SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Active Ingredient(s)	JNJ-17027907; R279741 (Trabectedin)

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 9 December 2015

Prepared by: Janssen Research & Development, LLC

Protocol No.: ET743-OVC-1004

Title of Study: An Open-Label, Multicenter, Pharmacokinetic Study of Trabectedin in Subjects with Advanced Malignancies and Hepatic Dysfunction

EudraCT Number: 2010-022719-21

NCT No.: NCT01273493

Clinical Registry No.: CR017542

Principal Investigator: [redacted], MD PhD

Study Center(s): This study was conducted at 7 sites in the US (3), Belgium (2), and Spain (2).

Publication (Reference): None

Study Period: 28 October 2010 to 29 April 2014; Database lock: 21 April 2015.

Phase of Development: 1/2a

Objectives: The primary objective of this study was to characterize the pharmacokinetics (PK) of trabectedin in subjects with advanced malignancies and hepatic dysfunction. The secondary objectives of this study were to assess survival and the safety of trabectedin when administered in subjects with hepatic dysfunction.

Methodology: This was an open-label, multicenter, single-dose, non-randomized study of trabectedin in 2 groups of subjects with advanced malignancies. One group of subjects had hepatic dysfunction, and the other group of subjects did not have hepatic dysfunction (the control group). The study included a screening phase (within 14 days prior to dosing), a treatment phase (a single-dose of trabectedin on Day 1), and a 30-day follow-up period following dosing. On Day 1, all subjects were pretreated with 20 mg of IV dexamethasone sodium phosphate (or equivalent) 30 minutes prior to the infusion of trabectedin. The dose of trabectedin administered to control subjects was 1.3 mg/m^2 (Initial Dose Level). The initial dose level of trabectedin for the hepatic dysfunction group was 0.58 mg/m^2 (Initial Dose Level, with the first 3 hepatic dysfunction subjects enrolled sequentially with at least 3 weeks separating dosing for each subject). The trabectedin dose in the hepatic dysfunction group was escalated or reduced using a "3+3" strategy. Decisions on dose escalation or reduction were made by the Study Evaluation Team (SET) which consisted of independent experts, the study principal investigator, the medical monitor, and the sponsor's clinical pharmacologist(s). No dose escalations above 0.9 mg/m^2 and no reductions below 0.3 mg/m^2 were to be permitted for subjects with hepatic dysfunction. Once the dose of trabectedin was

reduced from a particular dose level, no further escalation to that dose in subsequently enrolled subjects was permitted.

Study procedures, including adverse event (AE) assessments, physical exams, vital signs, and electrocardiograms (ECGs) were conducted according to the Time and Events Schedule. Pharmacokinetic sampling was performed prior to dosing on Day 1 and at 0.5, 1.5, 2.8, 3.5, 4, 5, 8, 24, 48, 72, 120, and 168 hours postdose. The PK data were used to inform the dose escalation or reduction decisions. End-of-study assessments were performed at the 30 day follow-up visit (Day 31). Subjects who completed the treatment phase (through Day 31, including the PK sampling through Day 8), and who in the opinion of the investigator could derive further clinical benefit, could have continued treatment with trabectedin in the optional extension phase (OEP). The dose and schedule of trabectedin in the OEP was modified by the treating physician, as appropriate for the type of malignancy being treated. In the OEP, all serious adverse events (SAEs) were to be collected until 30 days after the last dose of trabectedin. Beyond Day 31, only new AEs or SAEs were reported in the source documentation if deemed related to trabectedin. No additional data, except survival data, were reported in the electronic case report form after Day 31. Due to enrolment challenges with the hepatic dysfunction group, the Sponsor terminated the study early (28 January 2015).

Number of Subjects (planned and analyzed): Twenty-two subjects were planned to be enrolled so that 18 subjects (9 subjects with hepatic dysfunction and 9 subjects in the control group) completed the study. Fifteen subjects were enrolled in the study (9 subjects in the control group and 6 subjects in the hepatic dysfunction group). All 15 subjects were evaluated for safety and PK analysis.

Diagnosis and Main Criteria for Inclusion: Men or women, ≥18 years of age, with locally advanced or metastatic disease (ie, any solid tumor except hepatocellular carcinoma) were included. Subjects must have had relapsed or progressive disease following standard-of-care treatment with chemotherapy prior to enrolment, or were intolerant to prior standard-of-care treatment with chemotherapy. Subjects in the hepatic dysfunction group were selected based on baseline total serum bilirubin >1.5 to ≤3 times the upper limit of normal and serum AST and ALT <8 times the upper limit of normal. At screening, subjects were to have an Eastern Cooperative Oncology Group performance (ECOG) status of ≤2. Subjects who had previously been treated with trabectedin were not eligible for enrolment.

Test Product, Dose and Mode of Administration, Batch No.: Trabectedin was supplied as a white to off-white powder for reconstitution, dilution, and IV infusion. Each vial of trabectedin for injection was a single use vial, and it contained 1.0 mg of sterile lyophilized trabectedin. Trabectedin was reconstituted, diluted, and administered as a 3-hour IV infusion. The 9 control subjects were administered a single dose of trabectedin 1.3 mg/m^2; 3 subjects with hepatic dysfunction were administered 0.58 mg/m^2 trabectedin, and 3 subjects with hepatic dysfunction were enrolled at the increased dose of 0.9 mg/m^2 trabectedin. The supply of trabectedin used in this study is provided in the table below.

	Lot Numbers/Packaging Batch Numbers	Expiration dates
1.0 mg vial	8LZS02Q_2/4363155, 9FZS05P_1/4364092, AGZSG01/4364547, AGZSG01/4365270, AGZSG01/4365271, BEZUB00/4366385, BEZUB00/4367865, BEZUB00/4367863, BEZUB00/4367864, BKZS000/4367460, BKZS000/4367439, BKZS000/4367438, CJZS100/4369180, DDZSC00/4370017, DDZSC00/4370016	December 2011, June 2012, June 2013, June 2013, June 2013, April 2014, April 2014, April 2014, April 2014, October 2014, October 2014, October 2014, October 2014, September 2015, March 2016, March 2016, respectively

All subjects received 20 mg of IV dexamethasone sodium phosphate (or equivalent) 30 minutes prior to the infusion of trabectedin. Commercially available dexamethasone sodium phosphate for injection (or equivalent) was supplied by the study centers.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: Subjects received a single dose of trabectedin on Day 1. The total study duration (assuming a screening period of 14 days) was approximately 44 days. The duration of the OEP varied by subject, as treatment with trabectedin continued as long as he/she derived clinical benefit (ie, until there was clear evidence of disease progression or unacceptable toxicity, as judged by the investigator).

Criteria for Evaluation:

The following plasma trabectedin PK parameters were estimated for each subject: maximum plasma concentration (C_{max}), time to reach the maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve (AUC), apparent terminal elimination half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_z). Safety was evaluated by assessment of AEs, clinical laboratory tests (hematology and chemistry), vital sign measurements (blood pressure, temperature, and pulse), physical examination, and 12-lead ECGs. Subject survival was assessed.

Statistical Methods: The planned sample size of 18 subjects was based upon clinical considerations. A 90% 2-sided confidence interval (CI) was used to estimate the magnitude of the effect of hepatic impairment and aid in the interpretation that no effect of hepatic impairment was present if the 90% CI for the ratios of the log-transformed AUCs and C_{max} values of the test to reference fell within 80% to 125% ranges. Descriptive statistics (mean, standard deviation, median, minimum, maximum) were performed for age, body mass index, weight and height. Sex and race were tabulated.

Pharmacokinetics: All subjects with sufficient and interpretable data available for PK parameter estimations of trabectedin were considered PK-evaluable and were included in the PK analysis. Maximum plasma concentration and AUC were dose normalized for between-group comparisons. The plasma concentrations of trabectedin at each time point, PK parameters, and plasma protein binding were summarized by subject group with mean, median, standard deviation, minimum value, maximum value, and coefficient of variation. A mixed effects model with 1 of the estimated PK parameters of interest as the dependent variable, subject group as the fixed effect, and subject as a random effect was used to estimate the least squares means and intra-subject variability. For the formal statistical analyses, the endpoints AUC_{∞}, AUC_{last}, AUC_{48}, and C_{max} were log-transformed and analyzed using a general linear model. Hepatic dysfunction and control group were included in the model as a fixed effect. The contrast was computed between each test group and control group and a 90% 2-sided CI were formed. The difference and its CIs were then transformed back to the original scale to give the ratio of the geometric means for the 2 groups together with the corresponding 90% CI. The effect of hepatic impairment was estimated separately for selected PK parameters (AUC and C_{max}) using the ratio and its 90% CI. The relationship between PK parameters and hepatic function test (prothrombin time, bilirubin levels, albumin levels, and Child's Pugh score) at baseline was reported using Pearson's correlation. Descriptive statistics as well as the correlation coefficients and p-values were presented by each PK parameter.

Safety: The safety of trabectedin was evaluated from the signing of the informed consent through end-of-study/early withdrawal assessments by examining the incidence, severity, relationship to study medication, type of AEs, clinical laboratory test results, physical examination, vital sign measurements, and 12-lead ECGs. Data were summarized using descriptive statistics.

Efficacy: Survival data from the date of the first dose of trabectedin to the date of death due to any cause were summarized by treatment interval from 0 to 6 months, >6 to 12 months, >12 to 18 months, >18 to 24 months, >24 to 30 months, >30 to 36 months and >36 months. The number of subjects alive at the start of each interval, the number of subjects that died during each interval, and the number of subjects censored at each interval were provided.

RESULTS:

Study Population

Fifteen (15) subjects were enrolled in the study. Fourteen subjects completed the study (ie, completed the treatment phase through Day 31 [or death]); 1 subject was withdrawn due to disease progression (hepatic dysfunction group, 0.58 mg/m^2 dose cohort). The total study population consisted of 10 men and 5 women, and the majority were white (all 9 control subjects and 5 out of 6 hepatic dysfunction subjects were white). As required by protocol, all subjects had an ECOG score of 0 or 1, and all subjects had advanced malignancies. All tumor types were Stage IV except for 1 subject with Stage III ovarian cancer in the control group. All subjects in the hepatic dysfunction group met the NCI Organ Dysfunction Criteria at study entry (ie, described as having moderately impaired hepatic function). Six subjects in the control group and 1 subject in the hepatic dysfunction group (0.9 mg/m^2 cohort) entered the OEP.

Pharmacokinetics

All 15 subjects enrolled in the study had PK profiles that were considered evaluable. For both the control and hepatic dysfunction groups, the mean trabectedin plasma concentrations increased over the 3-hour infusion followed by a rapid decline after the infusion stopped. The results of statistical comparisons of the ln-transformed trabectedin dose normalized PK parameters are summarized in the table below. Geometric mean ratios (90% CI) for dose-normalized C_{max} was 1.40 (0.99, 1.99) in subjects with hepatic dysfunction (n=6) compared with control subjects (n=9) and 1.97 (1.20; 3.22) for dose-normalized AUC_{last}.

Summary of Comparison of Trabectedin PK Parameters Across Treatments

				Treatment Comparison		
PK Parameter	**Treatment**	**n**	**Geometric Mean**	**Ratio of Geo.Means (Hepatic Dysfunction /Control)**	**90% CI for Ratio of Geo. Mean[a]**	**Total CV (%)[b]**
C_{max} (ng/mL/mg)	Trabectedin Control (1.3 mg/m^2)	9	4.10			40.45%
	Trabectedin Hepatic Dysfunction (0.58 mg/m^2)	3	5.52	134.81	(84.88, 214.10)	
	(0.9 mg/m^2)	3	5.98	145.90	(91.87, 231.72)	
	(0.58 mg/m^2 and 0.9 mg/m^2)	6	5.75	140.25	(98.83, 199.02)	
AUC_{48} (ng h/mL/mg)	Trabectedin Control (1.3 mg/m^2)	9	16.13			50.28%
	Trabectedin Hepatic Dysfunction (0.58 mg/m^2)	3	24.30	150.65	(85.70, 264.83)	
	(0.9 mg/m^2)	3	33.11	205.28	(116.77, 360.86)	
	(0.58 mg/m^2 and 0.9 mg/m^2)	6	28.36	175.86	(113.61, 272.21)	
AUC_{last} (ng h/mL/mg)	Trabectedin Control (1.3 mg/m^2)	9	23.35			55.07%
	Trabectedin Hepatic Dysfunction (0.58 mg/m^2)	3	35.12	150.42	(81.61, 277.25)	
	(0.9 mg/m^2)	3	60.12	257.48	(139.70, 474.58)	
	(0.58 mg/m^2 and 0.9 mg/m^2)	6	45.95	196.80	(120.33, 321.87)	
AUC_{∞} * (ng h/mL/mg)	Trabectedin Control (1.3 mg/m^2)	6	29.19			64.46%
	Trabectedin Hepatic Dysfunction (0.58 mg/m^2)	2	39.09	133.90	(52.55, 341.18)	

*AUC_{∞} was not calculated if r^2adjusted (ie, an estimate of goodness of fit for the terminal phase of the concentration-time curve) was below 0.8 or if $AUC_{\infty, extrapolated}$ was greater than 20%.

[a] Ratio of parameter means (expressed as a percent), transformed back to the linear scale. Trabectedin used a reference.

[b] Total CV was calculated based on a model with 3 treatments (ie, the control group and the 2 hepatic dysfunction cohorts).

Pearson's correlation was performed to evaluate the potential for a relationship between the PK and baseline parameters of hepatic function. Pearson's correlation was positive both for C_{max} and AUC and measures of hepatic function at baseline, except for the correlation between AUC_{∞} and albumin level (see table below). The correlation appeared strongest (highest r and lowest p-value) for bilirubin and the overall Child-Pugh Score, which combines 5 parameters associated with liver impairment, suggesting that increasing severity of liver impairment correlated with increasing exposure.

Relationship between PK Parameters and Hepatic Function Parameter[a]

		The Parameters of Hepatic Function Tests			
PK Parameter	**Statistics**	**Prothrombin Time**	**Bilirubin Level**	**Albumin Level**	**Child-Pugh Score**
C_{max} (ng/mL/mg)	r	0.230	0.429	0.120	0.336
	P-value	0.409	0.111	0.671	0.220
AUC_{48} (ng h/mL/mg)	r	0.323	0.491	0.249	0.467
	P-value	0.241	0.063	0.372	0.079
AUC_{last} (ng h/mL/mg)	r	0.345	0.497	0.287	0.502
	P-value	0.207	0.059	0.300	0.057
AUC_{∞} (ng.h/mL/mg)[b]	r	0.401	0.240	-0.517	0.126
	P-value	0.324	0.566	0.189	0.767

Note: Hepatic function test values at baseline were used. $AUC_{0-\infty}$, AUC_{last}, AUC_{48}, and C_{max} were log-transformed to calculate the Pearson's correlation coefficient. r is the univariate Pearson's correlation coefficient between PK parameter and Hepatic function parameter; P-value is obtained from 2-sided T-test of Pearson's correlation coefficient.

[a] Hepatic function values are the point scores (1, 2, or 3) as reported by the investigator on the Child-Pugh Classification CRF

[b] The $AUC_{0-\infty}$, was calculated for 8 subjects (n=8)

Safety

The SET committee reviewed the safety data (AEs and laboratory data) and PK data from the first 12 subjects enrolled in the study (9 control subjects administered a single dose of trabectedin 1.3 mg/m^2 and 3 subjects with hepatic dysfunction administered 0.58 mg/m^2 trabectedin [Dose Level 1]) on 17 November 2011. No dose limiting toxicities occurred, and the SET recommended enrolling 3 additional subjects in the hepatic dysfunction group, sequentially, at the increased dose of 0.9 mg/m^2 trabectedin (Dose Level 2). The SET committee reviewed the safety and PK data again on 23 May 2014, which included data from the 3 subjects with hepatic dysfunction who received 0.9 mg/m^2 trabectedin and the previously available data. The SET recommended enrolling an additional 3 hepatic dysfunction subjects at the same dose of 0.9 mg/m^2. However, due to recruitment challenges with the hepatic dysfunction group, no additional subjects were enrolled at the 0.9 mg/m^2 dose level.

A summary of the safety profile is provided in the table below. There were no unexpected safety signals noted between the control group (n=9) and the hepatic dysfunction group (n=6).

Safety Profile by Treatment; Treated Subjects Analysis Set (Study ET743-OVC-1004)

	Control Trabectedin 1.3 mg/m²	Hepatic Dysfunction Trabectedin Total*	0.58 mg/m² (Initial Dose Level 1)	0.9 mg/m² (Dose Level 2)
Analysis set: treated subjects	9	6	3	3
TEAEs	9 (100.0%)	6 (100.0%)	3 (100.0%)	3 (100.0%)
Drug-related	7 (77.8%)	4 (66.7%)	1 (33.3%)	3 (100.0%)
Grade 3, 4 TEAEs	6 (66.7%)	5 (83.3%)	3 (100.0%)	2 (66.7%)
Drug-related	3 (33.3%)	2 (33.3%)	0	2 (66.7%)
Serious TEAEs	4 (44.4%)	3 (50.0%)	1 (33.3%)	2 (66.7%)
Drug-related	2 (22.2%)	1 (16.7%)	0	1 (33.3%)
Grade 3, 4	3 (33.3%)	2 (33.3%)	1 (33.3%)	1 (33.3%)
TEAE leading to treatment termination	1 (11.1%)	0	0	0
Drug-related	0	0	0	0
Total death	8 (88.9%)	5 (83.3%)	3 (100.0%)	2 (66.7%)
Deaths within 30 days of dosing	1 (11.1%)	1 (16.7%)	0	1 (33.3%)
Deaths due to TEAE	1 (11.1%)	0	0	0
Progressive disease	0	1 (16.7%)	0	1 (33.3%)
Other	0	0	0	0

TEAE = Treatment-emergent adverse event.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Note: MedDRA Version 16.1 is used
Subjects enrolled in the hepatic dysfunction group received 0.58 mg/m^2 or 0.9 mg/m^2 (separate dose cohorts).
*The total column is the sum of both cohorts with hepatic dysfunction.

All subjects (100%) in the control and hepatic dysfunction groups experienced at least 1 treatment-emergent adverse events (TEAE), with the most common TEAEs (≥50% of subjects in either group) being nausea, vomiting, ALT increased, decreased appetite, and anemia. Within the hepatic dysfunction group, the incidence of the most common TEAEs was higher in the 0.9 mg/m^2 dose cohort as compared to the 0.58 mg/m^2 dose cohort (nausea, vomiting, ALT increased, and decreased appetite). As noted in the table above, drug-related TEAEs were reported in 7/9 (77.8%) subjects in the control group and 4/6 (66.7%) subjects in the hepatic dysfunction group, and were consistent with the well-characterized toxicity profile of trabectedin. Within the hepatic dysfunction group, the number of subjects with drug-related TEAEs was higher in the 0.9 mg/m^2 cohort as compared to the 0.58 mg/m^2 cohort.

There were no notable changes from baseline in the clinical laboratory values, vital signs or ECGs.

Two subjects died within 30 days of dosing. Neither death was considered by the investigator to be related to trabectedin. One subject in the control group had a TEAE of sepsis which led to discontinuation of study drug; this subject subsequently died on Study Day 22 due to this TEAE. One subject in the hepatic dysfunction group (0.9 mg/m^2 cohort) died on Study Day 16 due to progressive disease (respiratory failure).

Survival Follow-Up

An additional 11 deaths were reported during the survival follow-up period. None of the deaths were considered by the investigator to be related to trabectedin. Nine subjects died within 0 to 6 months of receiving the dose of trabectedin, 3 subjects died between 6 to 12 months, and 1 subject died between 12 to 18 months of receiving the dose of trabectedin. The survival status of the remaining 2 subjects was unknown.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- Hepatic impairment is associated with increased trabectedin exposure. The geometric mean ratio for dose-normalized C_{max} was 1.40 in subjects with hepatic dysfunction compared with control subjects and 1.97 for dose-normalized AUC_{last}.
- No unexpected safety concerns were observed when trabectedin was administered to subjects with hepatic dysfunction at the protocol specified doses.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed Product. Some information in this posting may differ from the approved labeling for the Product. Please refer to the full prescribing information for indications and proper use of the product.