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RESEARCH**

*APPLICATION NUMBER:*

**207953Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Review - Addendum

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<b>NDA</b>	207,953
<b>Submission Date:</b>	November 24, 2014
<b>PDUFA Date:</b>	October 24, 2015
<b>Brand Name:</b>	Yondelis®
<b>Generic Name:</b>	Trabectedin
<b>Formulation/Strength:</b>	Lyophilized powder for injection; 1.0 mg single-use vial for reconstitution
<b>Sponsor:</b>	Janssen Products LP
<b>Submission Type; Code:</b>	Original NDA; NME
<b>Dosage Regimen:</b>	1.5 mg/m <sup>2</sup> as a 24-hour IV infusion administered every 3 weeks
<b>Proposed Indication:</b>	(b) (4)
<b>OCP Reviewer:</b>	Sriram Subramaniam, Ph.D.
<b>OCP Team Leader:</b>	Hong Zhao, Ph.D.
<b>OCP Division:</b>	Division of Clinical Pharmacology V
<b>ORM Division:</b>	Division of Drug Oncology Products

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This is an addendum to the Clinical Pharmacology review dated May 15, 2015 (DARRTS Reference ID 3757253) to address dosing in patients with hepatic impairment and to clarify our clinical pharmacology recommendations with regard to the concomitant use of strong CYP3A inhibitors and strong CYP3A inducers with YONDELIS.

### I. Labeling Recommendation for Patients with Hepatic Impairment

Given the observed hepatotoxicity of YONDELIS in clinical studies and exclusion of patients with the total bilirubin greater than upper limit of normal (>ULN) in the clinical trials with YONDELIS, we recommend to include the following statement in the YONDELIS label in Section 2 under DOSAGE AND ADMINISTRATION:

#### **2 DOSAGE AND ADMINISTRATION**

Do not administer YONDELIS to patients with total bilirubin greater than the upper limit of normal [(see *Dose Modifications (2.3)*)].

Since the pharmacokinetics of trabectedin has not been evaluated in patients with a total bilirubin>ULN, we recommend to revise Section 8.6 under Hepatic Impairment and Section 12.3 under Specific Populations in the YONDELIS label as follow (revisions highlighted):

#### **8.6 Hepatic Impairment**

The pharmacokinetics of trabectedin has not been evaluated in patients with a total bilirubin greater than the upper limit of normal [see *Clinical Pharmacology (12.3)*].

#### **12.3 Specific Populations**

The following population characteristics are not associated with a clinically significant effect on the pharmacokinetics of trabectedin: sex, age (19 to 83 years), body weight (36 to 148 kg), body surface area (0.9 to 2.8 m<sup>2</sup>), and mild to moderate renal impairment. The effect of (b) (4) degree (b) (4) of hepatic impairment, severe renal impairment, or end stage renal disease on trabectedin exposure is unknown.

## II. Labeling Recommendation Regarding Concomitant Use of Strong CYP3A Inhibitors and Inducers

We recommend to revise Section 7 under DRUG INTERACTIONS in the YONDELIS label as follows (revisions highlighted):

### **7 DRUG INTERACTIONS**

#### **7.1 Effect of Cytochrome CYP3A Inhibitors**

Coadministration of YONDELIS with ketoconazole, a strong CYP3A inhibitor, increases systemic exposure of trabectedin by 66%. **Avoid use of strong CYP3A inhibitors** (e.g., oral ketoconazole, itraconazole, posaconazole, voriconazole, clarithromycin, telithromycin, indinavir, lopinavir, ritonavir, boceprevir, nelfinavir, saquinavir, telaprevir, nefazodone, conivaptan) **in patients taking YONDELIS**. **Avoid taking grapefruit or grapefruit juice during YONDELIS treatment**. **If a strong CYP3A inhibitor for short-term use (i.e., less than 14 days) must be used, administer the strong CYP3A inhibitor 1 week after the YONDELIS infusion, and discontinue it the day prior to the next YONDELIS infusion [see Clinical Pharmacology (12.3)].**

#### **7.2 Effect of Cytochrome CYP3A Inducers**

Coadministration of YONDELIS with rifampin, a strong CYP3A inducer, decreased systemic exposure of trabectedin by 31%. **Avoid administering strong CYP3A inducers** (e.g., rifampin, phenobarbital, St. John's wort) **to patients who are taking YONDELIS [see Clinical Pharmacology (12.3)].**

Routinely, we recommend to avoid concomitant use of strong CYP3A inhibitors and strong CYP3A inducers for a sensitive CYP3A substrate drug; and if the use is unavoidable, we recommend dose adjustment based on the observed magnitude change in the exposure of the drug that is CYP3A substrate to reduce the risk of increased toxicity or decreased activity. For YONDELIS, if a strong CYP3A inhibitor must be used for short term (i.e., less than 14 days), we recommend that strong CYP3A inhibitors be administered 1 week after the YONDELIS infusion, and discontinued the day prior to the next YONDELIS infusion. This recommendation is made based on following information:

- Modification of YONDELIS dose with the strong CYP3A inhibitors and strong CYP3A inducers is complicated by the:
  - YONDELIS dose level at the time of administration of strong CYP3A inhibitors and strong CYP3A inducers. The recommended YONDELIS dose of 1.5 mg/m<sup>2</sup> can be reduced to 1.2 mg/m<sup>2</sup> and then to 1 mg/m<sup>2</sup>, based on adverse events.
  - Timing of administration of strong CYP3A inhibitors and strong CYP3A inducers relative to administration of YONDELIS. Trabectedin has a rapid decline phase and an additional slower exponential phase with a terminal half-life of ~ 175 hours, and after seven days following YONDELIS administration, the exposure of trabectedin drops by 93% (i.e., only 7% of exposure is remaining).
    - Therefore, the effect of strong CYP3A inhibitors and strong CYP3A inducers will vary depending on when they are administered relative to administration of YONDELIS.
- A low rate of concomitant use of strong CYP3A inhibitors (0.06%: 4 of 7001) and strong CYP3A inducers (0.03%: 2 of 7001) was identified in the clinical trials with YONDELIS.
- CYP3A inducers need to administered 6-7 days prior to administration of YONDELIS in order to exert the CYP3A induction effect.
- YONDELIS is recommended for administration once every 3 weeks.

**Signatures:**

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**Division of Clinical Pharmacology V**

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**Hong Zhao, Ph.D.**  
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**DCP-5: Reviewer - S Subramaniam; TL- H Zhao; DDD - B Booth; DD - A Rahman**

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/s/  
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SRIRAM SUBRAMANIAM  
10/06/2015

HONG ZHAO  
10/06/2015  
I concur.

NAM ATIQUR RAHMAN  
10/06/2015  
I concur.

## Clinical Pharmacology Review

<b>NDA</b>	207,953
<b>Submission Date:</b>	November 24, 2014
<b>PDUFA Date:</b>	October 24, 2015
<b>Brand Name:</b>	Yondelis®
<b>Generic Name:</b>	Trabectedin
<b>Formulation/Strength:</b>	Lyophilized powder for injection; 1.0 mg/25 mL single-use vial
<b>Sponsor:</b>	Janssen Products LP
<b>Submission Type; Code:</b>	Original NDA; NME
<b>Dosing regimen:</b>	1.5 mg/m <sup>2</sup> as a 24-hour IV infusion administered every 3 weeks
<b>Indication:</b>	(b) (4)
<b>OCP Reviewer:</b>	Sriram Subramaniam, Ph.D.
<b>OCP Team Leader:</b>	Hong Zhao, Ph.D.
<b>OCP Division:</b>	Division of Clinical Pharmacology V
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## 1 Executive Summary

This new molecular entity (NME) NDA submission is for trabectedin

(b) (4)

In the registration trial, patients with advanced L-type sarcoma (liposarcoma, and leiomyosarcoma subtypes) previously on anthracycline regimen (n=587) were 2:1 randomized to either trabectedin (1.5 mg/m<sup>2</sup> as a 24-hour intravenous infusion, once every 3 weeks) or dacarbazine (1 g/m<sup>2</sup> 20-120 minute intravenous infusion, once every 3 weeks). Trabectedin arm demonstrated 2.7 month improvement in progression-free survival (PFS) compared to dacarbazine arm. Overall incidence of Grade 3-4 treatment-related adverse events (AEs) was higher (76.2% vs. 51.6%) in the trabectedin arm compared to the dacarbazine arm, with the most common Grade3-4 toxicities for trabectedin being laboratory-related AEs, including bone marrow toxicities and hepatotoxicity that were transient, non-cumulative, and managed by appropriate dose reductions or dose delays.

No exploratory exposure-response analyses for efficacy endpoints and toxicities could be conducted because no PK samples were collected in the registration trial. However, exposure-response relationships for toxicities (neutropenia, elevation in transaminases, and hyperbilirubinemia) were identified using data from early clinical studies. The proposed dose adjustment from 1.5 mg/m<sup>2</sup> to 1.2 mg/m<sup>2</sup> and then to 1 mg/m<sup>2</sup> was based on AEs in the registration trial of trabectedin. The dose reduction rate was 35% in trabectedin arm and 10% in the dacarbazine arm.

Trabectedin is extensively metabolized in liver by CYP3A4 and mainly excreted to feces. Trabectedin exposure (i.e., AUCt) increased by 66% with coadministration of strong CYP3A4 inhibitor (i.e., ketoconazole) and decreased by 31% with coadministration of strong CYP3A4 inducer (i.e., rifampin). Therefore, a strong CYP3A4 inhibitor or strong CYP3A4 inducer should be avoided, or if there is no alternative medication, the trabectedin dose should be reduced based on the dose prior to the initiation of the strong CYP3A4 inhibitor, or increased based on the dose prior to the initiation of the strong CYP3A4 inducer as recommended in table below. Based on population PK analysis, no dose adjustment is necessary for patients with mild to moderate renal impairment and mild hepatic impairment. The PK of trabectedin has not been evaluated in patients with moderate to severe hepatic impairment, and in patients with severe renal impairment. Trabectedin clearance is not influenced by sex, age, body weight, and body size.

If YONDELIS Dose Prior to Strong CYP3A Inhibitor/Inducer is	Reduce YONDELIS Dose with Strong CYP3A Inhibitor to	Increase YONDELIS Dose with Strong CYP3A Inducer to
1.5 mg/m <sup>2</sup>	0.9 mg/m <sup>2</sup>	2.0 mg/m <sup>2</sup>
1.2 mg/m <sup>2</sup>	0.7 mg/m <sup>2</sup>	1.7 mg/m <sup>2</sup>
1.0 mg/m <sup>2</sup>	0.6 mg/m <sup>2</sup>	1.5 mg/m <sup>2</sup>

### 1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this NDA.

Decision	Sufficiently Supported?	Comment
Overall	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	
Evidence of effectiveness†	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	Registration trial and supportive trials

Proposed dose for general population	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	The proposed dose 1.5 mg/m <sup>2</sup> as a 24 hour IV infusion, once every 3 weeks has been demonstrated to be efficacious and safe in the proposed patient population.
Proposed dose adjustment in Specific patients or patients with comedications	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	<u>Labeling Recommendations</u>  (b) (4)
Proposed dose modification for others	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	One postmarketing requirement study in patients with hepatic impairment.
Pivotal bioequivalence	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> NA	
Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA	

## 1.2 PHASE IV REQUIREMENTS

1. Submit the final study report for the ongoing hepatic impairment study as postmarketing requirement (PMR) study.

### Signatures:

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**Sriram Subramaniam, Ph.D.**  
Reviewer  
Division of Clinical Pharmacology V

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**DCP-5: Reviewers – S Subramaniam, R Charlab Orbach; TL H Zhao; DDD - B Booth; DD - A Rahman**

### 1.3 CLINICAL PHARMACOLOGY SUMMARY

Trabectedin, a novel tris tetrahydroisoquinoline alkaloid binding to the guanine in the minor groove of DNA, is being developed for intravenous use (b) (4)

*Clinical Dose Selection:* The dose-escalation study using a 24-hr q3wk dosing regimen identified a maximum tolerated dose of 1.8 mg/m<sup>2</sup> with a recommended Phase 2 dose of 1.5 mg/m<sup>2</sup>. The dosing regimen for the registration trial (ET743-SAR-3007) is 1.5 mg/m<sup>2</sup> 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 (qw) for 3 weeks every 4 weeks] in patients with liposarcoma or leiomyosarcoma subtypes.

*Clinical Pharmacology Program:* The applicant has conducted 38 clinical studies in cancer patients to evaluate the safety and pharmacokinetics (PK) of trabectedin. Of the 38 clinical studies, 32 were included in a previous NDA for trabectedin (b) (4)

In the current NDA, the Applicant provided DDI studies to evaluate the effect of CYP3A4 inducers and inhibitors on the PK of trabectedin, and a dedicated QT study to evaluate the QTc prolongation potential of trabectedin. The hepatic impairment study will be submitted as a post marketing requirement study.

*Pharmacokinetics of Trabectedin:* The T<sub>max</sub> 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<sub>max</sub>; 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.

No exploratory exposure-response analyses for efficacy endpoints and toxicities could be conducted because no PK samples were collected in the registration trial. However, exposure-response relationships were identified for neutropenia, elevation in serum transaminases, and hyperbilirubinemia using trabectedin data from early trials. The applicant's proposed dose adjustment from 1.5 mg/m<sup>2</sup> to 1.2 mg/m<sup>2</sup> and then to 1 mg/m<sup>2</sup> was empirically derived based on adverse events (AEs) in the registration trial of trabectedin. Nonetheless the proposed dose reductions are likely to decrease toxicity based exposure-toxicity relationships.

## 2 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

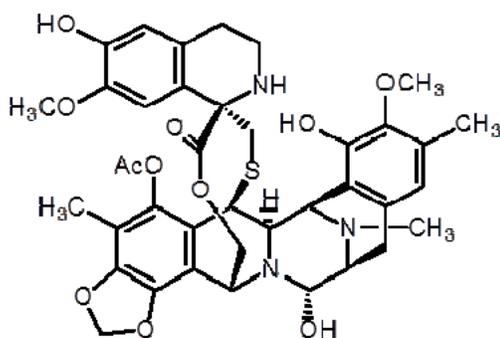
#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Trabectedin is a novel tris tetrahydroisoquinoline alkaloid originally isolated from the marine tunicate, *Ecteinascidia turbinata*. Trabectedin has poor aqueous solubility and pH-dependent solution stability. Initially, (b) (4) formulations (b) (4) were used in majority of early clinical trials. However, a sucrose-based (b) (4) trabectedin IV formulation was used in the registration trial (ET743-SAR-3007) and this formulation is the proposed to-be-marketed formulation. (b) (4)

The to-be-marketed trabectedin formulation is supplied as a lyophilized white to off-white powder in sterile single-use vial containing 1 mg of (b) (4)-trabectedin, sucrose (400 mg) and potassium dihydrogen phosphate (27.2 mg), as well as phosphoric acid and potassium hydroxide (Module 3.2.P.1). Each vial is to be reconstituted with Sterile Water for Injection and further diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

#### Physico-chemical properties

##### 1. Structural formula:



2. Established name: Trabectedin, Ecteinascidin 743 (ET-743)
3. Molecular Weight: 761.84
4. Molecular Formula: C<sub>39</sub>H<sub>43</sub>N<sub>3</sub>O<sub>11</sub>S
5. Chemical Name (CAS): (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-trimethyl-spiro[6,16-(epithio propanoxymethano)-7,13-imino-12H-1,3-dioxolo[7,8]isoquino[3,2-b][3]benzazocine-20,1'(2'H)-isoquinolin]-19-one
6. Solubility: practically insoluble in apolar organic solvents (hexane) and water; its solubility increases in acidic media.
7. Log P: 2.5±0.3 (in n-octanol-aqueous buffer).

### 2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Trabectedin binds to the minor groove in DNA, which in turn affects several transcription factors, DNA binding proteins, and DNA repair pathways that results in disruption of the cell cycle and inhibition of cell proliferation. Trabectedin also modulates tumor microenvironment.

The proposed indication for YONDELIS<sup>®</sup> is for the treatment of patients (b) (4)

### 2.1.3 What are the proposed dosage and route of administration?

Trabectedin is administered at a dose of 1.5 mg/m<sup>2</sup> as a 24-hour IV infusion once every three weeks (q3w) through a central venous line. All patients receiving YONDELIS must be premedicated with corticosteroids such as dexamethasone 20 mg IV, 30-minute prior to infusion of YONDELIS.

## 2.2 GENERAL CLINICAL PHARMACOLOGY

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Thirty-eight clinical studies were submitted in NDA 207953 to support the clinical pharmacology of trabectedin. Except for 6 Phase I studies (ET743-OVC-1001, ET743-OVC-1002, ET743-OVC-1003, 10045020, 10045030, and ET-A-010-01) and simulation report 14/J&J/018/1250a, the other clinical studies, and population PK and PK/PD analyses to support clinical pharmacology were reviewed as part of a previously submitted and later withdrawn NDA (attached in Appendix 3.1).

The studies used to support dosing or claims are summarized in the Table 1. Briefly, following three Phase 2 studies (ET-B-005-98, ET-B-008-98, and ET-B-017-99) in advanced STS patients with a trabectedin dosing regimen of 1.5 mg/m<sup>2</sup> 24-hr IV q3wk, the Applicant conducted a Phase 2 study (ET743-ST5-201) to compare two trabectedin dosing regimens (1.5 mg/m<sup>2</sup> 24-hr IV q3wk and 0.58 mg/m<sup>2</sup> 3-hr IV qwk for 3 weeks every 4 weeks) in L-subtype STS patients. The trabectedin dosing regimen of 1.5 mg/m<sup>2</sup> 24-hr IV q3wk was used in the registration trial (ET743-SAR-3007). Dose escalations study was conducted with a 24-hr IV q3wk dosing regimen over the dose range of 0.05mg/m<sup>2</sup> to 1.8 mg/m<sup>2</sup> (ET-A-002-95) in patients with solid tumors.

**Table 1. Clinical Studies Supporting Proposed Indication and Dosing Regimen\*.**

Study	Design	Dosing Schedule	Subjects <sup>a</sup>		
Pivotal ET743-SAR-3007	Randomized, open label	Trabectedin: q3wk 24-h dose	345		
		Dacarbazine: q3wk 20- to 120-min dose	173		
Trabectedin					
Supportive ET743-ST5-201	Randomized, open label	qwk 3-h dose group	134 <sup>a</sup>		
		q3wk 24-h dose group	136 <sup>a</sup>		
Trabectedin			L-sarcoma <sup>b</sup>	Other	All
Initial Phase 2			100	83	183
ET-B-005-98	Single arm	q3wk 24-h dose	49	50	99
ET-B-008-98	Single arm	q3wk 24-h dose	28	22	50
ET-B-017-99	Single arm	q3wk 24-h dose	23	11	34

<sup>a</sup> Subjects evaluable for efficacy

<sup>b</sup> L-sarcoma: liposarcoma and leiomyosarcoma

\*All of the above studies used a trabectedin dosing regimen of 1.5 mg/m<sup>2</sup> 24-hr IV infusion q3wk. Study ET743-ST5-201 also included a trabectedin dosing regimen of 0.58 mg/m<sup>2</sup> 3-hr IV infusion qwk for 3 wks every 4 wks.

Source: Summary of Clinical Efficacy, Table 1

**2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?**

The primary endpoint of the registration trial ET743-SAR-3007 was overall survival (OS). The study was designed to detect a difference between a median OS of 10 months in the dacarbazine group and 13.5 months in the trabectedin group (HR=0.74) at an overall 2-sided significance level of 0.05 with a power of 80% requiring 376 events. Based on the EOP2 meeting on July 23, 2012, the Applicant provided progression-free-survival (PFS) and response rate data as a basis for possible accelerated approval.

PFS was defined as the time between randomization and occurrence of disease progression or death. Disease status was to be assessed using radiographic techniques, including computed tomography (CT) scans of the chest (with lung views), abdomen, and pelvis, or if necessary, magnetic resonance imaging (MRI) scans. Tumor assessments were to be done every 6 weeks for the first 36 weeks and then every 9 weeks until disease progression for both treatment arms. Measurable disease and response criteria used in the protocol were per RECIST guidelines and were to be based on radiologic assessments by independent radiologists using imaging only.

**2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Trabectedin, the active moiety, was measured in the plasma, feces, and urine for the PK characterization and exploratory analysis of exposure response relationships. N-desmethyl-trabectedin (ET-729) is the only identified active metabolite *in vitro*, with circulating plasma concentrations below the limit of quantification of 0.1 ng/mL. For details refer to Appendix 3.1 (Section 2.2.3).

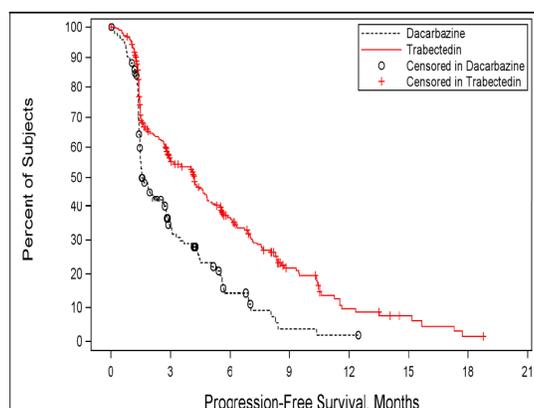
**2.2.4 Exposure-response**

Trabectedin arm demonstrated 2.7 month improvement in PFS compared to Dacarbazine arm in the registration study ET743-SAR-3007 (FIGURE 1). Because no PK samples were collected in this study. Therefore, no exploratory exposure-response analysis for safety and efficacy was conducted for the registration trial. However, exposure-toxicity relationships for neutropenia, and elevation of serum transaminases, and hyperbilirubinemia were identified based on trabectedin data from Phase 1 and 2 studies (refer to Section 2.2.4.2.2). (b) (4)

The proposed dose adjustments (from 1.5 mg/m to 1.2 mg/m and then to 1.0 mg/m ) in the registration trial was based on toxicity and tolerability.

1

(b)  
(4)



**FIGURE 1:** Kaplan Meier plot for progression free survival for trabectedin and dacarbazine arms of the registration study ET743-SAR-3007.

**2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

No PK samples were collected in the registration study ET743-SAR-3007; therefore, no exploratory exposure-response analysis for safety and efficacy was conducted.

**2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?**

**2.2.4.2.1 Applicant’s analyses**

The Applicant developed PK/PD models to describe exposure-toxicity relationship for neutropenia, and elevation of serum transaminases, and hyperbilirubinemia based on the trabectedin data from Phase 1 and 2 studies. The models and simulations suggest dose reductions can decrease toxicities of trabectedin. Please see Appendix 3.1 (Sections 2.2.4.2.1 and 5) for description of the models and the results.

Briefly, the highlights of the results of PK/PD analysis for neutropenia include:

- Neutropenia is not dependent on  $C_{max}$  (i.e., duration of infusion).
- The magnitude and duration of neutropenia are related to the trabectedin dose and AUC.
- Magnitude of neutropenia also governed by dosing frequency, with larger and infrequent dosing regimens resulting in higher fluctuations in absolute neutrophil counts (ANC) (e.g., higher doses given over fewer intervals lead to more severe neutropenia).
- A proportional reduction in the trabectedin dose or exposure will lead to a more than proportional reduction in the ANC nadir.

The highlights of the results of PK/PD analysis for ALT elevation include:

- ALT elevation is transient.
- Magnitude of ALT elevation is independent of duration of infusion.
- Development of tolerance to the ALT elevation.
- The absence of concomitant administration of dexamethasone was the only measurable patient characteristic that explains some portion of the variability in ALT elevation. The magnitude of the trabectedin stimulatory effect on the release rate of ALT from hepatocytes to plasma was approximately reduced by 60% in presence of dexamethasone. Model-based simulations indicated that, within the first 12 weeks of trabectedin treatment, dexamethasone co-administration would reduce the overall incidence of grade 4 toxicities by 32% for patients receiving 1.5 mg/m<sup>2</sup> given as

24- hr infusion every 3 weeks.

#### 2.2.4.2.2 Is there evidence of exposure-response for safety?

Yes. Neutropenia (Grade 4) and ALT elevation ( $\geq$  Grade 3) were some of the major toxicities in trabectedin treatment arm of the registration study ET743-SAR-3007 (Table 2), and exposure-response relationships were described for these toxicities. In addition, transaminase elevation and neutropenia were the major toxicities that required dose reductions (Table 3). Of the 36% patients with AEs leading to dose reductions, 21% of the patients experienced transaminase elevations and 3.5% of patients experienced neutropenia in the registration study (Table 3).

**Table 2.** Drug-Related AEs in study ET743-SAR-3007.

AEs in $\geq$ 20% of Patients	Dacarbazine (n=155), %		Trabectedin (n=340), %	
	Any	Grade 3/4	Any	Grade 3/4
All AEs	85.2	36.8	94.7	64.7
ALT increased	4.5	0	42.9	25.6
AST increased	3.9	0	33.2	12.4
Neutropenia	16.8	11	28.2	21.5
Neutrophil count decreased	13.5	9.7	24.1	18.5
Blood alkaline phosphatase increased	5.8	0	17.9	1.2
Thrombocytopenia	18.7	9.7	16.8	8.5

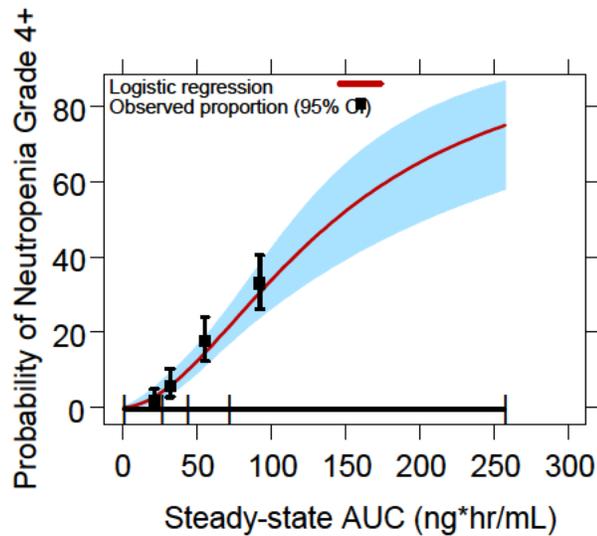
Source: CSR, Tables 43 and TSFAE03B

**Table 3.** Neutropenia and ALT/AST elevation leading to dose reduction in study ET743-SAR-3007.

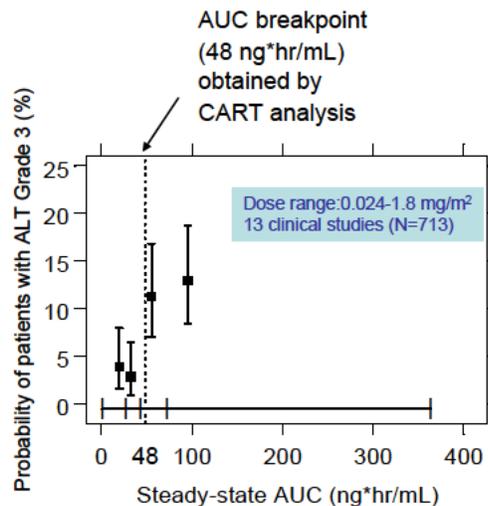
	Dacarbazine (n=155) n, (%)	Trabectedin (n=340) n, (%)
Subjects with AEs leading to DR	17 (11.0%)	123 (36.2%)
ALT increased	0	50 (14.7%)
AST increased	0	22 (6.5%)
ALP increased	3 (1.9%)	15 (4.4%)
Neutropenia	3 (1.9%)	12 (3.5%)

Source: CSR, Table 51

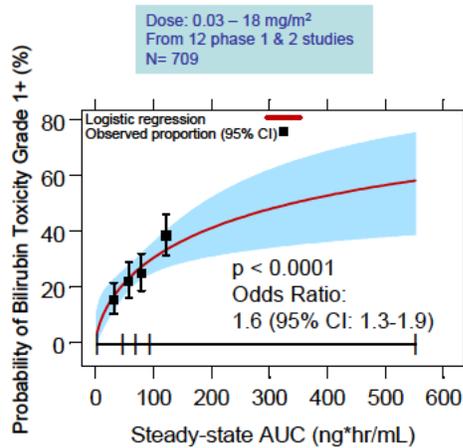
The FDA analysis of trabectedin exposure (AUC) based on trabectedin monotherapy data of all cancer types from 13 Phase 1 and 2 studies identified exposure-response relationships for neutropenia (grade  $\geq$ 4) (FIGURE 2), and alanine aminotransferase (ALT) elevation ( $\geq$  grade 3) (FIGURE 3) and hyperbilirubinemia (FIGURE 4) (refer to Appendix 3.1, Sections 3.3 to 3.5 for details of the analyses and results).



**FIGURE 2:** The probability of neutropenia (Grade 4) vs trabectedin exposure based on 13 trabectedin monotherapy studies (N=704 patients) with a dose range of 0.024 - 1.8 mg/m<sup>2</sup>. The horizontal bars represent AUC quartiles. The dots represent the median AUC in each quartile. The vertical bars represent the 95% CI of the probability of neutropenia.



**FIGURE 3:** The probability of ALT elevation (≥ grade 3) vs trabectedin exposure based on 13 trabectedin monotherapy studies (N=713 patients) with a dose range of 0.024-1.8 mg/m<sup>2</sup>. The horizontal bars represent AUC quartiles. The dotted line is optimal AUC breakpoint (calculated by CART analysis) that maximally distinguishes the low risk from high risk of toxicity. The dots represent the median AUC in each quartile. The vertical bars represent the 95% CI of the probability of ALT elevation.



**FIGURE 4:** The probability of hyperbilirubinemia ( $\geq$  grade 1) vs trabectedin exposure based on 12 trabectedin monotherapy studies (N=709 patients) with a dose range of 0.03-1.8 mg/m<sup>2</sup>. The horizontal bars represent AUC quartiles. The dots represent the median AUC in each quartile. The vertical bars represent the 95% CI of the probability of hyperbilirubinemia.

**2.2.4.2.3 Are the proposed dose adjustment based on toxicities appropriate?**

The reduction in trabectedin dose decreases the risk for toxicity and improves treatment tolerability. Although exploratory exposure-response analyses for toxicities are not conducted for the registration study due to lack of PK sampling collection in the trial, exposure-toxicity relationships using trabectedin data from Phase 1 and 2 studies suggest that a reduction in dose will decrease the risk of toxicity.

The monotherapy model (FIGURE 2) predicted a decrease in neutropenia from 14.4% to 7.6% when dose was reduced from 1.1 mg/m<sup>2</sup> to 0.75 mg/m<sup>2</sup> (refer to Appendix 3.1, Section 2.2.4.2.3 for details). Therefore, based on the shape of the relationship, a relatively higher difference will be expected for dose reductions from 1.5 mg/m<sup>2</sup> to 1 mg/m<sup>2</sup>.

Applicant’s simulation results (14/J&J/018/1250a) using population PK and PK/PD models predicted reduction in incidence rates of Grade 3-4 neutropenia at steady state from about 45% to 38% when dose was reduced from 1.5 mg/m<sup>2</sup> to 1.2 mg/m<sup>2</sup> and further reduction of the incidence rate to 32% when dose was reduced to 1 mg/m<sup>2</sup>.

Applicant’s comparison of the estimates of the incidence of ALT toxicity (grade  $\geq$ 3) using the semi-physiological population PK/PD model (for ALT elevation), with and without dose reduction strategy (1.5 mg/m<sup>2</sup> 24-hr q3wk to 1.2 mg/m<sup>2</sup> and to 1 mg/m<sup>2</sup> in Study ET743-STS-201), suggested that the dose reduction strategy reduced incidence of ALT elevation. Also, per the Applicant, comparison of estimates of incidence of ALT toxicity, using dose reduction, from simulated and pooled data from Phase 2 studies involving administration of 1.5 mg/m<sup>2</sup> of trabectedin as a 24-hr IV infusion q3wk, suggested that the model-based estimated and observed incidence of grade  $\geq$  3 ALT elevation values were comparable (refer to Appendix 3.1, Section 3.2 for details).

As stated in Table 3, adverse events, primarily transaminase elevations and neutropenia, were the cause of dose reductions in the registration Study ET743-SAR-3007. Dose reductions occurred in 35% of the patients treated with trabectedin, of which 11% of the patients required two dose reductions (see table below).

	Dacarbazine (n=155)	Trabectedin (n=340)
Dose Reductions	9.7% (15)	35.0% (119)

1	8.4% (13)	24.2% (83)
2	1.3% (2)	10.6% (36)

Source: CSR, Table 22

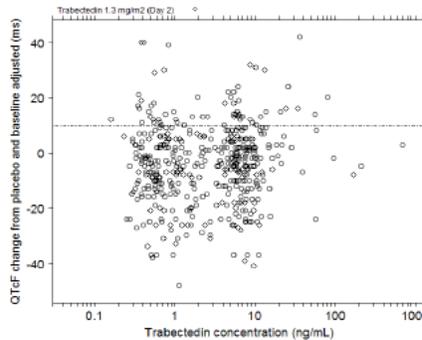
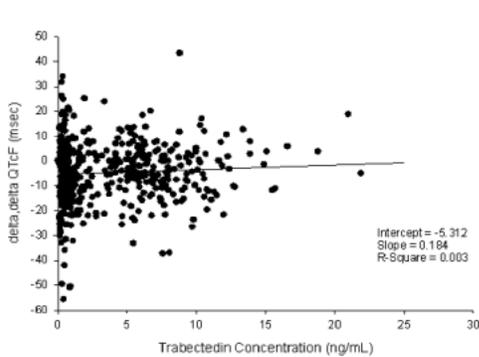
**2.2.4.2.4 Is the proposed (b) (4) supported by the data?**

No. (b) (4)

(b) (4)

**2.2.4.3 Does this drug prolong the QT or QTc interval?**

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/m<sup>2</sup>) 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. Refer to Appendix 3.2 for details.



**FIGURE 5:** Relationship between  $\Delta\Delta QTcF$  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  $\Delta\Delta QTc$  (along with 90% confidence intervals) was estimated at the mean trabectedin  $C_{max}$  values based on this model. FDA's plot of  $\Delta\Delta QTc$  vs. log trabectedin concentrations (right).

The tested dose of 1.3 mg/m<sup>2</sup> as a 3-hr infusion resulted in higher trabectedin  $C_{max}$  concentrations compared to the dose of 1.5 mg/m<sup>2</sup> 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  $C_{max}$  concentrations expected with a strong CYP3A4 inhibitor following a trabectedin dose of 1.5 mg/m<sup>2</sup> as a 24-hr infusion are lower than those of trabectedin alone at a dose of 1.3 mg/m<sup>2</sup> as a 3-hr infusion.

#### **2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

During the trabectedin development program, different infusion lengths (1-hour, 3-hours, 24-hours, and 72-hours) and different dosing regimens (Day 1 of a 21-day cycle, Days 1, 8, and 15 of a 28-day cycle, and Days 1, 2, 3, 4, and 5 of a 28-day cycle) were investigated in nine single-agent dose-finding studies with various dose ranges of trabectedin (0.006-1.8 mg/m<sup>2</sup>). The dose-escalation study performed for the 24-hr q3wk dosing regimen at dose range of 0.5 to 1.8 mg/m<sup>2</sup> identified a maximum tolerated dose of 1.8 mg/m<sup>2</sup> with a recommended Phase 2 dose of 1.5 mg/m<sup>2</sup> (ET-A-002-95). No exposure-efficacy response relationship has been established to support the dosing regimen used in the registration study (ET743-SAR-3007). The 1.5 mg/m<sup>2</sup> 24-hr infusion q3wk dosing regimen used in the registration study was supported by the efficacy and safety outcome of three Phase 2 studies in advanced, relapsed STS patients with trabectedin dosing regimen at 1.5 mg/m<sup>2</sup> via 24-hr q3wk (ET-B-005-98, ET-B-008-98, and ET-B-017-99). Further, a Phase 2 study (ET743-STC-201) dosing regimen of 1.5 mg/m<sup>2</sup> via 24-hr infusion q3wk was found superior to 1.3 mg/m<sup>2</sup> via 1 hr infusion qwk for 3 weeks regimen in L-subtype sarcoma. Also see Section 2.2.1.

While the basis for selection of the dose has not been sufficiently addressed from a clinical pharmacology perspective (i.e., as no exposure data was collected in the registration study), there are no unresolved dosing and administration issues.

#### **2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites**

##### **2.2.5.1 What are the *single dose and multiple dose* PK parameters?**

The PK of trabectedin in humans has the following features:

- The maximum concentrations of trabectedin in plasma were typically observed to the end of the infusion. The plasma drug concentrations then declined in a multi-exponential manner: a rapid initial decline followed by a more prolonged distribution and terminal phases.
- The PK of trabectedin is independent of cycles when it is administered every three weeks (Studies (b) (4) ET-A-002-9 (b) (4))
- The plasma  $C_{max}$  and AUC values of trabectedin are dose-proportional within the dose range of 0.58-1.8 mg/m<sup>2</sup> when administered as a 3-hr or 24-hr intravenous infusion (Section 2.2.5.8).
- The inter-subject variability of plasma clearance was approximately 50%.

As the recommended dosing regimen in the proposed labeling is 24-hr infusion, the following results are the trabectedin PK parameters for a 24-hr infusion regimen:

**Table 4.** Summary of single-dose trabectedin pharmacokinetic parameters following a 24-hour intravenous infusion in patients with cancer during 21-day treatment Cycle 1 and Cycle 2.

Dose (mg/m <sup>2</sup> )	Cycle	C <sub>max</sub> (ng/mL)	AUC <sub>0-∞</sub> (ng·h/mL)	CL (L/h)	V <sub>z</sub> (L)	Terminal t <sub>1/2</sub> (h)
0.05	1	0.06 ± 0.04 n=3	1.18 ± 0.69 n=3	82.3 ± 41.9 n=3	629 ± 419 n=3	8.88 ± 10.6 n=3
0.1	1	0.08 ± 0.05 n=3	2.29 ± 1.89 n=3	110.5 ± 73.7 n=3	2165 ± 1320 n=3	27.9 ± 34.3 n=3
0.2	1	0.19 ± 0.08 n=3	3.82 ± 1.54 n=3	103.9 ± 46.2 n=3	3435 ± 1769 n=3	26.4 ± 18.2 n=3
0.4	1	0.76 ± 0.49 n=3	23.5 ± 18.3 n=3	41.5 ± 21.8 n=3	1425 ± 180 n=3	30.7 ± 20.1 n=3
0.6	1	0.56 ± 0.22 n=3	12.0 ± 4.53 n=3	94.4 ± 51.5 n=3	3484 ± 3882 n=3	20.6 ± 14.0 n=3
0.9	1	0.95 ± 0.20 n=5	28.4 ± 4.48 n=5	62.0 ± 10.4 n=5	2546 ± 541 n=5	29.4 ± 10.1 n=5
1.2	1	1.45 ± 0.65 n=4	33.5 ± 14.0 n=2	74.4 ± 34.5 n=2	3915 ± 2073 n=2	36.8 ± 17.0 n=2
	2	1.43 ± 0.91 n=23	34.6, 44.5 <sup>a</sup> n=24	62.1, 44.7 <sup>a</sup> n=24	5011, 2264 <sup>a</sup> n=24	55.9, 35.1 <sup>a</sup> n=24
	1	1.84 ± 1.12 n=20	56.8 ± 24.9 n=20	54.7 ± 23.5 n=20	7509 ± 3412 n=20	103.2 ± 41.8 n=20
1.5	2	1.72 ± 1.44 n=4	58.1 ± 49.0 n=4	71.0 ± 51.2 n=4	5655 ± 3142 n=4	77.4 ± 57.3 n=4
	5	0.99 ± 0.23 n=4	31.7 ± 8.96 n=4	81.0 ± 19.7 n=4	4698 ± 2604 n=4	45.1 ± 36.4 n=4
1.8	1	2.82 ± 1.40 n=4	60.2 ± 24.5 n=4	57.4 ± 28.7 n=4	8369 ± 7032 n=4	91.8 ± 27.9 n=4
	2	1.10 ± 0.07 n=4	65.7 ± 24.5 n=4	47.4 ± 12.0 n=4	8002 ± 963 n=4	126.0 ± 46.9 n=4

<sup>a</sup> Individual values provided  
 Note: Results provided as mean ± standard deviation  
 Source: Annex 7 of the corresponding clinical study report

### 2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. All studies with trabectedin were done in cancer patients.

### 2.2.5.3 What are the characteristics of drug absorption?

Absorption is not applicable as trabectedin is administered via the intravenous infusion.

### 2.2.5.4 What are the characteristics of drug distribution?

Trabectedin is highly protein bound (97.5%), has a blood-to-plasma ratio of 0.89, is extensively distributed extravascularly (V<sub>ss</sub> of 5000 to 6000 L), and is a substrate for P-glycoprotein. Please refer to Appendix 3.1 (Section 2.2.5.4) for information on distribution characteristics.

### 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The human mass balance study (Study ET-A-013-01) suggests that trabectedin and its related metabolites are eliminated mainly by biliary excretion into the feces. Negligible quantities of unchanged drug were recovered in urine and feces confirming the extensive metabolism of trabectedin *in vivo*. Please refer to Appendix 3.1 (Sections 2.2.5.5 and 2.2.5.7) for information. Also see Section 2.2.5.6.

### 2.2.5.6 What are the characteristics of drug metabolism?

Based on *in vitro* studies, trabectedin undergoes extensive metabolism, predominately by CYP3A4. 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 patients administered trabectedin as a 3-h or 24-h infusion in 6 Phase 1 and 2 studies. Please refer to Section 2.2.5.6 of Appendix 3.1 for more information on *in vitro* and *in vivo* studies relating to metabolism of trabectedin.

### 2.2.5.7 What are the characteristics of drug excretion?

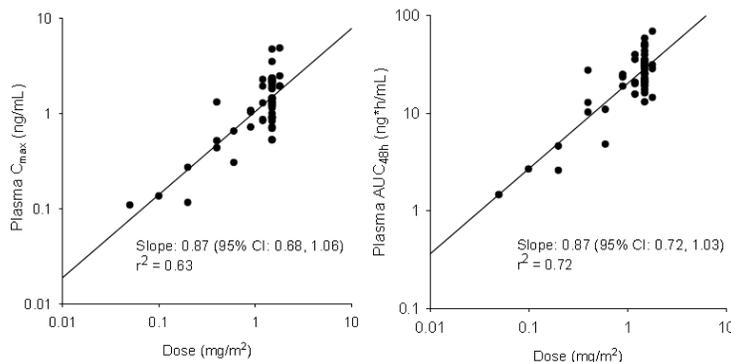
Trabectedin is eliminated primarily through the biliary route, has a plasma clearance of ~31 L/hr, and an elimination half-life of ~ 175 hours based on population PK analysis. Please refer to Appendix 3.1 (Section 2.2.5.7) for more information on elimination, clearance, and half-life of trabectedin.

### 2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

Trabectedin demonstrated linear PK in patients with cancer in terms of dose proportionality (Figure 6) and time independence (Appendix 3.1, Section 2.2.5.9).

#### **Dose proportionality**

The plasma  $C_{max}$  and AUC ( $AUC_{48h}$ ) values of trabectedin are dose-proportional when administered as a 24-hr intravenous infusion based on a linear regression model (FIGURE 6). As the null hypothesis (i.e., slope of the regression line =1) was not rejected, the PK parameters of trabectedin were deemed dose-proportional.



**FIGURE 6:** Dose proportionality in terms of AUC and C<sub>max</sub> following 24-hour IV infusions of trabectedin in the dose range of 0.05 to 1.8 mg/m<sup>2</sup> in patients with STS and solid tumors.

### 2.2.5.9 How do the PK parameters change with time following chronic dosing?

Accumulation was not observed with q3wk dosing regimen and PK parameters of trabectedin are cycle-independent. Please refer to Appendix 3.1 (Section 2.2.5.9) for more information.

### 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-individual and intra-individual variability in clearance of trabectedin were 50% and 31%, respectively in patients with cancer. Please refer to Appendix 3.1 (Section 2.2.5.10) for details.

## 2.3 INTRINSIC FACTORS

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Population PK analysis results indicate trabectedin clearance is not influenced by sex, age, body weight, and BSA (see Sections 2.3.2.1 to 2.3.2.4). Renal function (creatinine clearance range of 30.3 to 150 mL/min) did not significantly correlate with trabectedin clearance (see Section 2.3.2.6). Hepatic dysfunction is expected to affect PK of trabectedin as trabectedin is extensively metabolized in liver by CYP3A4 and mainly excreted through biliary route to feces. An ongoing hepatic impairment study is to be submitted as a post marketing requirement (PMR) (see Section 2.3.2.5). Please refer to Appendix 3.1, Section 2.3.1 for details of the effect of intrinsic factors on the PK of trabectedin.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

No dose adjustments were proposed for the specific populations. In the proposed labeling, the dose adjustments of trabectedin from 1.5 mg/m<sup>2</sup> to 1.2 mg/m<sup>2</sup> and then to 1.0 mg/m<sup>2</sup> or dose discontinuation were based on the toxicities in the registration study. See Sections 2.2.4.2.2 and for more details.

**2.3.2.1 Pediatric patients**

[REDACTED] (b) (4)

**2.3.2.2**

[REDACTED] (b) (4)

**2.3.2.3 Sex**

Population PK analyses did not reveal a clinically meaningful correlation between sex and plasma clearance. Sex was associated with the trabectedin central volume of distribution (V<sub>c</sub>: males 16.1 L and females 13.9 L), which is not considered clinically meaningful. [REDACTED] (b) (4)

Please refer to Appendix 3.1 (Section 3.2) for details.

**2.3.2.4 Elderly**

The population PK analysis indicated that the trabectedin plasma clearance and volume of distribution are not influenced by subject age (range, 19 to 83 years). Please refer to Appendix 3.1 (Section 3.2) for more information on population PK analysis.

**2.3.2.5 Hepatic Impairment**

As trabectedin is extensively metabolized by CYP 3A4 in liver, hepatic dysfunction is expected to affect trabectedin PK. A hepatic impairment study to determine the dose regimen in patients with hepatic impairment is ongoing and the final study report will be submitted as a post marketing requirement (PMR). Population PK analysis indicated that no relationship was observed between measures of hepatic function (AST, 0.15 to 3.49 x ULN; ALT, 0.03 to 4.76 x ULN; ALP, 0.17 to 6.82 x ULN; LDH, 0.25 to 20.38 x ULN; total bilirubin, 0.08 to 4.00 x ULN) and the plasma clearance of trabectedin (Appendix 3.1, Section 3.2). Also, in Phase I study (ET-A-006-00) in 33 cancer patients with liver metastasis, stratified based on serum alkaline phosphatase (ALP) concentrations (Strata I: ULN < ALP ≤ 1.5xULN, II: 1.5xULN < ALP ≤ 2.5xULN, III: ALP > 2.5xULN), and administered 1.3 mg/m<sup>2</sup> to 0.75 mg/m<sup>2</sup> of trabectedin, did not show a significant difference in the PK of trabectedin between strata. Therefore, same starting dose is recommended for mild hepatic impairment or liver metastasis. However, since the effect of moderate to severe hepatic impairment has not been studied and hepatotoxicity is observed with trabectedin, the labeling criteria for trabectedin treatment excludes patients with moderate to severe hepatic impairment.

### 2.3.2.6 Renal Impairment

Only 5.8% of the administered dose of trabectedin is eliminated renally, and a population PK analysis suggested renal function, as measured by creatinine clearance (with a range of 30.3 to 150 mL/min), has no significant correlation with the trabectedin clearance. Therefore, dose adjustments for mild and moderate renal impairment do not appear necessary. However, no PK data is available for patients with severe renal impairment and this patient population is excluded from the labeling criteria for trabectedin treatment based on safety concerns. Please refer to Appendix 3.1 (Section 3.2).

### 2.3.2.7 Race/Ethnicity

The potential effects of race/ethnicity on the PK of trabectedin were not formally investigated. The safety profile of trabectedin in the registration study ET743-SAR-3007, as assessed by the incidence of AEs in white and non-whites, appeared unaffected by race. Due to the small number (n=76, 22%) of the non-white subjects in the study, the results should be deemed as inconclusive. Also, trabectedin exposure in Japanese sarcoma patients (10045020 and 10045030) at 1.2 mg/m<sup>2</sup> dose was similar to those in western sarcoma patients at 1.5 mg/m<sup>2</sup>. However, definitive conclusions cannot be drawn based on these results due to the small sample sizes in the Japanese studies (n = 9 and 37) and potential differences in conduct when cross-comparing studies conducted at different global locations.

### 2.3.2.8 What pregnancy and lactation use information is there in the application?

Trabectedin is a (b) (4) may cause serious birth defects when administered during pregnancy. No data are available for the exposure of trabectedin on pregnancy and in human milk. Please refer to Appendix 3.1, Section 2.3.2.8. Because of the potential for serious adverse reactions from trabectedin in breastfed infants, it is recommended that nursing woman discontinue nursing during treatment with trabectedin.

## 2.4 EXTRINSIC FACTORS

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD (ALT elevation) of trabectedin.

### 2.4.2 Drug-drug interactions

#### 2.4.2.1 Is there an *in vitro* basis to suspect *in-vivo* drug-drug interactions?

Yes. As CYP3A4 is the major CYP isozyme for the metabolism of trabectedin, inhibitors and inducers of CYP3A4 are expected to affect the pharmacokinetics of trabectedin.

*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.

Please see sections 2.4.2.2, 2.4.2.3, 2.4.2.4, and 2.4.2.7.

#### 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

CYP3A4 is the major CYP450 isozyme responsible for the metabolism of trabectedin at clinically relevant concentrations. However, due to metabolism by other CYPs observed at supratherapeutic concentrations, the contribution of other CYPs to the metabolism of trabectedin in humans cannot be ruled out. The genetic polymorphisms of CYP3A4 are not expected to influence the metabolism of trabectedin in humans. Please refer to Appendix 3.1 (Section 2.4.2.2) for details.

#### **2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?**

In vitro and in vivo studies indicate that trabectedin is not likely to be an inhibitor of CYP450 enzymes or cause drug-drug interactions via CYP450 inhibition with co-administered drugs that are metabolized by CYP450 enzymes *in-vivo*. Please refer to Appendix 3.1 (Section 2.4.2.3) for details.

#### **2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?**

Trabectedin is a substrate for P-glycoprotein (P-gp). The effect of modulation of P-gp activity on trabectedin is not clear. In P-gp knock-out mice administered <sup>14</sup>C-labeled trabectedin, increases in levels of total radioactivity were found in brain tissue and to lesser extent in the testes, small intestines, and heart relative to control mice, but trabectedin clearance was not different, nor were liver levels of trabectedin and total radioactivity, or urinary and fecal excretion of total radioactivity. The potential effects of trabectedin on the function of P-glycoprotein in humans have not been studied. Please refer to Appendix 3.1 (Section 2.4.2.4) for details.

#### **2.4.2.5 Are there other metabolic/transporter pathways that may be important?**

None has been identified.

#### **2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?**

Dexamethasone is used as premedication to remedy the hepatotoxicity. In a Phase 2 double-blind crossover study (ET-B-010-99) in STS patients (trabectedin starting dose of 1.65 mg/m<sup>2</sup> 3-hr q3wk, and later reduced to 1.5 mg/m<sup>2</sup> and 1.3 mg/m<sup>2</sup>), the plasma CL of trabectedin was 28.2% higher and the terminal t<sub>1/2</sub> was 21.3% shorter with concomitant dexamethasone therapy (4 mg, twice daily) relative to placebo. Please refer to Appendix 3.1 (Section 2.4.2.6) for study details. Also, population PK analyses suggest that the plasma CL of trabectedin was 19% higher in patients who received any concomitant dexamethasone administration. However this difference was not statistically significant due to relatively small number of subjects receiving trabectedin alone (n=58) compared to those receiving trabectedin plus dexamethasone. The inter-subject variability of plasma CL of trabectedin was large (50%). Further, PK/PD analysis indicated that dexamethasone reduces ALT elevation by 60%.

All patients enrolled in the registration study ET743-SAR-3007 received a substantially different regimen of dexamethasone (a single 20-mg IV dose administered at 30 minutes prior to the administration of trabectedin) compared to that used in study ET-B-010-99 (4 mg of dexamethasone twice daily). Also, in majority of the Phase 2 studies, trabectedin was coadministered with dexamethasone.

#### **2.4.2.7 Are there any *in-vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

To evaluate the effect of co-administration of strong CYP3A4 inhibitor and inducer on the PK of trabectedin, the Applicant conducted multicenter, randomized, open-label, 2-way crossover drug-drug interaction studies with ketoconazole (a strong CYP3A4 inhibitor: ET743-OVA-1003) and rifampin (a strong CYP3A4 inducer: ET743-OVA-1002) in patients with advanced malignancies per the FDA drug-drug interaction guidance.

##### Coadministration with Strong CYP3A4 Inducer

The treatment phase of study ET743-OVA-1002 consisted of 2 single-dose trabectedin treatment cycles (one cycle with and one cycle without rifampin coadministration). In the cycle involving coadministration with rifampin, each patient received 600 mg of rifampin for 6 consecutive days. On the 6th day rifampin was administered immediately before the start of the trabectedin infusion. Trabectedin was administered as a 3-hour IV infusion at a starting dose of 1.3 mg/m<sup>2</sup>. All patients received 20 mg of IV dexamethasone 30 minutes prior to the infusion of trabectedin regardless of whether they received rifampin. Nine patients completed both treatment cycles, and 8 were PK evaluable. Trabectedin

clearance increased by 50% from 39.6 L/h to 59.8 L/h and the dose-normalized  $C_{max}$  and  $AUC_{last}$  of trabectedin decreased by 22% and 32%, respectively when trabectedin was coadministered with rifampin (Table 5). One patient apparently had aberrantly high trabectedin levels compared to other patients, however, the decrease in dose-normalized exposures when coadministered with rifampin were similar with and without exclusion of data from this patient.

**Table 5.** Study ET743-OVA-1002: Plasma pharmacokinetic parameters of trabectedin with and without rifampin (top) and statistical comparison of  $C_{max}$  and  $AUC_{last}$  of trabectedin with and without rifampin (bottom)

PK Parameters	Mean (SD)	
	Trabectedin Alone (N=8)	Trabectedin + Rifampin (N=8)
DN_ $C_{max}$ , ng/mL/mg	3.98 ± 1.75	3.05 ± 0.970
$t_{max}$ , h	2.83 (1.50-2.88)	2.23 ( 0.50-2.85)
DN_ $AUC_{4h}$ , ng·h/mL/mg	17.0 ± 8.65	12.3 ± 4.12
DN_ $AUC_{last}$ , ng·h/mL/mg	24.5 ± 14.5	15.8 ± 5.16
DN_ $AUC_{co}$ , ng·h/mL/mg	32.6 ± 24.8	18.1 ± 6.10
$t_{1/2term}$ , h	105 ± 34.3	80.6 ± 18.7
CL, L/h	39.6 ± 14.5	59.8 ± 15.3
$Vd_z$ , L	5462 ± 1693	6786 ± 1886

Note (1): Results presented as mean ± standard deviation; Median (min, max) values reported for  $t_{max}$

Note (2): DN: dose-normalized

Source: Table 13 of the corresponding clinical study report

Parameter	Geometric Means		Estimated Ratio (%)	90% Confidence Intervals (%)
	Trabectedin Alone (n=8)	Trabectedin + Rifampin (n=8)		
DN_ $C_{max}$ (ng/mL)	3.74	2.94	78.48	(70.65, 87.17)
DN_ $AUC_{last}$ (ng·h/mL)	22.2	15.2	68.51	(60.57, 77.49)

DN: dose-normalized

Source: Table 14 of the corresponding clinical study report

#### Coadministration with Strong CYP3A4 Inhibitor

In study ET743-OVA-1002 8 patients were randomly assigned to treatment Sequence 1 (trabectedin+ketoconazole followed by trabectedin alone) or Sequence 2 (trabectedin alone followed by trabectedin+ketoconazole). All patients received 20 mg of IV dexamethasone 30 minutes prior to the infusion of trabectedin regardless of whether they received ketoconazole. Trabectedin was administered as a 3-hour IV infusion at a dose of 1.3 mg/m<sup>2</sup> when given alone. When trabectedin and ketoconazole were coadministered, trabectedin was administered as a 3-hour IV infusion at final dose of 0.58 mg/m<sup>2</sup> and 200 mg of ketoconazole was administered twice daily. Specifically, patients received 200 mg of ketoconazole 12 hours prior to trabectedin administration, immediately prior to trabectedin administration, and then continuing every 12 hours up to 156 hours after the start of the trabectedin infusion (15 consecutive doses). Based on the ratios of the geometric means, the dose-normalized  $C_{max}$  and  $AUC_{last}$  of trabectedin increased by approximately 21% and 66%, respectively when ketoconazole was coadministered with trabectedin e (Table 6).

**Table 6.** Study ET743-OVA-1003: Plasma pharmacokinetic parameters of trabectedin with and without ketoconazole (top) and statistical comparison of C<sub>max</sub> and AUC<sub>last</sub> of trabectedin with and without ketoconazole (bottom)

PK Parameters	Mean (SD)	
	Trabectedin Alone (N=8)	Trabectedin + Ketoconazole (N=8)
DN_C <sub>max</sub> , ng/mL/mg	5.80 ± 3.34	7.03 ± 3.90
t <sub>max</sub> , h	2.83 (0.50-2.87)	2.83 (1.50-2.87)
DN_AUC <sub>48h</sub> , ng·h/mL/mg	28.6 ± 15.8	42.3 ± 24.6
DN_AUC <sub>last</sub> , ng·h/mL/mg	49.2 ± 34.1	82.9 ± 55.8
CL, L/h	20.3 ± 13.1	12.7 ± 7.46

Note (1): Results presented as mean ± standard deviation; Median (min, max) values reported for t<sub>max</sub>

Note (2): DN: dose-normalized

Parameter	Geometric Means		Estimated Ratio (%)	90% Confidence Intervals (%)
	Trabectedin Alone (n=8)	Trabectedin + Ketoconazole (n=8)		
DN_C <sub>max</sub> (ng/mL)	5.16	6.27	121.45	(95.95, 153.73)
DN_AUC <sub>last</sub> (ng·h/mL)	41.5	68.9	165.87	(122.70, 224.23)

In conclusion, the available data indicates that coadministration of strong CYP3A4 inhibitors will increase which is likely to increase toxicity based on exposure-toxicity relationships, and coadministration of strong CYP3A4 inducers will decrease trabectedin exposure which may affect efficacy. Therefore, it is recommended to avoid coadministration with strong CYP3A4 inhibitors or inducers, or if an alternative medication is not available, the trabectedin dose should be reduced based on the dose prior to the initiation of a strong CYP3A4 inhibitors or inducers as recommended in table below.

If YONDELIS Dose Prior to Strong CYP3A Inhibitor/Inducer is	Reduce YONDELIS Dose with Strong CYP3A Inhibitor to	Increase YONDELIS Dose with Strong CYP3A Inducer to
1.5 mg/m <sup>2</sup>	0.9 mg/m <sup>2</sup>	2.0 mg/m <sup>2</sup>
1.2 mg/m <sup>2</sup>	0.7 mg/m <sup>2</sup>	1.7 mg/m <sup>2</sup>
1.0 mg/m <sup>2</sup>	0.6 mg/m <sup>2</sup>	1.5 mg/m <sup>2</sup>

## 2.5 GENERAL BIOPHARMACEUTICS

### 2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable.

### 2.5.2 What is the composition of the to-be-marketed formulation?

Trabectedin for injection is supplied in a single-use vial containing 1 mg of trabectedin as a sterile lyophilized white to off-white powder for reconstitution. Sucrose-based formulation (b) (4) was used for the registration trial and is proposed as the to-be-marketed formulation. The composition of the trabectedin for injection is shown in Table 7.

**Table 7.** Composition of the to-be-marketed trabectedin for injection.

Component	Quality Reference	Function	Unit Quantity (per Vial) 1.0-stg Vial	Lyophilized Cake/Powder (% w/w)
Trabectedin*	DMP 21755	Active ingredient	1.0 mg	(b) (4)
Sucrose	NF	(b) (4)	400 mg	(b) (4)
Potassium dihydrogen phosphate	NF	(b) (4)	27.2 mg	(b) (4)
Phosphoric acid (b) (4)	NF	pH adjustment	q.s. to pH 3.6-4.2	(b) (4)
Potassium hydroxide (b) (4)	NF	pH adjustment	q.s. to pH 3.6-4.2	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

### **2.5.3 What moieties should be assessed in bioequivalence studies?**

Not applicable.

### **2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

Trabectedin is administered intravenously. Therefore, an evaluation of food effect is not necessary.

### **2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in-vivo* performance and quality of the product?**

Not applicable.

## **2.6 ANALYTICAL SECTION**

### **2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?**

During the drug development of trabectedin, 5 different bioanalytical methods were used. Four of the 5 methods have been reviewed earlier in Appendix 3.1 (Section 2.6.1). The fifth method (PRA) was a LC/MS/MS method used in the drug interaction studies (ET743-OVA-1002 and ET743-OVA-1003). This method used a stable isotope of trabectedin (D<sub>3</sub>-trabectedin) as the internal standard (IS). The lowest limit of quantification (LLOQ) for the assay was 25 pg/mL.

### **2.6.2 Which metabolites have been selected for analysis and why?**

No metabolites have been selected for analysis. ET-729 is the only identified pharmacologically active metabolite of trabectedin, with plasma concentrations below the LLOQ. Please refer to Appendix 3.1 (Section 2.6.2) for details.

### **2.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?**

Total drug was measured for trabectedin. Measurement of total drug is acceptable as protein binding of trabectedin is independent of the drug concentrations at the clinically relevant range. Please refer to Appendix 3.1 (Section 2.6.3) for details.

### **2.6.4 What bioanalytical methods are used to assess concentrations?**

The bioanalytical methods used in the early clinical Phase 1 and 2 studies have been described in an earlier review (Appendix 3.1, Section 2.6.4)

In the drug-drug interaction studies (ET743-OVA-1002 and ET743-OVA-1003), plasma samples were assayed for trabectedin using a validated liquid chromatography tandem mass spectrometry method (LC/MS/MS). Briefly, trabectedin was isolated from 200 µl aliquots of plasma by solid phase extraction. The extract was evaporated under nitrogen and the residue reconstituted in 100 µl of acetonitrile: formic acid (10:90), a 5 mM ammonium acetate/methanol (50/50; v/v) mixture. The extracts were injected onto chromatography column, and trabectedin was isocratically eluted with a mixture of 0.005 M ammonium acetate and detection was by LC/MS/MS operated in the positive mode. Trabectedin and the IS were measured at mass transitions  $m/z$  744.2 → 495.2 and 747.3 → 496.3, respectively.

#### **2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?**

In the early clinical Phase 1 and 2 studies using trabectedin as single agent, the calibration range was originally 10-2500 pg/mL. However, when the method was revalidated with the new internal standard,

the lower quantification limit was raised to 25 pg/mL to obtain a better signal to noise ratio. Please refer to Appendix 3.1 (Section 2.6.4.1) for details.

The calibration range in the drug interaction studies was 25-25,000 pg/mL with 9 non-zero calibrators. The bias of the individual back-calculated values for the calibrators should be within 15.0 %, except for at the LLOQ within 20%. Not more than 25% of the non-zero calibrators could be rejected. The calibration curves were calculated by least-squares linear regression. Correlation coefficients (r) of 0.993 or better were obtained. For drug concentrations beyond the upper limit of the quantification (ULOQ: 25,000 pg/mL), the sample dilution with control human plasma (1:10) was shown to with acceptable accuracy and precision (<1%).

#### **2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ ULOQ)?**

The ULOQ and LLOQ for bioanalytical methods used in the early clinical Phase 1 and 2 studies have been described in Appendix 3.1 (Section 2.6.4.2).

The ULOQ and LLOQ for trabectedin assay in the drug interaction studies (ET743-OVA-1002 and ET743-OVA-1003) are 25,000 pg/mL and 25 pg/mL, respectively.

#### **2.6.4.3 What are the accuracy, precision and selectivity at these limits?**

Selectivity of trabectedin assay in the drug interaction studies: Six batches of control human plasma were tested with and without spiking with 25 pg/mL of trabectedin. The peak area of the analyte in the unspiked lots was  $\leq 20.0\%$  of the average peak area of the analyte in the 6 samples spiked at 0.0250 ng/mL and the peak area of the IS was  $\leq 5\%$  of the average peak area of the IS in the spiked samples.

The acceptance criteria for the standard curve in each run is that the bias should be within the range of  $\pm 20\%$  at the LLOQ, and within the range of  $\pm 15\%$  at the other concentration levels. There should be at least 6 validated standard levels including both extremes with no more than 15% of the values excluded. The overall precision and accuracy of all in-study QCs should be within 15% CV and within 15% of nominal concentration, respectively.

#### **2.6.4.4 What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)**

Stock stability at room temperature (dark and light),  $+4^{\circ}\text{C}$  and  $-20^{\circ}\text{C}$  in methanol was validated for 3 days, 1 month and 6 months, respectively. Bench-top stability in plasma was validated for 4 hours at ambient temperature. Freeze/thaw stability in plasma (at  $-20^{\circ}\text{C}$ ) was validated for 3 cycles. Analyte in whole blood was stable for 24 hours at  $4^{\circ}\text{C}$  and 2 hours at room temperature. Long-term stability was validated for 352 days at  $-20^{\circ}\text{C}$  and for 162 days at  $-70^{\circ}\text{C}$ .

#### **2.6.4.5 What is the QC sample plan?**

Quality control (QC) samples were prepared at 3 levels (75, 1,250 and 20,000 pg/mL) in duplicate in each analytical runs in the drug interaction studies. The QC acceptance criteria require that the accuracy is within  $\pm 15\%$  of the nominal concentrations for at least  $2/3^{\text{rd}}$  of the total QCs and at least one QC at each level within a run. For dilution integrity, QCs were independently prepared at a 200,000 pg/mL.

The QC analysis plans in the early clinical Phase 1 and 2 studies have been described in Appendix 3.1 Section 2.6.4.5).

## **2.7 LABEL RECOMMENDATIONS**

Only relevant clinical pharmacology sections are included. Underlines indicate content that was added by the agency and ~~strikethroughs~~ indicate content taken out by the agency.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Recommended Dose and Schedule

(b) (4)



### 2.2 Premedication

(b) (4)



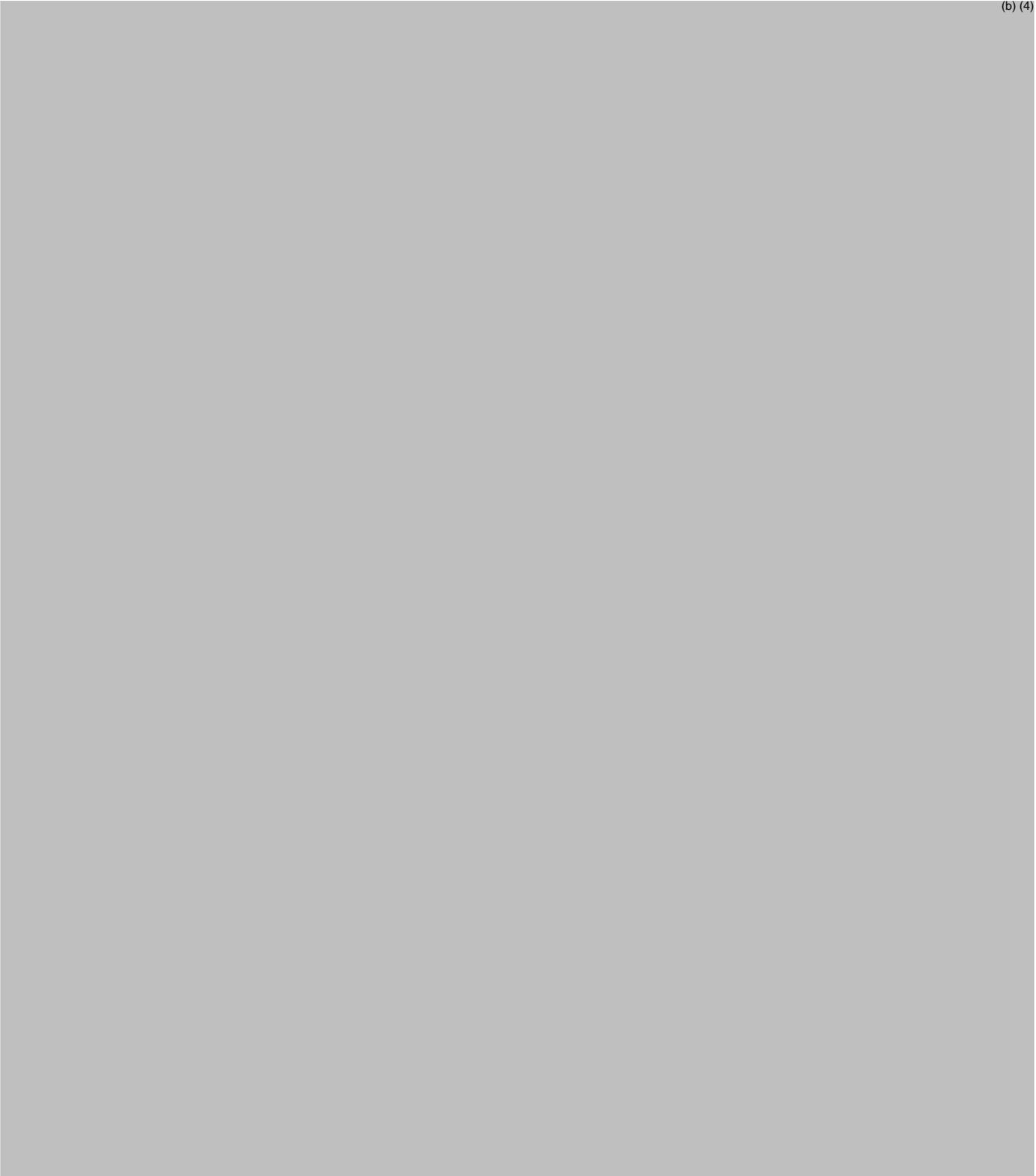
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NDA 207,953 Review - trabectedin

### 3 Appendices

3.1 [Redacted] (b) (4)



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### 3

#### 3.2 QT-IRT REVIEWS

Interdisciplinary Review Team: QT Study Review dated January 27, 2012

#### Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>IND</b>	50286
<b>Brand Name</b>	YONDELIS
<b>Generic Name</b>	Trabectedin
<b>Sponsor</b>	Johnson & Johnson
<b>Indication</b>	Cytotoxic chemotherapy for solid tumors
<b>Dosage Form</b>	Solution for intravenous infusion
<b>Drug Class</b>	Cytotoxic antiproliferative
<b>Therapeutic Dosing Regimen</b>	(b) (4) mg/m <sup>2</sup> as a 3-h infusion every 3 weeks
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	1.1 mg/m <sup>2</sup> as a 1-h infusion (single agent) 1.1 mg/m <sup>2</sup> as a 3-h infusion (in combination with DOXIL 30 mg/m <sup>2</sup> ) 1.8 mg/m <sup>2</sup> as a 3-h infusion (single agent)
<b>Submission Number and Date</b>	July 19, 2010
<b>Review Division</b>	DDOP / HFD 150

## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect was detected in this dedicated QT study following a 3-h intravenous infusion of trabectedin 1.3 mg/m<sup>2</sup> in patients with locally advanced or metastatic solid tumors. The largest upper bound of the 2-sided 90% CI for the mean difference between trabectedin 1.3 mg/m<sup>2</sup> and placebo was below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. However, because of the lack of demonstrated assay sensitivity, the results should be interpreted as having ruled out an effect of about 20 ms.

In this non-randomized, single-blind, placebo controlled, sequential design study, 75 patients with locally advanced metastatic tumor received placebo and trabectedin (1.3 mg/m<sup>2</sup>) as a 3-h infusion on days 1 and 2, respectively.

Overall summary of findings is presented in Table 26.

**Table 26: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Trabectedin (1.3 mg/m<sup>2</sup>) (FDA Analysis)**

Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Trabectedin (1.3 mg/m <sup>2</sup> )	1	-0.3	(-2.8, 2.3)

The tested dose of 1.3 mg/m<sup>2</sup> as a 3-h infusion is higher than the trabectedin dose administered during the pivotal Phase 3 study in patients diagnosed with ovarian cancer (1.1 mg/m<sup>2</sup> as 3-h infusion in combination with doxorubicin every three weeks). The dose used for the treatment of soft tissue sarcoma is 1.5 mg/m<sup>2</sup> as a 24-h infusion with three week interval cycles and would result in lower exposures compared to 1.3 mg/m<sup>2</sup> as a 3-h infusion. Within the range of concentrations observed in this study, no apparent concentration-QT relationship was observed.

Based on in-vitro results, trabectedin metabolism is primarily mediated by CYP3A4. No devoted in-vivo drug-drug interaction studies have been performed. It is anticipated that subjects that receive concomitant CYP3A4 inhibitors may have higher exposures to trabectedin than those observed in this study. Based on population pharmacokinetic analysis age, sex, and body size did not have influence on the clearance of trabectedin. A hepatic impairment study resulted in no PK differences between varying degrees of hepatic impairment. A renal impairment study has not been performed since a minor fraction of the trabectedin dose is excreted in the urine. As the dose is administered intravenously, therefore food effects are not relevant.

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

The dose used by the sponsor in this QT study (1.3 mg/m<sup>2</sup> as a 3-h infusion) is only 18% higher than the therapeutic dose (1.1 mg/m<sup>2</sup> as a 3-h infusion). Based on the information provided at the protocol review stage of this IND, the dose to be tested was 1.3 mg/m<sup>2</sup> as a 3-h infusion, which was also the MTD (See IRT review dated 03/19/2008 for more details). However, based on the current information, the MTD is higher than 1.3 mg/m<sup>2</sup> as a 3-h infusion. Since this QT study was a single agent study, the sponsor could have utilized MTD dose (1.8 mg/m<sup>2</sup> as a 3-h infusion or 1.1 mg/m<sup>2</sup> as a 1-h infusion) for this study.

## 2 BACKGROUND

### 2.1 PRODUCT INFORMATION

YONDELIS®, also known as trabectedin (and ET-743 throughout early development) is a tris, tetrahydroisoquinoline alkaloid isolated from the marine ascidian ecteinascidin turbinate. It is the first of a new class of antitumor agents with a unique mechanism of action that involves the transcription-dependent nucleotide excision repair system and it is currently developed as an antineoplastic agent.

### 2.2 MARKET APPROVAL STATUS

In September 2007, trabectedin (under the tradename YONDELIS) received marketing authorization in the EU for the treatment of patients with advanced soft tissue sarcoma (STS), after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. As of 17 March 2011, trabectedin is approved for the treatment of STS in 61 countries. Trabectedin is not approved for any indication in US.

In October 2009, the European Commission granted approval of the Marketing authorization for YONDELIS in combination with CAELYX (pegylated liposomal doxorubicin, also known as DOXIL) for the treatment of patients with relapsed platinum-sensitive ovarian cancer. As of 17 March 2011,

trabectedin is approved for the treatment of patients with relapsed platinum-sensitive ovarian cancer in 48 countries.

### 2.3 PRECLINICAL INFORMATION

From IB (August 2011)

“Trabectedin had no relevant effect on the potassium channel in human ether-a-go-go related gene (hERG)-transfected cells up to a concentration of  $10^{-5}$ M (7,618 ng/mL).

“The effects of trabectedin on cardiovascular and respiratory function have been investigated in vivo (anesthetized Cynomolgus monkeys). A 1-hour infusion schedule was selected to attain maximum plasma levels ( $C_{max}$  values) in the range of those observed in the clinic. The plasma trabectedin levels attained were  $10.6 \pm 5.4$  ng/mL ( $C_{max}$ ) and similar to those reached after administration of 1.1 mg/m<sup>2</sup> by 3 hour-infusion ( $C_{max}$  of  $7.9 \pm 2.0$  ng/mL). Trabectedin had no relevant effects on heart rate, lead II electrocardiogram (ECG) variables (PR, QT, QTcF and QTcV intervals, and QRS duration), ECG gross morphology and rhythm, left ventricular alterations, cardiac output, stroke volume, and arterial blood or respiratory alterations. Trabectedin tended to reduce arterial blood pressure (mean systolic and mean diastolic) between 60 minutes and 240 minutes after the onset of infusion; this was ascribed to the sodium pentobarbitone anesthesia that is known to depress the baroreceptor. The maximum plasma trabectedin levels in this study were similar to, or higher than, those reached in patients.”

### 2.4 PREVIOUS CLINICAL EXPERIENCE

From IB (August 2011)

“As of 17 March 2011, approximately 7,933 subjects with advanced malignancies have been treated with trabectedin, administered either as a single agent or in combination with other chemotherapeutic agents.

“Trabectedin is well tolerated with prolonged administration. Myelosuppression, with neutropenia as its primary component, elevated ALT and AST, and fatigue were the major dose-limiting toxicities (DLTs) reported in Phase 1 studies. Anemia, thrombocytopenia, leukopenia, and lymphopenia were less frequently reported components of myelosuppression. Although neutropenia is commonly reported with trabectedin treatment, drug-related infection, mucositis, or stomatitis were infrequently reported. No evidence of cumulative toxicity was noted.

“Mild (Grade 1 or Grade 2) transient and reversible elevations of serum CPK were noted with trabectedin treatment. Irreversible renal failure and fatal rhabdomyolysis have been rarely reported. Rhabdomyolysis appears to be an uncommon event with an incidence of approximately 0.5% of total exposure (Summary of Clinical Safety of Trabectedin 2009).

“However, abnormalities in CPK of any grade (Grade 1 to 4) were reported at least once in (b) (4) or in 23% of subjects

receiving trabectedin as a single agent in the integrated Phase 2 safety analysis set, according to clinical laboratory data, warranting adequate monitoring of this clinical laboratory abnormality and its potential manifestations (ie, myalgia) prior to and during treatment.

“Cardiovascular Safety. Cardiac-related AEs were reported for 100 (8%) of 1,199 subjects in the integrated Phase 2 safety analysis set; the lowest occurrence of these events (9 [3%] of 258 subjects) was in the q3wk 3-h treatment arm. Tachycardia (27 [2%] subjects) was the only cardiac-related AE reported by  $\geq 2\%$  of subjects in the integrated Phase 2 safety analysis set. Across all treatment arms, cardiac-related AEs were serious for 27 (2%) subjects in the integrated Phase 2 safety analysis set, with congestive heart failure (5 [ $<1\%$ ] subjects), tachycardia (4 [ $<1\%$ ] subjects), atrial fibrillation (3 [ $<1\%$ ] subjects), and cardiac failure (3 [ $<1\%$ ] subjects) being those serious cardiac-related events reported for more than 2 subjects. Fourteen (1%) subjects were withdrawn due to cardiac-related AEs. (b) (4)

“Cardiac-related AEs that were serious or resulted in discontinuation were infrequent in both treatment

arms. Cardiac-related AEs led to discontinuation of study treatment for 7 (2%) subjects in the trabectedin + DOXIL arm and 1 subject (<1%) in the DOXIL monotherapy arm.”

*Reviewer’s comments: No syncope, seizures, sudden death or ventricular arrhythmias were reported. No clinically relevant ECG changes were reported. There were reports of decrease ventricular ejection fraction decreases after administration of trabectedin.*

## **2.5 CLINICAL PHARMACOLOGY**

Appendix 5.1 summarizes the key features of trabectedin’s clinical pharmacology.

## **3 SPONSOR’S SUBMISSION**

### **3.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 50286. The sponsor submitted the study report ET743-OVC-1001-OLE for the study drug, including electronic datasets and waveforms to the ECG warehouse.

### **3.2 TQT STUDY**

#### **3.2.1 Title**

A Single-Blind, Multicenter, Placebo-Controlled, Sequential Design Study Evaluating the Potential Effects of a Single-Dose Administration of Trabectedin on the QT Intervals of the Electrocardiogram

#### **3.2.2 Protocol Number**

Protocol ET743-OVC-1001 (Phase 1/2<sup>a</sup>)

#### **3.2.3 Study Dates**

Date study initiated (first subject enrolled): 14 October 2008

Date study completed (date of last observation for last subject recorded as part of the database): 14 December 2009

#### **3.2.4 Objectives**

- The primary objective of this study was to assess the effects of trabectedin on the QT/QTc interval duration in subjects with advanced solid tumor malignancies when administered at a therapeutic dose.
- The secondary objectives of this study were to assess the safety and pharmacokinetics of trabectedin and its effect on subject survival.

#### **3.2.5 Study Description**

##### **3.2.5.1 Design**

This was a single-blind, multicenter, placebo-controlled study that included a treatment phase of 2 single-

dose sequential treatments. The study consisted of a screening phase (within 21 days before the first study drug administration on Day 1) followed by a single blind period (SBP) of 2 days. Subjects who completed the SBP were given the option to continue taking trabectedin in an open label extension for a minimum of 6 cycles (if clinical benefit seen). Enrollment was planned for at least 60 subjects to ensure at least 52 evaluable subjects completed all required assessments, up to and including the 24-hour triplicate ECG recordings and pharmacokinetic blood samples collected after trabectedin administration on Day 2. Across the 2 treatment days, the times of study drug administrations, 12-lead ECG recordings, and pharmacokinetic blood sample collections were obtained and to be time-matched. Subjects' safety was monitored throughout the study.

### 3.2.5.2 Controls

The sponsor used a placebo control. A positive control (moxifloxacin) was not included in the study.

### 3.2.5.3 Blinding

There was no randomization in the single blind period of this study since all subjects received the same treatment sequence. Infusions were blinded to the subject for both intravenous infusions.

## 3.2.6 Treatment Regimen

### 3.2.6.1 Treatment Arms

Subjects with locally advanced or metastatic solid tumors who had received 3 or fewer prior lines of systemic chemotherapy were included in the study and received the following:

Day 1: trabectedin placebo (normal saline) administered as a 3-h i.v. infusion

Day 2: 1.3 mg/m<sup>2</sup> of trabectedin as a 3-h i.v. infusion

Each subject received the infusions at the same time of day on the Days 1 and 2. The placebo and trabectedin were administered as constant rate intravenous infusions over a period of 3 hours.

### 3.2.6.2 Sponsor's Justification for Doses

“The potential effects of a 1.3 mg/m<sup>2</sup> dose of trabectedin given as a 3-hour intravenous (i.v.) infusion on the QT/QTc interval duration was to be assessed. This is higher than the trabectedin dose administered (1.1 mg/m<sup>2</sup> as a 3-hour i.v. infusion) in combination with DOXIL to subjects diagnosed with ovarian cancer, during pivotal Phase 3 study OVA 301. Although higher doses have been administered to sarcoma cancer patients (e.g., 1.5 mg/m<sup>2</sup> given as a 24-hour intravenous infusion), the 3-hour infusion of 1.3 mg/m<sup>2</sup> was expected to produce concentrations in plasma that are higher than those observed with infusions of longer duration (e.g., 24 hours).”

*(Source: Investigational Brochure: Section 2.1 Study Design Rationale, page 16)*

*Reviewer's Comments: The sponsor could have utilized 1.8 mg/m<sup>2</sup> as a 3-h infusion (MTD) for this dedicated QT study. The 1.3 mg/m<sup>2</sup> is less than the maximum tolerated dose (1.8 mg/m<sup>2</sup>) but slightly higher than the intended therapeutic dose (1.1 mg/m<sup>2</sup>). We note, however, that trabectedin is extensively metabolized by CYP3A. It is anticipated that subjects that receive concomitant CYP3A inhibitors may have higher exposures to trabectedin than those observed in this study. Trabectedin is not approved in US but the EMA approved label states that “In vivo interaction studies have not been performed. Since*

*trabectedin is metabolized mainly by CYP3A4, co-administration of substances that inhibit this isoenzyme e.g. ketoconazole, fluconazole, ritonavir, clarithromycin or aprepitant could decrease metabolism and increase trabectedin concentrations. If such combinations are needed, close monitoring of toxicities is required”.*

*A hepatic impairment study resulted in no PK differences between varying degrees of hepatic impairment. A renal impairment study has not been performed since a minor fraction of the trabectedin dose is excreted in the urine.*

### **3.2.6.3 Instructions with Regard to Meals**

There are no instructions with regards to meals.

*Reviewers Comment: Trabectedin is administered by i.v. infusion so food effects are not anticipated.*

### **3.2.6.4 ECG and PK Assessments**

On Days 1 and 2 serial ECGs were collected in triplicate at each of the following time points: predose and at 1, 2, 2.75, 4, 6, and 8 h after the start of the infusion. ECGs were also collected 24 h after trabectedin administration on Day 2. The predose ECG assessments began within 30 min before the dose of study drug (trabectedin and placebo).

With regard to PK, peripheral venous blood samples (4 mL) for determination of trabectedin plasma concentrations were collected predose and following placebo and trabectedin administration on Days 1 and 2, respectively. Samples were time-matched to the ECG measurements and collected within 5 min of when the last ECG tracing was recorded. Samples were taken at the following time points for trabectedin: Predose, 1, 2, 2.75, 4, 6, 8, and 24 hour.

*Reviewer’s Comment: The timing of the ECGs is reasonable to capture the QT at peak concentrations of trabectedin (right after infusion ends,  $T_{max}$  ~ 3 hours) and to account for any delayed effects.*

### **3.2.6.5 Baseline**

The ECG tracings collected at predose on each day served as the baseline for comparison with all ECG tracings collected postdose for 24 hours.

### **3.2.7 ECG Collection**

On Days 1 and 2 serial ECGs were collected in triplicate (three 10-second digital ECGs in close succession) at each of the following time points: before dosing (i.e., predose) and at 1, 2, 2.75, 4, 6, and 8 hours after the start of the infusion. ECGs were also collected 24 hours after trabectedin administration on Day 2. There was a maximum of 2 minutes between each of the triplicate ECG measurements. The predose ECG assessments began within 30 minutes before the dose of study drug (trabectedin and placebo).

Advanced and automated electrocardiograms capturing a 12-lead surface ECG signal with the capacity for digital signal processing were used.

All digital ECG tracings were blinded and sent to a third-party central ECG laboratory (with a paper and electronic copy to the sponsor) for measurement of intervals, diagnostics of abnormalities and review of ECG waveform morphology. For the triplicate ECGs collected at each time point, the mean of 3 measurements for each ECG parameter was considered for all listing and statistical analyses described below.

## 3.2.8 Sponsor's Results

### 3.2.8.1 Study Subjects

Of the 75 enrolled subjects, 24 (32%) were men and 51 (68%) were women.

**Table 27: Demographics and Baseline Characteristics (Study ET743-OVC-1001: All Treated Subjects Analysis Set)**

	Total (N=75)
<b>Sex, n (%)</b>	
Female	51 (68)
Male	24 (32)
<b>Race, n (%)</b>	
White	51 (68)
Asian	23 (31)
Other	1 (1)
<b>Age (Years)</b>	
Mean (SD)	50.1 (11.03)
Median	52.0
Range	(22;68)
<b>Baseline Weight (Kg)</b>	
Mean (SD)	69.8 (16.34)
Median	66.0
Range	(38;111)
<b>Height (Cm)</b>	
Mean (SD)	164.9 (9.62)
Median	165.0
Range	(143;192)
<b>Baseline ECOG Performance Status, n (%)</b>	
0	31 (41)
1	44 (59)
<b>Baseline BMI (kg/m<sup>2</sup>)</b>	
Mean (SD)	25.6 (5.45)
Median	24.8
Range	(14;42)
<b>Baseline BSA (m<sup>2</sup>)</b>	
Mean (SD)	1.8 (0.22)
Median	1.7
Range	(1;2)

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Source: CSR, Table 7

The most common tumor types were sarcoma (25 subjects/75 subjects, 33%) and ovarian cancer (23 subjects/75 subjects, 31%).

### 3.2.8.2 Statistical Analyses

#### 3.2.8.2.1 Primary Analysis

“A small decrease in mean-placebo corrected changes from baseline in QTcF ( $\Delta\Delta$ QTcF) was observed at most postdose time points. The  $\Delta\Delta$ QTcF ranged from -1.4 at 1 hour to -9.8 ms at 24 hours during the 24-hour monitoring period.

“Changes from baseline in QTcB with trabectedin relative to placebo were generally smaller in the magnitude than those with QTcF and were not consistently negative. The  $\Delta\Delta$ QTcB ranged from -2.0 at 2

hours to 3.4 ms at 4 hours during the 24-hour monitoring period.

“The upper limits of the 90% confidence intervals for all mean  $\Delta\Delta\text{QTcF}$  and  $\Delta\Delta\text{QTcB}$  values were below 10 ms (actually  $\leq 6.65$  ms) at all time points. Thus, non-inferiority of trabectedin to placebo with respect to QTc prolongation can be concluded. The lower limit of the 90% CI for mean  $\Delta\Delta\text{QTcF}$  ranged from -12.65 at 24 h to -3.35 ms at 1 h after the start of the trabectedin infusion based on mean  $\Delta\Delta\text{QTcF}$ . The lower limit of the 90% CI was -4.83 ms at 24 h to 0.07 ms at 4h for  $\Delta\Delta\text{QTcB}$ .”

Source: CSR Section 3.3.1.3

**Table 28: Least Square Mean and 90% CI of Difference in Change from Baseline in QTcF Intervals (Sponsor’s Results)**

QTc Interval (ms)-Friderica Correction	Trabectedin 1.3 mg/m <sup>2</sup> (Day 2) Minus ----- Placebo (Day 1) ----- L.S.Means <sup>a</sup> SE 90% CI		
	1h	-1.4	1.16
2h	-3.7	1.22	(-5.68; -1.63)
2h45min	-4.5	1.25	(-6.55; -2.40)
4h	-5.8	1.42	(-8.19; -3.45)
6h	-4.2	1.21	(-6.26; -2.22)
8h	-2.3	1.52	(-4.82; 0.26)
24h	-9.8	1.71	(-12.65; -6.99)

Source: CSR, Table 14

### 3.2.8.2.2 Categorical Analysis

“No subject had a maximum individual increase of QTcF from baseline ( $\Delta\text{QTcF}$ ) exceeding 60 ms for any treatment group. Two subjects (101507, 910202) had changes ( $\Delta\text{QTcF}$ ) greater than 30 ms during placebo treatment, and 2 subjects (700211, 910201) had changes ( $\Delta\text{QTcF}$ ) greater than 30 ms during trabectedin treatment.

“No subject had a maximum individual postdose QTcF greater or equal to 480 ms in any treatment group; 4 of the subjects in the trabectedin treatment group and 6 subjects in the placebo treatment group with greater than 450 ms for the QTcF interval.

“No subject had a maximum decrease from baseline ( $\Delta\text{QTcF}$ ) exceeded 60 ms for any treatment group. Three subjects had decreases in the QTcF interval of  $<30$  ms after receiving trabectedin (Subjects 340102, 100601, and 820102).

“One subject (910101) had QTcF values of  $<360$  ms during placebo treatment and 1 subject (101504) during trabectedin treatment. None of the subjects had QTcF values that were  $<320$  ms in either treatment period.”

Source: CSR Section 3.3.1.4

### 3.2.8.2.3 Additional Analyses

“Two subjects (101507, 820403) had PR intervals  $>200$  ms during placebo and trabectedin treatments and 1 subject (320201) had a PR interval  $>200$  ms during the placebo treatment only. There was only 1 subject (330201) who had an abnormal QRS intervals of  $>120$  ms in both groups.”

Source: CSR Section 3.3.2

### 3.2.8.3 Safety Analysis

Seventy-one (95%) of the 75 subjects in the study experienced treatment-emergent adverse events (Table 24). The most frequent events were in the Gastrointestinal Disorders system organ class (SOC) (72%; 54/75) with nausea (55%, 41/75) and vomiting (52%, 39/75) being the most common events. In addition, in descending order, the incidence of General Disorders and Administration Site Conditions events were 51% (asthenia, 27%; fatigue, 16%); Blood and Lymphatic Disorders events were 27% (neutropenia, 16%; anemia, 9%; leucopenia, 7%).

Nineteen percent of the subjects experienced serious adverse events, most of these being vomiting, nausea, and asthenia (3% to 5%).

The most frequent adverse events by Grades 3-4 toxicity grade were: neutropenia (Grade 3, 5.3% Grade 4, 5.3%); asthenia (Grade 3, 4%), vomiting (Grade 3, 4%), nausea (Grade 3, 4%), and abnormal hepatic function (Grade 3, 18.7%; Grade 4, 4%).

Three deaths were reported within 30 days of study treatment (Day 2). In 1 subject (101504) with oropharyngeal cancer, death was reported as due to progressive disease 12 days after receiving study drug; in 1 subject (910104) with ovarian cancer, death was due to adverse events (vomiting and asthenia) 3 days after receiving study drug. The relationship to drug is doubtful; in 1 subject (320303) with linitis plastica, death resulted from assisted suicide administered 30 days after study drug due to progressive disease.

In drug-related toxicity categories Grades 3 and 4, the most frequent adverse events were abnormal hepatic function (16%), and neutropenia (8%).

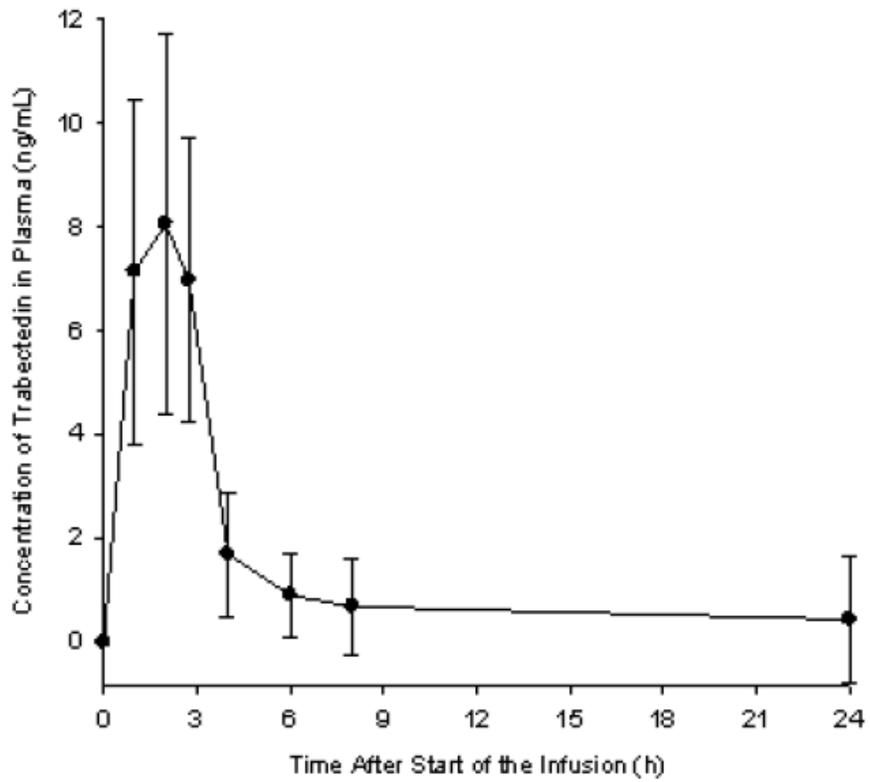
There were no subjects with cardiac disorders in the SBP of the study. No adverse events were reported suggestive of proarrhythmic potential as specified in the ICH E14 Guidelines.

### 3.2.8.4 Clinical Pharmacology

#### 3.2.8.4.1 Pharmacokinetic Analysis

The sponsor reported the estimated average (SD)  $C_{max}$  for trabectedin to be 9.24 ng/mL (3.75 ng/mL). Maximum concentrations were observed at an average (SD) of 2.22 h (0.65 h) after the start of the trabectedin infusion. The mean drug concentration-time profile is illustrated in Figure 31.

Figure 31: Mean Trabectedin Concentration-Time Profile for a 3-h Infusion of 1.3 mg/m<sup>2</sup>



Mean (SD) of 67 to 73 subjects represented at each time point

(Source: Study Report for Protocol ET743-OVC-1001, page 50, figure 1)

**Table 29: Descriptive Statistics of Trabectedin PK Concentrations**

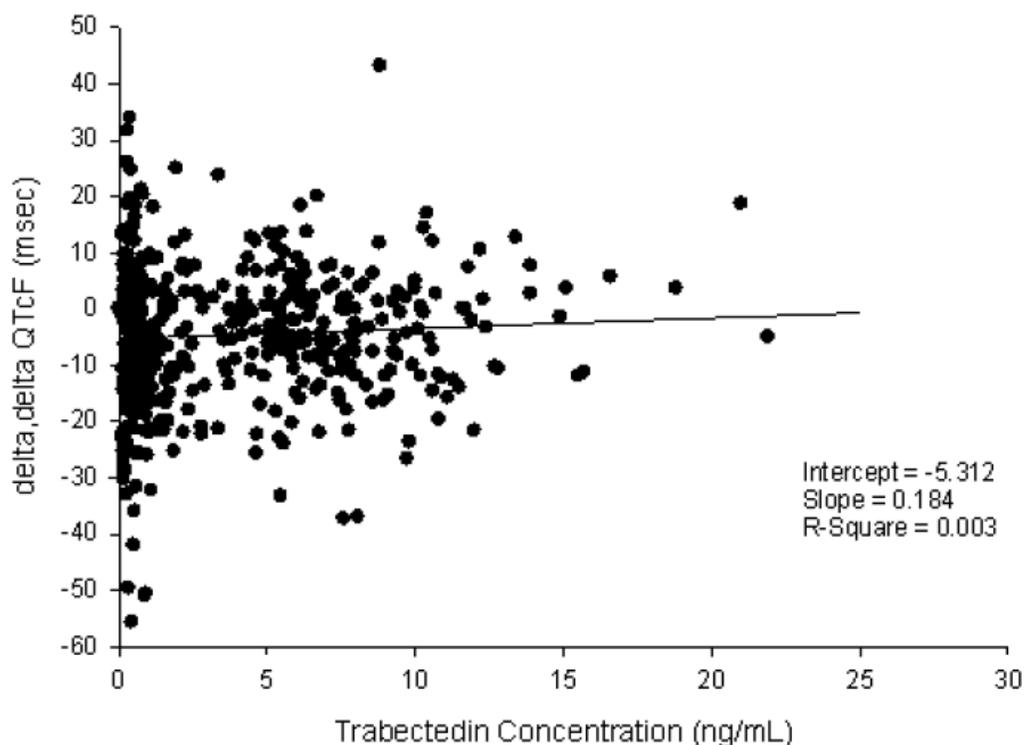
Trabectedin (ng/mL, Plasma)								
Scheduled Day	Day 2							
Sched. Time / SubjID	Predose	1 hr	2 hr	2 hr 45 min	4 hr	6 hr	8 hr	24 hr
820105	NAv	7.27	8.80	10.6	1.55	0.672	0.511	0.277
820106	BQL	5.10	4.20	5.89	5.51	0.472	0.344	0.147
820202	BQL	24.7	4.37	2.30	2.66	2.19	1.08	1.20
820203	BQL	7.04	9.18	9.32	1.54	0.611	0.511	0.276
820204	0.0572	5.51	6.03	2.24	0.547	0.396	0.342	0.175
820206	BQL	4.48	5.18	6.09	0.836	0.395	0.389	0.213
820207	BQL	5.23	6.81	6.15	0.934	0.575	0.428	0.211
820301	BQL	6.37	5.12	6.06	5.49	0.559	0.388	0.231
820302	BQL	3.56	4.18	4.52	1.04	0.434	0.356	0.189
820303	BQL	10.0	18.8	10.7	1.65	0.837	0.549	0.290
820402	BQL	6.13	7.55	7.70	0.966	0.481	0.394	0.253
820403	BQL	6.05	6.23	6.15	0.827	0.419	0.386	0.154
820404	BQL	7.98	8.99	10.0	1.01	0.569	0.383	0.157
910101	BQL	12.2	39.7	4.36	1.21	1.11	0.772	0.314
910102	BQL	13.9	13.9	26.1	1.29	1.37	0.951	0.349
910104	BQL	21.9	7.26	28.8	2.38	0.922	0.783	0.203
910108	BQL	58.7	23.4	706	19.6	1.54	1.90	0.554
910109	BQL	8.07	7.59	5.47	5.57	0.590	0.405	0.921
910201	BQL	4.10	21.0	56.9	3.93	1.72	1.31	0.352
910202	BQL	13.4	11.8	34.9	4.67	2.91	1.87	0.446
910203	BQL	7.92	15.1	1.42	1.77	0.800	0.591	0.285
n	73	74	74	73	74	74	74	73
Mean	BQL	11.3	11.5	18.2	4.47	1.19	1.09	0.653
SD	-	22.0	24.6	82.0	13.6	2.55	2.52	1.79
%CV	-	194.6	214.5	451.2	303.3	214.1	230.7	274.3
Median	BQL	6.36	7.53	6.91	1.29	0.672	0.511	0.254
Min	BQL	2.13	1.55	1.42	0.486	0.233	0.161	0.104
Max	11.7	173	215	706	97.7	21.7	16.7	11.6

*Reviewer's Comment: Summaries of trabectedin concentrations are provided in Table 29; the AUC exposure metric was not provided by the sponsor.*

### 3.2.8.4.2 Exposure-Response Analysis

The sponsor examined the relationship between  $\Delta\Delta\text{QTcF}$  and trabectedin plasma concentrations using a linear mixed effects modeling approach, with  $\Delta\Delta\text{QTc}$  as dependent variable and trabectedin concentration as a predictor and subjects as random effect. 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  $C_{\text{max}}$  values of trabectedin based on this model. The sponsor concluded there was a weak linear exposure-effect relationship for  $\Delta\Delta\text{QTcF}$  (Figure 32).

**Figure 32: Individual  $\Delta\Delta\text{QTcF}$  vs. trabectedin plasma concentrations**



(Source: Study Report for Protocol ET743-OVC-1001, page 65, figure 8)

Reviewer's Comments: Sponsor analysis of trabectedin concentration and  $\Delta\Delta QTcF$  is presented above. We provide our independent analysis in section 5.3. A plot of  $\Delta\Delta QTcF$  vs. drug concentrations generated from the FDA analysis is presented in Figure 35.

## 4 REVIEWERS' ASSESSMENT

### 4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

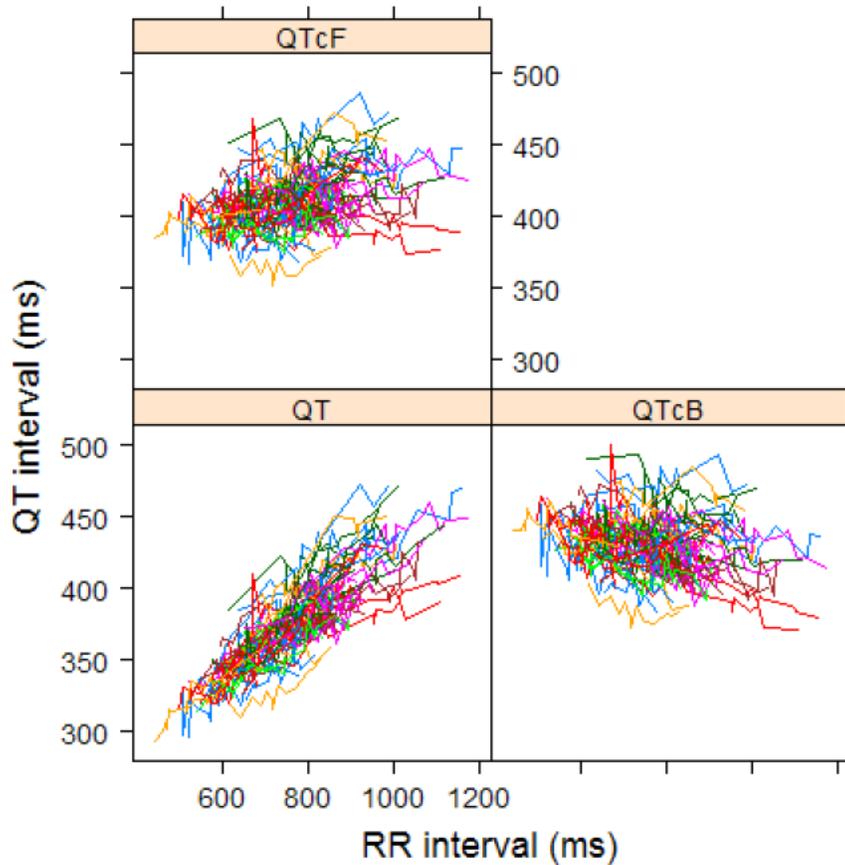
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 30, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

**Table 30: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Method	Treatment					
	Placebo		Trabectedin		All	
	N	MSSS	N	MSSS	N	MSSS
QTcB	75	0.0106	75	0.0140	75	0.0103
QTcF	75	0.0037	75	0.0045	75	0.0026

The relationship between different correction methods and RR is presented in Figure 33.

**Figure 33: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)**



#### 4.1.1 QTc Analysis

##### 4.1.1.1 The Primary Analysis for Trabectedin

The statistical reviewer used linear regression model to analyze the  $\Delta\Delta\text{QTcF}$  effect. The model includes time points, sex and baseline values as covariates. The analysis results are listed in the following table.

**Table 31: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group = Trabectedin**

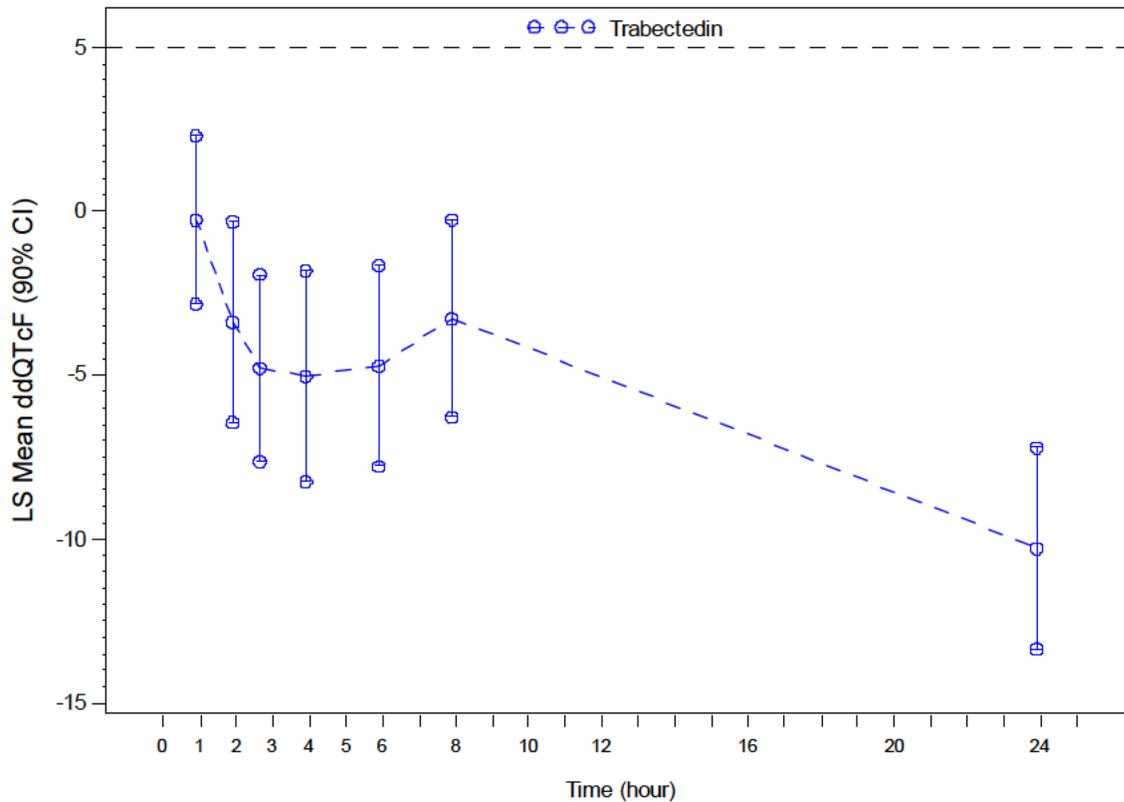
	Trabectedin $\Delta$ QTcF	Placebo $\Delta$ QTcF	$\Delta\Delta$ QTcF	
Time/(hour)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	0.8	1.1	-0.3	(-2.8, 2.3)
2	1.2	4.6	-3.4	(-6.5, -0.3)
2.75	2.0	6.8	-4.8	(-7.6, -1.9)
4	4.0	9.0	-5.0	(-8.2, -1.8)
6	0.3	5.0	-4.7	(-7.8, -1.7)
8	-0.3	2.9	-3.3	(-6.3, -0.3)
24	-5.8	4.4	-10.3	(-13.3, -7.2)

The largest upper bound of the 2-sided 90% CI for the mean difference between trabectedin and placebo was 2.3 ms.

#### 4.1.1.2 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcF for trabectedin.

**Figure 34: Mean and 90% CI  $\Delta\Delta$ QTcF Timecourse**



#### 4.1.1.3 Categorical Analysis

Table 32 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 500 ms.

**Table 32: Categorical Analysis for QTcF**

Treatment Group	Total N		Value $\leq 450$ ms		450 ms < Value $\leq 480$ ms		480 ms < Value $\leq 500$ ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	75	150	72 (96.0%)	146 (97.3%)	3 (4.0%)	4 (2.7%)	0 (0.0%)	0 (0.0%)
Placebo	75	524	70 (93.3%)	508 (96.9%)	5 (6.7%)	16 (3.1%)	0 (0.0%)	0 (0.0%)
Trabectedin	75	524	70 (93.3%)	506 (96.6%)	4 (5.3%)	17 (3.2%)	1 (1.3%)	1 (0.2%)

Table 33 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 60 ms.

**Table 33: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	75	524	71 (94.7%)	516 (98.5%)	4 (5.3%)	8 (1.5%)
Trabectedin	75	524	71 (94.7%)	520 (99.2%)	4 (5.3%)	4 (0.8%)

**4.1.2 HR Analysis**

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 34. The largest upper limits of 90% CI for the HR mean differences between trabectedin and placebo is 11.8 bmp.

**Table 34: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group = Trabectedin**

Time/(hour)	Trabectedin	Placebo	$\Delta\Delta$ HR	
	$\Delta$ HR	$\Delta$ HR	Diff LS Mean (bpm)	Mean (bpm)
1	-3.5	-3.0	-0.5	( -2.2, 1.2)
2	-2.1	-4.0	1.9	( -0.1, 3.9)
2.75	0.6	-3.4	4.1	( 1.9, 6.3)
4	8.4	-0.5	8.9	( 6.1, 11.8)
6	12.4	5.2	7.2	( 4.5, 10.0)
8	9.6	5.7	4.0	( 1.1, 6.8)
24	5.1	-3.3	8.5	( 6.3, 10.7)

**4.1.3 PR Analysis**

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in the following table. The largest upper bound of the 2-sided 90% CI for the mean difference between trabectedin and placebo was 2.8 ms

**Table 35: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = Trabectedin**

	Trabectedin $\Delta$ PR	Placebo $\Delta$ PR	$\Delta\Delta$ PR	
Time/(hour)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	Mean (ms)
1	0.7	1.4	-0.7	( -3.0, 1.6)
2	-0.2	-0.4	0.2	( -2.4, 2.8)
2.75	-1.2	-0.4	-0.8	( -3.3, 1.7)
4	-2.2	-2.0	-0.2	( -2.7, 2.3)
6	-3.7	-1.5	-2.2	( -4.9, 0.5)
8	-4.9	-0.7	-4.1	( -6.7, -1.5)
24	-3.3	1.1	-4.4	( -7.4, -1.4)

**4.1.4 QRS Analysis**

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in following table. The largest upper bound of the 2-sided 90% CI for the mean difference between trabectedin and placebo was 1.8 ms

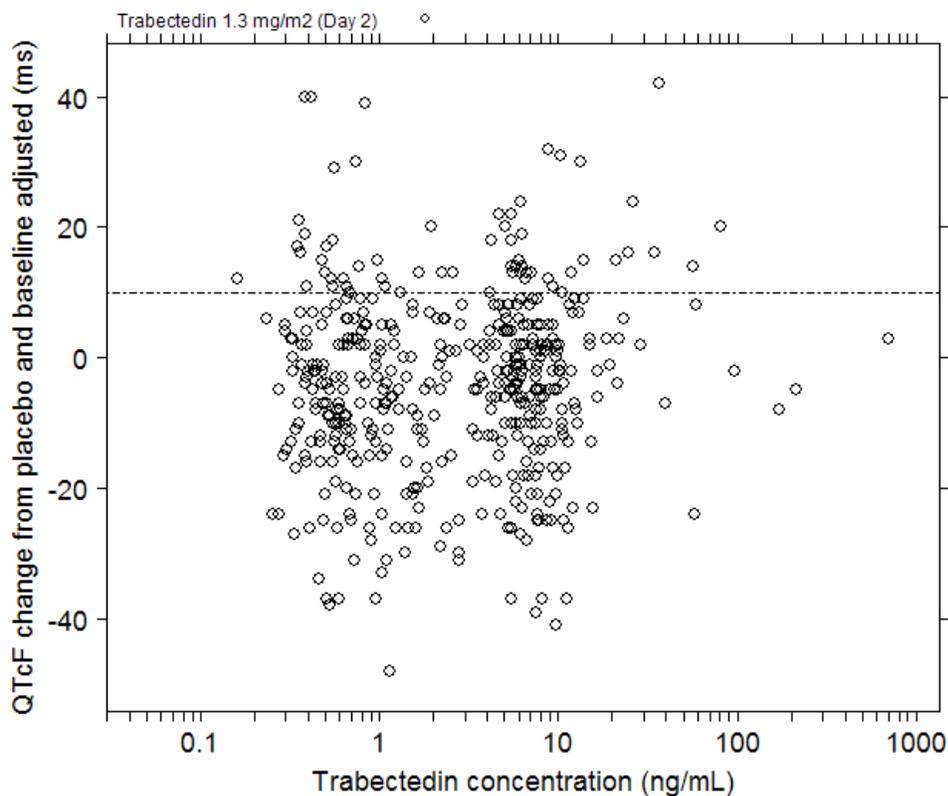
**Table 36: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = Trabectedin**

	Trabectedin $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
Time/(hour)	Mean (ms)	Mean (ms)	Diff LS Mean (ms)	Mean (ms)
1	-0.4	-1.0	0.6	( -0.7, 1.8)
2	-0.5	-0.7	0.2	( -1.1, 1.4)
2.75	-1.5	-0.3	-1.2	( -2.2, -0.2)
4	-1.5	-0.5	-1.0	( -2.1, 0.1)
6	-2.0	-0.7	-1.3	( -2.5, -0.0)
8	-2.6	-1.4	-1.2	( -2.4, 0.0)
24	0.3	3.1	-2.8	( -4.0, -1.6)

## 4.2 CLINICAL PHARMACOLOGY ASSESSMENTS

A plot of  $\Delta\Delta Q_{Tc}$  vs. log trabectedin concentrations generated from the FDA analysis is presented in Figure 35. No relationship was observed. The clinical pharmacology assessments are outlined in section 4.2.8.4.

Figure 35:  $\Delta\Delta Q_{TcF}$  vs. Trabectedin Concentration



## 4.3 CLINICAL ASSESSMENTS

### 4.3.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### 4.3.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 96.5% of the ECGs were annotated in the primary lead II, with less than 98% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

### **4.3.3 PR and QRS Interval**

Two subjects had PR > 200 ms while none exceeded 210 ms. Four subjects had QRS > 110 ms at baseline without postbaseline increases.

## 5 APPENDIX

### 5.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic Dose	<sup>(b) (4)</sup> mg/m <sup>2</sup> as 3-hr infusion q3wk	
Maximum Tolerated Dose	1.1 mg/m <sup>2</sup> as a 1-hr infusion 1.8 mg/m <sup>2</sup> as a 3-hr infusion 1.1 mg/m <sup>2</sup> as a 3-hr infusion* 1.8 mg/m <sup>2</sup> as a 24-hr infusion *MTD of trabectedin administered in combination with 30 mg/m <sup>2</sup> DOXIL (Study ET743-USA-11). All other values are from single agent studies.	
Principal Adverse Events	Hepatic toxicity, neutropenia (with possible infection), thrombocytopenia and bleeding disorders, cardiac disorders, renal and urinary disorders, rhabdomyolysis and creatine phosphokinase (CPK) elevations, myelodysplasia and acute myeloid leukemia, and respiratory disorders.	
Maximum Dose Tested	Single Dose	1.8 mg/m <sup>2</sup>
	Multiple Dose	1.9 mg/m <sup>2</sup> (0.38 mg/m <sup>2</sup> qd x 5 days)
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (SD) C <sub>max</sub> = 1.2 (6.84) Mean (SD) AUC = 71.3 (37.8)
	Multiple Dose	Mean (SD) C <sub>max</sub> = 4.42 (1.13) Mean (SD) AUC = 12.0 (7.25)
Range of Linear PK	0.024 to 1.8 mg/m <sup>2</sup> administered as 3- and 24-h infusions	
Accumulation at Steady State	Little or no accumulation of trabectedin in plasma is observed or expected (based on population pharmacokinetic simulations) upon repeat administration at 3-week intervals, irrespective of the infusion duration.	
Metabolism	Trabectedin is oxidatively metabolized by various routes that produce a wide range of metabolites upon incubation with human hepatic sub-cellular fractions and hepatocytes. No appreciable glucuronidation of trabectedin was demonstrated. In vivo metabolites of trabectedin have not been conclusively identified. Studies with pooled human liver microsomes suggest CYP3A4 is the predominant cytochrome P450 enzyme responsible for the hepatic metabolism of trabectedin.	
Absorption	Absorption is not a pertinent factor in the administration and treatment with trabectedin since it is given as a solution via the intravenous route.	
Distribution	Vd/F or Vd	Estimates of the distribution volume at steady state from the population

		analyses are close to or exceed 5000 L.
	% bound	The mean free (unbound) fraction, evaluated by equilibrium dialysis, was 2.23% and 2.72% at 10 ng/mL and 100 ng/mL, respectively.
Elimination	Route	<p>Following the single-dose administration of <sup>14</sup>C-labeled trabectedin, a majority of the radioactivity excreted was recovered in the feces (57.6% of the dose) and smaller amounts recovered in the urine (5.8% of the dose) over a collection interval of up to 24 days and 10 days, respectively.</p> <p>Negligible quantities of unchanged drug were recovered in urine (&lt;1% of the dose) and feces.</p>
	Terminal t <sub>1/2</sub>	175 h (mean of the values for males [181 h] and females [168 h]).
	CL/F or CL	The typical value of trabectedin plasma clearance and the corresponding intersubject variability, from the final population pharmacokinetic model, were approximately 31 L/h and 50%, respectively.
Intrinsic Factors	Age	A population pharmacokinetic analysis indicated that the plasma clearance and distribution volume of trabectedin are not influenced by subject age (range, 19 to 83 years).
	Sex	A clinically meaningful relationship between sex and the plasma clearance was not observed during a population pharmacokinetic analyses and simulations.
	Race	Effect of race has not been formally evaluated. The majority of subjects studied were white.
	Body Size	Various measures of body size included in the population analyses, such as total body weight (range, 36-148 kg) and body surface area (range, 0.9-2.8 m <sup>2</sup> ),

		<p>did not explain the inter-subject variability in the plasma clearance of trabectedin.</p>
	<p>Hepatic &amp; Renal Impairment</p>	<p>A Phase 1 study (ET-A-006-00) assessed the pharmacokinetics of trabectedin in patients with hepatic impairment defined by alkaline phosphatase concentrations at screening. A high degree of overlap was observed in pharmacokinetic parameters and differences between groups were not statistically significant. The population pharmacokinetic analysis showed no relationship between the concentration of liver enzymes and trabectedin plasma clearance.</p> <p>No formal clinical study in patients with renal impairment has been conducted since only a minor fraction of the total trabectedin dose is excreted in urine.</p>
<p>Extrinsic Factors</p>	<p>Drug interactions</p>	<p>Effect of other drugs on trabectedin:</p> <ul style="list-style-type: none"> <li>• A population analysis was performed that included trabectedin pharmacokinetic data from 15 Phase 1 and Phase 2 studies. The systemic clearance values of trabectedin in a subset of patients who were enrolled in 2 global, multicenter studies during which a limited number of pharmacokinetic samples were collected from each patient after trabectedin administration (b) (4) [redacted] as a single-agent (Study ET743-STS-201) were compared. The median clearance values were [redacted] (b) (4) [redacted] 37.5 L/h for the 211 patients in Study ET743-STS-201. The</li> </ul>

		<p>apparent difference is not expected to be clinically relevant in light of the reported between-patient variability in trabectedin systemic clearance (approximately 50%, expressed as percent coefficient of variation).</p> <ul style="list-style-type: none"> <li>The potential effects of dexamethasone pretreatment on the pharmacokinetics of trabectedin were evaluated using population methods. The median plasma clearance values of trabectedin were comparable for those patients who were given a single i.v. dose of 10 mg or 20 mg dexamethasone just before trabectedin and those who received trabectedin without dexamethasone pretreatment (38.3 L/h [n=290] and 34.1 L/h [n=37], respectively).</li> </ul> <p>Effect of trabectedin on other drugs:</p> <ul style="list-style-type: none"> <li>Based on results of nonclinical studies, trabectedin is not expected to affect the metabolic clearance of other coadministered drugs. Trabectedin exhibited limited inhibitory activity on the following human hepatic microsomal CYP enzymes: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4. Trabectedin also had a limited induction potential for the following human CYP enzymes: CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1,</li> </ul>
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		<p>3A4, and 3A5.</p> <ul style="list-style-type: none"> <li>Results of Phase 1 Study ET743-USA-11 also suggested that concomitant administration with trabectedin (dose range, 0.4 to 1.3 mg/m<sup>2</sup>) does not influence the plasma pharmacokinetics of DOXIL, based on comparisons made with previously published single-agent studies. (b) (4)</li> </ul> <p>(b) (4)</p>
	Food Effects	Food effects are not pertinent since trabectedin is administered intravenously.
Expected High Clinical Exposure Scenario	<p>The effects of trabectedin on the QT/QTc interval were assessed in patients with locally advanced or metastatic solid tumors. Patients were administered 3-hour intravenous infusions of placebo (saline) on day 1 and trabectedin (1.3 mg/m<sup>2</sup>) on day 2. Time-matched serial triplicate ECG recordings and pharmacokinetic blood samples were collected over 24 hours on both days. Heart-rate corrected mean QT intervals and changes from predose baseline in QTc (<math>\Delta</math>QTc) were assessed. The difference in <math>\Delta</math>QTc between trabectedin and placebo was calculated at each time point (<math>\Delta\Delta</math>QTc). Trabectedin did not prolong the QTc interval. The upper limits of the 90% confidence interval for <math>\Delta\Delta</math>QTcF and <math>\Delta\Delta</math>QTcB at all time points were less than the prespecified noninferiority margin of 10 ms (<math>\leq 6.65</math> ms). No patient had a QTc &gt;500 ms or a time-matched increase from baseline in QTc &gt;60 ms at any time point. Regression</p>	

	analyses indicated $\Delta\Delta QT_c$ was poorly correlated with trabectedin concentration.
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QT Interdisciplinary Review Team memorandum dated March 03, 2015



## Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 15, 2015

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Anuja Patel, RPM  
DOP2

Subject: QT-IRT Consult to NDA 207953

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/20/2015 regarding your labeling consultation for trabectedin. The QT-IRT received and reviewed the following materials:

- Your consult
- QT-IRT's previous review for Study ET743-OVC-1001-OLE under IND 50286 (1/27/2012)
- Proposed YONDELIS (trabectedin) label

#### 4 QT-IRT COMMENTS FOR DOP2

The following is the sponsor's proposed labeling language related to QT.

## 12.2 Pharmacodynamics

### Cardiac Electrophysiology

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill, obscuring the text under the 'Cardiac Electrophysiology' heading.

*QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.*

## 12.2. Pharmacodynamics

### Cardiac Electrophysiology

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill, obscuring the text under the 'Cardiac Electrophysiology' heading.

Thank you for requesting our input into the development of this product under NDA 207953. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cderdcrpqt@fda.hhs.gov](mailto:cderdcrpqt@fda.hhs.gov)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SRIRAM SUBRAMANIAM  
05/15/2015

HONG ZHAO  
05/15/2015  
I concur.

NAM ATIQR RAHMAN  
05/15/2015

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT**

**Office of Clinical Pharmacology**

*NDA or BLA Filing and Review Form*

General Information about the Submission

	Information		Information
NDA/BLA Number	207953	Brand Name	Yondelis
OCP Division (I, II, III, IV, V)	V	Generic Name	Trabectedin
Medical Division	DOP2	Drug Class	Hedgehog inhibitor
OCP Reviewer	Sriram Subramaniam, Ph.D.	Indication(s)	(b) (4)
OCP Team Leader	Hong Zhao, Ph.D.	Dosage Form	Injection, for IV Infusion
Pharmacometrics Reviewer	Sriram Subramaniam, Ph.D. Liang Zhao, Ph.D.	Dosing Regimen	1.5 mg/m <sup>2</sup> as 24 hr IV infusion, every 3 weeks
Date of Submission	November 24, 2014	Route of Administration	Intravenous
Estimated Due Date of OCP Review	April 25, 2015	Sponsor	Janssen
DARRTS Due Date		Priority Classification	Priority
PDUFA Due Date	July 24, 2015	<a href="\\CDSESUB1\evsprod\NDA207953\207953.enx">\\CDSESUB1\evsprod\NDA207953\207953.enx</a>	

*Clin. Pharm. and Biopharm. Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			(b) (4)
Reference Bioanalytical and Analytical Methods	x	12		
<b>I. Clinical Pharmacology</b>				
Mass balance:	x	1		
Isozyme characterization:	x	4		
Active Metabolites	x	2		
Transporters	x	2		
Blood/plasma ratio:	x	1		
Plasma protein binding:	x	2		

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

(b) (4)

<b>Pharmacokinetics (e.g., Phase I) -</b>			
<b>Healthy Volunteers-</b>			
single dose:			
multiple dose:			
<b>Patients-</b>			
single dose:	x	8	
multiple dose:	x	9	
<b>Dose proportionality -</b>	x	12	
fasting / non-fasting single dose:			
fasting / non-fasting multiple dose:			
<b>Drug-drug interaction studies -</b>			
In-vivo effects on primary drug:	x	4	
In-vivo effects on primary drug	x	10	

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

In-vivo effects of primary drug	x	10		(b) (4)
In-vitro:	x	7		
<b>Subpopulation studies -</b>				
Ethnicity:	x	3		
Age: elderly	x	1		
gender:	x	5		
Body weight & size	x	1		
Pediatrics:		Waiver		
Cancer type	x	1		
Renal impairment:	x	1		
Hepatic impairment:	x	1		
<b>PD -</b>				
Phase 1 and/or 2:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	x	3		
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data: rich	x	7		

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

sparse:	x	9		(b) (4)
<b>II. Biopharmaceutics</b>				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
Bio-waiver request based on BCS				
BCS class				
<b>III. Other CPB Studies</b>				
Genotype/phenotype studies	x	3		
Pediatric development plan	x			
Literature References				
Total Number of Studies		40 (Clinical) 14 (In vitro)		

**Highlight** - denotes studies not submitted in the original NDA

(b) (4)

On **initial** review of the NDA/BLA application for filing:

<b>Criteria for Refusal to File (RTF):</b> This OCP checklist applies to NDA, BLA submissions and their supplements					
No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for	x			

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

	each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?				
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
<b>Complete Application</b>					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	x			
	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
<b>Studies and Analyses</b>					
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
7	Are the pediatric exclusivity studies adequately			x	

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT

	designed to demonstrate effectiveness, if the drug is indeed effective?				
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
<b>General</b>					
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.**

All clinical pharmacology information discussed during the pre-NDA meeting held on October 17, 2014, were submitted, except the following.

1. Study report for Study 10045020 (Japanese study) and the related concentration-time and derived pharmacokinetic (PK) parameter datasets as SAS transport files were not provided. Only a synopsis was provided for the study.
2. It was agreed that the study report for the hepatic impairment study (ET743-OVC-1004) would not be included in the NDA. Janssen was asked to provide a description and timeline for post marketing requirements related to this study during the pre-NDA meeting. The requested information was not included in the NDA.

An information request will be sent to Janssen to request these items.

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

Not applicable.

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

An information request needs to be sent to Janssen. We request a response in two weeks.

1. Submit to the NDA a description of the proposed hepatic impairment study as post marketing requirement (PMR), including your proposed timelines for completion of the study and submission of the final study reports, as requested during the pre-NDA meeting held in October 17, 2014.
2. Submit to the NDA the study report for Study 10045020, and the related concentration-time and derived pharmacokinetic (PK) parameter datasets as SAS transport files (\*.xpt) with description of each data item (in a define.pdf file).

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA/SUPPLEMENT**

**Signatures:**

Sriram Subramaniam  
\_\_\_\_\_  
Reviewing Clinical Pharmacologist Date

Hong Zhao  
\_\_\_\_\_  
Team Leader/Supervisor Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SRIRAM SUBRAMANIAM  
01/08/2015

HONG ZHAO  
01/08/2015  
I concur.