Office of Clinical Pharmacology Review

NDA or BLA Number	NDA207953/SDN264
Link to EDR	\\CDSESUB1\evsprod\NDA207953\207953.enx
Submission Date	NDA
Submission Type	*Priority Review*
Brand Name	YONDELIS®
Generic Name	Trabectedin
Dosage Form and Strength	1 mg sterile lyophilized powder
Route of Administration	Intravenous infusion
Proposed Indication	Treatment for unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen
Applicant	Janssen Research and Development, LLC
Associated IND	*IND050286*
OCP Review Team	*Edwin Chiu Yuen Chow, Ph.D.* *Jeanne Fourie Zirkelbach, Ph.D.*

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1. EXECUTIVE SUMMARY

Janssen Research and Development, LLC submit a supplement to NDA207953 in response to a Written Request for pediatric studies of trabectedin for pediatric exclusivity determination (Pediatric Written Request issued on November 7, 2017; Reference ID:4175838).

Trabectedin is an alkylating drug approved for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen. Based on few instances of disease response and disease control observed in trabectedin-treated pediatric subjects with sarcoma across the studies included in the current supplement, an indication for this population is not being requested. The supplement includes proposed language to update Section 8.4 *Pediatric Use* of the US prescribing information to describe the findings from the pediatric studies included in the Pediatric Written Request (PWR).

Pharmacokinetics were characterized in 4 open-label studies (age range: 2 years to 18 years, N=35). Non-compartmental pharmacokinetic (PK) analyses were performed in 30 pediatric patients. Due to the limited sample size and age population, the population pharmacokinetic model was not reviewed. Plasma clearance in pediatric subjects was relatively consistent when corrected for BSA in the dose level range of 1.1 to 1.5 mg/m^2 used in the pediatric studies. Clearance in pediatric patients tended to increase with increasing BSA or age, but remained constant when corrected for BSA. Exposure parameters, dose-normalized to the 1.5 mg/m^2 adult clinical dose, were generally similar between the adult and pediatric populations. The results showed that the PK parameters in pediatric patients (aged 3 to 17 years), normalized to 1.5 mg/m^2 dose, were within the range of values previously observed in adults given the same dose per body surface area.

1.1 Recommendations

This efficacy supplement fulfills the clinical pharmacology components of the WR as summarized in the table below. For labeling recommendations regarding use of trabectedin in pediatric patients, please refer to Section 2.4.

Pediatric Written Request (WR) Component	Sufficiently Supported?	Relevant Language in WR
Pharmacokinetic Endpoints	☒Yes ☐ No Refer to 3.2	Pharmacokinetic data must be appropriately analyzed to obtain relevant pharmacokinetic parameters (for example AUC, Cmax, Clearance, and volume of distribution, etc). The effect of age and body size on the pharmacokinetics of trabectedin in pediatric patients must be evaluated. If appropriate, combine data from the Phase 1 and Phase 2 studies to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

1.2 Post-Marketing Requirements and Commitments

There is no clinical pharmacology requested postmarking requirements (PMRs) or postmarketing commitments (PMCs).

Signatures:

Edwin Chiu Yuen Chow, PhD Reviewer Division of Clinical Pharmacology V	Jeanne Fourie Zirkelbach, PhD Team Leader Division of Clinical Pharmacology V

Cc: OHOP: RPM - **A Zack-Taylor;** MTL - **S Demko**; MO - **A Barone**
DCP-V: Deputy DD - **B Booth;** DD - **A Rahman**

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Refer to package insert of YONDELIS®.

2.2 Dosing and Therapeutic Individualization

The applicant did not propose an indication or a new dosing regimen for pediatrics.

2.2.1 General dosing

This section is not applicable for this NDA.

2.2.2 Therapeutic individualization

This section is not applicable for this NDA.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

Only relevant clinical pharmacology sections are included. The Applicant's proposed labeling change are in BLUE and modifications are made by the Agency in RED.

8 USE IN SPEICIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

For brevity, only QBR questions related to the current submission are addressed below. For additional details, please refer to the original NDA 207953 (SDN1, receipt date of 11/24/2014) and the corresponding clinical pharmacology review in DAARTS (DARRTS date 5/15/2015).

PERTINENT REGULATORY HISTORY

- On December, 4 2000, a formal PWR for trabectedin (known as ecteinascidin) was issued under IND050286. The request was issued to the manufacturer, PharmaMar, requesting that information from Phase 1 and 2 studies be submitted in support of an indication for trabectedin in children for the treatment of refractory or relapsed pediatric malignancies, with at least 1 study specifically in pediatric patients with refractory brain tumors.
- On October 4, 2010, a revised PWR was issued, as the previous PWR dated May 19, 2004 had expired. The PWR was issued to applicant requesting information from Phase 1 and 2 studies in support of an indication to use trabectedin in children for the treatment of soft tissue sarcoma (STS).
- On November 7, 2017, a new original Written Request was issued with a due date of March 31, 2018 replacing the March 15, 2012 Written Request. The original Written Request (March 15, 2012) had expired because the July 31, 2017 Amended Written Request was not issued prior to the date of expiration (March 31, 2017).

3.2 Clinical Pharmacology Questions

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

Table 1 lists the clinical studies included in the application. PK data were obtained in pediatric subjects ranging in age from 2 to 18 years in 2 Phase 1 (ET-A-008-00, ET743-SAR-2004) and 2 Phase 2 studies (ET-B-019-099, ET743-SAR-2005).

Table 1: Clinical Studies Conducted in Pediatric Subjects with Sarcoma

Study	Design	Tumor Type (Enrolled)	Dosing Schedule	No. of Pediatric Subjects (Pediatric Subjects Evaluable for PK)
Phase 1 ET-A-008-00	Non-randomized, open-label, dose-escalation study in children with refractory solid tumors	Osteosarcoma Ewing's sarcoma Wilms Tumor Hepatoblastoma Rhabdomyosarcoma Synovial sarcoma	Trabectedin: q3wk; 3-h regimen Starting dose: 1.1 mg/m^2 Escalation dose: 1.3 mg/m^2	Total=12 (8 PK evaluable) 6 (4 PK evaluable) 6 (4 PK evaluable)
Phase 1 ET743-SAR-2004	Non-randomized, open-label, limited-escalation study in children and adolescents with relapsed or refractory solid tumors	Desmoplastic small round cell Sarcoma NOS Synovial sarcoma Neuroendocrine carcinoma Nasopharyngeal carcinoma Osteosarcoma Ewing's sarcoma Peripheral nerve sheath tumor Brain stem glioma Chondrosarcoma	Trabectedin: q3wk; 24-h regimen Starting dose: 1.1 mg/m^2 Escalation doses: 1.5 mg/m^2 1.7 mg/m^2	Total=12 (5 PK evaluable) 3 (1 PK evaluable) 6 (3 PK evaluable) 3 (1 PK evaluable)
Phase 2 ET-B-019-99	Non-randomized, open-label study to evaluate efficacy (ORR), PK, and safety of trabectedin in subjects with previously treated osteosarcoma	Osteosarcoma	Trabectedin: q3wk; 24-h, 1.5 mg/m^2	Total=13 (9 PK evaluable)
Phase 2 ET-B-023-00	Non-randomized, open-label study to evaluate the efficacy and safety of trabectedin in subjects with previously treated advanced or recurrent sarcoma	Soft tissue sarcoma Osteosarcoma Ewing's sarcoma Rhabdomyosarcoma	Trabectedin: q3wk; 3-h, 1.5 mg/m^2 Starting dose: 1.5 mg/m^2 Starting dose: 1.3 mg/m^2 for subjects with prior high dose methotrexate exposure or high dose therapy requiring blood progenitor therapy	Total=12 subjects (PK not part of study design)
Phase 2 ET743-SAR-2005	Non-randomized, open-label study to evaluate the efficacy, PK, and safety of trabectedin in children with recurrent or refractory rhabdomyosarcoma, Ewing's sarcoma/peripheral PNET, and NRSTS.	Rhabdomyosarcoma Ewing's sarcoma/peripheral PNET Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS)	Trabectedin: q3wk; 24-h regimen 1.3 mg/m^2 1.5 mg/m^2	Total=50 (10 PK evaluable)[a] 8 (0 PK evaluable) 42 (10 PK evaluable)[a]

No.=number; NOS=not otherwise specified; NRSTS=non-rhabdomyosarcoma soft tissue sarcoma; ORR=objective response rate; PK=pharmacokinetic; PNET=primitive neuroectodermal tumors; q3wk=once every 21 days

[a] N=8 in the reanalysis of PK.

Cross reference: Mod5.3.3.3/ET-A-008-00, Mod5.3.3.2/ET743-SAR-2004, NDA207953/0000/Mod5.3.5.4/ET-B-019-99, NDA207953/0000/Mod5.3.5.2/ET-B-023-00, Mod5.3.5.1/ET743-SAR-2005, and Mod5.3.5.3/NCA-PK-Peds

Source: 2.7.3 Summary of Clinical Efficacy, Table 1, Page 10.

- Study ET-A-008-00 is a Phase 1, nonrandomized, open-label, dose-escalation study that evaluated the maximum tolerated dose (MTD), PK, antitumor activity, and safety of trabectedin in pediatric subjects with refractory solid tumors. Twelve pediatric patients (aged 2 to 17 years) were administered trabectedin via a 3 hours intravenous infusion dosed at 1.1 and 1.3 mg/m^2 Q3W. The maximum tolerated dose (MTD) was defined as 1.1 mg/m^2 in this study. The PK sampling time includes pre-dose, and 2, 2.4, 3.5, 4, 27, 51, and 75 hours after the start of infusion. Overall, PK sampling was collected in 12 pediatric patients. The PK descriptive summary of the nnNon-compartmental PK analyses excluded data from 4 patients due to unreliable PK data (suspected infusion blockage or problems). The PK descriptive summary of PK parameters ($AUC_{0\text{-}inf}$, CL, $t_{1/2}$, and V_{ss}) obtained from non-compartmental PK analyses excluded data from an additional 4 patients due to the r^2 adj < 0.80 of terminal phase or AUC_{extrap} > 20%.
- Study ET743-SAR-2004 is a Phase 1, nonrandomized, open-label, limited-escalation study that evaluated the MTD, PK, antitumor activity, and safety of trabectedin in children and adolescents with relapsed or refractory solid tumors. 5 pediatric patients (aged 13 to 16 years) were administered trabectedin via a 24 hour intravenous infusion dosed at 1.1, 1.5 and 1.7 mg/m^2 Q3W. The MTD was defined as 1.5 mg/m^2 in this study. The PK sampling time includes pre-dose, and 4, 8, 23.9, 24.5, 25, 27, 30, 47.75, 48, 95.75, 96, 119.75, 120, 167.75, 168 hours after the start of infusion for the 1.1 and 1.5 mg/m^2 dose group and pre-dose, and 4, 12, 23.9, 34.5, 25, 27, 30, 47.75, 48, 95.75, 96, 119.75, 120, 143.75, and 144 hours after the start of infusion for the 175 mg/m^2 dose group and. Overall, PK sampling was collected in 5 pediatric patients. The PK descriptive summary of the PK parameters ($AUC_{0\text{-}inf}$, CL, $t_{1/2}$, and V_{ss}) obtained from the non-compartmental PK analyses excluded data from 2 patients due to r^2 adj < 0.80 of terminal phase and/or AUC_{extrap} > 20%.
- Study ET-B-019-99 is a Phase 2, nonrandomized, open-label study that evaluated the efficacy (objective response rate), PK, and safety of trabectedin in subjects with previously treated osteosarcoma. Subjects enrolled in this study were to be ≥13 years of age. Nine pediatric patients (aged 12 to 17 years) were administered trabectedin via 24 hours intravenous infusion dosed at 1.5 mg/m^2 Q3W. The PK sampling time includes pre-dose, and 2, 23.5, 24.5, 25, 48, and 72 hours after the start of infusion. Overall, PK sampling was collected in 9 pediatric patients. The PK descriptive summary ofPK parameters ($AUC_{0\text{-}inf}$, CL, $t_{1/2}$, and V_{ss}) obtained from non-compartmental PK analyses excluded data from 2 patients due to r^2 adj < 0.80 of terminal phase and/or AUC_{extrap} > 20%).
- Study ET743-SAR-2005 is a Phase 2, nonrandomized, open-label study that evaluated the efficacy, PK, and safety of trabectedin in pediatric subjects with recurrent or refractory rhabdomyosarcoma, Ewing sarcoma/peripheral primitive neuroectodermal tumors, and non-rhabdomyosarcoma STS. Ten pediatric patients (aged ≥ 5 to 17 years) were administered trabectedin via 24 hours intravenous infusion dosed at 1.5 mg/m^2 Q3W. The PK sampling time includes pre-dose, and 1.5, 8, 23.5, 24.5, 26, 30 72, and 192 hours after the start of infusion. Overall, PK sampling was obtained in 10 pediatric patients, but data from 1 patient were not included in analysis as the patient did not have any demographic or safety data. The PK descriptive summary excluded PK parameters ($AUC_{0\text{-}inf}$, CL, $t_{1/2}$, and V_{ss}) obtained from non-compartmental PK analyses from 6 patients due r^2 adj < 0.80 of terminal phase and/or AUC_{extrap} > 20%.
- There was no PK collection in Study ET-B-023-00.

3.2.2 How is trabectedin measured across studies?

The four pediatric studies with PK information were conducted by different pediatric cancer research groups, with different PK sampling schedules (stated earlier). Two different bioanalytical methods were used across the 4 studies. The bioanalytical method (LC-MS/MS) used in Studies ET-A-008-00 and ET-B-019-99 was developed by the Massachusetts General Hospital Cancer Centre, whereas the method used

Studies ET743-SAR-2004 and ET743-SAR-2005 was developed by Johnson & Johnson. Although, a relevant additive error and higher variability were observed for the LC MS assay used for ET-A-008-00 and ET-B-019-00 when compared to the Slotervaart LC-MS/MS assay, these data were summarized and pooled with data from the other studies by the applicant. The estimates of clearance corrected for BSA were generally comparable across the four studies (see Figure 2), even with differences in blood sampling and assay methodologies.

3.2.3 What is the PK characteristics of the drug?

The PK parameters obtained from non-compartmental analyses across the 4 studies are summarized in Table 2. Due to the differences in infusion time and PK sampling time across the four studies, the PK results from the analyses are interpreted with caution. Overall, no clear differences were observed in individual clearance at dose levels between 1.1 and 1.5 mg/m^2, which suggest the PK to be linear at over this dose range.

Table 2: PK parameters across pediatric studies

Study	ET-A-008-00			ET743-SAR-2004		ET-B-019-99	ET743-SAR-2005
Age:	2 to 16 years			13 to 16 years		12 to 17 years	5 to 18 years
Dose	1.1 mg/m^2; 3-h IV infusion	1.3 mg/m^2; 3-h IV infusion	1.1 mg/m^2; 24-h IV infusion	1.5 mg/m^2; 24-h IV infusion	1.7 mg/m^2; 24-h IV infusion	1.5 mg/m^2; 24-h IV infusion	1.5 mg/m^2; 24-h IV infusion
n	4	4	1	3	1	9	8
C_{max} (ng/mL)	6.57 (3.28)	11.5 (5.00)	0.638	1.19 (0.415)	2.20	1.36 (0.715)	2.53 (2.41)
t_{max} (h)	2.00 (1.98 – 2.08)	2.00 (1.98 – 2.03)	24.05	8.00 (4.03 – 8.00)	12.00	23.43 (1.58 – 23.58)	23.5 (8.00 – 30.00)
$AUC_{0-\tau}$ (ng·h/mL)	26.1 (15.4)	39.9 (16.7)	16.2	26.2 (10.1)	59.2	35.0 (13.2)	48.5 (23.0)[e]
AUC_{∞} (ng·h/mL)	28.1[a]	62.7 (25.7)[b]	28.7	36.5; 60.4[c]	NR[d]	46.0 (14.8)[e]	81.7 (39.6)[b]
CL (L/h/m^2)	39.1[a]	24.2 (12.7)[b]	38.3	24.8; 41.1[c]	NR[d]	36.2 (13.9)[e]	21.0 (8.56)[b]
V_{ss} (L/m^2)	1600[a]	768 (441)[b]	2998	1866; 3304[c]	NR[d]	674 (391)[e]	1111 (743)[b]
$t_{1/2term}$ (h)	49.9[a]	50.9 (14.3)[b]	94.8	83.2; 104.3[c]	NR[d]	24.4 (7.6)[e]	63.1 (11.1)[b]

(mean [SD], t_{max}: median [range])
NR: Not reported; SC: standardized criteria for NCA. Standardized NCA criteria applied to raw data across all 4 studies.
$AUC_{0-\tau}$ where τ= 24h for ET-A-008-00 and τ=48h for ET743-SAR-2004, ET-B-019-99 and ET743-SAR-2005.
[a] n=1, individual value shown
[b] n=3
[c] n=2, individual values shown, separated by semi-colon
[d] Accurate determination of extrapolated parameters not possible as r^2adj <0.80 and/or $\%AUC_{\infty,ex}$ >20%.
[e] n=7

Source: 5.3.5.3 Noncompartmental pharmacokinetics report, Appendix 2, page 45

The dose-normalized PK parameters are summarized in Table 3, taking into account that trabectedin is dose-proportional in adults. In general, the mean clearance ranged from 21.0 L/h/m^2 to 36.2 L/h/m^2 when trabectedin was administered as a 24-hour infusion across Studies ET743-SAR-2004, ET-B-019-99, and ET743-SAR-2005. Trabectedin plasma clearance was also similar (27.9±12.8 L/h/m^2) when the trabectedin was given as a 3-h infusion in Study ET-A-008-00. Estimates of half-lives and V_{ss} varied between studies and are interpreted with caution due to the differences in the sampling schedule ranging from 72 hours to 192 hours after the start of infusion.

Table 3: Mean PK parameters across pediatric studies dose-normalized to 1.5 mg/m^2

	Based on Re-Analysis [SC]			
	ET-A-008-00 (2 to 16 years)	**ET743-SAR-2004 (13 to 16 years)**	**ET-B-019-99 (12 to 17 years)**	**ET743-SAR-2005 (5 to 18 years)**
Parameter	**3-hour infusion**	**24-hour infusion**	**24-hour infusion**	**24-hour infusion**
n	8	5	9	8
t_{max}, h; median (range)	2.00 (1.98 to 2.08)	8.00 (4.03 to 24.05)	23.43 (1.58 to 23.58)	23.5 (8.00 to 30.00)
C_{max}, ng/mL	11.1±5.30	1.27±0.494	1.36±0.715	2.53±2.41
$AUC_{0-\tau}$ ng·h/mL	40.8±19.4	30.6±14.2	35.0±13.2	48.5±23.0 [c]
AUC_{∞}, ng·h/mL	63.9±29.6 [a]	45.4±13.1 [b]	46.0±14.8 [c]	81.7±39.6 [b]
CL, L/h/m^2	27.9±12.8 [a]	34.7±8.72 [b]	36.2±13.9 [c]	21.0±8.56 [b]
V_{ss}, L/m^2	976±550 [a]	2,723±758 [b]	674±391 [c]	1,111±743 [b]
$t_{1/2term}$, h	50.7±11.7 [a]	94.1±10.6 [b]	24.4±7.6 [c]	63.1±11.1 [b]

mean ±SD, t_{max}: median [range]; NR: Not reported; SC: standardized criteria for NCA.

$AUC_{0-\tau}$ where τ= 24h for ET-A-008-00 and τ=48h for ET743-SAR-2004, ET-B-019-99 and ET743-SAR-2005.

a n=4.

b n=3.

c n=7.

Source: 5.3.5.3 Noncompartmental pharmacokinetics report, Table 9, page 31

The PK parameters obtained from the four pediatric studies were also compared to historical adult data reviewed in the original NDA submission as shown in Table 4 and Figure 1. Exposure was similar between pediatric and adult when trabectedin was administered as a 24-hour IV infusion (n=22 in the pooled pediatric population and n=51 for historical adult data). When trabectedin was administered as a 3-hour IV infusion (dose-normalized to a 1.5 mg/m^2 adult clinical dose), the mean exposure (C_{max} and truncated AUC) tended to be higher in the pooled pediatric population (n=8 pediatric subjects) compared to historical adult data (n=74 subjects); however, the range of data showed a substantial overlap between pediatric and adult values. Overall, the data support that trabectedin administered at a dose of 1.5 mg/m^2 as a 24-hour IV infusion every 3 weeks in pediatric subjects results in similar exposure as thesame dosage administered in adults.

Table 4: Pharmacokinetic results of trabectedin dose-normalized to administration of 1.5 mg/m2 trabectedin as a 3 or 24 hours IV infusion in the pediatric and adult population

Pharmacokinetics of trabectedin (mean [SD])	**3-hour IV Infusion**		**24-hour IV Infusion**	
	Pooled Pediatric Data	**Historical Adult Data**	**Pooled Pediatric Data**	**Historical Adult Data**
N	8	74	22	51
C_{max} (ng/mL)	11.1 (5.30)	8.08 (3.33)	1.76 (1.55)	1.79 (0.974)
AUC (ng·h/mL)[a]	40.8 (19.4)	29.4 (12.2)[b]	38.3 (17.7)[c]	32.9 (15.5)

[a] AUC_{0-24h} or AUC_{0-27h} reported for 3-hour infusion, AUC_{0-48h} reported for 24-hour infusion

[b] n=73 for AUC_{0-24h}

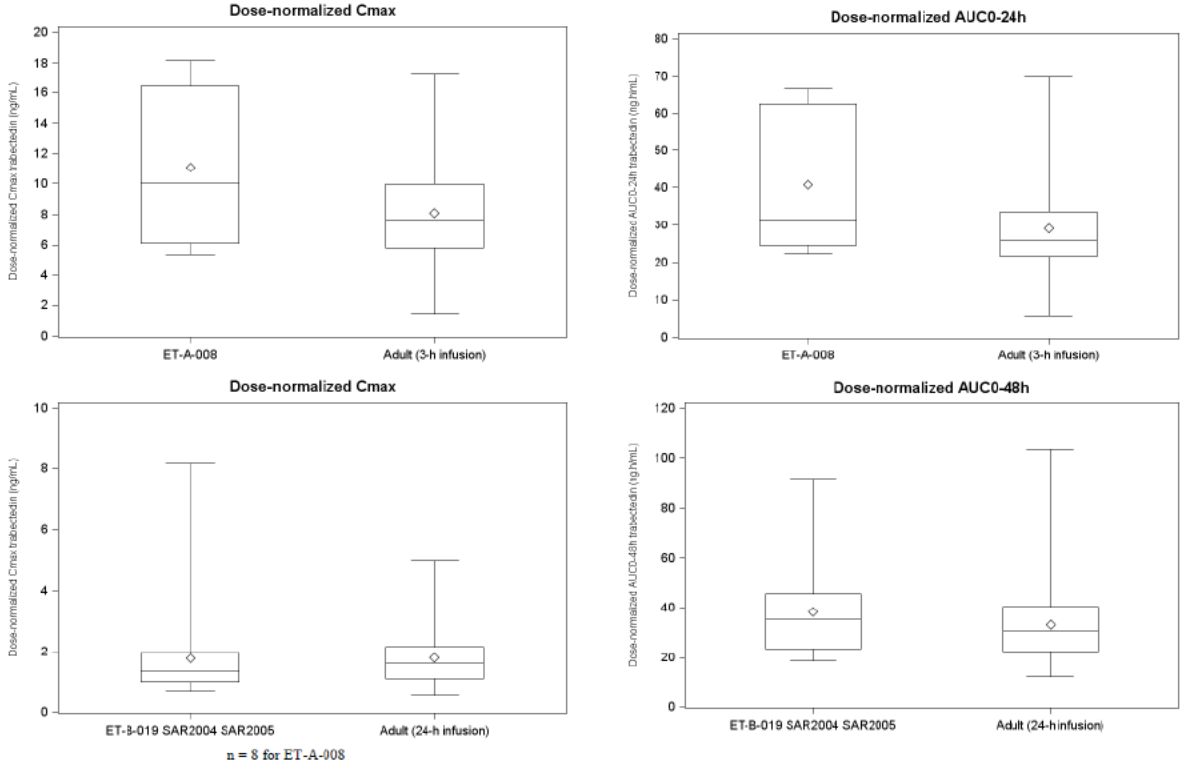
[c] n=21 for AUC_{0-48h}

Pharmacokinetic parameters dose-normalized to a 1.5 mg/m^2 adult clinical dose.

Source: 5.3.5.3 Noncompartmental pharmacokinetics report, Table 11, page 38

Figure 1: Boxplot of dose-normalized (to 1.5 mg/m^2 dose) C_{max} and truncated AUC comparing pediatrics and adult population

(Study ET-B-019-99, ET-A-008-00, ET743-SAR-2004, ET743-SAR-2005: Pharmacokinetics Data Analysis Set)

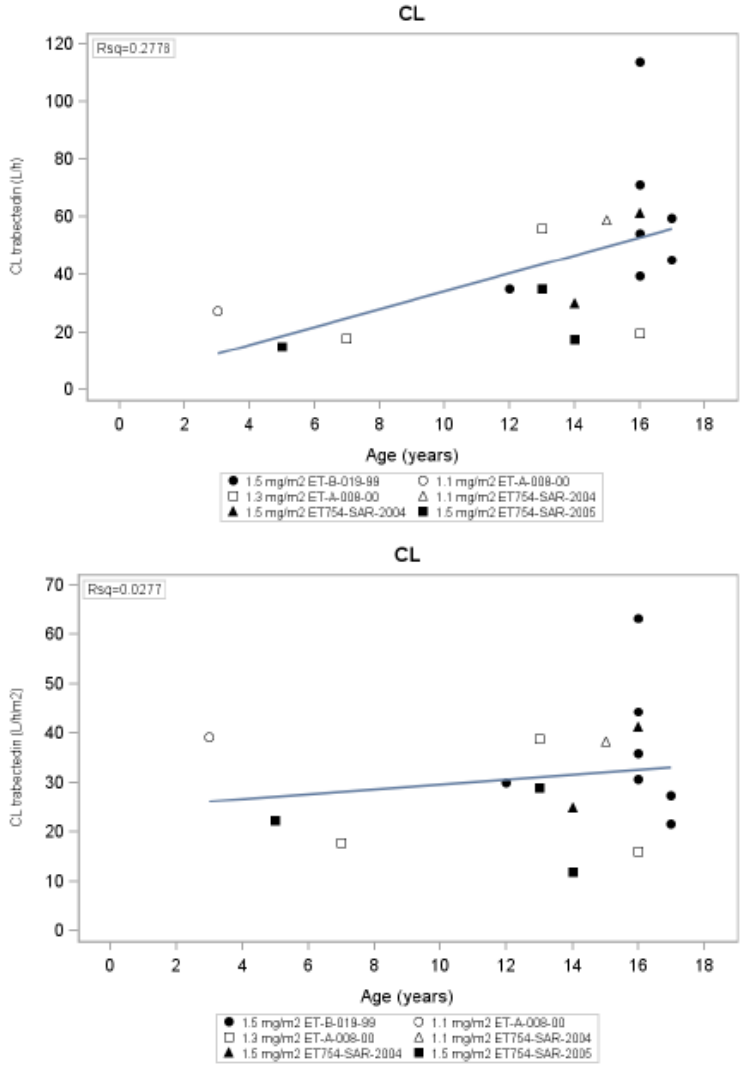


n = 8 for ET-A-008
n = 74 for Adult (3-h infusion)
n = 22 for ET-B-019 SAR2004 SAR2005
n = 51 for Adult (24-h infusion)
Legend: The bottom and top edges of the box indicate the intra-quartile range (the 25th and 75th percentiles). The diamond indicates the mean value. The line inside the box indicates the median value. The whiskers indicate the entire range of values.

Source: 5.3.5.3 Noncompartmental pharmacokinetics report, Figure 9 and 10, pages 39 and 40

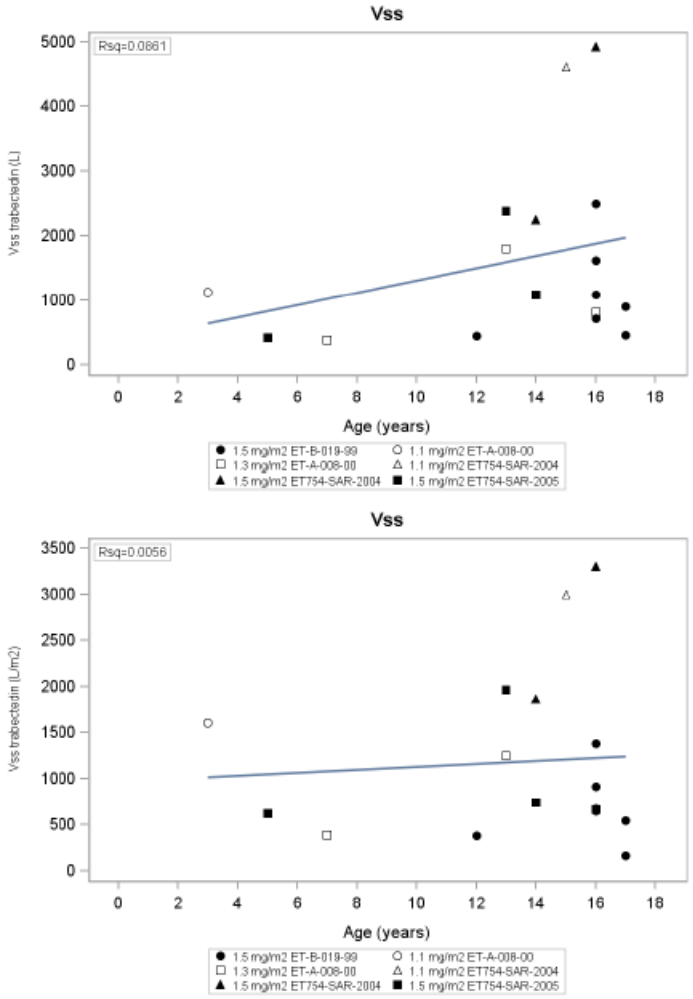
PK parameters such as CL and V_{ss} from the different pediatric studies were also evaluated in the function of BSA and age. The clearance of trabectedin showed a trend towards an increase with increasing BSA and age. When corrected for BSA, no clear difference in clearance was observed and clearance appeared to be independent of the age of the pediatric subject (Figure 2). For V_{ss}, trends versus BSA and age were less evident than for clearance. However, the correlation coefficients were higher for V_{ss} compared with those corrected for BSA (Figure 3). These relationships were generally consistent across studies, despite differences in age population, sampling scheme, bioanalytical method andinfusion duration. It should be noted that the majority of pediatric subjects were adolescent (≥ 12 years), with data available for only 3 children <12 years of age.

Figure 2: Scatterplot of clearance of trabectedin in function of age (in L/h and L/h/m²)



Source: 2.7.2 Summary of Clinical Pharmacology Studies, Figure 8, Page 35.

Figure 3: Scatterplot of V_{ss} of trabectedin in function of age (in L/h and L/h/m²)



Source: 2.7.2 Summary of Clinical Pharmacology Studies, Figure 9, Page 36.

Due to limited number of pediatric patients less than 12 years old, population pharmacokinetic analyses may not be reliable to evaluate the PK in the younger age group. Thus, the population PK model submitted by the applicant for pediatrics was not evaluated.

3.2.4 What are the characteristics of the exposure-response relationship for efficacy?

There was no efficacy observed in this pediatric population (see clinical review for more details), and therefore, no exposure-response analyses were performed for pediatrics in the current submission.

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/s/

EDWIN C CHOW
06/12/2018

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06/12/2018