

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207953Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA#: 207,953

Drug Name: Yondelis® (Trabectedin)

Indication(s): [REDACTED] (b) (4)

Applicant: Janssen Products, LP (Janssen)

Date(s): Submission: 11/24/2014
PDUFA: 10/26/2015

Review Priority: Priority

Biometrics Division: Division of Biometrics V

Statistical Reviewer: Huanyu (Jade) Chen

Concurring Reviewers: Kun He, Team Leader
Rajeshwari Sridhara, Division Director

Medical Division: Division of Oncology Products 2

Clinical Team: Amy Barone, Medical Reviewer
Marc Theoret, Team Leader
Patricia Keegen, Division Director

Project Manager: Anuja Patel

Keywords: log-rank test, K-M curve, audit method

Table of Contents

1	EXECUTIVE SUMMARY	5
2	INTRODUCTION	6
2.1	OVERVIEW.....	6
2.1.1	<i>Class and Indication</i>	6
2.1.2	<i>Regulatory History</i>	7
2.1.3	<i>Study Reviewed</i>	8
2.2	DATA SOURCES	8
3	STATISTICAL EVALUATION OF STUDY 3007.....	8
3.1	DATA AND ANALYSIS QUALITY.....	8
3.2	EVALUATION OF EFFICACY IN STUDY 3007.....	8
3.2.1	<i>Objective</i>	8
3.2.2	<i>Study Design</i>	9
3.2.3	<i>Efficacy Measures</i>	11
3.2.4	<i>Sample Size Considerations for OS</i>	11
3.2.5	<i>Interim Analysis for OS</i>	11
3.2.6	<i>Sample Size Considerations for PFS</i>	11
3.2.7	<i>Statistical Methodologies</i>	12
3.2.8	<i>Applicant's Results and FDA Statistical Reviewer's Findings / Comments</i>	13
3.3	EVALUATION OF SAFETY	20
3.4	BENEFIT/RISK RATIO.....	20
4	FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	20
4.1	GENDER, RACE, AGE, AND COUNTRY.....	20
5	SUMMARY AND CONCLUSIONS	21
5.1	STATISTICAL ISSUES	21
5.2	COLLECTIVE EVIDENCE.....	22
5.3	CONCLUSIONS AND RECOMMENDATIONS	22
5.4	LABELING RECOMMENDATION	22
6	REFERENCE.....	22

LIST OF TABLES

Table 1 FDA Approved Products for Advanced STS.....	6
Table 2 Statistical Regulatory History Related to Study 3007 Design	7
Table 3 Patient Population (ITT).....	13
Table 4 Patient Disposition, n (%).....	14
Table 5 Baseline Demographics Characteristics and Stratification Factor (ITT).....	14
Table 6 Baseline Disease Characteristics (ITT).....	15
Table 7 PFS Analyses (ITT).....	16
Table 8 Sensitivity Analyses of PFS	17
Table 9 OS Interim and Final Analysis Results (ITT).....	18
Table 10 ORR Results (ITT)	19
Table 11 DoR Results	19
Table 12 Summary of Mean MDASI Symptom Severity Scores	19
Table 13 PFS Analysis by Baseline Demographic Characteristics.....	20
Table 14 PFS Analysis by Baseline Disease Characteristics.....	21

LIST OF FIGURES

Figure 1 Study 3007 Scheme	9
Figure 2 K-M Curves for PFS (ITT).....	16
Figure 3 K-M Curves for OS Interim and final Analysis (ITT).....	18

1 EXECUTIVE SUMMARY

In this original New Drug Application (NDA), the applicant is seeking an approval of Yondelis® (Trabectedin) lyophilized powder for the treatment of patients ^{(b) (4)} liposarcoma or leiomyosarcoma ^{(b) (4)} who have received previous chemotherapy.

The study ET743-SAR-3007 (3007) to support the application was a randomized, open-label, parallel-group, active-controlled, multicenter phase III study evaluating the efficacy and safety of trabectedin (1.5 mg/m² IV over 24 hour Q3wkl) relative to dacarbazine (1200 mg/m² IV over 1 hour Q3Wkl). The efficacy measures included overall survival (OS), progression-free survival (PFS) per investigator assessment, and overall response rate (ORR). A total of 518 patients were randomized in a 2:1 allocation (trabectedin: 345; dacarbazine: 173).

The trial was originally designed using OS as the primary endpoint. At the study design phase, FDA did not agree with the proposal of using PFS as the primary endpoint. On March 20, 2012, the Oncologic Drug Advisory Committee (ODAC) discussed pazopanib and agreed with the magnitude of a 2.6 months improvement in median PFS to be clinically meaningful. After this ODAC meeting, the applicant submitted a protocol amendment to use PFS for supporting an approval before the first interim analysis of OS was performed as originally designed in the trial since the regulatory standard for approval of this indication changed.

The data and analyses from the study 3007 demonstrated that trabectedin had statistically significant improvement in PFS when compared with dacarbazine. The unstratified log-rank test p-value for PFS comparison was < 0.0001 with HR 0.55 (95% CI: 0.44, 0.70). The median PFS was 4.2 months (95% CI: 3.0, 4.8) for trabectedin and 1.5 months (95% CI: 1.5, 2.6) for dacarbazine. PFS results were consistent with an auditing analysis of the radiologic scans by independent radiologists blinded to treatment assignment, sensitivity analyses, and subgroup analyses of PFS.

Statistically significant improvement in OS was not demonstrated. The unstratified log-rank test p-value was 0.49 with HR 0.93 (95% CI: 0.75, 1.15). Additionally, there was no improvement in ORR (trabectedin: 9.9%; dacarbazine: 6.9%).

The issue is that the major protocol/ statistical analysis plan (SAP) changes were submitted after the completion of patient enrollment, and the final SAP was finalized after the clinical cut-off date. Whether the data and analyses from trabectedin demonstrated an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

2 INTRODUCTION

In this New Drug Application (NDA), the applicant is seeking an approval of Yondelis® (Trabectedin) for the treatment of patients with (b) (4) liposarcoma or leiomyosarcoma (b) (4), who were previously treated (b) (4) anthracycline containing regimen (b) (4). This submission was primarily supported by results from a randomized, open-label, parallel-group, active-controlled multicenter phase III study 3007 (ET743-SAR-3007) under Investigational New Drug (IND) 50,286.

2.1 Overview

2.1.1 Class and Indication

STS constitutes a heterogeneous group of over 50 subtypes. The most frequent histopathological types are leiomyosarcoma and liposarcoma (L-type sarcoma), which account for approximately 40% to 50% of all STS with estimated median overall survival (OS) of 8 to 13 months. The National Cancer Institute (NCI) estimates that there are 11,930 new cases and 4,870 deaths from STS in the U.S. in 2015^[1]. The reported international incidence rates range from 1.8 to 5 per 100,000 per year. Approximately 50% of patients present with or develop metastatic disease and despite chemotherapy.

Doxorubicin with or without ifosfamide is the standard systemic treatment option for patients with metastatic STS. Pazopanib is the only approved treatment for recurrent STS that has progressed after doxorubicin. On March 20, 2012, the Oncologic Drug Advisory Committee (ODAC) discussed pazopanib application and agreed with the magnitude of a 2.6 month improvement in median progression-free survival (PFS) to be clinically meaningful. Table 1 presents FDA approved products for advanced STS.

Table 1 FDA Approved Products for Advanced STS

Product	Indication	Efficacy Endpoint
Pazopanib (2012)	STS after prior chemotherapy (Limitation-adipocytic)	PFS: Median PFS (4.5 vs 1.9 months) HR 0.35, p<0.001 Control: placebo
Doxorubicin (2005)	Metastatic STS	ORR*: 10-25% (Single-agent) ORR: 46% (in combination)

*: ORR: overall response rate; HR: hazard ratio

According to the applicant's report, trabectedin is a new chemical entity firstly isolated, identified and characterized from the marine tunicate Ecteinascidia turbinata. Trabectedin was granted marketing authorization (MA) under "exceptional circumstances" by the EMA in 2007 for the treatment of patients with STS who have progressed after both anthracycline and ifosamide treatment or for whom these treatments are unsuitable, under Study ET743-ST-201 which FDA considered to be exploratory given the limitations in design and conduct.

In the current NDA submission, the proposed indication is for treatment of patients with (b) (4) This indication was supported by randomized, open-label, parallel-group, active-controlled multicenter phase III study.

2.1.2 Regulatory History

(b) (4)

Table 2 presents statistical regulatory history related to Study 3007 design.

Table 2 Statistical Regulatory History Related to Study 3007 Design

Date	Action
October 18, 2000	Type B, End-of-Phase 2 (EOP2) meeting to discuss the development of trabectedin (b) (4) FDA stated that the primary endpoint of the trial should be OS.
November 23, 2010	Type C meeting to discuss the design of the proposed Phase 3 study 3007 <ul style="list-style-type: none"> FDA agreed with OS as the primary endpoint with dacarbazine as the comparator Sponsor stated that patients would not be allowed to crossover to trabectedin arm
May 27, 2011	Study 3007 begins
July 23, 2012	EOP2 meeting to discuss the (b) (4) . FDA acknowledged that the applicant could submit the mature PFS and ORR results from the study 3007 as a basis for possible accelerated approval (b) (4)
June 7, 2013	Type C (Written Response), FDA acknowledged that Janssen sought approval based on PFS and ORR and may propose a detailed auditing plan including a strategy to detect potential assessment bias
July 15, 2013	Janssen submitted estimate power, medians and hazard ratio for PFS per investigator (INV) assessment based on planned sample size
September 16, 2013	Interim OS clinical data cut-off
November, 2013	Completed patient enrollment
January 9, 2014	<ul style="list-style-type: none"> Janssen submitted interim results for OS, PFS and ORR for Study 3007 Janssen estimated that 160 (80%) image data was estimated to be available for blinded independent radiologist review committee (BIRC) Janssen submitted a proposed auditing plan for the radiographic PFS (rPFS) endpoint in approximately 60% of the patients from sites enrolled ≥ 9 patients at the time of the interim analysis of OS (accepted on February 18, 2014)
March 17, 2014	Janssen submitted SAP addendum for Study 3007 (drafted on October 22, 2013) <ul style="list-style-type: none"> Implement the audit plan and describe the analysis methods for comparisons between rPFS per INV and BIRC using the 1st stage audit method by Dodd et. Al² Symptomatic deterioration, in the absence of radiographic evidence of progression, would not be considered a disease progression event
July 7, 2014	Type C meeting to discuss the audit results of rPFS for Study ET743-SAR-3007 as assessed by BIRC. <ul style="list-style-type: none"> FDA stated that the PFS effect was similar in magnitude to a recent approval of Pazopanib for treatment of STS and agreed that the result may support accelerated approval
October 17, 2014	Pre-NDA meeting
11/24/2014	NDA Submission
January 05, 2015	Final OS clinical data cut off

2.1.3 Study Reviewed

Study 3007 was a randomized, open-label, active-controlled, parallel group, multicenter phase III study comparing the efficacy and safety of trabectedin with dacarbazine for patients with advanced STS with prior chemotherapy. This study was conducted at 84 centers within 4 countries (Australia, Brazil, New Zealand, and the U.S. [94%]) from December 23, 2010 to January 05, 2015. The clinical data cut-off date was May 27, 2011 for the PFS analysis (interim OS analysis) and January 05, 2015 for the final OS analysis.

A total of 518 patients were randomized in a 2:1 allocation (trabectedin: 345; dacarbazine: 173) to receive either:

- Trabectedin: 1.5 mg/m², q3wk 24-hour IV or
- Dacarbazine: 1 g/m² as a 20-120 minute IV infusion q3wk

The planned primary endpoint originally designed in the trial was OS. The key secondary endpoints included PFS, TTP, and objective response rate (ORR).

2.2 Data Sources

The electronic submission including protocols, SAP, clinical study reports (CSR), and analysis datasets for this NDA submission are located on the network with network path: \\cdsesub1\evsprod\nda207953\0000\m5.

3 STATISTICAL EVALUATION OF STUDY 3007

Part of the text, tables, and figures presented in this section are adapted from the applicant's CSR.

3.1 Data and Analysis Quality

The data and analysis quality were acceptable. This reviewer was able to duplicate the analysis variable derivation and summary statistics.

3.2 Evaluation of Efficacy in Study 3007

3.2.1 Objective

The primary efficacy objective of the study 3007 was to compare OS between the treatment arms. The secondary efficacy objectives included comparisons for PFS, TTP, ORR, and Patient Reported Outcomes (PRO) between the treatment arms.

Reviewer's Comments:

- Detailed regulatory history is presented in Table 1. At the study design phase, FDA did not agree with the proposal of using PFS as primary endpoint. On March 20, 2012, the Oncologic Drug Advisory Committee (ODAC) discussed Pazopanib and agreed with the magnitude of a 2.6 months improvement in median progression-free survival (PFS) to be

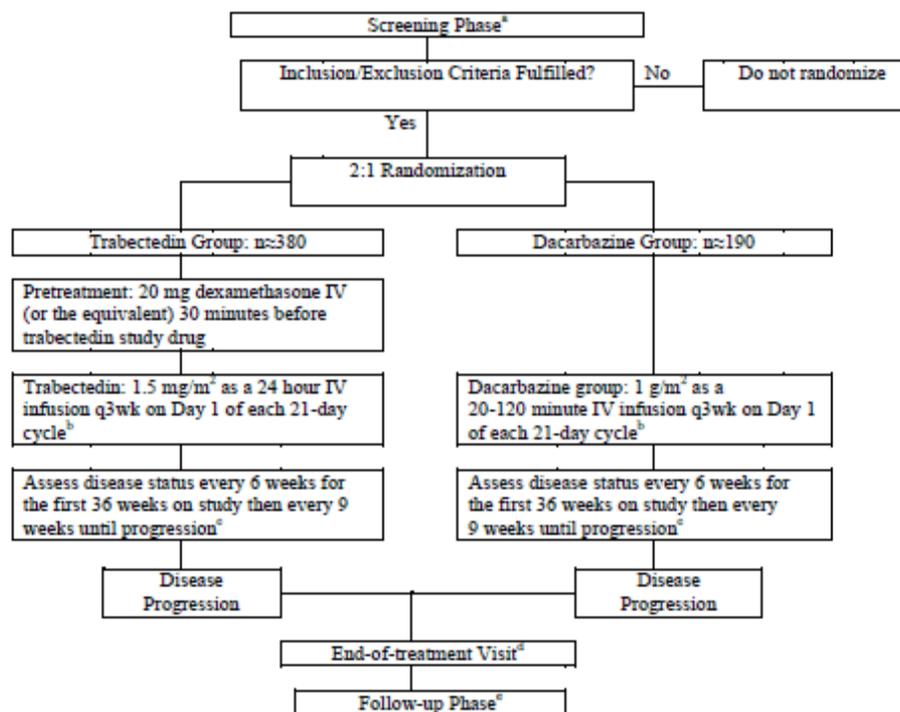
clinically meaningful. After this ODAC meeting, the applicant submitted a protocol amendment to use PFS for supporting an approval before the first interim analysis of OS as originally designed in the trial.

- This reviewer focuses on the evaluation of PFS, OS, ORR, and PRO.

3.2.2 Study Design

The study 3007 was designed to evaluate the efficacy and safety of trabectedin compared to dacarbazine in patients 15 years of age and older with unresectable, locally advanced or metastatic L-sarcoma, who were previously treated (in any order) with at least an anthracycline and ifosfamide containing regimen or an anthracycline containing regimen and 1 additional cytotoxic chemotherapy regimen. Figure 1 presents the study schema.

Figure 1 Study 3007 Scheme



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

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

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

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

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

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

Source: CSR Figure 1

According to the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, tumor radiographic assessments (computed tomography [CT] or magnetic resonance imaging [MRI]) were performed at baseline (within 21 days prior to randomization), every 6 weeks for the first

36 months of treatment, and every 9 weeks thereafter. Investigators reviewed physical findings and the results of clinical laboratory tests before each dose of study drug and, if required, delay administration or reduce the dose according to predefined guidelines. Patients received study treatment until radiographic or symptomatic documented progressive disease (PD) or unacceptable toxicity, withdrawal of consent, received subsequent anticancer therapy, death, investigator's decision, or pregnancy. Follow-up information regarding further anticancer treatment, assessment of radiographic disease assessments, and survival were collected at least every 60 days for the first two years and every 90 days thereafter.

Approximately 570 patients (age ≥ 15 years) were planned to be randomized based on a permuted-block randomization method using a 2:1 allocation. The randomization was centralized and stratified by three baseline factors: the number of lines of prior chemotherapy (1 vs. ≥ 2), Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (0 vs. 1), and L-sarcoma subtype (liposarcoma vs. leiomyosarcoma). An Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) was used to randomly assign patients to study treatment, and dispense study drug.

The main inclusion criteria included patients:

- Was 15 years of age or older
- With measurable disease at baseline per RECIST Version 1.1
- Had histologically proven, unresectable, locally advanced or metastatic liposarcoma (dedifferentiated, myxoid round cell, or pleomorphic) or leiomyosarcoma
- Was treated in any order with at least:
 - an anthracycline and ifosfamide containing regimen, or
 - an anthracycline-containing regimen and 1 additional cytotoxic chemotherapy
- Had pathology specimens
- Had an ECOG PS of 0 or 1
- Had adequate recovery from prior therapy; all side effects (except alopecia) were to have resolved to Grade 1 or less (NCI-CTCAE, Version 4.0)
- Had adequate organ function
- Had adequate hepatic function

The main exclusion criteria included patients:

- Had prior exposure to trabectedin or dacarbazine
- Were less than 3 weeks from last dose of systemic cytotoxic therapy, radiation therapy, or therapy with any investigational agent
- Had another malignancy within the past 3 years
- Had known significant chronic liver disease
- Had a myocardial infarct within 6 months before enrollment, New York Heart Association Class II or greater heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, clinically significant pericardial disease, or electrocardiographic evidence of acute ischemic or active conduction system abnormalities
- Had uncontrolled intercurrent illness

3.2.3 Efficacy Measures

PFS, assessed by investigator, was defined as the time from the date of randomization until the date of radiographic or clinical PD per investigator assessment as defined by RECIST 1.1, or death due to any cause, whichever occurred first.

OS was defined as the time from the date of randomization to the date of death from any cause. Patients were censored at the last date the patients were known to be alive if not known to have died on or before the clinical cut-off date. Patients were censored at the date of randomization if no additional follow-up data were obtained.

rPFS was defined as the time between randomization and radiology disease progression or death regardless of the cause of death, whichever occurred first. Symptomatic deterioration, in the absence of radiographic evidence of progression, was not considered as a progression event.

ORR was defined as the proportion of randomized patients achieving a best overall response of complete response (CR) or partial response (PR).

PRO was evaluated by M.D. Anderson Symptom Inventory (MDASI) scores across 13 different measures of symptoms (Symptom Severity) and 6 measures of physical and mental function. The MDASI scores were used to assess patient's perceived symptom burden and to determine the impact of treatment on symptom change or stability (Symptom Interference) prior to dosing on day 1 of each cycle.

3.2.4 Sample Size Considerations for OS

This study was designed to have 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. It was estimated that 376 OS events were needed at the final OS analysis, which could be expected from a total accrual of 570 patients.

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

3.2.5 Interim Analysis for OS

An interim efficacy analysis 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.

3.2.6 Sample Size Considerations for PFS

In the protocol amendment, the applicant submitted estimate sample size considerations on PFS per INV 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.

3.2.7 Statistical Methodologies

Intent to Treat (ITT) population was defined as all randomized patients. The ITT population was planned to be the primary analysis population for the efficacy analyses.

Efficacy Analysis Method for OS

The analysis for OS was performed using an unstratified log-rank test. The median OS with corresponding 95% confidence interval (CI) and survival curve were estimated 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. Un-stratified log-rank test was planned as supportive analysis.

Efficacy Analysis Method for PFS

The analysis method for PFS was identical to OS analysis.

Audit Plan for rPFS Subset

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 plan². Comparisons between rPFS based on BIRC vs. INV assessment and unaudited subset vs. audited subset were planned.

Efficacy Analysis Method for ORR

The analysis for ORR was performed using the Fisher's exact test. Response rate and the associated 95% CI were performed for each treatment arm.

Efficacy Analysis Method for PRO

The PRO analysis was the change from baseline in mean score of all symptom severity items, mean score of all symptom interference items and each individual item scores. The change in these PRO scores between baseline and post baseline assessment were summarized.

Reviewer’s Comments:

Many changes were made after the completion of patient enrollment and the final SAP was finalized after the clinical cut-off date for PFS analysis. The following is a list of major changes before and after the clinical cut-off date for PFS analysis (see Table 2 for more details):

1. Protocol/SAP addendums before the clinical cut-off date
 - a. On June 7, 2013, FDA required a detailed auditing plan
 - b. On July 15, 2013, estimate power, medians and hazard ratio for PFS was submitted
2. Protocol/SAP addendums after the clinical cut-off date
 - a. On January 9, 2014, the applicant submitted SAP addendum 1 to implement estimate power, medians and hazard ratio for PFS and proposed auditing plan for rPFS
 - b. On March 17, 2014, the applicant submitted SAP addendum 2 to implement FDA agreed audit plan on rPFS

3.2.8 Applicant’s Results and FDA Statistical Reviewer’s Findings / Comments

3.2.8.1 Patient Population and Disposition

A total of 518 patients were randomized in a 2:1 allocation (trabectedin plus paclitaxel: 345; dacarbazine: 173). Table 1 presents the study population.

Table 3 Patient Population (ITT)

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

Reviewer’s Comments:

- Five patients randomized to the trabectedin arm and eighteen patients randomized to the control arm did not receive their allocated treatment. In the dacarbazine arm, the most common reason for not receiving the study drug was withdrawal of consent (8%).
- At the clinical cut-off date, 28% patients in the trabectedin arm and 15% in the placebo arm were still on study treatment

- *During the collection of radiographic scans for patients from sites selected in the audited subset, 3 patients' radiographic scans were not available for independent radiologist review. These patients were included in the unaudited subset.*

Table 4 presents the study disposition.

Table 4 Patient Disposition, n (%)

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

Reviewer's Comments:

The majority of the discontinuations were associated with PD and AEs, which were slightly imbalanced between the trabectedin and the dacarbazine arms. The placebo arm had more PDs, and trabectedin arm had more AEs.

3.2.8.2 Baseline and Demographic Characteristics

Table 5 presents the patient baseline demographic characteristics and stratification factors.

Table 5 Baseline Demographics Characteristics and Stratification Factor (ITT)

	Trabectedin (N=345)	Dacarbazine (N=173)
Age (yr) Mean (SD)	56.2 (10.9)	54.5 (11.8)
Median (min - max)	56 (17-79)	57 (18-81)
≥ 65	81 (23%)	34 (20%)
Female	238 (69%)	126 (73%)
Race White	269 (78%)	125 (72%)
Asian	44 (13%)	19 (11%)
Black	9 (3%)	10 (6%)
US	323 (94%)	166 (96%)
Stratification Factors		
Line of prior chemo: 1	39 (11%)	19 (11%)
>=2	306 (89%)	154 (89%)
ECOG PS: 0	169 (49%)	86 (50%)
1	176 (51%)	87 (50%)
Sarcoma: Liposarcoma	93 (27%)	47 (27%)
Leiomyosarcoma	252 (73%)	126 (73%)

Table 6 presents the important baseline disease characteristics and prior treatment in the ITT population.

Table 6 Baseline Disease Characteristics (ITT)

	Trabectedin (N=345)	Dacarbazine (N=173)
Leiomyosarcoma: Uterine	134(38.8%)	78(45.1%)
Nonuterine	118(34.2%)	48(27.7%)
Liposarcoma: Myxoid with or without round cell	38(11.0%)	19(11.0%)
Pleomorphic	10(2.9%)	3(1.7%)
Dedifferentiated	45(13.0%)	25(14.5%)
BMI \geq 30 kg/m ²	142 (41%)	61 (35%)
Prior surgery, n (%)	327 (94.8%)	158 (91.3%)
Prior radiotherapy, n (%)	176 (51.0%)	80 (46.2%)
Time from last PD, Med (min-max) Month	0.85 (0.03-13.7)	0.82 (0.07-9.82)
Time from Last Diag, med (min-max) Month	38.2 (4.7-318.5)	26.2 (10.4-162.0)
ORR (CR/PR) in last line of chemo	32 (8.5%)	17 (9.8%)
PD in last line of chemo	198 (57.4%)	103 (59.5%)

Reviewer's Comments:

Baseline characteristics appear to be balanced between the two treatment arms except uterine leiomyosarcoma and body mass index (BMI) \geq 30 kg/m².

- More patients in the dacarbazine arm have uterine leiomyosarcoma compared to those in the treatment arm.*
- More patients in the trabectedin arm have BMI \geq 30 kg/m²*

3.2.8.3 PFS Analysis

Table 7 presents the efficacy analysis for PFS per investigator assessment with a total of 329 events. The trabectedin arm demonstrated a statistically significant difference in PFS compared with the placebo arm based on the unstratified log-rank test with a p-value <0.001. The median PFS was 4.2 months (95% CI: 3.0, 4.8) for the trabectedin arm and 1.5 months (95% CI: 1.5, 2.6) for the placebo arm. The median PFS difference was 2.7 months with a HR of 0.55 (95% CI: 0.44, 0.70).

Table 7 PFS Analyses (ITT)

	Trabectedin (N=345)	Dacarbazine (N=173)
Number of PFS Events, n (%)	217 (62.9%)	112 (64.7%)
PD, n (%)	204 (59.1%)	109 (63.0%)
Radiographic PD only	170 (49.3%)	82 (47.4%)
Clinical PD only	21 (6.1%)	16 (9.2%)
Both Radiographic and Clinical PD	13 (3.8%)	11 (6.4%)
Death, n (%)	13 (3.8%)	3 (1.7%)
Number of Censored	128 (37.1%)	61 (35.3%)
Permanently Censored	30 (8.7%)	35 (20.2%)
2 Consecutive Missing	4 (1.2%)	1 (0.6%)
Anti-Cancer Therapy	19 (5.5%)	14 (8.1%)
No Tumor Assessment	0	1 (1.6%)
No Post Baseline Tumor Assessment	7 (2.0%)	17 (9.8%)
Withdrew Follow-up Consent	0	2 (1.2%)
Clinical Cut Off Date	98 (28.4%)	26 (15.0%)
Median PFS in Months (95% CI)	4.2 (3.0, 4.8)	1.5 (1.5, 2.6)
Unstratified Cox HR (95% CI)	0.55 (0.44, 0.70)	
Unstratified Log-Rank Test P-value	<0.001	

Figure 2 presents the Kaplan-Meier Curves for PFS.

Figure 2 K-M Curves for PFS (ITT)

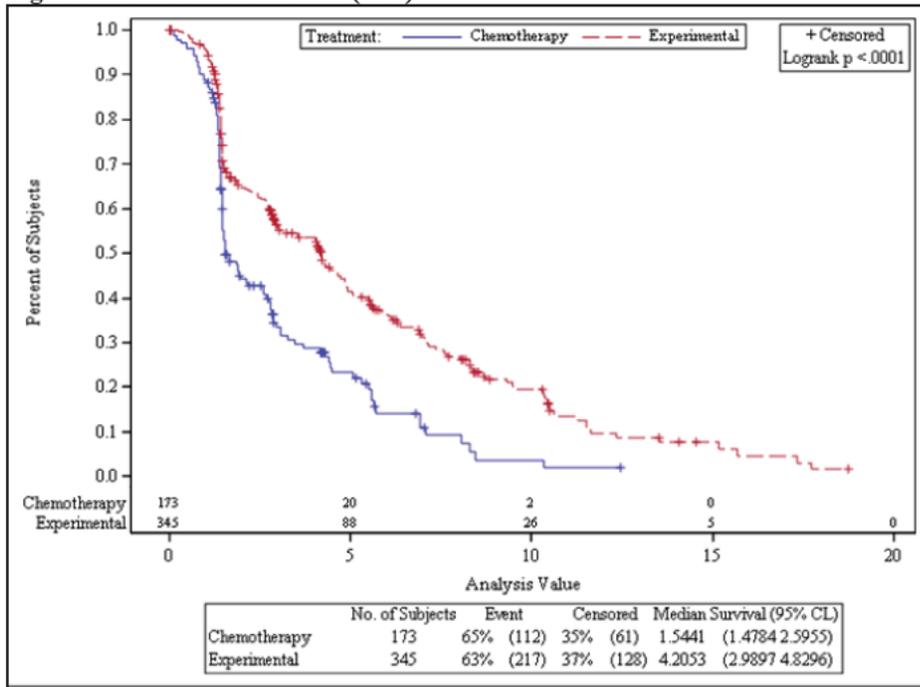


Table 8 presents the SAP pre-specified sensitivity analyses results for PFS.

Table 8 Sensitivity Analyses of PFS

Method	HR (95% CI)	P-Value
PFS (INV) ITT (unstratified)	0.55 (0.44, 0.70)	<0.0001
PFS (INV) ITT (stratified)	0.55 (0.44, 0.70)	<0.0001
PFS (INV) ITT (unstratified) adjust by factors in Tables 5 and 6	0.56 (0.45, 0.72)	<0.0001
PFS (INV)Site WITH >=9 PAT	0.55 (0.37, 0.80)	0.0014
PFS (INV)Site WITH< 9 PAT	0.55 (0.41, 0.75)	0.0001
rPFS (INV) ITT	0.57 (0.47, 0.73)	<0.0001
rPFS (IRC) audit subgroup	0.55 (0.40, 0.75)	0.0001
rPFS (INV) audit subgroup	0.58 (0.43, 0.79)	0.0004
rPFS (INV) unaudit subgroup	0.54 (0.37, 0.80)	0.0018
Overall rPFS (BRIC) – 1st stage of Dott et. al	0.54 (0.41, 0.71)	

Reviewer's Comments:

- *The PFS sensitivity analyses results were similar as the primary analysis of PFS. The HRs ranged from 0.54 to 0.58.*
- *The estimated overall HR for rPFS per BIRC assessment was 0.54 (95% CI: 0.41, 0.71), which appears consistent with the investigator based analyses.*

3.2.8.4 OS Analysis

Table 9 presents the applicant's efficacy analysis for OS at the planned interim analysis and the final analysis. The applicant submitted OS final analysis at the 120-Day Safety Update (clinical cut-off date: January 5, 2015). Neither interim nor final OS analysis demonstrated a statistically significant difference in OS compared with the dacarbazine arm based on the unstratified log-rank test with p-values 0.37 and 0.49 respectively.

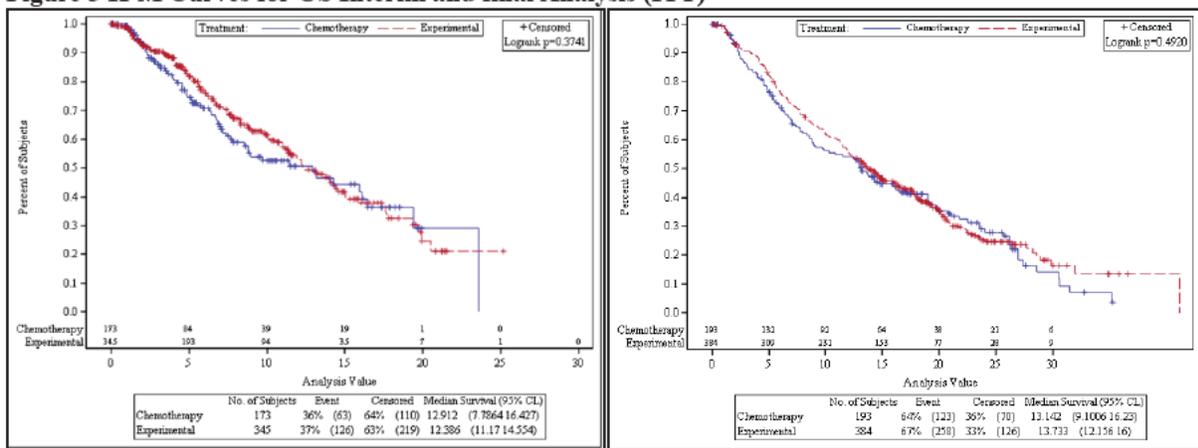
At the final OS analysis, there were a total of 381 deaths. The median OS was 13.7 months (95% CI: 12.2, 16.0) for the trabectedin and 13.1 months (95% CI: 9.1, 16.2) for the dacarbazine. The median OS difference was 0.6 months with a HR of 0.93 (95% CI: 0.75, 1.15).

Table 9 OS Interim and Final Analysis Results (ITT)

	Trabectedin (N=345)	Dacarbazine (N=173)
Interim Analysis		
Number of deaths, n (%)	126 (36.5%)	63 (36.4%)
Median OS in months (95% CI)	12.4 (11.2, 14.6)	12.9 (7.8, 16.4)
Unstratified Cox HR (95% CI)	0.872 (0.64, 1.18)	
Unstratified Log-Rank Test P-value	0.3471	
Final Analysis		
	N=384	N=173
Number of deaths, n (%)	258 (67.2%)	123 (63.7%)
Median OS in months (95% CI)	13.7 (12.2, 16.0)	13.1 (9.1, 16.2)
Unstratified Cox HR (95% CI)	0.93 (0.75, 1.15)	
Unstratified Log-Rank Test P-value	0.49	

Figure 3 present the Kaplan-Meier (K-M) Curves for OS Interim and final analysis.

Figure 3 K-M Curves for OS Interim and final Analysis (ITT)



OS Interim Analysis

OS Final Analysis

Reviewer's Comments:

Per protocol, patients in the dacarbazine were prohibited to cross over to the trabectedin. After reviewing the summary results for the final analysis of PFS, updated OS analysis (with 6 ongoing patients in the decarbozine arm), ORR, and DoR in the Pre-NDA meeting package, FDA agreed with the option for patients randomized to the dacarbazine to cross over to receive treatment with trabectedin. Neither interim nor final OS analysis demonstrated a statistically significant difference in the trabectedin arm compared to decarbozin. The lack of treatment effect was not confounded by patients (no more than 6 patients) in the dacarbazine arm crossing over to receive trabectedin.

3.2.8.5 ORR Analysis

Table 10 presents the results of ORR based on the INV measurements.

Table 10 ORR Results (ITT)

	Trabectedin (N=345)	Dacarbazine (N=173)
Overall Response	34 (9.9%)	12 (6.9%)
Complete Response	0	0
Partial Response	34 (9.9%)	12 (6.9%)
95% CI	(3.6%, 11.8%)	(6.9%, 13.5%)
Odds Ratio (95% CI)	1.47 (0.72 - 3.20)	
CMH P-value	0.33	

Duration of response (DoR) was defined for responders (CR or PR) and was calculated from the date of the first documentation of response to the date of PD or all cause death, whichever occurs first. Table 11 presents the median and its 95% CI for DoR.

Table 11 DoR Results

	Trabectedin	Dacarbazine
Number of responder, n	34	12
Median DoR in months (95% CI)	6.47 (3.58, 7.62)	4.17 (2.14, NE)

3.2.8.6 PRO Analysis

Patients experience regarding 3 core MDASI items of pain, fatigue, and nausea, which also correlate with frequently reported adverse events in this study, were representative of the other symptom severity measures, and are summarized in Table 12.

Table 12 Summary of Mean MDASI Symptom Severity Scores

Timepoint	Pain		Fatigue		Nausea	
	Dacarbazine	Trabectedin	Dacarbazine	Trabectedin	Dacarbazine	Trabectedin
Baseline	2.61	2.68	3.16	3.04	0.91	0.90
Cycle 2	2.86	2.89	3.73	3.67	1.17	1.90*
Cycle 3	2.56	2.20	3.92	3.20	1.25	1.48
Cycle 4	2.61	2.22	3.49	3.27	1.08	1.64
Cycle 5	2.61	1.91	3.10	2.86	0.91	1.40
Cycle 6	1.84	1.90	2.64	2.73	0.68	0.99
Cycle 7	2.11	1.74	2.44	2.86	1.11	0.90
Cycle 8	2.07	1.82	2.50	2.37	1.07	0.99

Source: CSR Table 40

Reviewer's Comments:

- *The MDASI mean baseline scores were observed to be low for all symptoms measured at baseline for both treatment arms.*
- *The MDASI scores failed to show meaningful difference in change from baseline between treatment arms across 13 different symptom measures, and 6 different functional measures in both treatment groups.*

3.3 Evaluation of Safety

Please refer to the clinical review of this application for safety evaluation.

3.4 Benefit/Risk Ratio

Trabectedin demonstrated a statistically significant improvement in PFS compared with dacarbazine. Trabectedin failed to demonstrate a statistically significant improvement in OS and ORR compared with dacarbazine. Whether the submission demonstrated an overall favorable benefit vs. risk profile for trabectedin arm is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Country

Table 13 presents the subgroup analysis of PFS by baseline demographic characteristics.

Table 13 PFS Analysis by Baseline Demographic Characteristics

Subgroup		Trabectedin (Censored/Event)	Dacarbazine (Censored/Event)	HR (95%)
age65	>=65	37/ 44	9/ 25	0.40 (0.23, 0.69)
	<65	91/173	52/ 87	0.60 (0.46, 0.79)
race	WHITE	96/173	43/ 82	0.52 (0.39, 0.68)
	BLACK	22/ 22	8/ 11	0.54 (0.25, 1.19)
	ASIAN	4/ 5	2/ 8	1.05 (0.21, 5.29)
sex	Female	97/141	45/ 81	0.57 (0.43, 0.76)
	Male	31/ 76	16/ 31	0.55 (0.34, 0.87)
country	USA	118/205	59/107	0.55 (0.43, 0.70)

Reviewer's comment:

- *The HRs of PFS by baseline demographic characteristics are less than 1 except in the Asian subgroup.*
- *These analyses are exploratory due to small sample size. Since no hypothesis and power calculation are pre-specified in the subgroups presented in this section, all results are considered exploratory. Thus, this reviewer strongly recommends* (b) (4)

Table 14 presents the subgroup analysis of PFS by baseline disease characteristics.

Table 14 PFS Analysis by Baseline Disease Characteristics

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

Reviewer's comment:

- The HRs of PFS by baseline disease characteristics are less than 1. These analyses are exploratory due to small sample size.
- These analyses are exploratory due to small sample size. Since no hypothesis and power calculation are pre-specified in the subgroups presented in this section, all results are considered exploratory. Thus, this reviewer strongly recommends (b) (4)

5 SUMMARY AND CONCLUSIONS**5.1 Statistical Issues**

Major protocol/SAP changes were submitted after the completion of patient enrollment and the applicant submitted final SAP after the clinical cut-off date. Whether the data and analyses from the current submission demonstrated an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

5.2 Collective Evidence

The data and analyses from the study 3007 demonstrated that trabectedin had statistically significant improvement in PFS when compared with dacarbazine. The unstratified log-rank test p-value for PFS comparison was <0.0001 with HR 0.55 and 95% CI (0.44, 0.70). The median PFS was 4.2 months (95% CI: 3.0, 4.8) for trabectedin and 1.5 months (95% CI: 1.5, 2.6) for dacarbazine. PFS results were consistent with an audit of the radiologic scans by independent radiologists blinded to treatment assignment and subgroup analyses of PFS.

Statistically significant improvement in final OS analysis was not demonstrated with the unstratified log-rank test p-value of 0.49 and HR 0.93 (95% CI: 0.75, 1.15), and there was no improvement in ORR (trabectedin: 9.9%; dacarbazine: 6.9%).

5.3 Conclusions and Recommendations

Patients treated with trabectedin demonstrated a statistically significant improvement in the PFS but improvement in OS and ORR were not observed. Whether trabectedin demonstrated an overall favorable benefit vs. risk profile for the treatment of advanced STS patients is deferred to the clinical team reviewing this submission.

5.4 Labeling recommendation

1. The results of PFS (INV) analysis will be included in the label.
2. The results of final OS analysis will be included in the label.
3. The ORR and DoR results will be included in the label.

6 Reference

[1] **National Cancer Institute**: PDQ® Adult Soft Tissue Sarcoma Treatment. Bethesda, M.N.C.I.D.1 m.A.a.h.c.g.c.p.

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

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

/s/

HUANYU CHEN
07/23/2015

KUN HE
07/23/2015

RAJESHWARI SRIDHARA
07/23/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 207953

Applicant: Janssen

Stamp Date: 11/24/2014

Drug Name: Yondelis

NDA Type: Priority

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	√			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

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

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			
Appropriate references for novel statistical methodology (if present) are included.	√			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

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

/s/

HUANYU CHEN
01/08/2015

KUN HE
01/08/2015