SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	YONDELIS®
Name of Active Ingredient(s)	trabectedin

Protocol No.: ET743-SAR-3002

Title of Study: A Multicenter, Open-Label Single-Arm Study of YONDELIS® (trabectedin) for Subjects With Locally Advanced or Metastatic Soft Tissue Sarcoma Who Have Relapsed or are Refractory to Standard of Care Treatment

Publication (Reference): None

Study Period: First Patient Enrolled: 04 August 2005; Data Cutoff: 01 October 2010.

Phase of Development: 3b

Objectives: The objective of this study was to facilitate access to trabectedin for eligible previously treated subjects with soft tissue sarcoma (STS), who could not be expected to benefit from currently available therapeutic options but who may have benefited from treatment with trabectedin. The safety profile of trabectedin was further evaluated.

Methods: This was a multicenter, open-label, single-arm study. During the Treatment Phase, eligible subjects were to receive a dose of 1.5 mg/m^2 trabectedin intravenous (i.v.) formulation administered as a 24-hour infusion on Day 1 of each suggested 21-day treatment cycle. All subjects were to be pretreated with 20 mg of dexamethasone i.v. on Day 1 of each treatment cycle about 30 minutes prior to each infusion of trabectedin i.v. formulation.

Number of Subjects (planned and analyzed): Planned enrollment included approximately 3,000 subjects with a documented histopathologic diagnosis of STS who fulfilled all eligibility requirements.

A total of 1,895 subjects were enrolled as of the data cutoff date of 01 October 2010 and contributed data to this analysis. Of these, 1,803 subjects were included in the safety "all-treated" analysis set, defined as subjects who received at least 1 dose of trabectedin. Nine hundred and forty-seven subjects were included in the efficacy "all evaluable" analysis set, defined as subjects who received at least 1 dose of trabectedin with an available overall best response evaluation. Nine hundred and three subjects were included for survival follow-up, defined as subjects who received at least 1 dose of trabectedin and who consented to overall survival (OS) follow up.

Diagnosis and Main Criteria for Inclusion: Subjects were 18 years of age or older with unresectable advanced or metastatic histologically documented STS. Subjects must have relapsed or had progressive disease following standard of care treatment with chemotherapy prior to enrollment or were intolerant to prior standard of care treatment with chemotherapy due to safety issues.

Test Product, Dose and Mode of Administration, Batch No.: Trabectedin lyophilized powder was provided in 0.25 mg/20 mL vials (Manufacturing lot numbers: 4M102, 4M101, 5E104, 5E105, 5E103, 5E104, and 7J106) and 1.0 mg/100 mL vials (Manufacturing lot numbers: 4M203, 4L202, 5E206, 5K209, 6J210, 9AZS4, 8LZS02Q, 8LZS02Q_2, and 9FZS05P_1).

Reference Therapy, Dose and Mode of Administration, Batch No.: None

Duration of Treatment: The number of treatment cycles was not specified for this study. Subjects could continue to receive treatment as long as they derived an overall clinical benefit as determined by the investigator.

Criteria for Evaluation:

Efficacy: Best overall response and OS were collected for subjects enrolled up to and including Amendment 4. For subjects enrolled after Amendment 5 (06 May 2010), efficacy evaluations were performed at the discretion of the investigator and institutional guidelines. No efficacy data were collected or analyzed by the sponsor. Tumor assessment was to be performed prior to administration of the first dose (Cycle 1, Day 1) and thereafter approximately every 2 cycles according to institutional standards. Additional tumor assessments could be performed, if clinically indicated. Safety: Safety evaluations were performed as per the treating physician based on prior experience with monitoring patients receiving cytotoxic anticancer chemotherapy. Adverse events (AEs) and serious adverse events (SAEs) were collected for subjects enrolled up to and including Amendment 4. For subjects enrolled after Amendment 5, no safety data outside of SAEs were collected or analyzed by the sponsor.

Statistical Methods: No statistical tests were used to determine the sample size of this study and no statistical hypotheses were tested. The aim of this protocol was to provide expanded access to trabectedin for appropriate patients with no other acceptable medical alternatives.

Efficacy was analyzed using an all evaluable analysis set. Objective response (defined as having a complete response [CR] or partial response [PR] as best overall response) rate was calculated as the number of objective responders divided by the number of subjects in the all evaluable analysis set. A tabulation of the best overall response by investigator assessment, as well as a summary of objective response rate was provided. Overall survival, analyzed by Kaplan-Meier, was provided for all treated subjects with data, as well as by sarcoma subtypes.

Safety analyses were based on an all treated analysis set. Incidences of treatment-emergent abnormalities were tabulated. Descriptive statistics were used to summarize treatment-emergent adverse events (TEAEs) by intensity or severity grade (NCI-CTCAE, Version 3) and drug relationship. Serious adverse events, Grades 3 and 4 AEs, events resulting in treatment discontinuation, and number of subjects who died within 30 days of the last dose of trabectedin i.v. formulation were summarized using descriptive statistics. The first occurrence of Grade 3 and 4 adverse events was reported by cycle. A frequency table for AEs leading to a cycle delay, a reduction in dose, a skipped dose, or the withdrawal of study drug was provided. Adverse events leading to a discontinuation of study drug and AEs with an outcome of death were presented by drug relatedness (possibly, probably, or very likely).

No analyses were provided for clinical laboratory tests, vital signs, electrocardiograms, or physical examination findings.

RESULTS:

The expanded access study enrolled a total of 1,895 subjects; of these, 92 (5%) subjects did not receive treatment. The 1,803 (95%) subjects who received at least 1 dose of trabectedin were included in the all treated analysis set, 947 (50%) subjects with overall best response data were included in the all evaluable analysis set, and 903 (48%) subjects were included for OS. Of the 1,803 subjects in the all treated analysis set, a total of 1,635 (91%) subjects terminated treatment as of the clinical data cutoff of 01 October 2010. The most common reason for treatment termination was disease progression (1,138 [63%] subjects). Other reported reasons for treatment termination included adverse events and subject choice (8% each), other (6%), death (4%), and lost to follow-up (1%).

The majority of subjects in the all treated analysis set were white (88%), women (59%), and <65 years of age (81%; median age of 54 years). Of the 1,080 (60%) subjects with a baseline Eastern Cooperative Oncology Group (ECOG) performance score, the majority of subjects had an ECOG score of 0 (36%; 389/1080) or 1 (58%; 630/1080).

The most common (frequency ≥10%) histology types in the all treated analysis set were L-type sarcomas: leiomyosarcoma (40%) and liposarcoma (21%). Median time from initial diagnosis to the first dose of trabectedin was 31 months, from initial diagnosis to the first recurrence or occurrence of metastatic disease was 14 months, and from last recurrence or occurrence of metastatic disease to the first dose of trabectedin was 5 months.

The majority of subjects in the all treated analysis set received treatment for <3 months (1,056 [59%] subjects) with a median treatment duration of 70 days. A total of 614 (34%) subjects received between 3 and 12 months of treatment, with 133 (7%) subjects receiving treatment for >1 year. Subjects received a median of 3 cycles of therapy; 420 (23%) subjects received >6 cycles. The median cumulative dose was 4.2 mg/m^2 with a median intensity of 1.3 mg/m^2 per cycle and a median relative dose intensity of 86%.

Overall, 1,508 (84%) subjects received at least 2 treatment cycles. Among these 1,508 subjects, 969 (64%) and 810 (54%) subjects, respectively, did not experience a delay in dosing or a reduction in dose of trabectedin. The most commonly reported reason for both cycle delays and dose reductions was drug-related AEs (353 [23%] subjects and 501 [33%] subjects, respectively).

EFFICACY RESULTS

Best Overall Response:

A total of 391 (41%) subjects experienced either a CR (4 [<1%] subjects), PR (44 [5%] subjects), or stable disease (SD; 343 [36%] subjects) as a best overall response. Among all evaluable subjects, the objective response rate (ORR) was 5.1% (95% CI: 3.8, 6.7). For L-type versus non L-type sarcomas, best overall responses were the following: CR, 4 (1%) vs. 0 (0%) subjects; PR, 29 (5%) vs. 12 (3%) subjects; and SD, 225 (42%) vs. 102 (27%) subjects. The ORR for each histology tumor type was 6.1% (95% CI: 4.2, 8.4) for L-type sarcomas and 3.2% (95% CI: 1.7, 5.5) for non L-type sarcomas. Two (1%) subjects in each of the leiomyosarcoma and liposarcoma groups had a CR, with PR experienced by 22 (6%) subjects with leiomyosarcoma and 7 (4%) subjects with liposarcoma. The ORR was 6.6% (95% CI: 4.3, 9.7) for leiomyosarcoma and 5.0% (95% CI: 2.3, 9.2) for liposarcoma, respectively.

Overall Survival:

A total of 903 subjects in the all treated analysis set were assessed for OS. Among these subjects, the median survival time was 11.9 months (95% CI: 11.2, 13.8). The median survival by histology tumor type was longer for subjects with L-type sarcomas compared with subjects with non L-type sarcomas (16.2 months [95% CI: 14.1, 19.5] and 8.4 months [95% CI: 7.1, 10.7], respectively) and for subjects with liposarcoma (18.1 months [95% CI: 15.0, 26.4] compared with subjects with leiomyosarcoma (16.2 months [95% CI: 11.7, 24.3]).

SAFETY RESULTS:

Treatment-emergent adverse events seen in at least 10% of subjects by body system and preferred term included: gastrointestinal disorders: nausea (29%), vomiting (17%), and constipation (12%); investigations: increased blood alkaline phosphatase (ALP) (20%), increased alanine aminotransferase (ALT) (19%), and increased aspartate aminotransferase (AST) (12%); blood and lymphatic system disorders: neutropenia (24%), anaemia (18%), and thrombocytopenia (15%); and general disorders and administration site conditions: fatigue (23%). Grade 3 and 4 TEAEs reported in at least 5% of subjects, were nausea, increased ALT, neutropenia, anaemia, thrombocytopenia, and fatigue. Toxicities were managed by dose adjustment, either dose delays or dose reductions. The most common serious TEAEs were nausea, vomiting and dehydration in 4% of subjects and pneumonia, dyspnoea, pyrexia, and anaemia in 3% of subjects, respectively.

Deaths due to adverse events that occurred during treatment or within 30 days of the last dose were infrequent, reported for 6% of subjects receiving trabectedin. Twenty-one (1%) subjects died due to an adverse event that was assessed by the investigator to be related to study treatment.

Among subjects who terminated treatment, the most commonly reported TEAEs that led to treatment termination were increased ALP, thrombocytopenia, respiratory failure, and fatigue. The most commonly reported TEAEs that led to a dose adjustment was increased ALP, followed by increased ALT, thrombocytopenia, neutropenia, fatigue, and increased AST. The most commonly reported TEAEs that led to treatment cycle delay was neutropenia (inclusive of decreased neutrophil count), followed by thrombocytopenia, and increased ALP.

No analyses were provided for clinical laboratory tests or electrocardiograms. Only clinically significant changes in vital signs and physical examination findings, noted as adverse events, were recorded. No analyses were provided.

STUDY LIMITATIONS: This is an expanded access study that facilitated access to trabectedin, only key safety and efficacy data were collected.

CONCLUSION:

In this large ongoing expanded access study, efficacy results of trabectedin in subjects with advanced STS are generally consistent with prior clinical studies. Importantly, it appears that the clinical outcomes (response rate and overall survival) are better in subjects with L-type sarcomas (liposarcoma and leiomyosarcoma) compared to subjects with non L-type sarcomas.

The toxicities experienced by subjects in this study were consistent with those seen throughout the development program of trabectedin. No new, unexpected, or unusual safety signals were noted.

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