SYNOPSIS

Issue Date: 13 August 2014

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	YONDELIS®
Name of Active Ingredient(s)	Trabectedin (R279741)

Protocol No.: ET743-OVC-1002

Title of Study: An Open-Label, Multicenter Study to Assess the Potential Effects of Rifampin on the Pharmacokinetics of Trabectedin in Subjects With Advanced Malignancies

NCT No.: NCT01273480

Clinical Registry No.: CR017536

Coordinating Investigators: Sunil Sharma, MD - Huntsman Cancer Institute, Salt Lake City, Utah; USA and Arthur P. Staddon, MD - Pennsylvania Oncology Hematology Associates, Philadelphia, Pennsylvania; USA

Study Center(s): Sunil Sharma, MD - Huntsman Cancer Institute, Salt Lake City, Utah; USA and Arthur P. Staddon, MD - Pennsylvania Oncology Hematology Associates, Philadelphia, Pennsylvania; USA.

Publication (Reference): None

Study Period: First subject enrolled: 11 January 2011; Last observation for the last subject recorded: 23 October 2012; Database lock: 1 February 2013.

Phase of Development: Phase 1/2a

Objectives: The primary objective of this study was to assess the potential effects of rifampin on the pharmacokinetics (PK) of trabectedin in subjects with advanced malignancies. Secondary objectives of this study were to assess survival and the safety of trabectedin when coadministered with rifampin.

Methodology: This was a multicenter, randomized, open-label, 2-way crossover, drug-drug interaction study in men and women with advanced malignancies. Subjects were to be screened to assess their eligibility to enter the study within 14 days prior to Study Day 1. The treatment phase of the study was consisted of 2 single-dose trabectedin treatment cycles (1 cycle with and 1 cycle without rifampin coadministration), then a 30-day follow-up period after the last dose of trabectedin in Cycle 2 (ending on Day 31, Cycle 2). Day 1 in Cycle 1 and Cycle 2 of the treatment phase were to be separated by 28 days. During the cycle in which trabectedin was coadministered with rifampin, each subject was to receive 600 mg of rifampin for 6 consecutive days. Specifically, subjects were to receive rifampin once-daily prior to trabectedin administration from Day R1 to Day R5 of the run-in phase (Sequence 1) that was to follow the screening phase (ie, for subjects receiving rifampin in Cycle 1) or from Day 24 to Day 28 of Cycle 1 (ie, for subjects receiving rifampin in Cycle 2 in Sequence 2). A 6^{th} dose of rifampin was to be administered on Day 1 immediately before the start of the trabectedin infusion. Safety was to be monitored throughout the study, and serial peripheral venous blood samples for PK analysis were to be collected at protocol-specified time points.

Decisions on dose adjustments in the treatment phase and early stopping of the study were to be made by the Study Evaluation Team (SET) which consisted of independent expert(s), the study principal investigator, the medical monitor, and the sponsor's clinical pharmacologist(s). The sponsor's statistician was to be consulted as needed. All decisions made by the SET were to be documented in a SET Decision Form that was to be sent to the study centers, kept in the Study Master File, and provided to the IEC/IRB, as requested.

Number of Subjects (planned and analyzed): At least 8 subjects were expected to complete all study procedures, including the collection of sufficient and interpretable PK assessments. Twelve subjects were enrolled into this study and randomized. Eleven of the randomized subjects were treated and comprised the safety population. Five subjects were randomized to Sequence 1 (trabectedin+rifampin followed by trabectedin alone), and 6 subjects were randomized to Sequence 2 (trabectedin alone followed by trabectedin+rifampin). Nine subjects completed both treatment cycles, and 8 were PK evaluable.

Diagnosis and Main Criteria for Inclusion: Men and women, 18 years of age or older, with any locally advanced or metastatic solid tumor except hepatocellular carcinoma, were eligible. Subjects had to have relapsed or progressive disease following standard of care treatment with chemotherapy prior to enrollment, or be intolerant to prior standard of care treatment with chemotherapy. At screening, subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance score of ≤2, adequate organ function, and had to be able to receive dexamethasone (or an equivalent IV corticosteroid).

Test Product, Dose and Mode of Administration, Batch No.: Trabectedin was supplied as a sterile lyophilized powder, 1.0 mg per vial (batch numbers: 363076, 363132 and 366024). Trabectedin was reconstituted, diluted, and administered as a 3-hour IV infusion at a starting dose of 1.3 mg/m^2. Rifampin (Rifadin, Sanofi-Aventis, Bridgewater, NJ) (batch numbers 363077, T137732 and T144721) was supplied as 300 mg capsules for oral administration. Rifampin was administered at a dose of 600 mg.

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

Duration of Treatment: The single-doses of trabectedin (1.3 mg/m^2 as a 3-hour IV infusion) were administered on Day 1 of Cycles 1 and 2 according to the subject's assigned treatment sequence. Rifampin (2 x 300 mg tablets) was administered orally once daily for 6 days according to the subject's assigned treatment sequence. The 6th dose of rifampin was administered prior to the single dose of trabectedin. Due to the run-in phase after screening, the total study duration for subjects enrolled in Sequence 1 was to be 78 days as compared with 73 days for subjects enrolled in Sequence 2.

Criteria for Evaluation: Pharmacokinetics: For the determination of plasma concentrations of trabectedin, peripheral venous blood samples were to be collected during and after dosing. The following plasma trabectedin PK parameters were to be estimated for each subject: maximum observed 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 (Vd_z). Safety: Safety was to be evaluated by assessment of adverse events, clinical laboratory tests (hematology and chemistry), vital sign measurements (temperature, pulse and blood pressure), physical examination, and 12-lead electrocardiograms (ECGs).

Statistical Methods:

Sample Size Determination: This study was designed to assess the potential effects of rifampin on the PK of trabectedin in subjects with advanced malignancies. At least 8 subjects were expected to complete all study procedures, including the collection of sufficient and interpretable PK assessments. The 90% confidence interval (CI) of the geometric means for PK parameters were used to help with the interpretation of the results.

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. A mixed-effects model with treatment, period, and sequence as fixed effects, and subject (sequence) as a random effect, was used to estimate the least squares means and intra-subject variance. For the formal statistical analyses, the endpoints $AUC_{0-\infty}$, AUC_{last}, AUC_{0-48}, and C_{max} were log-transformed. The ratio of mean C_{max} and AUC values with and without coadministration of rifampin and corresponding 90% CI were estimated using the estimated least square means and intra-subject SD from a mixed effects modeling of log-transformed PK parameters. The log-transformed PK parameter was modeled by means of a linear mixed effect model with sequence, period, treatment as fixed effects, and subject (sequence) as

a random effect. Descriptive statistics (geometric and arithmetic means, SD, CV%) were provided for all trabectedin PK parameters. Rifampin concentrations in plasma were summarized.

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, and type of adverse events; clinical laboratory test results; physical examination and vital sign measurements; and 12-lead ECGs. Data were summarized using descriptive statistics.

RESULTS:

STUDY POPULATION: Twelve subjects were randomized in this study, and 11 randomized subjects (1 man and 10 women) received rifampin and at least one cycle of trabectedin. One subject was withdrawn during the study due to an adverse event, and 1 subject was withdrawn due to progressive disease. Nine subjects completed the study. Eight subjects were PK evaluable. All subjects had locally advanced or metastatic disease (ie, any solid tumor except hepatocellular carcinoma), with sarcoma being the most common tumor type.

PHARMACOKINETIC RESULTS: The mean dose-normalized plasma trabectedin concentration-time profile of trabectedin was lower when trabectedin was coadministered with rifampin compared with trabectedin when administered alone. The dose-normalized exposure parameters C_{max}, AUC_{last} and AUC_{∞} of trabectedin were also lower by 22%, 31% and 38% respectively when trabectedin was coadministered with rifampin. Trabectedin clearance increased from 39.6 L/h to 59.8 L/h during the trabectedin+rifampin coadministration period compared with trabectedin alone. Coadministration of rifampin with trabectedin also resulted in a 23% shorter elimination half-life of trabectedin, compared with trabectedin alone.

Summary of Mean (SD) Dose-Normalized Plasma Pharmacokinetic Parameters of Trabectedin Administered With and Without Rifampin (Study ET743-OVC-1002: Pharmacokinetics Data Analysis Set)

	Mean (SD)	
PK Parameters	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_{48h}, 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_{∞}, 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)

*Median, (min, max) values reported for t_{max}
DN = dose-normalized; PK = pharmacokinetic; C_{max} = maximum plasma concentration; t_{max} = time to reach the maximum plasma concentration; AUC_{48h} = area under the plasma concentration-time curve 48 h after the start of trabectedin infusion; AUC_{last} = area under the plasma concentration-time curve to last quantifiable concentration; AUC_{∞} = area under the plasma concentration-time curve to infinite time; $t_{1/2term}$ = terminal half-life; CL = total clearance of drug after IV administration; Vd_z = apparent volume of distribution; SD = standard deviation

SURVIVAL FOLLOW UP: No subjects died during the study or within 30 days of the last dose of study. Four of 11 subjects died within 0-6 months of study start, and 3 subjects died within >6-12 months treatment duration.

SAFETY RESULTS: All treated subjects experienced treatment-emergent adverse events (TEAEs), of which 10 (90.9%) were reported as drug related. Nine of 11 subjects had TEAEs of Grade 3 or higher, with increased incidences reported in the trabectedin arm compared with the trabectedin+rifampin arm [8/10 (80%) vs. 5/11 (45.5%) respectively].

The incidence of blood and lymphatic system disorders events was higher in the trabectedin arm compared with the trabectedin+rifampin arm, most notably leukopenia (40.0% with trabectedin vs 18.2% with trabectedin+rifampin) and neutropenia (40.0% with trabectedin vs 27.3% with

trabectedin+rifampin). The incidence of hepatobiliary disorders was also higher in the trabectedin arm (60.0% with trabectedin vs 9.1% with trabectedin+rifampin).

The total incidence of serious adverse events was 36.4% and the incidence of serious adverse events leading to discontinuation was 9.1%. One subject was withdrawn from the study due to the adverse events of Grade 3 low white blood cell levels and Grade 3 thrombocytopenia while on trabectedin+rifampin treatment.

STUDY LIMITATIONS: The major protocol deviation of 4 hr sample not collected did not impact the study outcome.

CONCLUSION(S):

- In comparison with trabectedin alone, coadministration of rifampin resulted in reduced systemic exposure of trabectedin as measured by C_{max} and AUC_{last}. The coadministration of potent inducers of CYP3A4 with trabectedin has been shown to increase the metabolic clearance of trabectedin.
- No new safety signals were detected in subjects treated with trabectedin alone or in combination with rifampin.

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