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2. REPORT SYNOPSIS

Name of Sponsor/Company: Daiichi Sankyo Pharma Development	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: DJ-927 capsule	Volume:	
Name of Active Ingredient: DJ-927	Page:	

Title of Study:
A Phase II study of DJ-927 administered orally once every three weeks as second line therapy to subjects with locally advanced or metastatic non-small cell lung cancer after failure of a platinum-based non-taxane regimen.

Investigators:
[redacted]

Study Centers:
Seven centers in Europe participated in this study:
Center 01: Het Nederlands Kanker Instituut, Antoni van Leeuwenhoek Ziekenhuis (NKI-AVL), Plesmanlaan 121, 1066 CX, Amsterdam, The Netherlands.
Center 02: Asklepios Fachkliniken, München-Gauting, Onkologische Abteilung, München – Gauting, Station 02, Robert-Koch-Allee 2, 82131 Gauting, Germany.
Center 03: Mátrai Állami Gyógyintézet Bronchologia, H-3233 Mátraháza, Hungary
Center 04: Békés Megyei Képviselőtestulet Tüdőkórháza, H-5703 Gyula, Sitka u.1, Hungary.
Center 05: Országos Korányi Tbc és Pulmonológiai Intézet, H-1529 Budapest, Pihenő u.1, Hungary.
Center 06: Katedra i Klinika Pneumonologii, Onkologii i Alergologii, Akademii Medycznej im. prof. Feliska Skubiszewskiego w Lublinie, 20-950 Lublin, ul. Jaczewskiego 8, Poland.
Center 07: Mazowieckie Centrum Leczenia Chorób Pluc i Gruźlicy, ul. Reymonta 83/91, 05-400 Otwock, Poland.

Publication (reference): Not applicable

Study Period	**Phase of Development:**
First Subject Enrolled: 18 Oct 2004 Last Subject Contacted: 18 Feb 2006	Phase II

Objectives:
Primary objective:

- To assess the anti-tumor activity of DJ-927 when administered orally in a capsule form once on Day 1 of a three-week course, to subjects with locally advanced or metastatic NSCLC who have failed previous treatment with a platinum-based (non-taxane) regimen for advanced disease.

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Secondary objectives:

- To assess the duration of response.
- To assess the Time to Tumor Progression (TTP).
- To assess the Time to Treatment Failure (TTF).
- To assess the Median Survival Time (MST) and the 12 month survival rate.
- To evaluate the quantitative and qualitative toxicities of DJ-927 with this dosing schedule.
- To evaluate the pharmacokinetics (PK) of DJ-927 in plasma.

Methodology:
This was a multi-center Phase II study, open-label, single arm, 27 mg/m^2 or 35 mg/m^2 dose. Treatment courses were to be continued until disease progression or the subject experienced unacceptable toxicity as evaluated by the Investigator, or the subject withdrew consent. A three-outcome single-stage design was to be applied for this study. Plasma PK analysis was to be performed on Days 1, 3, 8 and 22 of Course 1 in all subjects, with an additional three samples on Day 22 post second dose for those subjects who fulfilled dose escalation criteria.
Both hematological and non-hematological toxicities or adverse events (AEs) that were considered definitely, probably or possibly drug-related were to be monitored until resolution, or until no further change in the subjects' condition could reasonably be expected.

Number of Subjects (Planned and Analyzed):
It was planned to enroll up to 37 subjects to confirm the recommended Phase II dose (27 mg/m^2 or 35 mg/m^2) in this subject population.
Overall, 36 subjects were registered and included in the Intent to Treat (ITT) population, 34 subjects were included in the Safety population, and 28 subjects were included in the Efficacy population.
In the Safety population, 34/34 subjects (100.0%) received 27 mg/m^2 as their initial dose level.

Main Inclusion/Exclusion Criteria:
Inclusion criteria: Aged 18 years or over with histologically and/or cytologically confirmed locally advanced or metastatic NSCLC. No more than one prior systemic platinum-based (non-taxane) chemotherapy regimen for locally advanced or metastatic NSCLC. The subject should have measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), demonstrated tumor progression at time of entry into the study, and reasonable survival expectation (> 12 weeks). For subjects who had received prior radiotherapy, measurable disease must have been located outside the previously-irradiated field. Eastern Cooperative Oncology Group (ECOG)

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performance status of 0-2.
Exclusion criteria: No measurable disease. Continuing toxicities related to previous anti-tumor therapy and administration of concurrent or previous prior myelosuppressive therapy within 4 weeks (or 6 weeks for prior treatment with nitrosourea, mitomycin C or carboplatin). Prior taxane therapy or prior wide field radiotherapy within the previous 4 weeks or radiotherapy to limited portals within 2 weeks. History of known or suspected central nervous system metastases. History of other malignancy (except resected non-melanoma skin cancer or resected carcinoma *in situ* of the cervix), unless in complete remission and off all therapy for that disease for a minimum of 2 years. Concurrent serious infection or concurrent severe or uncontrolled underlying medical disease unrelated to the tumor that was likely to compromise subject safety and affect the outcome of the study. History of any severe or life-threatening hypersensitivity reaction. Clinically significant dysphagia or malabsorption that precludes the ability to comply with oral medication and absorption of DJ-927. Any contra-indication, including extensive intestinal surgery that would impair small intestinal absorption of taxanes.

Test Product, Dose and Mode of Administration, Lot Number:
DJ-927 was to be given as a single oral dose once every 21 days. In order to confirm the maximum tolerated dose (MTD), a first cohort of six subjects was to receive a dose of 27 mg/m^2 in Course 1. If fewer than two dose limiting toxicities (DLT) were observed at 27 mg/m^2 during the first course of treatment, a second cohort of six subjects was to be treated at a dose of 35 mg/m^2. If fewer than two DLTs were observed at 35 mg/m^2 during the first course of treatment, the study was to continue at that dose level. Otherwise, the dose was to be reduced and the study continued at 27 mg/m^2. DJ-927 was supplied as 10 mg capsules.
Lot numbers:
[redacted] (expiry date: 30 Sep 2005)
[redacted] (expiry date: 30 Sep 2007)

Reference Therapy, Dose and Mode of Administration, Lot Number:
Not applicable.

Duration of Treatment:
Subjects were to be treated until disease progression or unacceptable toxicity occurred or withdrawal of consent by subject.

Criteria for Evaluation:
Tumor response evaluation: RECIST.
Toxicity Evaluation: Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0.

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Efficacy:

The primary efficacy endpoint of this study was overall tumor response.

The secondary efficacy endpoints of this study were:

- Duration of response.
- Time to tumor progression.
- Time to treatment failure.
- Median survival time and the 12 month survival rate.
- Pharmacokinetics of DJ-927 in plasma.

Pharmacokinetics:

The primary pharmacokinetic endpoint was evaluation of PK of DJ-927 in plasma by calculating AUC, clearance (CL), C_{max}, T_{max} and $T_{1/2.}$

Safety:

The safety endpoints of this study were evaluating the quantitative and qualitative toxicities of DJ-927 (AEs, vital signs, weight, body surface area [BSA], ECOG performance status and clinical laboratory tests).

Statistical Methods:

All subjects who were registered in the study were considered eligible for the ITT population and were summarized for demographic, and primary and secondary efficacy variables. All subjects who received any study medication were considered eligible for the Safety population and were summarized for safety variables. All subjects who completed at least one course of DJ-927 (21 days), had measurable disease, and did not have any major Protocol deviations, were considered eligible for the Efficacy population and were summarized for all efficacy variables. The Efficacy population was the primary population for the efficacy variables.

The primary efficacy endpoint (best overall response) was analyzed for both the ITT and the Efficacy populations and 95% exact confidence intervals (CIs) were calculated using the Binomial distribution. All secondary efficacy endpoints were analyzed for the Efficacy population. Key secondary endpoints (TTP, TTF and MST) were analyzed for the ITT and Efficacy populations and Kaplan-Meier survival plots were presented. All safety variables were summarized for the Safety population.

The sample size was determined based on the following: Null H_0: response rate $\leq$ 3% versus alternative Ha: response rate was $\geq$ 15%. For this three-outcome, one-stage-design and $\alpha = 0.05$, a sample size of 28 subjects was to yield type II error $\beta \leq 0.2$, and power $\geq$ 80%.

SUMMARY-CONCLUSIONS

Disposition:

There were 36 subjects who were registered in the study and included in the ITT population. There were 34 subjects who received study medication and were

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included in the Safety population (Subjects 007 and 015 did not take any study drug and were excluded from the Safety population and the Efficacy population). There were 28 subjects who were included in the Efficacy population (six subjects [Subjects 001, 003, 009, 019, 027, and 036] did not complete one course of DJ-927 and were therefore excluded from the Efficacy population).

The most common reason for going off-study (9/34 subjects [26.5%]) was progression of the disease (NSCLC). Six subjects (17.6%) were discontinued due to an AE or unacceptable toxicity, 8/34 subjects (23.5%) requested to withdraw, 6/34 subjects (17.6%) died due to disease progression, 3/34 subjects (8.8%) died due to a cause other than disease progression, 1/34 subject (2.9%) was taken off-study due to non-compliance, and 1/34 subject (2.9%) was taken off-study due to an 'other' reason (clinical deterioration of general status [ECOG performance status of 4]).

Subjects received a total of 101 courses during the study (3 courses at a dose level of 18 mg/m^2, 71 courses at a dose level of 27 mg/m^2 and 27 courses at a dose level of 35 mg/m^2).

Demographics:

For the Efficacy population, mean age was 58.0 years and there were more subjects aged <65 years (21/28 subjects [75.0%]) than ≥65 years (7/28 subjects [25.0%]). There were more male (21/28 subjects [75.0%]) than female subjects (7/28 subjects [25.0%]). All subjects (28/28 subjects [100.0%]) were Caucasian. Mean height was 169.4 cm. At baseline, mean weight was 73.29 kg, and mean BSA was 1.835 m^2.

For the Efficacy population at baseline, the primary sites of the disease were left lung (18/28 subjects [64.3%]) and the right lung (10/28 subjects [35.7%]). The site of disease was located in the upper lobe in 18/28 subjects (64.3%), and the lower lobe in 10/28 subjects (35.7%). The majority of subjects (21/28 subjects [75.0%]) had metastatic disease at the time of study entry, whilst 7/28 subjects (25.0%) had locally advanced carcinoma. The lung (13/28 subjects [46.4%]) and lymph nodes (13/28 subjects [46.4%]) were the most common sites of metastases.

All subjects had prior chemotherapy. In the Efficacy population 15/28 subjects (53.6%) had prior chemotherapy only; 12/28 subjects (42.9%) had radiation therapy only; and 4/28 subjects (14.3%) had surgery only.

All subjects had one regimen of prior chemotherapy. The most common agents used were cisplatin (taken by 27/28 subjects [96.4%]), and gemcitabine (taken by 14/28 subjects [50.0%]). These medications were taken in combination (ie, cisplatin + gemcitabine) by 14/28 subjects (50.0%). Other common regimens used were carboplatin or cisplatin + navelbine (taken by 5/28 subjects [17.9%]) and cisplatin + etoposide (taken by 4/28 subjects [14.3%]).

Values were similar for the ITT and Safety populations.

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Efficacy Result:

One subject (3.6% [Efficacy population] or 2.8% [ITT population]) had a CR and one subject (3.6% [Efficacy population] or 2.8% [ITT population]) had a PR to treatment, giving an overall response rate of 7.1% (Efficacy population) or 5.6% (ITT population). For both the Efficacy and ITT populations, SD was shown by 17 subjects as a best overall response (60.7% [Efficacy population] or 47.2% [ITT population]). Progressive disease was the best overall response in 7 subjects (25.0% [Efficacy population] or 19.4% [ITT population]).

For the Efficacy population, the mean duration of response was 31.2 weeks (approximately 218 days) (range: 24.0 to 38.4 weeks) (based on the 2 subjects who had a response).

For the Efficacy population, the median TTP was 125 days (95% CI: 57 to 196 days); the median TTF was 78 days (95% CI: 47 to 118 days); and the MST was 160 days (95% CI: 118 to 353 days). The estimated survival rate was 0.0% at 12 months. Values for the ITT population were similar to those for the Efficacy population.

Pharmacokinetic/Pharmacodynamic Results:

The pharmacokinetics of DJ-927 was evaluated after administration of 27 mg/m^2. Following administration, DJ-927 was rapidly absorbed with a median T_{max} value of 2 hr. The terminal elimination half-life of DJ-927 was 167 ± 77 hr. At 27 mg/m^2 dose level, DJ-927 showed the following results, respectively:

(1) C_{max} of 42.72 ± 34.33 ng/mL;
(2) $AUC_{0\text{-}168}$ of 1752 ± 1355 ng/mL hr;
(3) Vdss/F of 2710 ± 1751 L/m^2;
(4) CL/F of 12.6 ± 7.3 $L/hr/m^2$.

Safety Results:

In the Safety population, 33/34 subjects (97.1%) had at least one treatment-emergent AE (total of 300 AEs). There were 29/34 subjects (85.3%) with a drug-related AE. There were a total of 191 drug-related AEs, of which 52/191 AEs were NCI-CTCAE grade 3-5.

The most frequent drug-related AEs were leukopenia (8 subjects [23.5%] with 21 AEs), neutropenia (11 subjects [32.4%] with 19 AEs), nausea (11 subjects [32.4%] with 18 AEs), fatigue (13 subjects [38.2%] with 17 AEs), and anemia (10 subjects [29.4%] with 15 AEs). Only laboratory abnormalities that required clinical intervention, further investigation, led to a change in administration of study drug or were part of a larger syndrome or disease process were reported as an AE.

Overall, 20/34 subjects (58.8%) had at least one treatment-emergent SAE during the study. In total there were 46 SAEs with 21 drug-related SAEs. There were 14/21 drug related SAEs which were NCI-CTCAE grade 3-5. The most frequent SAEs and drug-related SAEs were grade 2-3 anemia (3/34 subjects [8.8%] with 6 SAEs),

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grade 2-3 fatigue (3/34 subjects [8.8%] with 3 SAEs), and grade 4 neutropenia (2/34 subjects [5.9%] with 2 SAEs). In the Safety population, 6/34 subjects (17.6%) were discontinued due to an AE or unacceptable toxicity.
Twelve subjects died on-study, with the primary cause of death for 8/12 subjects disease progression and for 4/12 subjects (019, 021, 027, and 036) an AE. One subject died due to a drug-related AE off-study (Subject 011 died off-study due to pneumonia which was considered by the Investigator to be possibly related to the study medication).
There were 33/34 subjects (97.1%) with at least one laboratory abnormality. The most frequent laboratory abnormalities NCI-CTCAE grade 3-4 included neutropenia (18/34 subjects [52.9%]), low WBC counts (14/34 subjects [41.2%]), and anemia 6/34 subjects [17.6%]).

Conclusions:

- The recommended Phase II dose of DJ-927 was confirmed at 27 mg/m^2.
- Within the framework of the pre-specified null and alternative hypotheses for this three-outcome one-stage design, the result of 2 responses out of 28 is inconclusive and there is not strong enough evidence to reject either the null rate or the alternative rate. The response rate is likely between the null rate of 3% and the alternative rate of 15%.
- One subject had a CR and one subject had a PR to treatment, giving an overall response rate of 7.1% [Efficacy population] or 5.6% [ITT population] with SD the best overall response of 17 subjects (60.7% [Efficacy population] or 47.2% [ITT population]).
- The mean duration of response was 31.2 weeks (approximately 218 days) (Efficacy population).
- For the Efficacy population, the median TTP was 125 days (95% CI: 57 to 196 days), the median TTF was 78 days (95% CI: 47 to 118 days) and the MST was 160 days (95% CI: 118 to 353 days).
- The estimated survival rate was 0.0% at 12 months.
- Neutropenia, leukopenia and anemia were the main hematological toxicities and gastrointestinal toxicities and fatigue were the predominant non-hematological toxicities.