SYNOPSIS

Issue Date: 31 July 2013

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

Protocol No.: ET743-OVC-1003

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

NCT No.: NCT01267084

Clinical Registry No.: CR017539

Coordinating Investigators: Luc Dirix, MD, PhD - Oncologisch Centrum, Wilrijk; Belgium and Jean-Pascale Machiels, MD, PhD - Cliniques Universitaires UCL Saint-Luc, Brussels; Belgium

Study Center(s): Luc Dirix, MD, PhD - Oncologisch Centrum, Wilrijk; Belgium and Jean-Pascale Machiels, MD, PhD - Cliniques Universitaires UCL Saint-Luc, Brussels; Belgium

Publication (Reference): None

Study Period: First subject enrolled: 02 March 2011; Last observation for the last subject recorded: 28 November 2012; Database Lock: 27 March 2013.

Phase of Development: Phase 1/2a

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

Methodology: This was a multicenter, randomized, open-label, 2-way crossover, drug-drug interaction study in men and women with advanced malignancies. All subjects were screened to assess their eligibility to enter the study within 14 days prior to Study Day 1. The treatment phase of the study consisted of 2 single-dose trabectedin treatment cycles (1 cycle with and 1 cycle without ketoconazole coadministration), then a 30-day follow-up period after the last dose of trabectedin in Cycle 2 Day 31. Day 1 in Cycle 1 and Cycle 2 of the treatment phase were to be separated by 21 days. The study consisted of 2 separate parts; Study Part A and Study Part B. In Study Part A, 4 subjects were sequentially enrolled into Sequence 1 (trabectedin+ketoconazole followed by trabectedin alone). In Study Part B, 8 subjects were enrolled and randomly assigned to treatment Sequence 1 (trabectedin+ketoconazole followed by trabectedin alone) or Sequence 2 (trabectedin alone followed by trabectedin+ketoconazole). During the cycle in which trabectedin was coadministered with ketoconazole, each subject received 200 mg of ketoconazole twice daily. Specifically, subjects assigned to Study Part A received 200 mg of ketoconazole 12 hours prior to trabectedin administration, immediately prior to trabectedin administration, and then continuing every 12 hours up to 48 hours after the start of the trabectedin infusion (6 consecutive doses). Subjects assigned to Study Part B received 200 mg of ketoconazole 12 hours prior to trabectedin administration, immediately prior to trabectedin administration, and then continuing every 12 hours up to 156 hours after the start of the trabectedin infusion (15 consecutive doses).

Safety was monitored throughout the study, and serial peripheral venous blood samples for PK analysis were collected at protocol-specified time points.

Review of safety, and subsequent decisions regarding study continuation and dose adjustments in the treatment phase 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 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 Independent Ethics Committee and Institutional Review Boards, as requested.

Number of Subjects (planned and analyzed): At least 11 subjects (3 subjects for Study Part A and 8 subjects for Study Part B) were to complete all study procedures, including the collection of sufficient and interpretable PK data assessments. However, 12 subjects were enrolled and treated with study drug (4 subjects for Study Part A and 8 subjects for Study Part B). Twelve subjects completed both treatment cycles, though 1 subject did not complete the study. Eleven subjects 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 standard of care treatment with chemotherapy. At screening, subjects were to have an Eastern Cooperative Oncology Group (ECOG) performance status 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: 363132 and 365340). Trabectedin was reconstituted, diluted, and administered as a 3-hour IV infusion at a dose of 1.3 mg/m^2 when given alone. When coadministered with ketoconazole, trabectedin was administered as a 3-hour IV infusion at a starting dose of 0.2 mg/m^2 for Study Part A and final dose of 0.58 mg/m^2 for Study Part B. Ketoconazole (Nizoral®) (batch number: 364190) was supplied as 200 mg tablets for oral administration, and was administered twice daily for a total daily dose of 400 mg.

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

Duration of Treatment: The single doses of trabectedin (3-hour IV infusion) were administered on Day 1 of Cycles 1 and 2 according to the subject's assigned treatment sequence. Ketoconazole (200 mg tablets) was administered orally twice daily. Subjects assigned to Study Part A received 200 mg ketoconazole starting 12 hours prior to trabectedin administration, then immediately prior to trabectedin administration, and continuing every 12 hours up to 48 hours after the start of the trabectedin infusion (6 total consecutive doses). Subjects assigned to Study Part B received 200 mg of ketoconazole starting 12 hours prior to trabectedin administration, then immediately prior to trabectedin administration, and continuing every 12 hours up to 156 hours after the start of the trabectedin infusion (15 total consecutive doses). The scheduled duration of the study was to have been 66 days for a single subject.

Criteria for Evaluation: Pharmacokinetics: For the determination of trabectedin plasma concentrations, peripheral venous blood samples were collected before, during, and after trabectedin dosing. The following plasma trabectedin PK parameters were 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).

Survival Status: Subject survival was assessed. Safety: Safety was evaluated by assessment of adverse events, clinical laboratory tests (hematology and chemistry), vital sign measurements (temperature, pulse, blood pressure), physical examination, and 12-lead electrocardiograms (ECGs).

Statistical Methods:

Sample Size Determination: This study was designed to assess the potential effects of ketoconazole on the PK of trabectedin in subjects with advanced malignancies. For statistical analysis (Study Part B), at least 8 subjects were expected to complete all study procedures, including the collection of sufficient and interpretable PK assessments. A sample size of 8 was based upon feasibility and clinical considerations. The 90% confidence interval (CI) was 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. For summary statistics of concentrations at individual time-points, concentrations below the lower limit of quantification were assumed to be 0. If at least 1 value was 0 for the calculation of the geometric mean (and geometric CV%) then the geometric mean and geometric CV% were set to missing. The plasma concentrations of trabectedin at each time point and PK parameters were summarized by treatment (with and without coadministration of ketoconazole). The ratio of mean C_{max} and AUC values with and without coadministration of ketoconazole and corresponding 90% CI were estimated using the estimated least square means and intra-subject SD from a mixed effects model of log-transformed PK parameters. The log-transformed PK parameters were modeled by means of a linear mixed effect model with sequence, period, and 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. Ketoconazole concentrations in plasma were summarized.

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

RESULTS:

STUDY POPULATION: Twelve subjects were enrolled into this study, and all subjects (4 men and 8 women) received all the scheduled trabectedin and ketoconazole doses. Four subjects were sequentially assigned to Study Part A, and 8 subjects were randomly assigned to treatment Sequence 1 or 2 in Study Part B. Eleven subjects completed the study: one subject enrolled in Study Part B was withdrawn from the study, after having completed all study treatments, due to the adverse event of euthanasia, which was requested by the subject. Eleven subjects were PK evaluable, with the remaining subject (enrolled in Study Part A) unevaluable due to collection of PK blood samples in a manner inconsistent with the protocol. Ovarian cancer was the most common tumor type.

PHARMACOKINETIC RESULTS:

Part A

In general, the shapes of the dose-normalized plasma concentration-time profiles of trabectedin were similar for both treatment cycles but higher during the coadministration period. The dose-normalized exposure parameters (C_{max} and AUC) of trabectedin were higher when trabectedin was coadministered with ketoconazole. Based on arithmetic means, the dose-normalized C_{max} of trabectedin was 6.10 ng/mL/mg in the trabectedin alone treatment cycle and 7.67 ng/mL/mg in the trabectedin+ketoconazole treatment cycle. The dose-normalized AUC_{last} of trabectedin was 47.9 h.ng/mL/mg in the trabectedin alone treatment cycle and 66.4 h.ng/mL/mg in the trabectedin+ketoconazole treatment cycle. The absolute exposure parameters (C_{max} and AUC) of trabectedin were higher when trabectedin was administered alone, as compared with the trabectedin+ketoconazole treatment cycle. Per protocol, no statistical analysis was performed for Study Part A.

A review of the PK data during the conduct of the study from Study Part A did not show an increased systemic exposure of trabectedin when it was co-administered with ketoconazole at 0.2 mg/m^2, as compared with the trabectedin alone treatment cycle at 1.3 mg/m^2, and no dose-limiting toxicity in the trabectedin+ketoconazole treatment cycle compared with trabectedin alone. Therefore, it was determined by the SET that the subjects enrolled in Study Part B could be administered a higher dose of trabectedin (0.58 mg/m^2) in combination with ketoconazole.

Part B

The mean dose-normalized plasma concentration-time profile of trabectedin was increased when trabectedin was coadministered with ketoconazole compared with when trabectedin was administered alone. The dose-normalized exposure parameters (C_{max} and AUC) of trabectedin were also increased when trabectedin was coadministered with ketoconazole. Based on the arithmetic means, the dose-normalized C_{max} of trabectedin was 5.80 ng/mL/mg in the trabectedin alone treatment cycle and 7.03 ng/mL/mg in the trabectedin+ketoconazole treatment cycle. The dose-normalized AUC_{last} of trabectedin was 49.2 h.ng/mL/mg in the trabectedin alone treatment cycle and 82.9 h.ng/mL/mg in the trabectedin+ketoconazole treatment cycle based on the arithmetic means. The absolute exposure parameters (C_{max} and AUC) of trabectedin were increased when trabectedin was administered alone, as compared with the trabectedin+ketoconazole treatment cycle.

Based on the ratios of the geometric means, the dose-normalized C_{max} and AUC_{last} of trabectedin increased by approximately 21% and 66% respectively when trabectedin was coadministered with ketoconazole. The 90% CIs for the ratios of geometric means for AUC were outside of the upper end of the 80% to 125% equivalence range, indicating statistical difference between treatments. Intra-subject CV for the exposure parameters of trabectedin was approximately 25% for C_{max} and 32%, for AUC_{last}, which is comparable to previously reported values[6].

Summary of Mean (SD) Dose-Normalized Plasma Pharmacokinetic Parameters of Trabectedin Administered With and Without Ketoconazole, Study Part B (Study ET743-OVC-1003: Pharmacokinetics Data Analysis Set)

	Mean (SD)	
	Trabectedin Alone	Trabectedin + Ketoconazole
PK Parameters	(N=8)	(N=8)
DN_C_{max}, ng/mL/mg	5.80 (3.34)	7.03 (3.90)
t_{max}, h*	2.83 (0.50-2.87)	2.82 (1.50-2.87)
DN_AUC_{48h}, ng·h/mL/mg	28.6 (15.8)	42.3 (24.6)
DN_AUC_{last}, ng·h/mL/mg	49.2 (34.1)	82.9 (55.8)
CL, L/h	20.3 (13.1)	12.7 (7.46)

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

OVERALL SURVIVAL: Subject 003112 died within 30 days of the last dose of trabectedin. This subject experienced a treatment-emergent serious adverse event of Grade 5 euthanasia, which was requested by the subject, on Study Day 36. The event was reported by the investigator as being not related to trabectedin or ketoconazole. Four additional subjects died within 6 months of study start, and 7 additional subjects died within 12 months of treatment.

SAFETY RESULTS: All twelve treated subjects comprised the safety analysis set. All subjects (100%) experienced at least one treatment-emergent adverse event (TEAE), and at least one drug-related TEAE. A total of 6 subjects had TEAEs of Grade 3 or higher, with a higher incidence reported in the trabectedin alone treatment cycle (5 of 8 subjects, 62.5%) compared with the trabectedin+ketoconazole treatment cycle (3 of 8 subjects, 37.5%).

For subjects in Study Part B, TEAEs occurring at a higher incidence with trabectedin alone as compared with trabectedin+ketoconazole included decreased appetite (50% versus 12.5% respectively) and abnormal hepatic function (62.5% versus 0%, respectively).

The total incidence of serious adverse events was 66.7% with comparable incidences reported after both treatments (trabectedin+ketoconazole and trabectedin alone). No adverse events led to discontinuation from study treatment.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

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.