These Clinical Trial Results are provided for informational purposes only.

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REPORT SYNOPSIS

Name of Sponsor/Company: Daiichi Sankyo Pharma Development Name of Test Product: ARQ 197 Name of Active Ingredient: (3*R*,4*R*)-3-(5,6-dihydro-4*H*-pyrrolo [3,2,1-i*j*] quinolin-1-yl)-4(1*H*-indol-3-yl) pyrrolidine-2, 5-dione	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:	Multicenter Phase 2 Trial of ARQ 197 for Subjects with Relapsed or Refractory Germ Cell Tumors
Phase of Development:	Phase 2
Study Period:	First subject first visit date: 02 Feb 2010 Last subject last visit date: 30 Nov 2011
Investigator(s):	[redacted]
Study Center(s):	Study ARQ197-A-U251 was conducted in the United States (US) [redacted] New York, [redacted]; [redacted] Indianapolis, [redacted], Orlando, [redacted], St. Louis, [redacted], Los Angeles, [redacted], Boulogne [redacted] Lyon [redacted] and in the United Kingdom (UK) at [redacted], Sutton, Surrey and [redacted], Leeds, West Yorkshire.
Publication (reference):	Feldman DR, Einhorn LH, Quinn DI, Horwich A, Loriot Y, Joffe JK, et al. A Phase 2 Multicenter Evaluation Of ARQ 197 Monotherapy in Patients with Relapsed or Refractory Germ Cell Tumors (GCTs) (abstract). 2011 ASCO Annual Meeting; 03 Jun to 07 Jun, 2011; Chicago, IL Feldman DR, Einhorn LH, Quinn DI, Alan Horwich, Fizazi K, Joffe JK, et al. A Phase 2 Multicenter Evaluation of Tivantinib (ARQ 197) Monotherapy in Patients With Relapsed or Refractory Germ Cell Tumors (GCTs) (poster). 2011 ASCO Annual Meeting; 03 Jun to 07 Jun, 2011; Chicago, IL.
Study Objectives/Hypothesis:	The primary objective was to determine the objective response rate (ORR) after 4 cycles of therapy with ARQ 197 in subjects with germ cell tumors (GCTs). The secondary objectives were: • To determine the progression-free survival (PFS) rate at 12 weeks from enrollment • To determine the median overall survival (OS) among subjects treated with ARQ 197 • To determine the safety and tolerability of ARQ 197 in this subject population The planned exploratory objectives were: • To evaluate the dynamic changes in midkine and soluble c-Met in plasma. • To evaluate the expression of p-c-Met, total c-Met, downstream markers of c-Met signaling including p-FAK and

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	p-ERK1/2, and markers of cell proliferation (ki67) and apoptosis (TUNEL). • To evaluate the pharmacokinetic (PK)/pharmacodynamic relationship of ARQ 197. Population PK/pharmacodynamic analysis was conducted separately with pooling of data from other clinical studies of ARQ 197. • To explore the relationship between common genetic variants in CYP2C19 and UGT1A1 on primary and secondary endpoints as well as PK and pharmacodynamic measures.
Study Design/Methodology:	This was a multicenter, single-arm, Simon 2-stage, Phase 2 clinical study conducted in subjects with relapsed or refractory non-central nervous system (non-CNS) GCTs. Eligible subjects were treated with ARQ 197 at a dose of 360 mg twice a day (BID) (a total daily dose of 720 mg) orally in a continuous manner. The overall treatment period was divided into continuous 28-day cycles without treatment interruption. Disease status and tumor response were assessed per modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1 at screening (within 3 weeks before the first scheduled dose of study drug), in 4-week intervals while subjects were on treatment during the first 4 cycles and at 8-week intervals thereafter, or as clinically indicated until progression of disease, withdrawal of consent, death, or loss to follow-up. Tumor measurement was also performed during the end of treatment visit if it was not done within the previous 28 days. Subjects with progressive disease (PD) at any time during the treatment period discontinued study treatment. Subjects with stable disease, complete response (CR), or partial response (PR) were to continue treatment until disease progression and/or unacceptable toxicity and/or withdrawal of consent was documented. CRs and PRs were to be confirmed within 28 days after initial assessment. After discontinuation from study treatment, survival status was obtained by phone every 3 months until the subject died, withdrew consent, was lost to follow-up, or started a new therapy for a maximum of 12 months during the follow-up period. According to the Simon 2-stage optimal design, 21 subjects were enrolled in stage 1. If fewer than 2 (ie, 0 or 1) of the first 21 subjects had either a CR or PR, then the study was to be terminated early for futility. If 2 or more out of 21 subjects had either CR or PR, then enrollment was to be extended to a total of 41 subjects (20 additional subjects). Enrollment for stage 2 was not to be halted until the 21 subjects in the first stage had been assessed for response. After stage 2, the treatment was to be considered effective if 5 or more subjects had CR or PR, after 4 cycles of therapy, among 41 subjects enrolled.

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Duration of Treatment for Individual Subject:	There was to be no limit to the number of treatment cycles that were administered. Treatment was continued until there was objective evidence of tumor progression (as per the modified RECIST version 1.1 criteria) or until death; evidence of toxicities that were unacceptable, which required discontinuation of drug; withdrawal of subject consent; loss to follow-up; or at the Investigator's discretion.
Number of Subjects:	Planned: A minimum of 21 and maximum of 41 Screened: 33 Enrolled: 27 Discontinued: 27
Diagnosis and Main Criteria for Study Entry:	Subjects were male and 16 years of age or older with histologically confirmed non-CNS GCT, both seminomas and non-seminomas. Subjects must have had radiographically measurable disease as defined by RECIST version 1.1 and documented GCT progression based on radiographic measurements or elevated serum tumor markers in case of radiographically measured stable disease.
Investigational Product and Comparator Information:	Dosage Form: 120-mg capsules; a dose of 360 mg of ARQ 197 was administered by mouth BID once in the morning and once in the evening (a total daily dose of 720 mg), with a meal, in continuous 4-week cycles Route of Administration: oral Lot No.: [redacted], expiration date: Jan 2012; 9L078-P1, expiration date: Dec 2011; 0A002-P1, expiration date: Dec 2011. Packaging Information: supplied as 90-count bottles

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the ORR after 4 cycles of therapy with ARQ 197. The secondary efficacy variables were PFS rate at 12 weeks, median OS, duration of response, best overall response, and Eastern Cooperative Oncology Group (ECOG) status. Response data were obtained from serial radiography. Survival data were obtained from follow-up communications. Variables based on response to treatment were assessed in accordance with modified RECIST criteria, version 1.1.

Pharmacokinetics: Population PK/pharmacodynamic analysis was conducted separately by pooling of concentration and other relevant demographic data along with similar data from other clinical studies of ARQ 197. The outcome of the analysis was reported as a stand-alone report.

Biomarker: Tumor samples of archival, fresh core needle biopsy or fine needle aspiration were planned to be evaluated for the expression of p-c-Met, total c-Met, and downstream markers of c-Met signaling including p-FAK and p-ERK1/2, and markers of cell proliferation (ki67) and apoptosis (TUNEL). However, c-Met at baseline was the only tissue biomarker that was analyzed. Plasma samples were collected for the analysis of midkine and soluble c-Met.

Safety: Adverse events (AEs), laboratory evaluations, coagulation, physical examination findings, vital signs, and electrocardiogram (ECG).

Other: Pharmacogenomics and Optional Pharmacogenomic Sample Banking: Blood sample collected

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was genotyped for commonly known variants in CYP2C19.

Statistical Methods:

Primary Efficacy Analyses:

The primary efficacy variable was the ORR after 4 cycles of therapy. For purposes of determining the ORR, tumor response was based on the best overall response recorded for each subject from the date of enrollment. The ORR was calculated as the number of subjects with a confirmed CR or PR divided by the number of subjects who received study drug (ie, ORR = [CR+PR]/number of subjects). Point estimates as well as 95% confidence intervals (CI) were calculated for the ORR. Response assessment was performed according to modified RECIST criteria, version 1.1.

Secondary Efficacy Analyses:

- PFS rate at 12 weeks was estimated based on Kaplan-Meier (product-limit) method and the corresponding 95% CIs were presented.
- Median OS and the corresponding 95% CI were estimated based on Kaplan-Meier method. OS rates at 6 months and 1-year post-treatment were also calculated along with the corresponding 95% CIs.

Pharmacokinetic/pharmacodynamic Analyses:

Population PK/pharmacodynamic modeling analysis was conducted separately with pooling of data from other clinical studies of ARQ 197.

Biomarker Analyses and Pharmacogenomic Analyses:

Raw biomarker values, changes from baseline, and percent changes from baseline for exploratory plasma biomarkers were summarized for all subjects in the biomarker analysis set. Pharmacogenomic data were listed.

Safety Analyses:

Adverse events, laboratory evaluations, physical examination findings, vital signs, ECGs, and concomitant medications were listed and/or summarized. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 and assigned grades based on National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0.

Summary:

Efficacy Results:

There was no confirmed CR or PR after 4 cycles of treatment with ARQ 197 in the first 21 enrolled subjects (stage 1 of the Simon 2-stage design). In stage 1, the ORR after 4 cycles was 0.
Three subjects (14.3%) had stable disease, 16 subjects (76.2%) had PD, and 2 subjects (9.5%) were inevaluable for best overall tumor response. The study was terminated early for futility.

In stage 1 of the Simon 2-stage design, the PFS rate at 12 weeks from enrollment was 16.4% (95% CI: 4.1% to 35.9%). The median OS was 6.2 months (95% CI: 3.5 months to 7.7 months). The OS rates at 6 months and 1-year post-treatment were 50.6% (95% CI: 27.7% to 69.7%) and 0, respectively.

Safety Results:

All 27 subjects discontinued from the study. There were 22 deaths during the 1-year follow-up period. The primary reasons for deaths were disease progression (21 subjects) and clinical progression (1 subject).

No Grade 5 treatment-emergent AEs (TEAEs) were reported. Twelve subjects (44.4%) experienced Grade 3 or 4 TEAEs. Fifteen subjects (55.6%) experienced at least 1 treatment-related TEAE, and 2 subjects (7.4%) experienced treatment-related Grade 3 TEAEs.

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Treatment-emergent serious AEs (SAEs), which were all Grade 3 or 4, were experienced by 9 subjects (33.3%). One subject (3.7%) experienced a treatment-related treatment-emergent SAE of Grade 3 pneumonia. One subject (3.7%) had a treatment-emergent SAE of Grade 3 sciatica leading to death that was not related to ARQ 197. The primary reason of death was disease progression.

Three subjects (11.1%) discontinued study treatment due to TEAEs that were not related to ARQ 197. Two of these TEAEs were treatment-emergent SAEs. The primary reason of study treatment discontinuation was PD for all 3 subjects.

Hematology conditions with shifts from Grade ≤2 at baseline to worst post treatment Grade 3 were anemia (2 of 6 subjects [33.3%]), lymphocyte count decreased (6 of 20 subjects [30.0%]), and white blood cell decreased (1 of 24 subjects [4.2%]).

The only chemistry condition with a shift from Grade ≤2 at baseline to worst post treatment Grade 3 was hyponatremia (1 of 27 subjects [3.7%]).

There were no clinically meaningful changes in vital signs, ECGs, and physical examinations during the study.

Pharmacokinetic/Pharmacodynamic Results:

Population PK/pharmacodynamic modeling analysis and reporting were outside of the scope of the clinical study report (CSR) for this study.

Other Results:

Biomarker Results:

The plasma soluble c-Met level was essentially unchanged from baseline to the end of treatment (a slight increase of 0.868% in median). The plasma soluble midkine level increased from baseline to the end of treatment; the median percentage increase was 49.583%. Tissue biomarker of c-Met at baseline was analyzed. c-Met expression in tumor tissues was measured using immunohistochemistry. Among the 6 subjects with available tumor tissues, all tumors were c-Met negative as per the pre-defined criteria.

Conclusions:

ARQ 197 was generally tolerated when administered to subjects with relapsed or refractory GCTs.

Among the first 21 subjects enrolled in stage 1 of the Simon 2-stage design, no subjects had either a CR or PR; therefore, the study was terminated early for futility per the stopping rule of the Simon 2-stage design.

Date of the Report: 31 Jul 2012