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REPORT SYNOPSIS

Name of Sponsor/Company: Daiichi Sankyo Development Ltd (DSD) Name of Test Product: CS-7017 Name of Active Ingredient: CS-7017	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study:	A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of CS 7017 in Colorectal Cancer Patients Who Have Achieved Disease Control Following First-Line Chemotherapy
Phase of Development:	2
Study Period:	Date first subject enrolled: 31 Jul 2009 Date last subject completed: 29 Oct 2012
Investigator(s):	46 investigators (A list of investigators is provided in Appendix 16.1.4.)
Study Center(s):	46 study centers located throughout Europe
Publication (reference):	To date, there have been no publications based on this study.
Study Objectives/Hypothesis:	**Primary Objective:** The primary objective of the study was to compare the progression-free survival (PFS) of colorectal cancer patients treated with CS-7017 or placebo at 18 weeks in subjects who have achieved a response of Disease Control (DC; complete response [CR], partial response [PR] or stable disease [SD]) to standard first-line therapy. **Secondary Objectives:** The secondary objectives included: • Comparing the overall PFS and overall survival (OS) of patients treated with CS-7017 or placebo; • Comparing the safety parameters of patients treated with CS-7017 or placebo; and • Comparing the overall response rate (ORR), duration of response, best overall response, and changes in Eastern Cooperative Oncology Group (ECOG) status of subjects treated with CS-7017 or placebo.* **Exploratory Objectives:** The exploratory objectives of the study were to: • Analyse the population pharmacokinetics (PK) of CS-7017;* • Evaluate changes relative to study treatment for plasma/serum biomarkers associated with the activity of peroxisome proliferator-activated receptor gamma (PPAR-γ) including adiponectin, vascular endothelelial growth factor (VEGF) and caspase 3/7; • Evaluate the expression of baseline tumor biomarkers including PPAR-gamma/retinoid X receptor (RXR), adiponectin receptor, p21, pErk and pAkt using archived tumor; and • Profile critical genes in tumor using archived tumor (mRNA expression and DNA mutation analysis), e.g. PPAR-gamma gene, APC gene and K-ras gene; to bank whole blood DNA for genotype analysis. *Note: These analyses were specified in the Statistical Analysis Plan (SAP) as changes from the protocol-specified statistical analyses. In the

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	final version of the protocol (Ver. 3.0, 09 Feb 2011), the PK objective is listed as a pharmacokinetic objective (rather than an exploratory objective) and the secondary objectives of ORR, duration of response, best overall response, and changes in ECOG scores were not included. **Hypothesis:** Monotherapy with CS-7017 compared with placebo will improve the PFS of patients who achieved an objective response of Disease Control on standard first line therapy such as FOLFOX (folinic acid, fluoriuracil, oxaliplatin) or FOLFIRI (folinic acid, fluoriuracil, irinotecan).
Study Design/Methodology:	This randomized, double-blind, placebo-controlled Phase 2 Study was designed to compare CS-7017 versus placebo in colorectal cancer patients who have achieved disease control ([CR], [PR] or [SD]) following standard first-line chemotherapy. Study medication was to be started within 8 weeks of completing first line therapy. After written informed consent was obtained from a subject, baseline evaluations were performed. The duration of this screening/baseline period was up to 4 weeks before starting study treatment. Once it was determined that a subject satisfied all inclusion/exclusion criteria, that subject was randomized to CS-7017 (0.5 mg by mouth twice a day [PO BID]) or placebo (2 tablets PO BID) in a blinded fashion. Subjects were stratified based on response to first-line therapy (SD vs. PR/CR), ECOG Performance Status (0, 1 vs. 2) and dominant site of disease (liver vs. others). Subjects received study medication twice daily, and treatment cycles were 3 weeks in duration. Disease assessments were performed at baseline and at the end of every 2 cycles (every 6 weeks ± 2 days). The database was to be cleaned and locked for unblinded analyses after the last subject randomized (screening) had been assessed for disease progression at 18 weeks. After the blind was broken, subjects in the treatment arm who tolerated the drug and whose disease had not progressed were allowed to continue therapy in the open-label extension phase. Subjects who discontinued from the study were contacted at Week 18 and then every 3 months, until death or at least 18 weeks after the last subject was randomized to treatment (whichever came first), to obtain information about disease progression status (if applicable), subsequent treatment, and survival status.
Duration of Treatment for Individual Subject:	During the blinded study phase, each subject's treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. After the blind was broken, subjects receiving placebo were discontinued from the study, and subjects on the treatment arm who tolerated the drug and whose disease had not progressed were to be allowed to continue CS-7017 therapy in the open-label extension phase until disease progression, unacceptable toxicity, or withdrawal of consent.
Number of Subjects:	Planned: 170

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	Screened: 107 Enrolled/Randomized*:* 84 (83 received treatment) Completed/Discontinued: 82 (those who were randomized and discontinued from the study) Note: Following the interim futility analysis on 02 May 2012, the sponsor (DSD) made the decision to terminate the study early. This decision was based not on clinical findings from the study, but because of changes to the standard of care within the proposed market for CS-7017.
Diagnosis and Main Criteria for Study Entry:	Eligible subjects were at least 18 years with an ECOG performance status ≤ 2 at study entry. They were to have histologically-confirmed, metastatic or locally advanced colorectal cancer (CRC) (stages III or IV) and must have received standard first line combination chemotherapy consisting of a fluoropyrimidine based regimen. Subjects received their primary treatment until best response (disease control) had been reached, i.e., CR, PR or SD. Unless CR was achieved, subjects had a minimum of one unidimensionally-measurable target lesion according to RECIST (Response Evaluation Criteria in Solid Tumors, Version 1.0).[1] Subjects entered the trial within 8 weeks after completing first line therapy. Subjects who were concomitantly using other thiazolidinediones were excluded, as were subjects with a history of diabetes mellitus requiring treatment with insulin or oral agents. Clinically significant pleural or pericardial effusion was also reason for exclusion. Subjects were required to have adequate organ and bone marrow function as assessed by clinical laboratory evaluations outlined in the protocol.
Investigational Product and Comparator Information:	**Dosage Form:** 0.25 mg tablets **Route of Administration:** oral **CS-7017 Lot No.:** [redacted] **Packaging Information:** For both CS-7017 and placebo, primary packaging consisted of aluminum to aluminum blister. The blisters were then made into pre-labelled wallets/blister cards and placed into treatment kits, each wallet/blister card containing 56 tablets. **Placebo Lot No.:** [redacted]

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was PFS at 18 weeks, defined as the time from the date of randomization to the date of the first objective documentation of disease progression or death resulting from any cause, whichever came first. Objective documentation of disease progression was based upon tumor measurements. Tumor assessment data were obtained from serial radiographic disease assessments taken at baseline and at the end of every 2 cycles (every 6 weeks ± 2 days). Response to treatment was assessed in accordance with RECIST criteria, Version 1.0.

Secondary efficacy endpoints included PFS, OS, ORR, duration of response, best overall response, and changes in ECOG Performance Status (PS) status. Variables based on response to treatment, including requirements for confirmation of response by repeat scan (to be performed at least 4 weeks after initial documentation of response), were assessed in accordance with RECIST 1.0 criteria. Survival status data

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were obtained from reported deaths and follow-up communications at Week 18 (for subjects who discontinued prior to Week 18) and then every 3 months after a subject discontinued from the study. ECOG performance status was to be collected at each cycle.

Note: The efficacy variables of ORR, duration of response, best overall response, and changes in ECOG status were not presented in the protocol, but were presented in the Statistical Analysis Plan (SAP) (Version 1.0), dated 17 Jan 2012.

Pharmacokinetics/Pharamcodynamics:

Blood samples for population PK analyses of CS-7017 were collected at specified time points in the study. Plasma concentrations of the free form of CS-7017 (R-150033) were to be measured using validated assays. Analyses of these data will be reported separately rather than in this report.

Safety:

Clinical laboratory evaluations, vital signs, electrocardiograms, physical examinations, and recording of adverse events were assessed.

Other:

Biomarkers: Exploratory biomarkers, including adiponectin, VEGF, and caspase 3/7, were proposed in the study based on the potential mechanisms reported for TZDs. Blood samples for analysis of these biomarkers were collected at specified timepoints in the study. Archived tumor tissue provided at baseline was to be used for analysis of the following exploratory tumor biomarkers: expression of PPARγ/RXR, and adiponectin receptor. As a result of inconclusive findings from other CS-7017 clinical studies VEGF and caspase 3/7 biomarkers were not analysed. Other protocol-specified analyses (p21, Akt/pAkt, and Erk/pErk) were not performed.

Pharmacogenomics: For those subjects who consented, a blood sample taken on Day 1, Cycle 1 was banked for possible future pharmacogenomic analysis.

Statistical Methods:

General Considerations:

Summary statistics were presented by treatment. For continuous variables, number of available observations (n), mean, standard deviation, median, and range are provided. In addition, coefficient variation and geometric mean are provided for biomarkers. For categorical variables, the frequency and percentage in each category is displayed. The baseline value is defined as the last non missing value before randomization. All demographic and baseline data were analysed for the intent-to-treat analysis set, full analysis set (FAS), per protocol analysis set and safety analysis set.

Efficacy:

All efficacy analyses were performed on the FAS and per protocol analysis sets.

Point estimates as well as 95% confidence intervals of 18 weeks PFS status weregenerated for each treatment arm. Comparison between the 18-week PFS status will be made using z-test after Log (-log) transformation.

For secondary endpoints, PFS and overall survival, medians and 95% confidence intervals (CIs) were provided for each treatment arm. Kaplan-Meier estimates were plotted by treatment arm. The hazard ratios for treatment effect along with the corresponding 95% confidence intervals for PFS and OS were calculated using a Cox Regression Model. The effects of prognostic factors were also explored using Cox models.

The best overall tumor response, the objective response, and the percentage of subjects with a best overall response of SD or better were tabulated by treatment group. The number of subjects and the percentage in each treatment and category was provided along with the 95% CI of the percentage. In addition, the difference in the treatment percentages after adjusting for the stratification factors as

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well as the asymptotic 95% CIs for the difference in percentages is presented for ORR and for the proportion of subjects with a best overall response of SD or better. Duration of response and duration of stable disease were summarized for responding subjects by treatment using descriptive statistics. Median duration of response was estimated using Kaplan-Meier methods. Shift tables for change in ECOG performance status, by treatment arm, are also provided.

Safety:

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0 and summarised for the number and percentage of subjects reporting treatment-emergent AEs (TEAEs). AEs/toxicities reported by the subject or noted by the Investigator and laboratory test results (haematology and blood chemistry) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 3.0, and are listed and summarised. The two treatment arms were compared with respect to the incidence and severity of AEs and laboratory abnormalities.

Pharmacokinetics and Biomarkers:

Descriptive statistics for biomarker values were computed by treatment and evaluation time.

Population PK modelling analysis will be conducted separately from the Statistical Analysis Plan of this study with possible pooling of data from other clinical studies of CS-7017. Biomarker analyses were performed on the Biomarker Analysis Set. Raw biomarker values, change from baseline, and percent change from baseline for serum biomarkers were to be summarized by treatment group and scheduled time point. The relationship between baseline values of PPAR-gamma/RXR and the efficacy variables of PFS and OS was explored using Kaplan-Meier analysis and the Cox proportional hazards model.

Interim Analysis (for futility):

To ensure participating subjects had potential for continued clinical benefit a futility analysis was performed when about 50% of the subjects had been assessed for disease progression or death at 18 weeks. Interim results were used to evaluate only the potential clinical benefit of continuing the study. No provision was made for stopping for a claim of superior efficacy of CS7017 over placebo at interim.

Note: Following the interim futility analysis on 02 May 2012, the sponsor (DSD) made the decision to terminate the study early. This decision was based not on clinical findings from the study, but because of changes to the standard of care within the proposed market for CS-7017. Therefore, a confirmatory Phase 3 study with the same design would no longer be possible.

Sample size determination:

The emphasis of the efficacy analysis in this study was on estimating the magnitude of the treatment difference between the two arms. The primary endpoint was the proportion of patients who remained alive and progression free at 18 weeks.

Assuming that the placebo arm would have 50% PFS status at 18 weeks, a total of 170 subjects with 85 subjects per arm (resulting in 76 evaluable subjects per arm assuming a 10% drop out rate) would provide approximately 86% power with two sided alpha 5% to detect a 50% improvement (i.e., 75% PFS status) at 18 weeks in the CS-7017 arm over control arm. The calculation of sample size was based on a continuity-corrected Chi-squared test procedure in nQuery Version 7.0.

Efficacy analyses were performed on the FAS and per protocol analysis set. Safety analyses were performed using the safety analysis set. Analysis of PK parameters was based on PK set. Analysis of biomarkers was based on biomarker analysis set.

Results:

The data from this study are from the complete database lock after disease progression of the last subject

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randomized to CS-7017.

Efficacy:

The PFS rate at 18 weeks in the FAS, the primary efficacy endpoint, was significantly improved by study treatment: 39.863% (95% CI: 23.5, 55.7) for the CS-7017 arm compared with 25.000% (95% CI: 13.0, 39.0) for the placebo arm (two-sided p-value <0.0001). The hazard ratio at Week 18 was 0.66. Results were similar for the Per Protocol Analysis Set.

The overall PFS was statistically different between treatment arms (log-rank test two-sided p-value=0.0380) with a hazard ration of 0.576 (95% CI: 0.351, 0.946) favoring CS-7017. The median PFS duration for the FAS was 3.0 months (95% CI: 1.4, 4.2) for the CS-7017 arm versus 2.7 months (95% CI: 1.4, 2.8) for the placebo arm. Results were similar for the Per Protocol Analysis Set.

Treatment with CS-7017 was associated with a longer OS, although this difference was not statistically significant (log-rank test p=0.1213). The hazard ratio was 0.61. The median OS in the FAS was longer in the CS 7017 arm than in the placebo arm: 22.9 months (95% CI: 12.0, NA) compared with 12.8 months (95% CI: 10.7, 17.0).

Safety:

The predominant AE of CS-7017 was fluid retention (12.2%) and associated secondary effects (eg, weight gain [51.2%], anaemia [36.6%]). No Grade 4 or 5 AEs related to CS 7017 occurred during the study. The proportion of study discontinuations due to AE (15.7% overall) waslow and mostly due to fluid retention compared to the number of discontinuations due to progressive disease (76.2% overall).

No severe neutropenia was reported.

Two deaths occurred within 30 days after the last dose of study drug, both in the placebo arm. No Grade 4 events or deaths related to study drug occurred during the study.

There were no significant trends in ECG abnormalities, and vital sign measurements were generally similar between treatment groups.

Pharmacokinetic/Pharmacodynamic:

Mean (±SD) baseline concentrations for adiponectin were similar for both treatment arms: 9.39 ng/mL (±4.51) for the placebo arm and 7.91 ng/mL (±4.93) for the CS-7017 arm. From baseline to last observation on treatment, the mean concentration of adiponectin remained relatively constant for subjects in the placebo arm. As expected, the mean concentration for subjects in the CS-7017 arm increased greatly to 35.76 ng/mL (±27.797) at Cycle 2 and then to 89.697 ng/mL (±34.449) at Cycle 3. These results further support the strong PPARγ agonist activity of CS-7017 at these doses in humans.

As CS 7017 is a selective agonist of PPARγ, the expression of this biomarker (as well as its heterodimer RXRα) is of interest. Baseline expression was determined from archived tumor tissue samples. No subjects had high expression of PPARγ; however, 3 of 22 subjects (2 in the CS 7017 arm and 1 in the placebo arm) had high expression of RXRα.

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Conclusions: There was a significant PFS improvement (18-week PFS and median PFS) with CS-7017 treatment compared to placebo treatment. Overall survival was longer in the CS-7017 arm than in the placebo arm but not statistically different. As expected, the predominant AE of CS-7017 was fluid retention and associated secondary effects (eg, weight gain, anaemia). No Grade 4 or 5 AEs related to CS 7017 occurred during the study.		
Date of the Report: 21 August 2013		