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REPORT SYNOPSIS

Name of Sponsor/Company: **Daiichi Sankyo Pharma Development**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(for National Authority Use Only)***
Name of Test Product: **CS-7017**		
Name of Active Ingredient: **(*RS*)-5-(4-{[6-(4-Amino-3,5-Dimethylphenoxy)-1-Methyl-1*H*-Benzoimidazol-2-Yl] Methoxy}Benzyl)-1,3-Thiazolidine-2,4-Dione Dihydrochloride Monohydrate**		

Title of Study:	Phase 2 Study of CS-7017 and Erlotinib in Subjects with Advanced Non-Small Cell Lung Cancer Who Failed First Line Therapy
Phase of Development:	2
Study Period:	First subject first visit date: 06-Oct-2010 Last subject last follow-up date: 23-Apr-2013
Investigator(s):	[redacted]A listing of all investigators who participated in this study is available upon request.
Study Center(s):	19 sites in the US, Germany, India, and Korea
Publication (reference):	None
Study Objectives/Hypothesis:	The primary objective was to estimate the difference in efficacy, as measured by progression-free survival (PFS), between erlotinib in combination with CS-7017 and erlotinib alone. The secondary objectives were the following: • To estimate the overall survival (OS) in the two treatment arms; • To estimate the overall response rate (ORR) in the two treatment arms; • To estimate the plasma concentration of CS-7017 at scheduled time points; • To evaluate the safety profile of the combination of CS-7017 and erlotinib relative to that of erlotinib alone. The exploratory objectives were: • To explore the prognostic or predictive significance of immunohistochemical analysis of archived tumor tissue of key elements possibly including but not limited to peroxisome proliferator-activated receptor gamma (PPARγ), retinoid X receptor, E-cadherin, and adiponectin receptors in relationship to clinical benefit from subjects treated either in the erlotinib or combination arms. • To evaluate changes in plasma adiponectin levels and explore their correlation with the effects of study treatment. • To evaluate serum CYFRA 21-1 (cytokeratin-19 fragments) levels and explore their correlation with the effects of study

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	treatment. • To explore, using archived tumor tissue, deoxyribonucleic acid (DNA) mutation of critical genes, possibly including but not limited to Kras and epidermal growth factor receptor (EGFR), associated with the target pathway and disease. • To explore effects of CS-7017 on erlotinib pharmacokinetics (PK). It was hypothesized that CS-7017 in combination with erlotinib would significantly slow the progression of non-small cell lung cancer (NSCLC) compared to standard therapy for subjects with advanced metastatic NSCLC that had progressed after first-line therapy.
Study Design/Methodology:	This was a multicenter, open-label, active-controlled, parallel group Phase 2 study. Subjects were randomly assigned on a 1:1 basis to one of two treatment arms: • CS-7017 0.5 mg twice a day (BID) in combination with erlotinib 150 mg once daily (QD) • Erlotinib alone 150 mg QD The subjects were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 vs. 2) in both groups. Cycles were 21 days long, with radiologic evaluations performed at the end of every 2 cycles. Treatment continued without interruption in subjects with complete response (CR), partial response (PR), or stable disease (SD) in the absence of withdrawal of subject consent or unacceptable toxicity. After discontinuation from the study, follow-up information was obtained. The duration of the follow-up was until death or collection of OS data ended.
Duration of Treatment for Individual Subject:	The main study lasted until at least 4 months after the last subject was randomized to treatment, depending upon the number of PFS events. Thereafter, the study continued until disease progression, withdrawals of consent, or intolerable toxicities were experienced
Number of Subjects:	Planned: 90 (45 to CS-7017 plus erlotinib and 45 erlotinib) Screened: 109 Enrolled/Randomized: 90 (45 to CS-7017 plus erlotinib and 45 erlotinib) Completed/Discontinued: 90 (45 to CS-7017 plus erlotinib and 45 erlotinib)

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Diagnosis and Main Criteria for Study Entry:	• Histologically or cytologically confirmed stage IIIB or IV NSCLC previously treated with a platinum-based regimen • Progressive disease (PD) (either no response to treatment or subsequent relapse after an objective response) after the last anti-cancer therapy • Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, Version 1.1 • ≥18 years of age • ECOG performance status of 0, 1, or 2 • Adequate organ and bone marrow function • Resolution of any toxic effects of prior therapy (except alopecia) to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 Grade ≤1 • Agreement to use effective contraception while on treatment and for at least 3 months after end of treatment • No more than two prior chemotherapy regimens for advanced disease. Maintenance therapy did not count as a separate regimen if it was given after first-line therapy without intervening disease progression. • No prior treatment with EGFR inhibitors • No treatment with anticancer drug therapy within 3 weeks before study treatment • No therapeutic or palliative radiation therapy within 2 weeks or major surgery within 4 weeks before study treatment • No administration of other thiazolidinediones (TZDs) within 4 weeks before study treatment or need for concomitant use during the study • No uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals, known HIV infection, or active hepatitis B or C infection at time of screening • No history of any of the following conditions within 6 months before initiating study treatment: diabetes mellitus requiring treatment with insulin or TZD agents; myocardial infarction with significant impairment of cardiac function; severe/unstable angina pectoris; coronary/peripheral artery bypass graft; New York Heart Association class III or IV congestive heart failure; malabsorption syndrome, chronic diarrhea (lasting > 4 weeks), inflammatory bowel disease, or partial bowel obstruction • No pericardial effusion or pericardial involvement with the	

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	tumor. No clinically significant pleural effusion (ie, requiring drainage). Subjects with minimal pleural effusion may be eligible upon request by Investigator and approval by Sponsor. • Neither pregnant nor breast feeding
Investigational Product and Comparator Information:	Dosage Form: CS-7017: 0.25 mg tablets Erlotinib: 150 mg or 100 mg tablets Route of Administration: CS-7017 0.5 mg tablets were self-administered by mouth (PO) BID, every 12 hours (± 2 hours of the scheduled administration time without reference to meals). Erlotinib 150 mg or 100 mg tablets were self-administered PO QD. Erlotinib was taken in the morning, at the same time every day, on an empty stomach, 1 hour before or at least 2 hours after meals. Lot No.: [redacted] Packaging Information: CS-7017 was supplied as 0.25 mg tablets, packaged in aluminum/aluminum blister cards (20 tablets per blister card). Commercially available erlotinib was either provided from a central source or by prescription, per local site procedures. In Korea, commercially available erlotinib (Tarceva™, Roche Korea Co., Ltd.) purchased by Daiichi Sankyo in Korea was provided to the study site.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was PFS, defined as the time from the date of randomization until the date of the first objective evidence of disease progression or death from any cause, whichever occurred first. Disease progression was determined in accordance with RECIST criteria, Version 1.1.

The secondary efficacy endpoints were OS, ORR, duration of response, and best overall response. For purposes of determining the ORR, tumor response was based on the best overall response recorded for each subject from the date of the randomization.

Tumor response data was obtained from serial radiographic assessments at the end of every 2 cycles (±7days) and survival data was obtained from follow-up communications every 3 months (± 15 days). Variables based on response to treatment were assessed in accordance with RECIST criteria, Version 1.1.

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Pharmacokinetics/Pharmacodynamics:
Pharmacokinetics of CS-7017 was assessed in subjects who were randomized to CS-7017 plus erlotinib. The erlotinib level in plasma was also assessed in all subjects from both treatment groups.

Adiponectin was evaluated as a biomarker to assess the pharmacologic activity of CS-7017.

As part of this study, a blood sample was also banked for possible future pharmacogenomics analysis.

Safety: Safety assessments included clinical laboratory tests, vital signs, body weight, electrocardiograms, physical examinations, ECOG performance status, and recording of adverse events (AEs) and concomitant medications.

Other: Not applicable

Statistical Methods:

Summary statistics were presented by treatment group. For continuous variables, number of available observations (n), mean, standard deviation, median, and range were provided. In addition, the coefficient of variation and geometric mean were provided for biomarkers. For categorical variables, the frequency and percentage in each category was displayed. Disposition and reasons for discontinuation were listed and summarized for all subjects.

Study drug exposure and treatment duration were summarized using descriptive statistics by treatment group for the Safety Analysis Set.

Efficacy:
Efficacy analysis focused on determining the magnitude of treatment effect. In addition, hypothesis testing was generated for key efficacy variables.

The primary endpoint of this study, PFS status, was plotted using Kaplan Meier product limit estimates, by treatment group. Point estimates and the corresponding 95% confidence interval (CI) were provided for median PFS by treatment group. Comparisons of PFS between treatment groups were made using a stratified log-rank test as well as a Cox proportional hazard regression model adjusting for ECOG performance status (0, 1 vs. 2). Within the same Cox model, point estimates of hazard ratios (HR) and the 95% CI were obtained.

The key secondary endpoints were OS and ORR for this study. Kaplan Meier product limit estimates were plotted for OS by treatment group. Point estimates and the corresponding 95% CI were provided for median OS by treatment group. Cox proportional hazard regression model adjusting for ECOG performance status (0, 1 vs. 2) was used to compare OS between two treatment groups.

The best overall tumor response (CR, PR, SD, PD, and inevaluable), the ORR (the best response of CR or PR combined), and the percentage of subjects with a best overall response of SD or better were

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tabulated by treatment group. The difference in the treatment percentages after adjusting for the stratification factors as well as the asymptotic 95% CIs for the difference in percentages were presented for ORR and for the proportion of subjects with a best overall response of SD or better.

Safety:

Safety analyses were descriptive and were presented by treatment group in tabular format with the appropriate summary statistics.

The demographic and baseline characteristics such as baseline ECOG performance status, disease status, and other baseline characteristics were summarized by treatment group and overall.

Assessments of change from baseline to postbaseline or the ratio of postbaseline to baseline included only those subjects with both baseline and postbaseline measurements. The last value of a variable taken before the first dose of study drug was used as the baseline value, unless otherwise specified. In general, missing or dropout data were not imputed for the purpose of data analysis.

Pharmacokinetics/Pharmacodynamics:

Pharmacokinetics analysis was descriptive for the plasma concentration of CS-7017 and erlotinib.

Population PK analysis was conducted separately with possible pooling of data from other clinical studies of CS-7017.

Pharmacodynamic analyses were descriptive for applicable biomarker values (adiponectin and CYFRA 21-1) and were summarized by treatment group and scheduled time point.

Summary:

Efficacy Results:

For the primary efficacy endpoint of PFS, differences between treatment groups were not statistically significant (HR = 0.882; 95% CI = 0.534 to 1.456; p-value = 0.6086) with a median PFS of 4.1 months (95% CI = 2.7 to 6.7) for CS-7017 plus erlotinib v 3.0 months (95% CI = 2.2 to 5.3) for erlotinib alone.

The secondary efficacy endpoints of OS and ORR were also not significantly different between treatment groups. The median OS for CS-7017 plus erlotinib was shorter (7.6 months, 95% CI = 3.8 to 12.0) compared to erlotinib alone (11.4 months, 95% CI = 9.7 to 15.0), but the difference in OS was not significant (HR = 1.201; 95% CI = 0.736 to 1.960; p-value = 0.3126). The confirmed ORR was 20.5% for subjects in the CS-7017 plus erlotinib group and 20.0% for subjects in the erlotinib group. No subject had a confirmed or unconfirmed CR. Best overall response of SD or better was comparable in both treatment groups.

There was no improvement in duration of response over erlotinib alone nor percent change in tumor diameters.

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Safety Results:

All of the subjects receiving CS-7017 plus erlotinib reported a treatment-emergent AE (TEAE). Ninety-six percent (96%) of subjects receiving erlotinib alone reported a TEAE. There were more treatment-emergent serious AEs (SAEs), and discontinuations due to TEAEs in the CS-7017 plus erlotinib group. Serious AEs were reported in 54.5% of subjects in the CS-7017 plus erlotinib group, most commonly in the system organ classes of Blood and Lymphatic System Disorders (20.5% of subjects). Twenty-two TEAEs leading to death were reported, 15 (34.1%) in the CS-7017 plus erlotinib group and 7 (15.6%) in the erlotinib group. Grade 5 SAEs reported for two subjects in the CS-7017 plus erlotinib group were myocardial infarction and death (cause unknown). One subject in the CS-7017 plus erlotinib group was reported with a Grade 4 SAE of pericardial effusion. All three of these SAEs were reported to be related to CS-7017 plus erlotinib.

Greater mean reductions in hemoglobin from study start to end of treatment were observed in the CS-7017 plus erlotinib group compared with the erlotinib group.

In the CS-7017 plus erlotinib group, 56.8% of subjects had TEAEs associated with edema; the most common events were face edema (22.7%) and edema peripheral (38.6%).

No edema-related events were > Grade 3, and the only Grade 3 event reported in more than one subject in the CS-7017 plus erlotinib group was peripheral edema (2 subjects, 4.5%).

Pharmacokinetic/Pharmacodynamic Results:

Mean adiponectin levels increased more than 8-fold with the administration of CS-7017 0.5 mg BID, consistent with pharmacodynamic modeling, compared to a <10% change with erlotinib alone. This significant increase with CS-7017 administration confirms target engagement of the PPARγ inhibitors.

Conclusions:

- There was no statistically significant improvement in PFS (HR = 0.882; 95% CI = 0.534 to 1.456; p-value = 0.6086) or OS (HR = 1.201; 95% CI = 0.736 to 1.960; p-value = 0.3126) for the combination of CS-7017 plus erlotinib as compared to erlotinib alone.
- The ORR and best overall response (SD or better) were comparable in both treatment groups, with a confirmed ORR of 20.5% for the CS-7017 plus erlotinib group and 20.0% for the erlotinib group.
- Large increases in adiponectin levels with CS-7017 administration confirm target engagement of the PPARγ inhibitors.
- The safety and tolerability of CS-7017 plus erlotinib was acceptable, but certain AEs associated with fluid retention side effects of CS-7017 were reported at a higher incidence, including anemia, facial edema, peripheral edema, weight increase and

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pleural effusion. In addition, constipation, pyrexia, decreased appetite and pain in the extremities were also reported at a higher frequency.		
Date of the Report: 12-November-2014		