SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development, L.L.C. and Pharma Mar, S.A.
Name of Finished Product	YONDELIS®
Name of Active Ingredient(s)	trabectedin

Protocol No.: CR014917; **EudraCT Number**: 2008-004967-21

Title of Study: A Single-Blind, Multicenter, Placebo-Controlled, Sequential Design Study Evaluating the Potential Effects of a Single-Dose Administration of Trabectedin on the QT Intervals of the Electrocardiogram

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Publication (Reference): None

Study Period: Date Study Initiated [First subject enrolled]: 14 October 2008. Date Study Completed [Date of last observation for last subject]: 14 December 2009 **Phase of Development:** 1/2a

Objectives: The primary objective of this study was to assess the potential effects of trabectedin on the QT/QTc interval duration measured by electrocardiograms (ECGs) in subjects with advanced solid tumor malignancies when administered at a therapeutic dose. The secondary objectives of this study were to assess the safety and pharmacokinetics of trabectedin and its effect on subject survival.

Methodology: This was a single-blind, multicenter, placebo-controlled study that included a treatment phase of 2 single-dose sequential treatments. The study consisted of a screening phase (within 21 days before the first study drug administration on Day 1) followed by a single-blind phase (SBP) of 2 days. Subjects who completed the SBP were given the option to continue taking trabectedin in an open-label extension phase (OLE) for a minimum of 6 cycles, as long as they derived a clinical benefit (i.e., until there was clear evidence of disease progression or unacceptable toxicity, as judged by the investigator). Enrollment was planned for at least 60 subjects to ensure at least 52 evaluable subjects completed all required assessments, up to and including the 24-hour triplicate ECG recordings and pharmacokinetic blood samples collected after trabectedin administration on Day 2. A placebo control (intravenous [i.v.] normal saline given over 3 hours) was given on Day 1 to establish the frequency and magnitude of changes in clinical endpoints that could have occurred in the absence of active treatment. A therapeutic dose of 1.3 mg/m^2 trabectedin as a 3-hour i.v. infusion was administered on Day 2. The subjects were blinded to the contents of the i.v. solutions on Day 1 and Day 2. Serial triplicate 12-lead ECG recordings were to be obtained for each subject immediately before each pharmacokinetic blood sample collection. Across the 2 treatment days, the times of study drug administrations, ECG recordings, and pharmacokinetic blood sample collections were to be time-matched. Subjects' safety was monitored throughout the study. A pharmacogenomic blood sample was to be collected from subjects who consented separately to the pharmacogenomic component of the study. Subjects who completed the SBP were allowed to enter the OLE phase of the study and were given the option to continue taking trabectedin for a minimum of 6 cycles, as long as they derived a clinical benefit (i.e., until there is clear evidence of disease progression or unacceptable toxicity, as judged by the investigator). The duration for the OLE phase varied by subject. Subjects who continued taking trabectedin in the OLE began Cycle 2 approximately 21 days after completion of the SBP. The dose and schedule of trabectedin were to be modified for subsequent doses after the first dose in the SBP to be more appropriate for the type of malignancy being treated.

Number of Subjects (planned and analyzed): Sixty subjects were planned for enrollment in order to have 52 evaluable subjects. The final enrollment was 75 subjects with 74 of these subjects being evaluable.

Diagnosis and Main Criteria for Inclusion: Subjects had to satisfy the following criteria to be enrolled in the study:

- Men or women between 18 and 65 years of age, inclusive;

- Subjects with locally advanced or metastatic solid tumors who had received 3 or fewer prior lines of systemic chemotherapy;
- Subjects must have had relapsed or had progressive disease following standard of care treatment with chemotherapy prior to enrollment, or intolerant to prior standard of care treatment with chemotherapy;
- Subjects who had prior anthracycline totaling over 260 mg/m^2 should have left ventricular ejection fraction (LVEF) within normal limits, according to the institutional guidelines. A MUGA (multigated acquisition) scan or 2-D echocardiogram must be performed within 6 weeks before enrollment;
- Blood pressure (after the subject was supine for 10 minutes) between 90 and 140 mmHg systolic, inclusive, and no higher than 90 mm Hg diastolic;
- A 12-lead ECG consistent with normal cardiac conduction and function
- Non-smoker (has not used any tobacco products for at least 6 months before study drug administration);
- Adequate organ function as evidenced by the following peripheral blood counts or serum chemistry values within 7 days before Day 1
- Hepatic function variables:
  - total bilirubin ≤ULN. If total bilirubin was >ULN, measured indirect bilirubin to rule out Gilbert's syndrome (if indirect bilirubin was within normal range, subject was eligible).
  - total alkaline phosphatase (ALP) ≤1.5 ULN, or if >1.5 ULN, ALP liver fraction or 5' nucleotidase must be ≤ULN
  - AST and ALT must be ≤2.5 × ULN

  and
- Adequate recovery from surgery, at least 2 weeks from last dose of hormonal therapy, at least 3 weeks from prior chemo- or biological therapy, at least 3 weeks from receiving radiotherapy, at least 4 weeks after or a period 10 times the drug's half-life (approximately 75 days), whichever is longer, before the first dose of the study drug is scheduled from the last experimental anticancer therapy, and 6 weeks in the case of receipt of nitrosoureas or mitomycin C, provided all side effects from these therapies have resolved to grade 1 or less according to the National Cancer Institute-Common Terminology Criteria of Adverse Events (NCI_CTCAE, Version 3)

Test Product, Dose and Mode of Administration, Batch No.: Trabectedin (batch numbers: 6J210 and 7J106A) was supplied as an off-white powder for reconstitution, dilution in 500 mL of normal saline (NS), and given as an i.v. infusion using a calibrated infusion pump to deliver the drug over a 3-hour infusion period.

Reference Therapy, Dose and Mode of Administration, Batch No.: The matching placebo formulation was 500 mL of NS and was given as an i.v. infusion using a calibrated infusion pump to deliver the drug over a 3-hour period. The normal saline was available commercially.

Duration of Treatment: For the SBP, all subjects received the following treatment sequence:

- Dexamethasone (20 mg or equivalent) administered intravenously approximately 30 minutes prior to the infusion of placebo (Day 1) and trabectedin (Day 2).
- The treatment with anti-emetic drugs on Days 1 and 2 was with identical therapies when possible and given after dexamethasone. A protocol amendment allowed the use of granisetron and ondansetron as additional anti-emetics drugs. Granisetron could have been given approximately 30 minutes before initiation of the placebo (Day 1) and trabectedin (Day 2) infusion. Alternatively, ondansetron could have been given approximately 30 minutes before initiation of the placebo (Day 1) and trabectedin (Day 2) infusion. Dosing and route of administration for anti-emetics was at the discretion of the investigator.
- Day 1: trabectedin placebo (normal saline) administered as a 3-hour i.v. infusion
- Day 2: 1.3 mg/m^2 of trabectedin as a 3-hour intravenous infusion

Subjects who completed the SBP were allowed to enter the OLE phase of the study and were given the option to continue taking trabectedin for a minimum of 6 cycles, as long as they derived a clinical benefit. The duration for the OLE phase varied by subject.

Criteria for Evaluation:

Pharmacokinetics:

Sample Collection and Handling: During the SBP, peripheral venous blood samples (4 mL) for determination of trabectedin plasma concentrations were collected before dosing (i.e., predose) and following placebo and trabectedin administration on Days 1 and 2, respectively. Samples were time-matched to the ECG measurements and collected within 5 minutes of when the last ECG tracing was recorded. The exact dates and times of blood sample collection were recorded in the eCRF.

Analytical Procedures: The concentrations of trabectedin in plasma were determined by a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method. Only the plasma samples collected at 2 hours 45 minutes after dosing with the placebo (intravenous normal saline) were analyzed to verify that no measurable concentrations of trabectedin were present after placebo dosing on Day 1. All samples collected predose and after the Day 2 trabectedin administration were analyzed.

Pharmacodynamics: On Days 1 and 2 serial ECGs were collected in triplicate (three 10-second digital ECGs in close succession) at each of the following time points: before dosing (i.e., predose) and at 1, 2, 2.75, 4, 6, and 8 hours after the start of the infusion. ECGs were also collected 24 hours after trabectedin administration on Day 2. There was a maximum of 2 minutes between each of the triplicate ECG measurements. The predose ECG assessments began within 30 minutes before the dose of study drug (trabectedin and placebo). The ECG tracings collected at predose on each day served as the baseline for comparison with all ECG tracings collected postdose for 24 hours. Advanced and automated electrocardiograms capturing a 12-lead surface ECG signal with the capacity for digital signal processing were used. All digital ECG tracings were blinded and sent to a third-party central ECG laboratory (with a paper and electronic copy to the sponsor) for measurement of intervals, diagnostics of abnormalities and review of ECG waveform morphology. For the triplicate ECGs collected at each time point, the mean of 3 measurements for each ECG parameter was considered for all listing and statistical analyses described below. Quality assurance procedures were used to ensure high precision and consistency of QT interval measurements (refer to Attachment 6 in the study protocol). Several steps were taken to ensure that the central ECG laboratory remained blinded to treatment (day), time, and subject's sex during the blinded treatment phase (i.e., Days 1 and 2) of the study. Subject data sent to the ECG laboratory were assigned new identification numbers. Electrocardiogram recordings from a given day, except the screening ECG, were identified with a random date that revealed their order within the study. A third-party ECG laboratory read screening ECGs from the sites within 24 hours. For these ECGs, the time point was known.

Efficacy: No efficacy was reported in the Single-Blind Phase (SBP) or in the Open-label Extension Phase (OLE) of the study.

Safety: Safety evaluations were based upon the type, incidence, and severity of treatment-emergent adverse events reported throughout the study, and on changes in vital sign measurements, clinical laboratory test results, EKG's, and physical examinations. Treatment-emergent adverse events were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA) Version 11.1, using the lower-level term (LLT) as the description most closely related to the investigator's terminology, a preferred term describing a group of closely related LLTs, and the system organ class (SOC), which is the broad category including related preferred terms. Summary tables of treatment-emergent adverse events include: 1) the incidence of adverse events by SOC and preferred terms, 2) the incidence of adverse events by the investigator's rating of the maximum severity of the adverse event preferred term (toxicity grade), and 3) the incidence of adverse events by the investigator's rating of the relationship to drug therapy (not related, doubtful, possible, probable, or very likely). Adverse events were reported from the time the subject signs the informed consent form until 30 days after the administration of the last dose of study drug. All adverse events with the exception of disease progression, were to be reported from the time the subject signs the informed consent form until 30 days after the administration of the last dose of study drug in the SBP of the study. Those meeting the definition of serious adverse events were to be reported using the Serious Adverse Event Form, including those due to disease progression or serious adverse events spontaneously reported to the investigator. Beyond 30 days after last dose, only Grade 3 or Grade 4 adverse events considered drug-related and all serious adverse events were to be followed until resolution of the event, or until the event improved to Grade 2 or better. Neuropathic adverse events of Grade 2 or worse were to be followed until improvement to Grade 1 or better. The unresolved aforementioned events were followed for a maximum of 6 months. All new adverse events or serious adverse events beyond 30 days after last dose were to be reported if deemed related to study drug. The sponsor evaluated any safety information that is

spontaneously reported by an investigator beyond the time frame specified in the protocol. All adverse events, regardless of seriousness, toxicity grade, severity, or presumed relationship to study therapy, were recorded using medical terminology in the source document and the eCRF. Grades 4 to 5 hematologic toxicities, Grade 3 to 5 nonhematologic toxicities, and all toxicities related to the study therapy but not expected, were collected. These data should also document whether the abnormality resolved and the date of resolution. Whenever possible, diagnoses were to be given when signs and symptoms were due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators recorded in the eCRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management were recorded in the source document and reported according to sponsor instructions. The sponsor assumed responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor also reported to the investigator all serious adverse events that are unlisted and associated with the use of the drug. The investigator (or sponsor where required) reported these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

Pharmacokinetic/Pharmacodynamic Analyses: Plots of individual QTc and individual QTc changes from predose (ΔQTc) versus the corresponding trabectedin plasma concentrations were prepared to assess potential concentration-effect relationships. The data from the placebo day were included in these plots with an assigned a zero concentration value. The difference in ΔQTc between trabectedin and placebo (ΔΔQTc) were plotted against the corresponding trabectedin plasma concentrations (Ct). Analysis on linear mixed effects model was performed with ΔΔQTc as dependent variable and trabectedin concentration as a predictor and subjects as random effect. The random intercept model was selected as the best fit model and the predicted value of ΔΔQTc (along with 90% confidence intervals) was estimated at the mean C_{max} values of trabectedin based on this model. Outliers of trabectedin concentration values were identified based on PK criteria. The plots and analysis of the linear mixed model were performed on both full dataset and the reduced dataset after exclusion of outlying concentrations.

Pharmacogenomics: It was recognized that genetic variation could be an important contributory factor to inter-individual differences in drug exposure and response. Pharmacogenomic research would allow for genetic evaluation of mutations associated with ion channelopathies in case marked drug-related changes of the QT/QTc interval or safety of trabectedin were observed. Deoxyribonucleic acid (DNA) samples were to be used to potentially help address emerging clinical issues and to enable the development of safer, more effective, and ultimately individualized therapies in the future. Subjects who consented to take part in the pharmacogenomic component of the study had a 10 mL blood sample was collected from subjects on Day 1of the SBP. DNA collection was performed to allow for the genotyping of candidate genes related to trabectedin or cancer. These candidate genes were only to be genotyped, as necessary, if it was hypothesized that this may have helped resolve issues with the clinical data. No genes were genotyped during this study. Genotyping of any genes related to trabectedin or the indications for which it is developed, if performed in the future, would be reported in a separate report.

Statistical Methods:

Sample Size Determination:

The intrasubject standard deviation for ΔQTcF was assumed to be 10 ms. Using a standard deviation of 10 milliseconds (ms), for a sample size of 52 subjects (completers), the probability that the upper limit of the two-sided 90% confidence interval (1-sided upper 95% confidence interval) for the difference in mean ΔQTc between trabectedin and placebo (ΔΔQTc) at each time point falls below 10 ms was estimated to be 80%, when the true difference in means equals 5 ms. The enrollment of at least 60 subjects was planned to ensure that at least 52 evaluable subjects complete all required assessments, up to and including the 24-hour triplicate ECG recordings and pharmacokinetic blood sample collected after the Day 2 trabectedin administration.

Pharmacokinetic Analyses:

The plasma concentrations of trabectedin, individual maximum plasma values (C_{max}), and the times that C_{max} values were observed (t_{max}), were summarized using descriptive statistical analyses.

Pharmacodynamic (ECG) Analyses:

The Evaluable Analysis Set was defined as the analysis set consisting of all who received placebo on Day 1 and trabectedin on Day 2, had the paired assessment at predose (as baselines for placebo and trabectedin, respectively), and had at least 1 paired postdose assessment. The Evaluable Analysis Set was used for analysis on all ECG related variables. The QT, RR, QRS, and PR intervals measured, preferably from lead II of the 12-lead ECG, were to be used for data analysis.

- **QT Correction Methods**

Because the QT interval has an inverse relationship to heart rate, the measured QT interval is routinely corrected by means of various formulae to compensate. The primary method for calculating QTc interval in this study was Fridericia correction method (QTcF). For completeness and to satisfy the ICH E14 Guideline requirements, QT intervals were also corrected for heart rate using the Bazett's (QTcB) corrections method.

- **Calculation of QTc Variables – Correction Methods**

The Fridericia correction was used as the primary method to correct for the heart rate during the statistical evaluation of PD data. Bazett's Correction was used as the secondary method for statistical evaluation of PD data. With QT and RR intervals measured in ms, the formulae for the various correction methods are as follows:

1. Fridericia's Correction: $QTcF = \frac{QT}{(RR/1000)^{1/3}}$
2. Bazett's Correction: $QTcB = \frac{QT}{(RR/1000)^{1/2}}$

Pharmacodynamic Endpoints:

- **The Difference in ΔQTc Between Trabectedin and Placebo (ΔΔQTc)**

The primary pharmacodynamic parameter was the difference in the change from predose (ΔQTc) at each scheduled time point between trabectedin (Day 2) and placebo (Day 1). The predose time point on Day 2 was also the 24-hour time point for Day 1. For each subject, the difference in ΔQTc between trabectedin and placebo was calculated at each time point (ΔΔQTc = ΔQTc for trabectedin - ΔQTc for placebo for the subject at the same time point). Mean values for the difference and the 90% confidence interval (CI) (one-sided 95% CI) for mean differences were calculated at each time point. A mixed effect analysis of variance (ANOVA) model was fitted with the ΔQTc data as the dependent variable and treatment (trabectedin, placebo), scheduled time point of measurement, and treatment by scheduled time point of measurement interaction as fixed effects and subject as a random effect. Using the estimated least square means and intrasubject variance obtained from this model, 2-sided 90% confidence intervals (CI) was calculated for the difference in mean ΔQTc between trabectedin and placebo (ΔΔQTc) at each scheduled time point. Non-inferiority was concluded if at each scheduled time point the upper-limit of the two-sided 90% CI fell below 10 ms.

- **QT/QTc Intervals**

Mean QT and QTc intervals and mean change from baseline (ΔQT and ΔQTc) over time was summarized by using descriptive statistics at each time point and by treatment group; summary statistics were also be generated for each gender separately.

Categorical Analyses

- Incidence count and percentage of subjects with QTc increase from predose (ΔQTc) for each treatment, time point, and sex were summarized for the following categories:
  - QTc interval increase from baseline >30 ms
  - QTc interval increase from baseline >60 ms.
- Absolute QTc interval prolongation was summarized using the following limits for the evaluation of QT/QTc interval prolongation:
  - QTc interval >450 ms
  - QTc interval >480 ms

  - QTc interval >500 ms

- QRS, PR, and RR Intervals

RR, PR, and QRS intervals over time were listed for each subject and treatment. For each treatment group and time point of measurement, the data were summarized using descriptive statistics.

The number and percentage of subjects who experienced PR, or QRS interval abnormalities based on the criteria below were summarized by treatment:

- PR interval >200 ms
- QRS interval >120 ms

ST-Wave, T-Wave and U-Wave Morphology:

The number and percentage of subjects in each treatment having abnormal ST-wave, T-wave morphology and/or the occurrence of abnormal U-waves were summarized by treatment group and sex.

Heart Rate (HR):

Mean HR and corresponding changes from baseline were listed and summarized using descriptive statistics by treatment group and by time point. The incidence count and percentage of subjects with heart rate >100 bpm and <50 bpm were tabulated by treatment and by sex. To investigate any effect of treatment on heart rate a mean plot for ΔHR over time by treatment group was presented.

Supportive Analysis:

- **Relationship between QT, QTc, and RR**

To explore relationship between QT, QTc, and RR, a linear regression analysis of QT and QTc over RR were performed based on trabectedin-free time points. The analyses were based on log-transformed data.

- **Categorical Analysis Related to QTc Interval**

To evaluate the observed changes in the QT interval, categorical analysis was performed using following limits.

Incident rate at all time points:

Reduction from baseline in QTc Interval: >30 ms, > 60 ms.

Absolute QTc interval: <360 ms, and <320 ms

Incident rate at t_{max}:

Reduction from baseline in QTc Interval: >5 ms, >10 ms, >20 ms, >60 ms.

Absolute QTc interval: <410 ms, <400 ms, <390 ms, <350 ms, <300 ms

SUMMARY - CONCLUSIONS

SUBJECT INFORMATION: All enrolled subjects (N=75) were treated in the SBP of the study. Of these subjects, 72 completed end of treatment visit, and 3 subjects died within 30 days after study treatment. There were 74 subjects that were included in the Evaluable Analysis Set. One subject (101502) who received trabectedin in the reverse order (prior to placebo) was excluded from the Evaluable Analysis Set, but was included in the Treated Analysis Set. Of the 74 subjects in the Evaluable Analysis Set, 71 subjects completed the SBP of the study, with 3 deaths within 30 days after study treatment. Sixty-six subjects continued to the Open label Extension Phase. A listing of these subjects is provided in Appendix 3.1 of the clinical study report. Of the 75 enrolled subjects, 24 (32%) were men and 51 (68%) were women. Fifty-one subjects (68%) were white, 23 (31%) Asian, and 1 subject categorized as Other (1%). The median age was 52.0 years and the median baseline weight and height were 66.0 kg and 165.0 cm, respectively. At the end of the study, 49 (65%) subjects terminated the study after entering into the OLE due to: progressive disease (31, 41%), adverse events (6, 8%), death (4, 5%), investigator decision (4, 5%), and subject choice (4, 5%), even though 75 subjects were treated. Twenty-six (35%) subjects completed both phases of the study. Three subjects who completed the study died (1 due to progressive disease, and 2 due to "Other" [physician-assisted suicide]), within 30 days of their last treatment

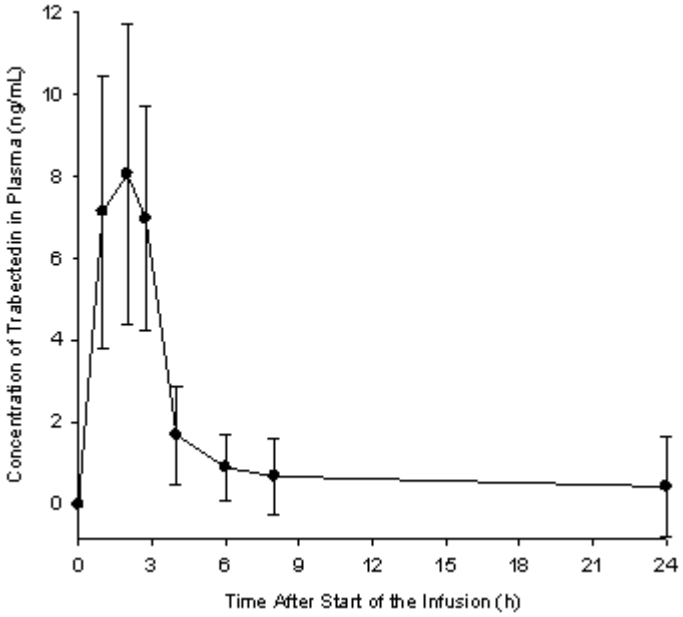
PHARMACOKINETICS: The trabectedin dosing information, the blood sampling times relative to the start of the trabectedin infusion, and the duration of trabectedin infusion on Day 2 of the study is presented in the clinical study report ET-743 OVC-1001. Data Sets Analyzed: Five hundred-ninety-seven plasma samples from 74 subjects were available for bioanalysis. A second descriptive statistical analysis was performed after excluding 24 plasma samples (4.0% of all available data) with concentrations greater than

2.5-times higher than the mean of those remaining. The pharmacokinetic results, including mean concentration-time data and t_{max} and C_{max} values, presented below (Figure 1 below) are based on the second descriptive statistical analysis.

Trabectedin Pharmacokinetics

Day 1 (Placebo): There were no measureable concentrations of trabectedin in all plasma samples collected at 2h 45 minutes after start of the placebo infusion on Day 1. Day 2 (trabectedin): The mean trabectedin concentrations in plasma increased over the course of the i.v. infusion (Figure 1 below). Maximum concentrations were observed at an average (SD) of 2.22 h (0.65 h) after the start of the trabectedin infusion. The mean (SD) C_{max} value was 9.24 ng/mL (3.75 ng/mL). The trabectedin concentrations initially declined rapidly upon cessation of the infusion and followed by a protracted decrease in the concentrations.

Figure 1: Plasma Concentration-Time Profile of Trabectedin
(Study ET743-OVC-1001: [Pharmacokinetics] Data Analysis Set With Exclusions)



Mean (SD) of 67 to 73 subjects represented at each time point

Pharmacokinetic Conclusions:

As expected, trabectedin C_{max} were attained towards the end of the 3-hour infusion. Much lower concentrations were observed by the 24-hour PK sample (i.e., 21 hours after cessation of the infusion).

PHARMACODYNAMICS (ECG) RESULTS SUMMARY

- A modest increase in heart rate was observed with trabectedin relative to placebo beginning 2 hours after start of the infusion and continuing through 24 hours. The maximum difference (14.1 bpm) was observed 4 hours after start of the infusion.
- Both Fridericia and Bazett correction methods yield similar correlation between QTc and RR interval values, but with opposite signs. The Bazett and Fridericia correction methods were equally appropriate for these data.
- Trabectedin (1.3-mg/m^2 administered as a 3-hour i.v. infusion) did not prolong the QTc intervals on assessment collected up to 24 hours after the start of the infusion. The upper limit of the 2-sided 90% confidence intervals for the mean difference for baseline between trabectedin and placebo (ΔΔQTc) at all time points was ≤6.65 ms, based on Fredericia's and Bazett's correction methods, which is below the predefined 10 ms limit.

- Categorical analyses revealed no subject with an absolute QTcF or QTcB value >500 ms or increase from baseline >60 ms. A comparable number of subjects exhibited QTcF and QTcB >450 ms and >480 ms or a change from baseline in QTcF and QTcB >30 ms with trabectedin compared with placebo.
- The results indicate that trabectedin shortens the QTc interval based on Fredericia's correction method. The mean ΔΔQTcF were below 0 ms throughout the 24-hour ECG monitoring period. The ΔΔQTcF ranged from -1.4 ms (90% CI, -3.35 to 0.51 ms at 1 hour) to -9.8 ms (90% CI,-12.65 to -6.99 ms at 24 hours) during the 24 hours after the start of the trabectedin infusion. Only at the 24-hour time point was the lower 90% confidence interval below -10 ms.
- A more modest degree of QTc shortening was observed based on Bazett's correction method, relative to Fredericia's method. The mean ΔΔQTcB intervals were below 0 ms for approximately one-half of the time points. The ΔΔQTcB ranged from -2.0 (90% CI, -4.65 to 0.65 ms at 2 hours) to 3.4 ms (90% CI, 0.07 to 6.65 ms at 4 hours) over the 24-hour intervals after the start of the trabectedin infusion.
- QTcF value was <360 ms in 1 subject in association with trabectedin and 1 subject with placebo. No subject had a QTcB value of ≤60 ms. Furthermore, no subject had a decrease from baseline in QTcF or QTcB, <30 ms. More subjects had decreases from baseline in corrected QT values ≥30 ms with trabectedin (n=2 for QTcF, n=6 QTcB) compared with placebo (n=2 for QTcF, n=4 for QTcB).
- Analysis of the T-wave morphological descriptors did not detect changes indicative of drug-induced impairment of cardiac repolarization. The available data also indicated the PR and QRS intervals were not affected by trabectedin. Trabectedin did not change cardiac autonomic regulation based on the absence of meaningful changes in heart rate.

EFFICACY RESULTS: No efficacy results were reported in the SBP or OLE phases of the study.

SAFETY RESULTS: Seventy-one (95%) of the 75 subjects in the study experienced treatment-emergent adverse events. The most frequent events were in the Gastrointestinal Disorders system organ class (SOC) (72%; 54/75) with nausea (55%, 41/75) and vomiting (52%, 39/75) being the most common events. In addition, in descending order, the incidence of General Disorders and Administration Site Conditions events were 51% (asthenia, 27%; fatigue, 16%); Blood and Lymphatic Disorders events were 27% (neutropenia, 16%; anemia, 9%; leukopenia, 7%). Three deaths were reported within 30 days of study treatment (Day 2). The most frequent drug-related adverse events were all grades of nausea (55%; Grades 3-4, 3%) and vomiting (52%; Grades 3-4, 3%), with asthenia (20%; Grade 3-4, 1%) and fatigue (16%; all were Grades 1-2) being less common. In drug-related toxicity categories Grades 3 and 4, the most frequent adverse events were abnormal hepatic function (16%), and neutropenia (8%). Nineteen percent of the subjects experienced serious adverse events, most of these being vomiting, nausea, and asthenia (3% to 5%). There were no subjects with cardiac disorders in the SBP of the study. No adverse events were reported suggestive of proarrythmic potential as specified in the ICH E14 Guidelines.

The safety profile of the administration of a single therapeutic dose of trabectedin (1.3 mg/m^2) as an i.v. infusion in this study was comparable to the known side effect profile of single agent trabectedin administered at 1.3 mg/m^2 over 3 hours. The pattern of hematological as well as non-hematological abnormalities reported by these subjects was consistent with the known safety profile of trabectedin. Incidences of adverse events were similar to or lower than in the other clinical studies of single agent trabectedin. A lower incidence may be due to the shorter exposure of a single dose. The most common adverse events were nausea and vomiting. There were no clinically noteworthy abnormal clinical laboratory values from Screening to End of Study. Similarly, changes in vital signs, ECGs, and physical examination changes were not associated with other clinical sequelae. No subject experienced cardiac toxicity in this study. As seen with single agent trabectedin treatment in the integrated phase 2 safety analysis (NDA No. 22-447, Module 5.3.5.3, Integrated Summary of Safety, submitted 19 November 2008), the laboratory abnormalities seen in this study were similar.

The safety profile of the administration of the single dose of trabectedin (1.3 mg/m^2) in study ET743-OVC-1001 was similar to that of single agent trabectedin administered at 1.3 mg/m^2 over 3 hours reported in previous clinical studies. The most commonly reported adverse events were asthenia, abnormal hepatic function, and vomiting which are consistent with the known safety profile of trabectedin. No adverse events suggestive of proarrhythmic potential were reported.

After the completion of the study, 74 (99%) of the 75 subjects in the study experienced treatment-emergent adverse events The most frequent events were in the Gastrointestinal Disorders system organ class (SOC) (76%; 57/75) with nausea (52%, 39/75) and vomiting (44%, 33/75) being the most common events. In addition, in descending order, the incidence of General Disorders and Administration Site Conditions events were 69% (asthenia, 36%; fatigue, 23%); Blood and Lymphatic Disorders events were 63% (neutropenia, 43%; anemia, 32%; thrombocytopenia, 21%, leukopenia, 12%).

During the OLE portion of the study the safety data continued to be consistent with data in the SBP of the study. There were no safety signals or trends in the data to indicate any increase in risk to subjects treated with trabectedin.

PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS:

The relationship between QTcF and QTcB intervals and the corresponding trabectedin concentrations were analyzed. The expected change from baseline in the QTcF and QTcB intervals (and corresponding 90% confidence intervals) at the observed mean trabectedin C_{max} were also seen. The individual ΔΔQTc intervals and corresponding trabectedin plasma concentrations exhibited a very weak linear relationship. Individual ΔΔQTcF values increased, whereas ΔΔQTcB values decreased, with an increase in the concentrations of trabectedin in plasma. For both analyses, the range of ΔΔQTc was quite wide as evidenced by the spread of the data around the regression line. No correlation was apparent based on the results of the regression analyses that included all available trabectedin concentrations (i.e., including the outlying trabectedin concentration). At the mean maximum trabectedin concentration of 9.2 ng/mL in plasma, the mean placebo-corrected change in QTcF and QTcB were predicted to be -2.53 msec and -0.68 msec, respectively, based on regression analyses that excluded the outlying plasma trabectedin concentration

PHARMACOGENOMICS: No pharmacogenomics results were reported in this study, but are to be presented in another report.

CONCLUSIONS:

- Trabectedin did not prolong the QTc interval as measured by ECGs in subjects with advanced solid tumor malignancies when administered at a therapeutic dose. The results of this study meet the criteria for a negative QT/QTc study.
- The safety and pharmacokinetic profile of trabectedin was similar to that observed in previous studies. No adverse events were reported suggestive of proarrhythmic potential
- The OLE portion of the study did not identify any additional safety issues.

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