed proprietary name, Yondelis, is acceptable.
- **OSE /Division of Medication Error Prevention and Analysis (DMEPA):** Dr. Otto Townsend, DMEPA, concluded the revised carton and container labeling was acceptable in the review dated September 11, 2015; DMEPA provided recommendations regarding the preparation and administration section of labeling.
- **Office of Prescription Drug Promotion (OPDP):** OPDP provided recommendations regarding text that may be considered promotion in Sections 5, 6, and 17.
- **Patient Labeling:** The FDA Patient Labeling team participated in labeling discussions of the Prescribing Information and the Patient Information. Refer to the FDA Patient Labeling NDA Reviews for their recommendations.
- **Maternal Health:** Maternal Health participated in labeling discussions and provided recommendations consistent with the Pregnancy and Lactation Labeling Rule (PLLR).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval

According to the review of the data submitted in the NDA, as amended, this reviewer recommends approval of trabectedin for the following indication:

Treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline containing regimen.

- Risk Benefit Assessment

Patients with unresectable or metastatic, leiomyosarcoma or liposarcoma have a serious and life-threatening disease with a high unmet medical need. Approximately 40-50% of patients will present with unresectable or metastatic disease, and once metastatic carries a grim prognosis—a median survival of approximately one year from time of diagnosis.

In general, FDA-approved treatment options in use for treatment of unresectable or metastatic STS inclusive of liposarcoma and/or leiomyosarcoma are limited to doxorubicin (metastatic STS) and pazopanib (advanced STS after prior chemotherapy); however, pazopanib is not indicated for patients with liposarcoma, which is noted as a limitation of use in pazopanib labeling. Pazopanib, when compared to a placebo, demonstrated a 3-month improvement in median PFS in patients with soft tissue sarcoma (excluding liposarcoma) who had received a

prior chemotherapy, a median PFS of 4.6 months with pazopanib as compared to a median PFS of 1.6 months with placebo (HR 0.35; 95% CI 0.26, 0.48; p-value <0.001). Pazopanib did not demonstrate an improvement in overall survival.

Progression-free survival as an endpoint to support approval in patients with advanced STS after prior chemotherapy was discussed at a March 20, 2012, ODAC convened to discuss pazopanib and overall the committee members supported PFS improvement of sufficient magnitude as a clinically meaningful endpoint. On April 26, 2012, FDA granted regular approval to pazopanib for “treatment of patients with advanced soft tissue sarcoma (STS) who have received prior chemotherapy. Limitation of Use: The efficacy of Votrient for the treatment of patients with adipocytic STS or gastrointestinal stromal tumors has not been demonstrated.”

The recommendation for approval of NDA 207953 (Yondelis) is primarily based on the results Trial ET743-SAR-3007, which demonstrated an improvement in investigator-assessed, progression-free survival (PFS) with a median PFS of 4.2 months (95% confidence interval (CI): 3.0, 4.8 months) on the trabectedin arm and 1.5 months (95% CI: 1.5, 2.6 months) on the dacarbazine arm, a median improvement of 2.7 months with a HR of 0.55 (95% CI: 0.44, 0.70; p < 0.001). The stated primary objective of the trial was overall survival. However, prior to the planned interim analysis of OS, FDA agreed that the final analysis of PFS at this time point could serve as a major efficacy outcome measure with the potential to support an initial approval of trabectedin (see Section 7). The final analysis of overall survival did not demonstrate superiority of the trabectedin arm compared with the dacarbazine arm with a HR of 0.93 (95% CI: 0.75, 1.15; p value = 0.49), but did not suggest a detriment in overall survival. The confirmed, investigator-assessed overall response rate (ORR) per RECIST version 1.1 was modest in both arms; the ORR in the trabectedin arm was 6.9% (95% CI: 4.5, 7.6) with a duration of response of 6.9 months (95% CI: 4.5, 7.6) and in the dacarbazine arm was 4.2% (95% CI: 2.9, not estimable) with a duration of response of 4.2 months (95% CI: 2.9, not estimable).

The primary safety risks of trabectedin were evaluated in safety analyses of the 755 patients with soft tissue sarcoma who received trabectedin at the recommended dosage; these were primarily described in analyses of Trial ET743-SAR-3007. The FDA clinical review of safety was also supplemented by evaluation of postmarketing safety information (foreign postmarketing information). Major safety risks with trabectedin are myelosuppression, predominantly neutropenic sepsis (including fatal cases), rhabdomyolysis (including fatal cases), hepatotoxicity (including hepatic failure), cardiomyopathy (including fatal cases), extravasation reactions and tissue necrosis, and allergic reactions (including anaphylaxis). Mitigation of these risks will be through product labeling

The risk-benefit assessment of trabectedin is favorable for the treatment of patients with unresectable or metastatic, leiomyosarcoma or liposarcoma who have received a prior anthracycline-containing regimen—a treatment refractory population which includes a population (liposarcoma) with no satisfactory available therapy. In this treatment refractory population, trabectedin at a dose of 1.5 mg/m² administered once every 3 weeks demonstrated an improvement in PFS of sufficient magnitude—a statistically robust, clinically meaningful 2.7 month median improvement and overall an approximate 45% reduction in PFS events compared with an active control—with an acceptable safety profile for patients with a serious

and life-threatening condition. The major safety risks with trabectedin were generally manageable with dose modifications and supportive care. FDA approval of trabectedin will represent a novel therapeutic option for treatment of the indicated population.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I agree with the recommendations of the NDA review team, including DRISK, that a REMS is not required to ensure safe use of trabectedin. Risk mitigation will occur through product labeling.

- Recommendation for other Postmarketing Requirements and Commitments

The following postmarketing requirements are recommended to assess a known serious risk of cardiac dysfunction with trabectedin, and to assess a signal of a serious risk of trabectedin toxicity in patients with impaired hepatic function:

1. Conduct a trial to characterize the risk of cardiomyopathy and its sequelae in patients receiving trabectedin; to identify risk factors for development of these sequelae; and to support labeling instructions for dose modification and monitoring. The design of the trial should include a patient population with previous exposure to anthracyclines and have sufficient cardiac monitoring to achieve these objectives. In addition, submit integrated safety analyses and supporting data including data from other trials that address these objectives.
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.”

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