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Report Synopsis

The synopsis of this report can be found in this file: CS1008-A-E202-e3-synopsis.pdf.

Name of Sponsor/Company: Daiichi Sankyo Development	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Test Product: CS-1008 Lyophilised Powder for Concentrate for Solution for Infusion		
Name of Active Ingredient: CS-1008		

Title of Study:	Randomised, double-blinded, placebo-controlled Phase 2 study of CS-1008 in combination with carboplatin/paclitaxel in chemotherapy naïve subjects with metastatic or unresectable non-small cell lung cancer
Phase of Development:	2
Study Period:	First subject first visit date: 24 Jun 2009 Last subject last follow-up date: 17 May 2011
Investigator(s):	[redacted] For other investigators, see Appendix 16.1.4
Study Center(s):	15 For other investigational sites, see Appendix 16.1.4
Publication (reference):	None at issue.
Study Objectives/Hypothesis:	The primary objective was: • To determine the difference in progression-free survival (PFS) in previously chemotherapy naïve subjects with Stage IIIB wet, or Stage IV NSCLC treated with CS-1008 plus carboplatin/paclitaxel versus subjects treated with placebo plus carboplatin/paclitaxel. The secondary objectives were as follows: • To evaluate the difference between the two treatment regimens CS-1008 plus carboplatin/paclitaxel and placebo plus carboplatin/paclitaxel with respect to: o Overall survival (OS) o Objective response rate (ORR) o Duration of response • To determine the safety and tolerability of CS-1008 administered in combination with carboplatin/paclitaxel to previously chemotherapy naïve subjects with Stage IIIB wet or Stage IV NSCLC. The exploratory objectives were to evaluate: • Changes in serum apoptosis biomarkers (ie, activated caspases 3/7, 8, cytochrome c, and M30

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	antigen), and, if archived tumour tissue was available, could have included: • protein expression of death receptor 5 (DR5), Bcl-2–associated X protein (Bax), Bcl-2-related protein (Bcl-x), cellular inhibitor of apoptosis (cIAP), galactosamine polypeptide Nacetylgalactosaminyltransferase (GALNT-14), and myeloid cell leukemia sequence 1 (Mcl-1) in archived tumour, and; • genotype/gene expression analysis of critical genes related to NSCLC or its treatment, possibly toinclude but not limited to DR5, Bax, Bcl-x, cIAP, GALNT-14, and Mcl-1, in archived tumour. Blood DNA was banked for pharmacogenomic analysis, including future analysis for leukocyte FcγR assessment. Additionally, population pharmacokinetics (PK) and pharmacodynamics (PD) modeling analysis to explore relationship of exposure vs. other biomarkers and treatment responses will be conducted in the future.
Study Design/Methodology:	This was a Phase 2, double-blind, placebo-controlled, randomised, two-arm, multicentre study of CS-1008 or placebo administered in combination with carboplatin/paclitaxel to adult chemotherapy-naïve subjects with Stage IIIB wet or Stage IV NSCLC. CS-1008 or placebo (infusion solution without investigational drug) was administered intravenously (IV) every 3 weeks (1 cycle). Commercially available carboplatin/paclitaxel was administered IV once every 3 weeks (1 cycle) for a total of 6 cycles unless there was unacceptable toxicity or progression of disease. Subjects who completed 6 cycles of CS-1008 or placebo in combination with carboplatin/paclitaxel and had at least stable disease (SD) were continued to receive CS-1008 monotherapy or placebo until the occurrence of progressive disease (PD) or unacceptable toxicity, at which time they were discontinued from the study. The proposed target dosing regimen was: • CS-1008: 10 mg/kg or placebo (infusion solution without investigational drug) at Week 1 of Cycle 1 and 8 mg/kg or placebo once every 3 weeks thereafter; • Paclitaxel: 175 mg/m^2 once every 3 weeks for a maximum of 6 cycles and; • Carboplatin: area under the concentration vs. time curve (AUC) of 6 once every 3 weeks for a maximum of 6 cycles. Before beginning dosing with the target regimen, a safety cohort was assessed. These subjects underwent dose escalation of CS-1008 and

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carboplatin.

Safety cohort:

This was the first study in which CS-1008 was administered to subjects once every 3 weeks instead of once weekly, the first 9 subjects enrolled in the study were enrolled sequentially on a dose escalation scheme and received CS-1008 on an open-label, non-randomised basis, with no placebo control. In this phase, the initial 10 mg/kg dose of CS-1008 in Cycle 1 was administered as 2 doses (i.e. 1 dose each week for 2 weeks). If CS-1008 was well tolerated, the first dose in Cycle 1 was escalated for the next 3-subjects group and the second dose was reduced, according to the scheme outlined below.

The first 3 subjects in the dose escalation phase received an initial dose of 6 mg/kg CS-1008 (Cycle 1, Week 1), followed by 4 mg/kg at Week 2. Provided CS-1008 was well tolerated at each dose level, the dose was increased as follows:

- 8 mg/kg at Week 1 of Cycle 2 and once every 3 weeks thereafter,

The next 3 subjects in the dose escalation phase received an initial dose of 8 mg/kg of CS-1008 (Cycle 1, Week 1), followed by 2 mg/kg at Week 2. Provided CS- 1008 was well tolerated at each dose level, the dose was continued as follows:

- 8 mg/kg at Week 1 of Cycle 2 and once every 3 weeks thereafter,

The next 3 subjects in the dose escalation phase received an initial dose of 10 mg/kg of CS-1008 (Cycle 1, Week 1). Provided CS-1008 was well tolerated at each dose level, the dose was continued as follows:

- 8 mg/kg at Week 1 of Cycle 2 and once every 3 weeks thereafter,

This was the first study of CS-1008 in combination with carboplatin/paclitaxel, the first 9 subjects enrolled in the study (Subjects 1 through 9, inclusive; safety cohort) received a lower dose of carboplatin in the first cycle.

These subjects received the following regimen on Week 1 of Cycle 1.

- CS-1008 at a dose as indicated above; paclitaxel at a dose of 175 mg/m^2, and carboplatin at a dose of AUC of 5.

If well tolerated, the dose of carboplatin was escalated to the target dose (AUC of 6) in Cycle 2 and subsequent treatment cycles.

On Day 1 of the first 6 cycles, CS-1008 was administered first

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	followed by paclitaxel and then carboplatin. After administration of CS-1008, subjects in the safety cohort were observed for adverse events (AEs) for 30 minutes before administration of paclitaxel and carboplatin. Subjects in the safety cohort were also observed for AEs for 2 hours after administration of all study drugs. The safety of this regimen in the 9 subjects in the safety cohort was reviewed by the Investigator and the Sponsor. Assuming that the regimen was found to be acceptable from a safety perspective, all subsequent subjects were randomised with regard to administration of CS-1008 or placebo and received the proposed target regimen as defined above. Stratification factors were "squamous" vs. "non-squamous" and "Stage IIIB wet" vs. "Stage IV". Subjects who completed 6 cycles of CS-1008 or placebo in combination with carboplatin/paclitaxel and had at least SD received CS-1008 or placebo monotherapy until disease progression, unacceptable toxicity, or consent withdrawal. After the study was unblinded for the purposes of the primary analysis, subjects who had completed 6 cycles of placebo+ carboplatin/paclitaxel regimen (i.e. those who were assigned to placebo treatment), no longer were given placebo. Upon unblinding, those subjects in the CS-1008 treatment arm who had tolerated CS-1008 and completed 6 cycles of carboplatin/paclitaxel, and whose disease had not progressed (i.e. SD or better), continued monotherapy with CS-1008 at the same dose. After unblinding, the study remained open and the subjects were followed for their survival information. After discontinuation from the study, subjects were contacted at 3 month intervals to obtain information about disease progression, if applicable, and survival status until the closure of the main study phase. Those subjects in the CS-1008 treatment arm, who had tolerated CS-1008, completed 6 cycles of carboplatin/paclitaxel, and whose disease had not progressed (i.e. SD or better) upon closure of the main study phase, continued monotherapy with CS-1008 in the extension phase at the same dose they received during the main study phase.
Duration of Treatment for Individual Subject:	Six cycles of CS-1008 or placebo in combination with carboplatin/paclitaxel and had at least SD, received CS-1008 or placebo monotherapy until disease progression, unacceptable toxicity, or consent withdrawal. The duration of participation for each subject was not defined as subjects who completed 6 cycles of treatment.
Number of Subjects:	Planned for randomization: 100

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	Planned for safety cohort: 9 Screened but not enrolled: 15 Enrolled but not dosed: 2 Randomised: 100 randomised with 99 subjects included in this study report. Included in the CSR: 99 (cut-off date: 31 May 2011) Full analysis set: 97 Per protocol analysis set: 92 Safety cohort: 9 Safety analysis set: 106 (includes 9 subjects of the safety cohort) Pharmacokinetic analysis set: 57 Biomarker analysis set: 105 Ongoing (cut off date: 31 May 2011): 2 Discontinued: 106
Diagnosis and Main Criteria for Study Entry:	Previously chemotherapy naïve subjects with Stage IIIB wet or Stage IV NSCLC and measurable disease who met study eligibility criteria.
Investigational Product and Comparator Information:	CS-1008 Lyophilised Powder for Concentrate for Solution for Infusion: Dosage Form: Supplied as a lyophilized powder for injection in single-use vials (single-strength only). Route of Administration: intravenous Lot No.: [redacted] and [redacted] Packaging Information: cartons containing 20 vials of a single strength of CS-1008 Lyophilised Powder for Concentrate for Solution for Infusion. Commercially available carboplatin and paclitaxel for IV administration: Both were locally sourced.
Criteria for Evaluation: Primary efficacy: Progression-free survival (PFS). Secondary efficacy: OS, ORR, duration of response, best overall response, and ECOG score. Exploratory: Changes of serum biomarkers of apoptosis: activated caspases 3/7, 8, cytochrome c, and M30 antigen; and outcomes of population PK and pharmacodynamic modeling analysis.	

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Additional exploratory: Protein expression and genotype/gene expression of critical genes related to NSCLC or its treatment, possibly including but not limited to DR5, Bax, Bcl-x, cIAP, GALNT-14, and Mcl-1, in available archived tumour samples.

Pharmacokinetics/Pharmacodynamics: See above (Exploratory)

Safety: AEs, clinical laboratory evaluations, physical examination findings, and vital sign measurements.

Other: None

Statistical Methods:

The Full Analysis Set (FAS) was defined as all subjects who were randomised and received at least one dose of study medication. All efficacy analyses were carried out on the FAS. A secondary analysis was performed using the per protocol analysis set, defined as subjects who were randomised, had no major violations in the eligibility criteria for randomisation, and received at least one dose of carboplatin/paclitaxel, and one dose of CS-1008 or placebo, and had no other major protocol violations.

Duration of PFS was defined as the time from the subject's randomisation (i.e. for randomised subjects) or date of first dose (for safety cohort subjects) to 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 recorded on the CRF page "overall tumor assessment".

Subjects who were alive and progression-free at the time of the PFS analyses were censored at the date of the last tumor evaluation.

A Cox proportional hazards model was employed to estimate the hazard ratio between the two treatment groups. The model included the treatment group as a factor as well as the stratification factors used in randomization which included the stage of the disease (stage IIIB wet versus stage IV) and type of NSCLC (squamous versus non-squamous). In addition, the following covariates were entered in a stepwise manner: age, gender, previous radiotherapy (yes/no), other cancer history (yes/no), and time from diagnosis. Within the framework of the proportional hazards model, the point estimate of hazard ratio was provided along with 80% and 95% CIs. In addition, a stratified log-rank test was employed to assess whether there was a difference between the two treatment arms, with a p-value presented for the comparison; the stratification factors are disease stage and histology type.

In addition, Kaplan-Meier product limit estimates for PFS were plotted for each treatment group, and estimates of median PFS was provided together with the 95% confidence interval (CI).

The statistical analysis for the secondary efficacy endpoints included:

- The hazard ratio for the treatment effect on OS was provided, together with the 80% and 95% CIs, and following the same method described for the PFS analysis
- Kaplan-Meier product limit estimates for OS was plotted for each treatment group and median OS estimated and;
- ORR and duration of response was summarised by treatment group with descriptive statistics. Duration of response was summarised only if the data warrant.

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For the examination of subgroups, prospectively the subgroups were defined as follows:

1. Cell histology based on squamous and non-squamous cell types. Subtypes within non-squamous cell histology will not be defined.
2. Genotypes based on FCGR2A-H131R and FCGR3A-V158F polymorphisms

   •Positive: FCGR2A-H131R (H/H) or FCGR3A-V158F (V/V)

   •Negative: Subjects who have genotyping data and who are neither V nor H homozygous

For each of the subgroups described above, the following exploratory analyses were performed in the FAS:

1. Within subgroups: A Cox regression analysis was performed that included treatment as the only model factor. Hazard ratio estimates for treatment effects are displayed graphically using a forest plot. A K-M analysis was also performed within each subgroup. Treatments were compared using the unstratified log rank test. P-values for subgroups, except for cell histology and FCGR2A-H131R, and FCGR3A-V158F polymorphisms, were interpreted as descriptive.
2. Interaction between treatment and subgroup classification factor: A Cox regression analysis was performed that included treatment, subgroup, and treatment × subgroup interaction as model factors. P-values for the interaction term are displayed. They were not interpreted for inferential purposes, but only as a measure of the strength of the interaction.

All analyses involving safety data (extent of exposure, AEs, laboratory results, vital signs and physical exam) were performed on the safety analysis set by source of CS-1008 and overall (all subjects).

Summary:

Efficacy Results:

The number of subjects with progressive disease or death was 34 (N=49) in the CS-1008 group and 34 (N=48) in the placebo group for the full analysis set. Median PFS was 5.4 months (95% CI 3.3; 6.6) for the CS-1008 group, and 4.3 months (95% CI 4.1; 5.8) for the placebo group of the full analysis set (p=0.5000 by log-rank test). Further, the number of subjects with progressive disease or death was 39 (N=49) in the CS-1008 group and 39 (N=48) in the placebo group for the sensitivity analysis (i.e., removing censoring of non-PFS discontinuations) of the full analysis set. For the sensitivity analysis, median PFS was 5.4 months (95% CI 3.3; 6.5) of the CS-1008 group, and 4.3 months (95% CI 4.1; 5.8) of the placebo group. Similar median PFS (months) values were observed for the cell histology subgroup (i.e. non-squamous and squamous).

The hazard ratio (treated:untreated) in the FcγR2A-H131R/FcγR3A-V158F polymorphism positive subgroup was 0.760 (95% CI 0.105; 5.512). However, no definitive conclusions regarding PFS

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benefit can be drawn in this subgroup due to the wide confidence interval.

The number of subjects who died was 29 (N=49) in the CS-1008 group and 32 (N=48) in the placebo group for the full analysis set. Median OS was 8.4 months (95% CI 6.9; 16.3) for the CS-1008 group, and 9.0 months (95% CI 7.6; 14.5) for the placebo group of the full analysis set (p=0.8491 by log-rank test). Further, the number of subjects who died was 27 (N=47) in the CS-1008 group and 29 (N=29) in the placebo group for the per protocol analysis set. For the per protocol analysis set, median OS was 9.1 months (95% CI 7.0; NA) of the CS-1008 group, and 9.7 months (95% CI 7.7; 15.8) of the placebo group.

Similar number of deaths and median OS values were observed between the two treatment groups for the cell histology subgroup (i.e. non-squamous and squamous), and the FcγR2A-H131R/FcγR3A-V158F polymorphism subgroups (i.e. positive and negative). In contrast to PFS, the hazard ratio (treated: untreated) in the FcγR2A-H131R/FcγR3A-V158F polymorphism positive subgroup is close to 1 (hazard ratio=0.906 (95% CI 0.304; 2.704)). Therefore, as with the comparable estimate for PFS, no firm conclusions can be drawn due to the breadth of the confidence interval.

No subject in either treatment group exhibited a confirmed complete response. However, 12 (24.5%) subjects in the CS-1008 group and 11 (22.9%) subjects in the placebo group exhibited a confirmed partial response. For the other response measures, percent differences ranged from -4.4% to 4.1% for confidence intervals, calculated for 95% confidence in the full analysis set.

Median values for duration of response (confirmed responses) were 20.71 weeks and 19.86 weeks for the CS-1008 group and the placebo group, respectively. For the confirmed and unconfirmed responses, median values were 23.14 weeks and 19.43 weeks of the CS-1008 group and the placebo group, respectively. Duration of stable disease median values was 19.14 weeks for the CS-1008 group and 23.86 weeks for the placebo group.

Safety Results: Ninety one (93.9%) subjects experienced at least one treatment emergent adverse events (TEAE). Within the safety cohort all subjects (100.0%) experienced at least one TEAE.

The most common TEAEs were fatigue (n=32/65.3%), followed by alopecia (n=30/61.2%), polyneuropathy (n=16/32.7%), and nausea (n=14/28.6%) in the CS-1008 group, whereas the most common TEAEs in the placebo group were alopecia (n=34/70.8%), fatigue (n=24/50.0%), polyneuropathy (n=22/45.8%), and nausea (n=21/43.8%). In the all combined CS-1008 (i.e., CS-1008 + safety cohort) group, the most common TEAEs with the highest percent subjects were fatigue (n=41/70.7%), alopecia (n=35/60.3%), polyneuropathy (n=21/36.2%), and nausea (n=20/34.5%).

In general, the type and incidence of the most frequent TEAEs were similar between the two treatment groups. However, in some instances there were more TEAEs in the CS-1008 group when compared to the placebo group. Of note, these were anaemia, neutropenia, and thrombocytopenia

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adverse events, indicating possibly mild myelosuppressive effect with CS-1008 treatment. Additionally, there were more pruritus and rash adverse events in the CS-1008 group, suggesting possible low grade hypersensitivity reaction with CS-1008, and there were more pleural effusion adverse events with CS-1008. Further, there were more grade ≥3 neutropenia treatment emergent events in the CS-1008 group when compared to the placebo group.

The most common treatment emergent SAEs were pleural effusion (n=4/8.2%), followed by pneumonia (n=3/6.1%) and anaemia (n=2/4.1%) in the CS-1008 group.

The number of deaths with any TEAEs for the safety analysis set were 3 (6.1%) in the CS-1008 group, 3 (6.3%) in the placebo group and none in the safety cohort group. All TEAEs were judged by the investigator as SAEs leading to death. None of these were related to CS-1008 or placebo treatment. The number of deaths, including deaths during follow-up period for the safety analysis set were 27 (55.1%) in the CS-1008 group, 29 (60.4%) in the placebo group, 8 (88.9%) in the safety cohort group, and 35 (60.3%) in the all combined CS-1008 group.

There were 26 (53.1%) subjects in the CS-1008 group and 19 (39.6%) subjects in the placebo group with TEAEs related to CS-1008/placebo treatment.

The number of subjects discontinuing CS-1008/placebo treatment due to TEAE related to CS-1008/placebo were 2 (4.1%) in the CS-1008 group and 3 (6.3%) in the placebo group, but none in the safety cohort group. The number of subjects discontinuing CS-1008/placebo treatment due to at least one treatment emergent SAE were 6 (12.2%) in the CS-1008 group and 6 (12.5%) in the placebo group, but none in the safety cohort group. Further, the number of subjects discontinuing CS-1008/placebo treatment due to treatment emergent SAE related to CS-1008/placebo were 2 (4.1%) in the CS-1008 group and 1 (2.1%) in the placebo group, but none in the safety cohort. Furthermore, there were no TEAEs leading to death related to CS-1008/placebo treatment.

Finally, no clinically meaningful mean changes from baseline in hematology, serum chemistry and urinalysis values were evident during the study.

Pharmacokinetic/Pharmacodynamic Results: PK data was not analyzed. The data collected from this study will be combined with PK data from other CS-1008 studies for population PK analyses and will be reported separately. No pharmacodynamic data collected and investigated.

Other Results:

Investigational Biomarkers: There was no apparent differentiation between subjects randomised in the CS-1008 group and the placebo group.

Human Anti-humanized Antibody: All samples assayed for HAHA were negative at each study visit prior to start of infusion of CS-1008, and 3 months after the end of treatment.

Conclusions:

The results of this Phase 2, placebo controlled, randomized, two-arm study showed that CS-1008 was not effective in this combination treatment and setting, in an unselected population.

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<tr><td colspan="3">The safety profile is good and further research of other combinations and populations may be considered.</td></tr>
<tr><td colspan="3">Date of the Report: 7 Aug 2012</td></tr>
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