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ORIGINAL ARTICLE

Population pharmacokinetics of trabectedin in adolescent patients with cancer

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Abstract

Purpose To characterize the trabectedin population pharmacokinetics in children and adolescent patients with cancer and compare it with the trabectedin pharmacokinetics in adults.

Methods Plasma concentrations from ten adolescent and three children with cancer (age range 4.0–17.0 years) treated with trabectedin at doses ranging from 1.1 to 1.7 mg/m^2, administered as a 24-h continuous intravenous infusion every 3 weeks, were available for the analysis. An external model evaluation was performed to verify whether a previously developed adult population pharmacokinetic model was predictive of the pediatric plasma concentrations of trabectedin. The maximum a posteriori estimation of the individual pharmacokinetic parameters for pediatric patients was conducted, after successful completion of the external evaluation step. The relationships between pharmacokinetic parameters and body size were evaluated.

Results External evaluation methods showed no major differences between the adult population and children and adolescent patients of this study. The mean ± standard deviation (SD) of the individual estimated clearance and central volume of distribution in these children/adolescent patients was 36.4 ± 16.1 L/h and 13.2 ± 6.54 L, respectively. These values were similar to the typical values reported for adult patients—37.6 L/h and 13.9 L (for females) and 16.1 L (for males). The median area under the plasma concentration versus time curve (AUC) in children/adolescent patients was 55.1 µg h/L, while in the adult population the median AUC was 61.3 µg h/L, both administered a 1.5 mg/m^2 dose regimen with mean (range) BSA for adults = 1.86 (0.90–2.80) vs children/adolescent patients = 1.49 (0.66–2.54).

Conclusions The adult population pharmacokinetic model adequately described the trabectedin plasma concentrations and its variability in the pediatric population of patients involved in this assessment that mostly comprised adolescents. The trabectedin systemic exposure achieved in this population was comparable (within 12%) to the exposure obtained in adult population when the same dose, expressed in mg/m^2, was administered.

Keywords Trabectedin · Cancer · Pediatric · Nonlinear mixed-effects modeling

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Introduction

Trabectedin is a tetrahydroisoquinoline compound isolated from the marine ascidian *Ecteinascidia turbinata* and currently synthetically produced [1]. The mechanisms of action of trabectedin seem to be unique and are still not completely elucidated. It has been reported that trabectedin interferes with several transcription factors, DNA-binding proteins, and DNA repair pathways resulting in G2-M cell cycle arrest and ultimately apoptosis [2, 3]. Moreover, trabectedin induces a significant downregulation of cytokines, chemokines, and inflammatory and angiogenic mediators, which modify the tumor microenvironment, contributing to the antitumor and antiangiogenic effects of trabectedin [4].

The clinical activity of trabectedin has been demonstrated in several clinical studies in adults [5–7]. In 2007, the European Medicines Agency (EMA) approved trabectedin for the treatment of patients with advanced soft tissue sarcomas following failure of first-line chemotherapy or as first-line treatment for patients unfit for anthracycline-based treatment, and later (2009) trabectedin was also approved in Europe for patients with relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin. In 2015, the US Food and Drug Administration (FDA) gave the marketing approval for trabectedin for the treatment of patients with unresectable or metastatic liposarcoma and leiomyosarcoma who received a prior anthracycline-containing regimen. The approved dose in adults is 1.5 mg/m^2 administered as an intravenous infusion over 24 h every 3 weeks in patients with normal hepatic function [8].

Trabectedin is extensively bound to human plasma proteins, mainly to albumin site I (total protein binding of 94.2%) [9]. The binding of trabectedin to albumin together with its large volume of distribution implies that it is highly unlikely that clinically relevant interactions will occur based on the displacement of trabectedin from plasma proteins. Because of the high association constant of trabectedin to albumin and the low trabectedin concentration relative to albumin, moderate changes in albumin concentration will also not change the fraction of bound trabectedin or elimination processes [9]. Moreover, as trabectedin is an intermediate-to-high hepatic extraction drug, changes in unbound fraction will not have a major impact on elimination processes.

In vitro and in vivo studies suggested that trabectedin is extensively metabolized by the liver. Experiments with human liver microsomes showed that CYP3A4 is the principle enzyme involved in the oxidative metabolism of trabectedin [10]. In a mass balance study of trabectedin in patients with cancer, 32–81% of the total radioactive dose of administered ^{14}C-trabectedin was recovered in the feces [11]. Less than 10% of the radioactivity was excreted in the urine, and less than 1% of the radioactivity corresponded to unchanged trabectedin.

The population pharmacokinetics (PK) of trabectedin in adults were characterized using data from 14 clinical studies conducted in patients with advanced cancer (five phase 1 studies) or soft tissue sarcoma, breast cancer, renal cancer, ovarian cancer, colorectal cancer and melanoma (nine phase 2 studies). A total of 603 patients receiving intravenous trabectedin as monotherapy at doses ranging from 0.024 to 1.8 mg/m^2 (administered as a 1-, 3- or 24-h infusion every 21 days; a 1- or 3-h infusion on days 1, 8 and 15 of a 28-day cycle; or a 1-h infusion daily for 5 consecutive days every 21 days) were included in this population PK analysis [12]. The integration of these phase 1/2 data demonstrated trabectedin linear elimination, dose proportionality up to 1.8 mg/m^2 and time-independent PK. The mean (SD) trabectedin terminal half-life was approximately 180 (61.4) h. Model-based simulations indicated that the median predicted trabectedin plasma concentrations did not differ significantly between cycle 1 and cycle 2 of treatment, suggesting limited accumulation when trabectedin is administered every 3 weeks [12]. Systemic clearance was estimated to be 31.5 L/h with an inter-individual variability [IIV; expressed as coefficient of variation (CV, %)] of 51%. The typical value of CL was 19.2% higher in patients receiving concomitant dexamethasone.

The typical values of the volume of distribution at steady state for male and female patients were 6070 L and 5240 L, respectively. None of the other covariates evaluated (age, body size variables, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, creatinine clearance, albumin, total protein, Eastern Cooperative Oncology Group performance status and presence of liver metastases) were statistically related to trabectedin PK parameters. Co-administration of dexamethasone (inducer of hepatic CYP3A4 enzymes at high dose) as an antiemetic and hepatoprotective agent did not have any meaningful impact on the PK profile of trabectedin [12].

Trabectedin intravenous infusion has been evaluated for the treatment of pediatric patients with solid tumors in two phase 1 studies [13, 14], and three phase 2 studies [15, 16] and results were submitted to the US FDA to address the use of trabectedin in the pediatric population. As part of the study assessments, trabectedin PK were evaluated in the two phase 1 studies [13, 14] and two of the phase 2 studies in pediatric patients [15, 16]. Trabectedin was administered in these studies as a 24-h intravenous infusion every 3 weeks or as a 3-h infusion every 3 weeks. One phase 1 study was conducted to determine the maximum tolerated dose, toxicity profile and PK characteristics of a 24-h continuous intravenous infusion of trabectedin as single agent at an initial starting dose of 1.1 mg/m^2, escalated to 1.5 and 1.7 mg/m^2 in three patient cohorts [13]. This study enrolled children and adolescents with refractory or relapsed solid tumors. The recommended dose of trabectedin determined in this phase 1 study was 1.5 mg/m^2 infused intravenous over 24 h every 21 days, the same to the recommended dose and schedule for adults. Non-compartmental PK analysis approach (NCA) was used to characterize the PK in children and adolescent patients and concluded that the disposition of trabectedin in this population was similar to adults [13]. The second phase 1 study was a nonrandomized, open-label, dose-escalation study that evaluated the maximum tolerated dose, PK, antitumor activity, and safety of trabectedin administered as a 3-h intravenous infusion every 21 days to pediatric patients with refractory solid tumors [14]. The PK were characterized with a mean half-life (± SD) of 43.8 ± 18.4 h, total body

clearance of 28.2 ± 10.5 L/h/m^2, and a steady-state apparent volume of distribution of 959 ± 807 L/m^2 [14].

Additionally, PK were obtained in a phase 2 study conducted in children with recurrent rhabdomyosarcoma, Ewing sarcoma, or non-rhabdomyosarcoma soft tissue sarcomas to determine the toxicity, efficacy and PK of trabectedin given over 24-h continuous intravenous infusion every 3 weeks [16]. The PK of trabectedin were reported in pediatric patients with mean clearance (± SD) of 24.3 ± 16.2 L/h/m^2 and mean half-life of 52.6 ± 18.4 h, similar to those observed in adults [16].

Thus far, no pooled PK analysis of the available trabectedin plasma concentrations from pediatric oncology population has been published. Therefore, the aim of the current analysis was to characterize the PK of trabectedin in pediatric patients with cancer following intravenous administration using a population PK analysis after pooling the data obtained from a phase 1 and a phase 2 study described above [13, 16]. These two studies were selected for the analysis as trabectedin plasma concentrations were determined using the standard assay used for the development of the population PK model in adult population [12]. The other two pediatric studies [14, 15] were excluded because a different bioanalytical method was used. In particular, the cross-validation of this method indicated that it was characterized by a significant analytical bias and a larger variability compared to the standard bioanalytical method.

For the characterization of PK in children and adolescent patients, the previous population PK model developed to describe the PK of trabectedin in adult population following intravenous administration was used.

Methods

Study designs, treatment, sample collection and bioanalytical method

Data were available from two clinical studies conducted in pediatric population, in accordance with the principles for human experimentation as defined in the Declaration of Helsinki [13, 16]. The two studies were approved by the Human Investigational Review Board of each study center and by the health authority of each country. Informed consent was obtained from each parent or guardian after being told about the potential risks and benefits, as well as the investigational nature of the study.

The phase 1, multicenter, open-label, non-randomized, dose-escalation study, planned to evaluate 1.1, 1.5 and 1.7 mg/m^2 of trabectedin, administered as a 24-h intravenous infusion on day 1 of each 21-day cycle [13]. The study included children and adolescents with several types of refractory solid tumors. PK data were collected during cycle 1 prior to infusion and at 4, 8, 16, 23.9, 24.5, 25, 27, 30, 48, 96 120, and 168 h after the start of the infusion at the three dose levels above. All patients were to be pre-treated with dexamethasone 2.5 mg/m^2 intravenously every 12 h × 8 doses beginning 12–24 h prior to the trabectedin infusion.

The phase 2 study was an open-label, multicenter, investigator-initiated study to evaluate the efficacy, safety, and PK of trabectedin in children with histologically documented recurrent or refractory rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, and Ewing sarcoma/peripheral primitive neuroectodermal tumors [16]. Trabectedin was administered as 24-h continuous intravenous infusion every 3 weeks. The study was performed in two parts: a limited dose escalation in Part 1 followed by an efficacy evaluation in Part 2. The dose-escalation phase evaluated three possible trabectedin dose levels, starting at 1.3 mg/m^2 and followed by either 1.5 mg/m^2 or 1.1 mg/m^2, depending on the toxicity observed. PK data were collected during cycle 1 prior to infusion and at 1.5, 4, 8, 23.5 and 26.5 h after the start of the infusion at the dose of 1.5 mg/m^2. Additional samples were collected up to 1 week after dosing. Dexamethasone 2.5 mg/m^2 was to be administered orally on the evening before trabectedin administration (day 0) and every 12 h on days 1, 2, and 3 of each cycle. On day 1, the first dose of dexamethasone was to be given immediately prior to the trabectedin infusion. Patients could receive dexamethasone intravenously if they were unable to take oral dexamethasone [16].

Plasma concentrations of trabectedin in both studies were determined using a bioanalytical high-performance liquid chromatography coupled to mass spectrometry/mass spectrometry (LC/MS/MS) method validated with the stable isotope-labeled internal standard (trabectedin-D3), with a calibration range from 25 to 50,000 pg/mL. In short, trabectedin was isolated from 200 µL aliquots of plasma by solid-phase extraction using Bond Elut Certify 130 mg columns (Varian) and elution with methanol/NH_4OH 25% (98/2 v/v). The extract was evaporated under nitrogen at 40 °C and the residue was reconstituted in 100 µL of methanol + 50 µL of ammonium acetate/formic acid. A 10 µL aliquot of this extract was injected onto the LC–MS/MS. Chromatography was on a 4.6 mm × 50 mm HILIC Silica (Atlantis™) 3 µm column; elution was with ammonium acetate/formic acid in methanol at a flow rate of 1 mL/min. Detection was by tandem mass spectrometry (Sciex AP4000) with Turbo Ionspray operated in the positive mode. Trabectedin and the internal standard were measured at mass transitions *m/z* 744.3 → 495.0 and 747.3 → 496.0, respectively. Both the intra- and inter-batch accuracies were within the limits of 85–115% (80–120% at the lower limit of quantification) with values between 97.6 to 113.6% for intra-batch accuracy and 101.1–108.4% for inter-batch accuracy. The intra- and inter-batch precision was within 15% (20% at the lower limit of

quantification) with values between 0.0% and 5.7% for the intra-batch precision and 1.2% and 4.8% for the inter-batch precision.

Pharmacokinetic analysis

Software

The data were analyzed by a nonlinear mixed-effects modeling approach using NONMEM software (version 7.3; Icon Development Solutions, Ellicot City, MD, USA) [17]. Dataset preparation, exploration, visualization, as well as graphical analysis of NONMEM outputs were conducted using R v.3.3.3 [18].

Pharmacokinetic model

The PK model previously developed by Perez-Ruixo et al. [12] in adult patients was used to assess the similarities in trabectedin PK between pediatric and adult patients. The concentration–time profiles of trabectedin following different dosing schedules and infusion durations in adult patients were well described by a four-compartment PK model with linear elimination (Fig. 1). The PK model consisted of a central plasma compartment and three peripheral compartments. Trabectedin was assumed to have linear and nonlinear distribution from the central compartment to the deep and shallow peripheral compartments, respectively. The model also included a catenary compartment representing a tissue compartment of the shallow peripheral compartment. The model was parameterized in terms of elimination clearance from the central compartment (CL), V_c for the central volume of distribution, and intercompartmental rate constants describing the distribution between the central compartment and peripheral compartments (k_{12}, k_{21}, k_{31}, k_{34}, and k_{43}). The transfer to one of the peripheral compartments was saturable and described by a Michaelis–Menten equation (V_m for maximum rate of distribution and K_m, the Michaelis–Menten constant, corresponding to the concentration that produces half of V_m). Gender and dexamethasone comedication intake were included as covariates in the PK model. Males had a 16.0% larger V_c relative to females. The plasma clearance of trabectedin was 19.2% higher in patients who received concomitant dexamethasone administration compared to those who did not.

The IIV in adults was modeled assuming a lognormal distribution. The same IIV model was used for estimation of the IIV in pediatric population. As only data for one cycle of administration were available for pediatric patients, inter-occasion variability (IOV) from the adult PK model was not included in the current analysis. The residual variability (RV) in adults was evaluated using an additive error model after natural logarithmic transformation of the measured plasma concentrations and model predictions [12] and for pediatric population, the same RV model was used. A mixture model for RV was used in adult population to distinguish between patients whose data were well described by the model versus others less well described by the model. Given the limited number of pediatric patients included in the current analysis and the rich PK profile available for most of the patients, the mixture model was removed from the model and only the random effect of lower magnitude was used for RV in pediatric population. Parameter values for the adult PK model, including IIV and IOV, are presented in Table 1.

External evaluation

The first step for the analysis of pediatric data was to perform an external model evaluation to verify whether

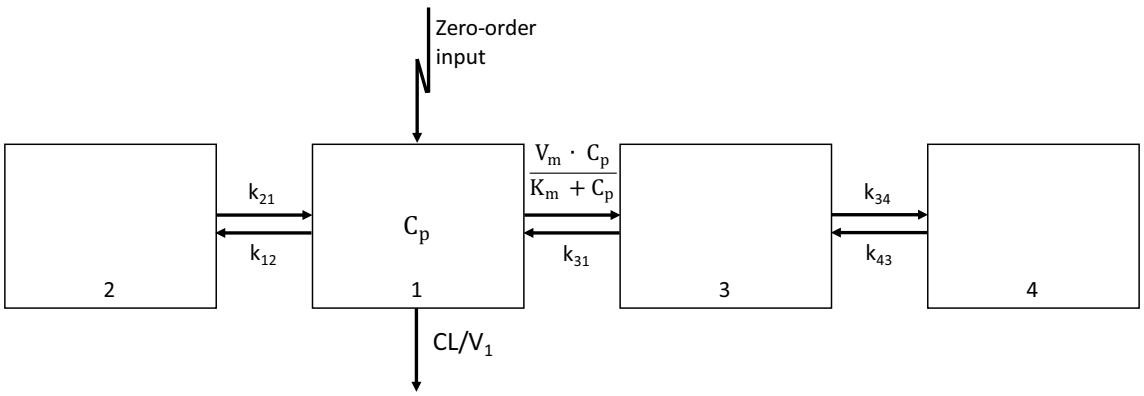

Fig. 1 Schematic representation of the trabectedin pharmacokinetic model for adults [12]. *CL* Clearance for central compartment, C_p plasma drug concentration, K_m Michaelis–Menten constant, corresponding to the concentration that produces half of V_m, k_{xy} intercompartmental rate constant from compartment x to compartment y, V_m volume of maximum rate of distribution, V_1 volume of the central compartment

Table 1 Final parameter estimates and standard errors for adult population pharmacokinetic model [9]

Pharmacokinetic parameter	Typical value		Inter-individual variability (%CV)		Inter-occasion variability (%CV)	
	Final estimate	% SEM	Final estimate	% SEM	Final estimate	% SEM
V_c (L)	13.9	7.8	34.06	17.40	29.72	21.60
Additive increase on Vc for males[a]	2.22	31.6	–	–	–	–
CL (L/h)	31.5	7.6	50.99	13.10	27.80	24.50
Additive increase on CL for taking dexamethasone[b]	6.05	34.4	–	–	–	–
Additive increase on CL for unknown dexamethasone status	4.60	54.1	–	–	–	–
k_{12} (h^{-1})	4.04	8.0	38.99	20.70	27.13	27.90
k_{21} (h^{-1})	0.0115	7.9	–	–	–	–
V_m (h^{-1})	3420	7.8	–	–	–	–
K_m (ng/mL)	557	Fixed	–	–	–	–
k_{31} (h^{-1})	1.03	7.1	28.64	32.90	–	–
k_{34} (h^{-1})	0.497	4.6	–	–	–	–
k_{43} (h^{-1})	0.156	6.5	–	–	–	–
RV fraction	0.634	5.6				
RV—subpopulation 1 (SD)	0.18	10.3	–	–	–	–
RV—subpopulation 2 (SD)	0.53	13.3	–	–	–	–

CL apparent total clearance, *CV* coefficient of variation *kxy*, intercompartmental rate constant from compartment *x* to compartment *y*, *RV* residual variability, *SD* standard deviation, *SEM* standard error of the mean, V_c volume of distribution of the central compartment

[a]Relative increase on Vc is approximately 16.0%. TVVc = 13.9 + (1 − SEXF) × 2.22 (SEXF = 0 for males)

[b]Relative increase on CL is approximately 19.2%. TVCL = 31.5 + DXM1 × 6.05 + DXM2 × 4.60 (DXM1 = 1 for patients taking dexamethasone. Otherwise DXM1 = 0; DXM2 = 1 for patients with unknown dexamethasone status. Otherwise DXM2 = 0)

the adult population PK model previously developed was predictive of the pediatric plasma concentrations of trabectedin. The adult population PK model developed from the original dataset was used to predict the trabectedin plasma concentrations in the validation dataset for pediatric patients [19]. For this purpose, the following tools were used:

1. *Visual Predictive Check* (*VPC*) The VPC was performed for visual comparison between distributions of simulated data using the currently available adult population PK model and the pediatric dataset [20]. A total of 500 replicates were generated and used for each analysis. Relative standard error of the adult parameter estimates was not considered in this analysis.
2. *Numerical Predictive Check* (*NPC*) Based on the parameter estimates for adult population, 500 replicates of the pediatric dataset were simulated. The NPC was performed on the mean, the percentile (25th, 50th and 75th), the SD and the CV of the exposure parameter area under the plasma concentration versus time curve (AUC), calculated as dose/clearance. These metrics reflect the central tendency and variability in the observed data in the analysis dataset. Therefore, these statistics were computed for each replicate, and then summarized across replicates and compared with the actual values observed in the pediatric dataset [20, 21].
3. *Goodness-of-fit plots* A maximum a posteriori estimation, using the population PK model for adults previously developed as prior information, was used to estimate the individual PK parameters in pediatric patients. This analysis was conducted using the MAXEVAL = 0 option in NONMEM. The goodness-of-fit plots were graphically assessed by the examination of scatterplots of observed trabectedin plasma concentrations versus population/individual predicted concentrations.

Estimation of pharmacokinetic parameters in pediatric patients

As the external validation step was successful, the adult PK model was used to get estimates of the individual Bayesian PK parameters of trabectedin in the pediatric patients using MAXEVAL = 0 option in NONMEM.

Results

Population pharmacokinetic sampling dataset

A total of 129 trabectedin plasma concentration samples were available for the PK analysis from 13 pediatric patients (5 from the phase 1 study and 8 from the phase 2 study). Summary statistics for baseline characteristics in pediatric patients are presented in Table 2. Overall the dataset included three children (23.1%), eight adolescents (61.5%) and two patients (15.4%) 17 years of age. The median age of children was 11 years (range 4–12) while for adolescents was 13.5 years (range 13–15). The median body weight was 26.3 kg (range 15.7–31.5 kg) for children and 51.4 kg (range 34.6–74.9 kg) for adolescents. For the two 17-year-old patients, the median body weight was 95.9 kg (47.4 and 144.3 kg).

Table 2 Summary of continuous and categorical covariates on the children and adolescent patient population

Patient characteristics (units)	Value ($N = 13$)	Missing covariates[a]
Age (years)	13.0 (4.0–17.0)	0 (0)
Body weight (kg)	47.4 (15.7–144.3)	0 (0)
Height (cm)	161.8 (101.7–177.5)	0 (0)
Body surface area (m^2)	1.49 (0.66–2.54)	0 (0)
Serum creatinine (mg/dL)	0.58 (0.38–0.70)	8 (61.5)
Creatinine clearance (mL/min/1.73 m^2)[b]	113.2 (86.6–177.7)	8 (61.5)
Lean body mass (kg)	38.1 (13.3–74.1)	0 (0)
Body mass index (kg/m^2)	17.6 (14.0–45.8)	0 (0)
Albumin (g/L)	0.36 (0.25–0.39)	8 (61.5)
Aspartate aminotransferase (U/L)	–	13 (100)
Alanine aminotransferase (U/L)	–	13 (100)
Alkaline phosphatase (U/L)	133.0 (63.0–597.0)	0 (0)
Total bilirubin (μmol/L)	8.55 (5.13–12.0)	8 (61.5)
Total protein (g/L)	0.63 (0.61–0.71)	8 (61.5)
Gamma glutamyltransferase (U/L)	–	13 (100)
Lactate dehydrogenase (U/L)	141 (130–161)	9 (69.2)
Sex		0 (0)
Male	4 (30.8)	
Female	9 (69.2)	
Race		0 (0)
White, not Hispanic or Latino	6 (46.2)	
Black	2 (15.4)	
White, Hispanic or Latino	2 (15.4)	
Others	3 (23.1)	
CYP3A4 inducers		8 (61.5)
Not taken	–	
Taken	5 (38.5)	
CYP3A4 inhibitors		8 (61.5)
Not taken	4 (30.8)	
Taken	1 (7.69)	
Liver metastases	–	13 (100)
Dexamethasone comedication		0 (0)
Not taken	0 (0.00)	
Taken	13 (100.0)	

Continuous variables were expressed as median (range), whereas categorical variables are expressed as counts (%)

[a]Missing covariates were expressed as number of patients (percentage) in the dataset with missing values

[b]Creatinine clearance was calculated using the Schwartz formula [27]

External evaluation

The time course of trabectedin plasma concentrations after intravenous infusion over 24 h is shown in Fig. 2a. After reaching a maximum plasma concentration (C_{max}) of around 1 ng/mL, concentrations declined following a three-compartment model, consistent with the pattern observed in adult patients [12]. Findings from the VPC, NPC and goodness-of-fit plots confirmed the ability of the adult population PK model to describe the time course of trabectedin plasma concentrations and its variability in children and adolescent patients with several types of cancer.

In the VPC (Fig. 2a), with 129 trabectedin plasma concentrations in the dataset, it was expected that 10% of the samples (~ 13) would be outside of the 90% prediction interval. In total, 13 plasma concentrations were beyond the 90% prediction interval, thus confirming the capacity of the adult PK model to describe the data in children and adolescent patients involved in this assessment, including its variability. Furthermore, in the NPC (Fig. 2b), the AUC metrics (25th,

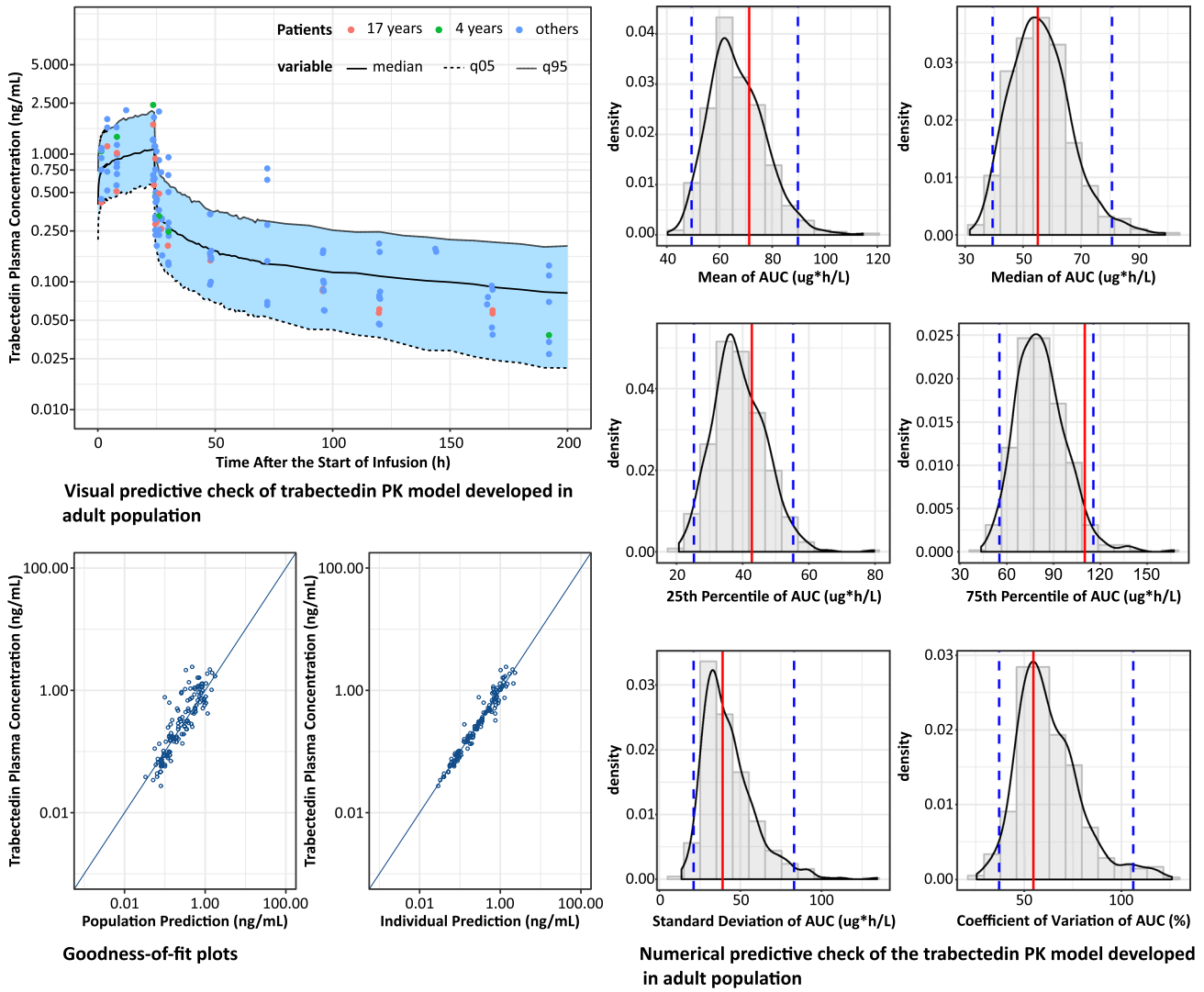

Fig. 2 External evaluation of the trabectedin population pharmacokinetic model developed in adult population. **a** The solid black line represents the median of 50th percentile and the dashed black lines represent the 5th and 95th percentiles, respectively. The blue shaded area represents the 90% prediction interval for the corresponding adult model-based predicted percentiles computed for each bin across time and replicates. The green filled circles represent the youngest patient (4 years of age, dose 1.5 mg/m^2) included in the dataset while the orange filled circles represent the oldest patients (17 years of age, dose 1.5 mg/m^2) and showed that data were contained within the PI. **b** The gray shaded area represents the histograms of the 500 replicates of the simulated AUC using the previous adult pharmacokinetic model. The vertical dashed blue lines represent the 95% CI of the simulated AUC while the vertical solid red line represents the observed AUC values (derived from individual predicted CL) in the pediatric population included in this analysis. **c** Observations plotted against population predicted concentrations (left panel) and against individual predicted concentrations (right panel). The solid line is the identity line

50th and 75th percentiles, the SD and CV) of trabectedin exposure in these children and adolescent patients were contained inside the corresponding 95% CI of the simulated AUC metrics confirming the appropriateness of the adult model in predicting PK in children and adolescents. In addition, the goodness-of-fit plots (Fig. 2c) showed a random normal scatter around the identity line indicating the absence of systematic bias for population and individual predictions, thus illustrating good predictive performance.

Population pharmacokinetic parameters

As the results of the external evaluation showed that the previously developed PK model of trabectedin in the adult population adequately described the PK in pediatric patients, the adult PK model was used to derive estimates of the individual PK parameters of trabectedin in these children and adolescent patients. In Table 3, estimates of the individual PK parameter for each patient and summary statistics are displayed.

The mean ± SD of the individual estimated clearance in children and adolescent patients was 45.1 ± 19.0 L/h/1.73 m^2 (i.e., 26.1 L/h/m^2). The individual trabectedin clearance estimates for each pediatric patient included in the present analysis normalized for a typical body surface area value in adults of 1.73 m^2 were plotted versus age (upper panel) or body surface area (lower panel) (Fig. 3). These plots provide evidence that PK of trabectedin in children and adolescent patients are similar to the PK of trabectedin in adults, and that further dose adjustment is not needed to achieve the same exposure as in the adult population when pediatric patients are dosed according to the body surface area.

Discussion

Collection of sizeable PK data in pediatric patients is often challenging due to ethical and logistic constraints [22]. Dosing regimens in pediatric patients are commonly derived empirically from adult doses using linear extrapolation based on age or body weight that may preclude the influence of nonlinear developmental factors and clinical conditions that are known to greatly impact PK [23, 24]. Population PK models are advanced tools that integrate Bayesian forecasting and nonlinear mixed-effects modeling approaches and improve empirical dose selections by involving clinical study simulations and evaluation of drug disposition under specific clinical conditions. This approach provides valuable information on sources of drug exposure variability that influence the efficacy and safety of a drug and have relevant implications in clinical practice. Trabectedin is an important therapeutic option for children with recurrent malignant sarcomas that are associated with dismal post-relapse survival rate of < 25% [25]. However, there are limited data characterizing the disposition of trabectedin in pediatric patients.

A population PK approach was used to characterize the trabectedin PK in children and adolescents with several types of refractory solid tumors or recurrent or refractory rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, and Ewing sarcoma/peripheral primitive neuroectodermal tumors. Due to the complexity of trabectedin disposition, the limited sample size of the patients included in these pediatric studies, and the sparse sampling obtained in pediatric patients, an external validation based on the adult PK model for trabectedin was used to describe the pediatric data and understand the similarities in trabectedin PK between pediatrics and adults. Three different and complementary tools (VPC, NPC, and goodness-of-fit) were used for this purpose. Overall, there were no major differences in the PK of trabectedin between adult and children/adolescent patient population involved in this assessment, which justified the use of the adult PK model to determine the individual PK parameters in the pediatric patients and, therefore, the exposure in this special population.

A four-compartment PK model was suitable to adequately describe the time course of trabectedin plasma concentrations in pediatric patients following 24-h intravenous infusion. The model included linear elimination, linear and nonlinear distribution to the deep and shallow peripheral compartments, respectively, and a catenary compartment representing a tissue compartment of the shallow peripheral compartment.

The PK parameters estimated for children and adolescent patients were similar to those obtained for adults and in the previous pediatric NCA [13, 14]. Thereby, for female and male patients included in the present analysis, the mean (SD) of V_c were 11.8 (4.0) L and 16.5 (10.3) L, respectively, close to the typical adult values (13.9 L and 16.1 L, respectively). The mean (SD) of the individual estimated clearance in children and adolescent patients was 36.4 (16.1) L/h similar to the value reported in adult patients (37.6 L/h). When normalized by body surface area, systemic clearance of trabectedin in children and adolescent patients from the current analysis (mean (SD) 45.1 (19.0) L/h/1.73 m^2] was within 25% of the previously reported values in adult patients receiving concomitant dexamethasone (estimate from final PK model in adults: 36.09 L/h/1.73 m^2). Moreover, the median of the AUC (normalized for a 1.5 mg/m^2 dose) determined in the children/adolescent patient population included in this analysis was determined to be 55.1 µg h/L, which is generally comparable (within 12%) to that obtained in adult population using the same dosing regimen (61.3 µg h/L) and also with those obtained after NCA PK analysis [26].

Table 3 Individual parameter estimates for children and adolescent patients

Patient #/sex	Dose (μg)	Age (years)	BSA (m^2)	Individual pharmacokinetic parameters									
				CL (L/h)	CL (L/h/1.73 m^2)	V_c (L)	V_c (L/1.73 m^2)	V_{ss} (L)	V_{ss} (L/1.73 m^2)	k_{12} (h^{-1})	k_{31} (h^{-1})	AUC (μg h/L)	AUC[a] (μg h/L)
1/M	1700	15	1.55	54.73	60.08	14.16	15.80	6617	7385	4.55	0.98	31.06	42.36
2/F	2200	17	1.48	51.40	48.23	13.57	15.86	6347	7419	4.52	0.82	42.80	42.80
3/F	2600	13	1.70	47.39	45.74	17.40	17.70	6979	7102	3.94	0.91	54.87	54.87
4/F	1800	14	1.20	31.73	26.95	7.08	10.21	3168	4567	3.51	1.36	56.73	56.73
5/F	3100	15	1.81	28.20	22.56	11.44	10.93	3598	3439	2.60	1.07	109.95	97.01
6/F	1700	12	1.14	14.87	51.89	9.92	15.06	3201	4858	2.54	0.44	114.35	114.35
7/F	1000	4	0.66	19.80	75.88	4.55	11.94	2017	5288	2.56	1.36	50.51	50.51
8/F	2400	13	1.58	69.30	38.80	12.54	13.73	5058	5538	3.71	1.03	34.63	34.63
10/M	2400	15	1.62	36.34	70.27	11.32	12.09	8739	9332	7.85	1.40	66.05	66.05
11/M	1500	11	1.02	41.43	20.03	8.82	14.97	3678	6238	3.48	1.19	36.20	36.20
12/M	4000	17	2.54	29.41	18.53	31.66	21.56	9896	6741	3.22	0.92	136.03	136.03
13/F	2200	13	1.49	15.96	46.34	13.99	16.24	2754	3197	1.43	0.66	137.88	137.88
14/F	1800	13	1.22	32.68	60.08	15.37	21.80	4971	7050	2.96	0.90	55.08	55.08
Mean	2184	13.2	1.49	36.40	45.11	13.22	15.22	5156	6012	3.61	1.00	71.24	71.12
Median	2200	13.0	1.46	32.68	46.34	12.54	15.06	4971	6238	3.48	0.98	55.08	55.08
Minimum	1000	4.0	0.66	14.87	18.53	4.55	10.21	2017	3197	1.43	0.44	31.06	34.63
Maximum	4000	17.0	2.54	69.30	75.88	31.66	21.80	9896	9332	7.85	1.39	137.88	137.88
SD	765.77	3.30	0.45	16.07	19.00	6.54	3.63	2419	1743	1.54	0.28	38.93	37.16
CV (%)	35.05	24.9	30.9	44.14	42.12	49.52	23.83	46.92	28.99	42.65	27.93	54.64	52.25

k_{21}, V_m, K_m, k_{34}, and k_{43} were fixed to the values obtained in the adult population PK model, i.e., 0.0115 h^{-1}, 3420 h^{-1}, 557 μg, 0.497 h^{-1} and 0.156 h^{-1}, respectively [12]

BSA body surface area, *Cl* apparent total clearance, *CV* coefficient of variation, *kxy* intercompartmental rate constant from compartment *x* to compartment *y*, *SD* standard deviation, V_c volume of distribution of the central compartment, V_{ss} volume of distribution at steady-state

[a]AUC dose normalized for a 1.5 mg/m^2 dose

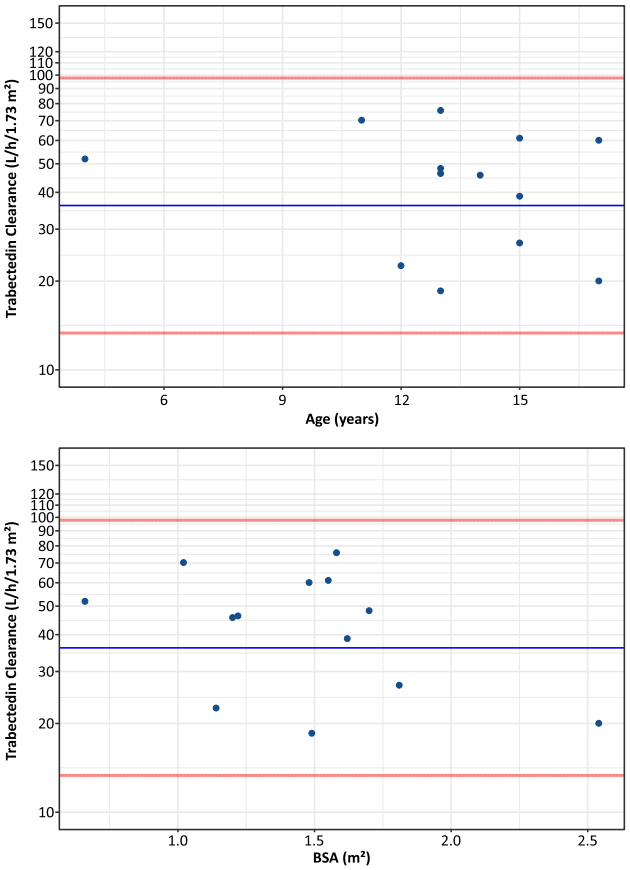

Fig. 3 Individual trabectedin normalized clearance estimates obtained using the population model plotted against age (upper panel) or body surface area (lower panel) of the children and adolescent patients. The filled circles represent the individual normalized clearance estimates. The horizontal blue line represents the normalized population clearance reported for adults and the red dashed lines represent the 95% prediction interval. *BSA* body surface area

Conclusions

The previously developed adult population PK model well predicts the trabectedin plasma concentrations and its variability in the pediatric population of patients involved in this assessment that mostly comprised adolescents. Based on these data, there is no relevant difference in trabectedin PK parameters between adult and pediatric populations ranging from 4 to 17 years of age when normalized based on the body surface area. Consequently, the trabectedin systemic exposure achieved in children and adolescent patients is comparable to the exposure obtained in adult population when the same dose, expressed in mg/m^2, is administered. Thus, the approved adult dose of 1.5 mg/m^2 dose regimen is expected to provide similar exposure when administered in children and adolescent patients with refractory cancers.

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Compliance with ethical standards

Conflict of interest IP is an employee of Janssen-Cilag, Italy; JJPR and VH are employees of Janssen Pharmaceutica NV, Belgium; DO and MG are employees of Janssen Research and Development, LLC, USA (parent company Johnson and Johnson). BV received fees from Janssen as a consultant on this analysis. EF was a government employee at the time of the clinical trial and is currently a faculty member at the Perelman School of Medicine at the University of Pennsylvania, she received no funding from Janssen Pharmaceutica or Johnson and Johnson for conduct of the clinical trial or preparation of this manuscript.

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