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# REPORT SYNOPSIS

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<tr><td>Name of Sponsor/Company:<br>Daiichi Sankyo Development LTD.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier<br>Volume:<br>Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Test Product:<br>CS-1008 Lyophilized Powder for Injection for Infusion</td></tr>
<tr><td>Name of Active Ingredient:<br>CS-1008</td></tr>
<tr><td>Title of Study:</td><td colspan="2">A Phase 2 Open-Label Randomised, Trial of CS-1008 in Combination with Irinotecan versus Irinotecan Alone in Subjects with Metastatic Colorectal Carcinoma Who Failed First Line Oxaliplatin Based Chemotherapy</td></tr>
<tr><td>Phase of Development:</td><td colspan="2">2</td></tr>
<tr><td>Study Period:</td><td colspan="2">First subject first visit date: 01 Sep 2010<br>Last subject last follow-up date: 18 Apr 2011</td></tr>
<tr><td>Principal Investigators:</td><td colspan="2">A full list of investigators is provided in Appendix 16.1.4</td></tr>
<tr><td>Study Centers:</td><td colspan="2">This study was conducted at 4 investigative sites in the United Kingdom; 4 additional sites did not enroll any subjects. Details are presented in Appendix 16.1.4.</td></tr>
<tr><td>Publication (reference):</td><td colspan="2">None</td></tr>
<tr><td>Study Objectives/Hypothesis:</td><td colspan="2">The primary objective of this study was to estimate the difference in treatment effect between CS-1008 administered in combination with irinotecan and irinotecan alone, as measured by progression-free survival.<br>Secondary objectives were to determine:<br>– Overall and median survival<br>– Objective response rate (ie, complete response and partial response rate)<br>– Safety and tolerability of CS-1008 administered in combination with irinotecan<br>– Incidence of anti-CS-1008 antibody</td></tr>
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formation

- Serum levels of CS-1008 at the scheduled time points

Exploratory objectives were to evaluate:

- Changes in serum apoptosis biomarkers (eg, activated caspases 3/7 and 8, cytochrome c, and M30 antigen) and in serum tumor markers (ie, carcinoembryonic antigen that may have correlated with the effects of study treatment. Exploratory tumor biomarkers, eg, death receptor 5, Bcl2-associated x protein, B cell lymphoma X (Bcl-x) protein, inhibitor of apoptosis (IAP) protein expression, and genotype/gene expression of critical genes, were evaluated using archived tumor tissue. Blood deoxyribonucleic acid was also banked for pharmacogenomic analysis.
- Relationship between serum exposure and biomarker responses versus clinical responses. Population pharmacokinetic and pharmacodynamic modelling analysis was also conducted separately to explore the relationship of serum exposure and biomarker responses versus treatment responses.

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| Study Design/Methodology: | This was planned to be a randomized, open-label, 2-arm, multicenter study of CS-1008 administered in combination with irinotecan versus single-agent irinotecan to subjects with metastatic colorectal cancer who have failed an oxaliplatin-based first-line treatment. All subjects |

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received irinotecan. During each 3-week cycle, irinotecan was administered as a 30- to 90-minute intravenous (IV) infusion (according to local custom) on Day 1 and CS-1008 (to subjects randomized to CS-1008) was administered as a 30-minute IV infusion once each week (ie, on Day 1 of each week or Days 1, 8, and 15 of each cycle). CS-1008 was administered before administration of irinotecan on the days where treatment coincided.

The first part of the study was a dose-escalation safety phase, during which subjects received both CS-1008 and irinotecan to determine the irinotecan dose to be used in the randomized phase. The dose of CS-1008 (loading dose of 6 mg/m$^2$ followed by 2 mg/m$^2$ once weekly) was fixed. Subjects were to receive irinotecan alone or in combination with CS-1008 during the randomized phase.

During the dose-escalation safety phase, the first 6 subjects received irinotecan (300 mg/m$^2$/q3wks [dose level -1 in the package insert]) and CS-1008 (loading dose of 6 mg/m$^2$ followed by 2 mg/m$^2$ once weekly). The first 2 subjects were to receive 1 full cycle (3 weeks) of treatment before additional subjects began study treatment. All 6 subjects in this initial safety cohort had to receive both study treatments in order for the toxicity of the combination to be thoroughly assessed. If a subject received only CS-1008, the subject was to be replaced. Based on the incidence rates of grade 3/4 toxicities and grade 4 toxicities in comparison with historical rates associated with irinotecan monotherapy, the dose of irinotecan could be increased in the next 6 subjects to 350 mg/m$^2$/q3wks or decreased to 250 mg/ m$^2$/q3wks.

Disease assessments were performed at baseline and at the end of every 2 cycles (6 weeks). Treatment continued

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| | until disease progression, unacceptable toxicity, or withdrawal of consent to treatment. All subjects who discontinued from the study, whether with or without documented disease progression, returned to the study site 4 to 6 weeks after the last dose of study treatment to complete toxicity assessments. Thereafter, for subjects who discontinued without disease progression, follow-up site visits occurred every 3 months to assess progression, by computerized tomography (CT) scan or clinical assessment, or if a CT scan was not performed, until disease progression or death. If follow-up site visits were not feasible, follow-up contact was by telephone. Following disease progression in all subjects, follow-up was by telephone for survival information until death or up to 1 year after the last subject was randomized.<br><br>After review of the incidence and severity of adverse events (AEs) observed at the irinotecan dose level of 300 $mg/m^2$/q3wks in combination with CS 1008, it appeared unlikely that the study would achieve its main goal of treating subjects with irinotecan at a dose of 350 $mg/m^2$/q3wks in combination with CS 1008. Therefore, the study was concluded after 8 subjects had been enrolled and treated in the dose-escalation safety phase. No subjects were enrolled in the randomized phase. |
| Duration of Treatment for Individual Subject: | Subject enrollment was anticipated to be completed in approximately 1 year. It was not possible to define exactly the duration of the study for a particular subject because there was no limit to the number of treatment cycles that could be administered to a subject (ie, treatment was to continue until disease progression, unacceptable toxicity, or withdrawal of consent to treatment). However, the median progression-free survival was expected to be less |

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| | than 3 months and median overall survival was expected to be 10 months for subjects on irinotecan alone. |
| Number of Subjects: | Planned: 6 to 12 (dose-escalation safety phase); 80 (randomized phase)<br>Screened: 12<br>Enrolled: 8<br>Discontinued: 8 |
| Diagnosis and Main Criteria for Study Entry: | Second-line therapy for previously-treated advanced or metastatic colorectal adenocarcinoma |
| Investigational Product and Comparator Information: | Investigational Product: CS-1008<br>Dosage Form: Lyophilized Powder for Injection for Infusion<br>Route of Administration: IV<br>Lot No.: [redacted]<br>Packaging Information: cartons containing 20 numbered vials of CS-1008 29.5 mg Powder for Injection for Infusion<br>Comparator: Irinotecan<br>Dosage Form: Solution<br>Route of Administration: IV<br>Packaging Information: Commercially available |

Criteria for Evaluation:

Efficacy: Efficacy was not evaluated in this study because the study was concluded after the dose-escalation safety phase.

Safety: Safety endpoints included adverse events (AEs), clinical laboratory

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evaluations, physical examination findings, and vital sign measurements.

Drug Concentration, biomarkers were not assessed since data were only collected for the 8 enrolled subjects.

Human Antihuman Antibody (HAHA): Concentrations of HAHA were not assessed since data were only collected for the 8 enrolled subjects.

Statistical Methods:

Safety: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 13) and summarized for the number and percentage of subjects reporting treatment-emergent adverse events (TEAEs). AEs/toxicities reported by the subject or noted by the Investigator and laboratory test results (hematology and blood chemistry) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0, and listed and summarized for each treatment group.

Summary:

Safety Results:

Eight subjects received CS-1008 in the study and 7 of these subjects also received at least 1 dose of irinotecan.

All 8 subjects had at least 1 TEAE. The most common TEAEs (at least 3 of 8 subjects) were diarrhea, nausea, alopecia, constipation, fatigue, and rectal hemorrhage, and anemia, decreased appetite, insomnia, hyperhidrosis, lethargy, neutropenia, pyrexia, and vomiting. The most common grade 3 or 4 TEAEs were rectal hemorrhage and neutropenia, each reported in 2 subjects.

There were no deaths during the treatment stage of the study or within 30 days of the last dose. Four of the 8 subjects died during the 1-year follow-up period.

SAEs were reported in 5 subjects including 2 with neutropenic sepsis, 1 with anaphylactic reaction, 1 with constipation, and 1 with constipation, retroperitoneal infection, sensory loss, and tumor perforation. Anaphylactic reaction was

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considered to be related to CS-1008 (the subject never received irinotecan) and the 2 SAEs of neutropenic sepsis were considered to be related to irinotecan.

Four subjects discontinued due to AEs of anaphylactic reaction, tumor perforation, neutropenic sepsis, and jaundice, respectively.

Shifts in hematology laboratory values from baseline grade ≤2 values to grade 3 or 4 values post-treatment were observed in 1 or 2 subjects for most parameters. Shifts in chemistry parameters from baseline grade ≤2 values to grade 3 values post-treatment were not consistent and no shifts to grade 4 were observed.

Based on the incidence and severity of observed AEs, the study was terminated before the randomized phase was initiated.

Conclusions:

After review of the incidence and severity of AEs observed at the irinotecan dose level of 300 mg/m$^2$/q3wks in combination with CS-1008 (6 mg/m$^2$ loading dose followed by 2 mg/m2 weekly) in the initial 8 subjects, it appeared unlikely that the study would achieve its goal of treating subjects with irinotecan at a dose of 350 mg/m2 in combination with CS-1008. Therefore, the study was terminated. As the randomized phase of the study was not initiated, the treatment effect of irinotecan and CS-1008 combined versus irinotecan alone was not evaluated.

Date of the Report: 15 Mar 2012