Report Synopsis

Sponsor name: Janssen Pharmaceutical K.K. Investigational drug: JNS002 Ingredient: doxorubicin hydrochloride Protocol No.: CR004867	Study summary table Corresponding section in the application data Volume No.: Page:	(Space for reviewing authorities)

Study title:

Phase II clinical study of JNS002 in patients with Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube, peritoneal carcinoma) having a history of platinum-based chemotherapy

Investigators:

A total of 31 investigators including Hidenori Kato, Department of Obstetrics and Gynecology, National Hospital Organization Hokkaido Cancer Center

Investigator Sites:

A total of 31 medical institutions in Japan including Department of Obstetrics and Gynecology, National Hospital Organization Hokkaido Cancer Center

Publications: No publications (For cited references, see Chapter 15)

Study period:	**Clinical Phase:**
[From date of informed consent obtained from first patient to completed date of observation in last patient]: January 18, 2005 to November 28, 2006	Phase II

Objectives:

1. To evaluate efficacy of JNS002 50 mg/m^2 intravenously administered every 4 weeks to patients with Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube, peritoneal carcinoma) having a history of platinum-based chemotherapy using best overall response (response rate) as a primary endpoint.
2. To evaluate safety (the incidence, severity, seriousness, and causality, etc. of adverse events and adverse reactions) of JNS002 50 mg/m^2 intravenously administered every 4 weeks.
3. To evaluate the time to response in response cases (patients with complete response [CR] or partial response [PR]).
4. To evaluate the duration of response in response cases (patients with CR or PR).

Study methods:

Multicenter, non-randomized, open-label study

After obtaining informed consent in writing from patients, the screening test was performed in patients. Then, the patients were enrolled as subjects at the Patient Registration Center, and treatment with JNS002 was started. JNS002 50 mg/m^2 was intravenously administered every 4 weeks (1 cycle), which was repeated at least twice (2 cycles) unless the patient met the discontinuation criteria.

Sample size (at planning and at analysis):

< At planning >

The target sample size was 80 patients consisting of the following two groups of patients as an efficacy analysis set.

1. Platinum-sensitive group (Pt-S group) (second-line platinum-sensitive subjects): 20 patients as the efficacy analysis set
2. Platinum-resistant group (Pt-R group) (second-line and third-line platinum-resistant subjects): 60 patients as the efficacy analysis set

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< At analysis >
1. Pt-S group: 11 patients
2. Pt-R group: 63 patients

As a result of discussions on JNS002 in the "Sixth Review Meeting for Problems of Unapproved Drugs" held on October 31, 2005, it was concluded that an early application for approval should be made based on the foreign clinical study results and the ongoing domestic phase II study (JNS002-JPN-02 study) in patients with advanced or relapsed ovarian carcinoma, and therefore we were requested to submit an early application. Meanwhile, to give the status of patient registration, as of December 28, 2005, 11 patients and 63 patients were registered in the Pt-S group and Pt-R group, respectively. Since the number of subjects in the Pt-S group is very small, the target number of registered patients was expected to be achieved at the end of November 2006. Under the above circumstances, we terminated the registration of patients for the Pt-S group when the registration for the Pt-R group was completed in order to make an early application.

The overall number of subjects in the study including both Pt-S group and Pt-R group was as shown in the following:

Number of registered patients: 74
Number of eligible patients: 73
Number of patients excluded as ineligible: 1

Number of patients in the efficacy analysis set
Full analysis set (FAS): 73
Per-protocol set (PPS): 71

Since, of 70 patients in the PPS, two patients – JNS-006 and JNS-053 had been treated with JNS002 at doses failing to comply with the protocol in some cycles, their efficacy data in cycle 4 and cycle 2 and later cycles were respectively excluded from the PPS analysis data.

Number of patients in the safety analysis set: 74

Diagnosis and major inclusion criteria:

1. Patients with a diagnosis of Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube, peritoneal carcinoma) established by a histologic examination.
2. Patients who received the first-line platinum-based chemotherapy (irrespective of the route of administration).
3. Patients who experienced 1-2 regimens in prior chemotherapy.
4. Patients with measurable lesions meeting “Response Evaluation Criteria In Solid Tumors (RECIST guidelines)” translated into Japanese by the Japan Clinical Oncology Group (JCOG).
5. Patients with the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-2.

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Diagnosis and major inclusion criteria: (continued)

6. Patients who meet all of the following criteria (1) to (4) and have major organ functions sufficiently being maintained for adequate evaluation of the efficacy and safety of JNS002.
   (1) Bone marrow function
   White blood cell count: 3.0 x 10^3/mm^3 - 12 x 10^3/mm^3
   Neutrophil count (total neutrophil count): ≥ 1.5 x 10^3/mm^3
   Hemoglobin: ≥ 9.0 g/dL
   Platelet count: ≥ 100 x 10^3/mm^3
   (2) Liver function
   Serum AST, ALT: ≤ 2.5 times the upper limit of institutional normal range
   Serum Al-P: ≤ 2.5 times the upper limit of institutional normal range
   Total bilirubin: ≤ the upper limit of institutional normal range
   (3) Renal function
   Serum creatinine: ≤ 1.5 times the upper limit of institutional normal range
   (4) Cardiac function
   Left Ventricular Ejection Fraction (LVEF): ≥ 50%
   Electrocardiograms: normal or asymptomatic change not requiring treatment
   Cardiac function evaluated by New York Heart Association (NYHA) classification at registration: No heart disease or having a heart disease of NYHA Class I
7. Patients who have not received treatment with colony stimulating factor (CSF) products or blood transfusion within 2 weeks from the day of hematological examinations at registration (until the same day of the week 2 weeks before the day of hematological examinations at registration)
8. Patients who meet all of the following criteria (1) to (3) as required duration from the completed day of prior therapy to the initial day of treatment in this study.
   (1) Surgery: ≥ 4 weeks
   (2) Radiotherapy: ≥ 4 weeks
   (3) Chemotherapy, immunotherapy, and hormone therapy
      1) Hormone agents, oral antimetabolites, immunotherapeutics: ≥ 2 weeks
      2) Nitrosoureas, Mitomycin C: ≥ 6 weeks
      3) Chemotherapies other than the above 1) and 2): ≥ 4 weeks
9. Patients who can be continuously hospitalized for 4 weeks from the initial day of treatment with JNS002.
10. Patients expected to have a life expectancy of ≥ 3 months.
11. Patients aged ≥ 20 years to < 80 years at registration.
12. Patients who voluntarily give written consent to participate in this study after being given a sufficient explanation about the contents of the study by the investigator (or subinvestigator) using a prescribed informed consent form and other explanatory documents.

Report Synopsis 3

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Investigational drug, dosage and treatment methods, lot numbers:

< Investigational drug >
JNS002 (formulation for intravenous administration containing doxorubicin hydrochloride enclosed in STEALTH® liposomes)

< Dosage and treatment methods >
JNS002 50 mg/m^2 was intravenously administered to each patient using an infusion pump at a rate of 1 mg/min. After the completion of treatment, a drug rest period for 28 days (4 weeks) was taken including the day of treatment. This was considered one cycle, and treatment was given to patients for at least two cycles unless the patient met the discontinuation criteria.

< Lot numbers >
03DE, 04EF, 05FE

Treatment period:
Treatment was started after obtaining informed consent. Four weeks was considered one cycle, and treatment was given to patients for at least two cycles, in principle. After the completion of treatment, an observation period was established as -4 days to +7 days from the 29th day from the last administration or the determined day of discontinuation, whichever came later.

Endpoints:
1. Primary endpoint
   Best overall response (response rate)
2. Secondary endpoints
   (1) Incidences, severity, seriousness, causal relationship, etc. of adverse events and adverse reactions
   (2) Median time to response and the range, etc. in patients with response (CR or PR).
   (3) Median duration of response and the range, etc. in patients with response (CR or PR)

Evaluation methods:
1. Efficacy
   Evaluation of tumor regression effects was conducted according to the RECIST guidelines.
   Evaluation procedures according to the RECIST guidelines:
   (1) Definitions of measurable lesion and non-measurable lesion
   1) Lesions that were applicable to any definition in the following table were considered measurable lesions.
      In this study, lesions observed by ultrasonography were not handled as measurable lesions.

X-ray films	Maximum diameter (major axis) ≥ 20 mm and being surrounded by the lung field (not contacting with the mediastinum or chest wall).
CT, MRI	Maximum diameter (major axis) ≥ slice thickness x 2 However, the lesion must have a maximum diameter (major axis) of ≥ 10 mm.
Direct measurement*	Maximum diameter (major axis) of ≥ 20 mm (skin metastasis, etc.)

*: Deep lesions were judged if they are measurable or not by CT, MRI, or X-ray examination.

If it is a superficial lesion that is difficult to be measured by CT, MRI, or X-ray, direct measurement was allowed. In the case of direct measurement, if there was a color picture of the lesion taken with a scale, it was considered an objective material, and the lesion was handled as a measurable lesion.

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Evaluation method: (continued)

2) All the lesions other than the above were handled as non-measurable lesions.
However, it was noted that the following lesions a) to h) should be handled as non-measurable lesions irrespective of test method and lesion size.
   a) Bone lesion
   b) Meningeal lesion
   c) Ascites
   d) Pleural effusion, pericardial effusion
   e) Cutaneous lymphopathy or pulmonary lymphopathy
   f) Abdominal mass not identifiable by diagnostic imaging
   g) Cystic lesion (lesion containing a cyst was considered measurable if its major axis not overlapping the cyst site could be measured)
   h) Lesions observed by ultrasonography

(2) Evaluation of tumor regression effects
For each cycle, evaluations of target lesions and non-target lesions were conducted by the same test methods as in screening according to the investigation items and investigation timings for efficacy and safety evaluations. The site of target lesion, test method, test date, major axis, sum of major axes, site of non-target lesion, test method, test date, and the presence or absence of disappearance or exacerbation were recorded in the case report form.

1) Evaluation of response in target lesion
   a) Complete response (CR)
   b) Partial response (PR)
   c) Progressive disease (PD)
   d) Stable disease (SD)
   e) Not evaluable (NE)

2) Evaluation of response in non-target lesion
   a) Complete response (CR)
   b) Incomplete response (IR)/Stable disease (IR/SD)
   c) Progressive disease (PD)
   d) Not evaluable (NE)

3) Overall Response
Overall Response was evaluated for each cycle based on the combined evaluations of target lesion and non-target lesion and the presence or absence of new lesion.

2. Safety

Safety of JNS002 was evaluated from "adverse events" that occurred during the study period. The adverse events were evaluated based on the investigation results related to safety during the study period (subjective symptoms, objective findings, physical examination, laboratory tests, cardiac function test, etc.).

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Statistical analyses:

< Efficacy >

The following tabulation and analyses in the efficacy analysis set (FAS) were conducted based on results of the response evaluation committee's final efficacy evaluation and results of the physician in charge's evaluation (In the efficacy evaluation, the results of tabulation and analysis in FAS were employed as major results based on results of the response evaluation committee's evaluation).

1. Primary endpoint

Of best overall response, the percentage of patients who had CR or PR (response rate)

The point estimate of the response rate and the two-sided 95% confidence interval in all patients of the efficacy analysis set were calculated.

The point estimate of the response rate and the two-sided 90% confidence interval were calculated separately for the Pt-S group (second-line Pt-S patient group) and Pt-R group (second-line and third-line Pt-R patient groups). A similar analysis in PPS was conducted for reference.

2. Secondary endpoints

The tabulation and analysis for the following items (1) to (6) were conducted as secondary efficacy endpoints. Descriptive statistics in each period were the median, minimum and maximum based on the Kaplan-Meier method.

(1) Survival analysis was performed for duration of CR, duration of PR, duration of overall response, time to response, time to progression, duration of stable disease, and survival by the Kaplan-Meier method to calculate descriptive statistics.
(2) The same analysis as in (1) was performed for duration of CR, duration of PR, duration of overall response, and time to response in patients with CA-125 response*.
(3) Best overall response was tabulated for each category. The same tabulation was performed in PPS.
(4) The percentage of patients with best overall response of CR, PR, or SD was calculated with the 95% confidence interval.
(5) The percentage of patients with CA-125 response* was calculated with the 95% confidence interval.
(6) The same tabulation and analyses as in the above (1) to (5) were performed with data stratified into Pt-S group and Pt-R group.

*: For patients with baseline CA-125 values > twice the upper limit of institutional normal range, the evaluation of CA-125 response was conducted according to the following criterion based on the CA-125 reduction rate.
CA-125 response: Patients who showed ≥ 50% reduction in CA-125 compared with baseline at least twice at an interval of ≥ 28 days after the start of treatment.

< Safety >

The following tabulation and analyses in the safety analysis set (SAS) were conducted.

1. The number of patients and the frequency (incidence) of each adverse event or adverse reaction were tabulated by treatment cycle and severity. Tabulation was conducted by setting subsets as needed.
For adverse event names, if the Japanese version of the Medical Dictionary for Regulatory Activities published by ICH (MedDRA/J) was used, the adverse event names were grouped by System Organ Class (SOC) and output in the order of SOC and in the order of frequency of Preferred Terms (PT).
2. Palmar-plantar erythrodysaesthesia syndrome, rash, stomatitis, nausea, white blood cell count decreased, neutrophil count decreased, platelet count decreased, and hemoglobin decreased were analyzed in detail based on descriptive statistics including the number of days to onset and the number of days to recovery, etc.
3. Reaction associated with intravenous infusion and cardiotoxicity were analyzed in detail by calculating the incidences, etc.
4. The same tabulation and analyses as in the above 1 to 3 were conducted with data stratified into the Pt-S group and Pt-R group.

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Summary/Conclusion

Efficacy results: The results of efficacy analyses at the data cut-off on March 31, 2006 were as shown in the following.
The antitumor effects (best overall response) in 73 patients in FAS were CR in 2 patients (2.7%), PR in 13 patients (17.8%), SD in 28 patients (38.4%), PD in 27 patients (37.0 %), and NE in 3 patients (4.1%). The response rate [number of patients with response] (two-sided 95% confidence interval) based on the best overall response evaluated according to the RECIST guidelines was 20.5% [15/73 patients] (12.0 - 31.6%). The response rates in individual patient groups [number of patients with response] (two-sided 90% confidence interval) were 27.3% [3/11 patients] (7.9 - 56.4%) in the Pt-S group and 19.4% [12/62 patients] (11.6 - 29.5%) in the Pt-R group. The median time to response in patients whose best overall response was CR or PR was 54.0 days, and there was no significant difference between the Pt-S group and Pt-R group.
Since the lower limit of confidence interval of the response rate in the FAS and Pt-R group exceeded the threshold response rate established beforehand, JNS002 was suggested to have antitumor effects in the patient groups.
The results of statistical analyses with all data including the data after data cut-off were confirmed to be similar to those of the above results in this study.

Safety results: Major safety results were as shown in the following.
Adverse events occurred in all the 74 patients in SAS, and 3,650 events in all were reported. Of the events, those whose causal relationship with JNS002 could not be ruled out were 3,449.
The adverse events that occurred with an incidence of > 50% were hematological toxicities, skin toxicities and gastrointestinal disorders. The hematological toxicities occurred most frequently in any tabulation for all adverse events, laboratory test values or by severity.
Among ≥ Grade 3 adverse events, hematological toxicities occurred most: neutrophil count decreased in 50 patients (67.6%), white blood cell count decreased in 45 patients (60.8%), lymphocyte count decreased in 35 patients (47.3%), hemoglobin decreased in 13 patients (17.6%), platelet count decreased in 5 patients (6.8%), and red blood cell count decreased in 3 patients (4.1%). Among ≥ Grade 3 non-hematological toxicities, the events that frequently occurred were palmar-plantar erythrodysaesthesia syndrome in 12 patients (16.2%) and stomatitis in 6 patients (8.1%). Grade 4 adverse events were only hematological toxicities, except for 1 patient with deep vain thrombosis.
Regarding major hematological toxicities (white blood cell count decreased, neutrophil count decreased, platelet count decreased, and hemoglobin decreased), among the events whose outcome was recovery, the median duration required for recovery was within 1 cycle (10.5 – 16.0 days) in all the patients for any event. The median duration required for recovery to the grade according to the criteria for treatment initiation in the next course was 7.0 – 8.0 days in all the patients for any event. The major hematological toxicities were suggested to meet the criteria for treatment initiation in the next course relatively early after the onset of the event and show a recovery within 1 cycle.
Palmar-plantar erythrodysaesthesia syndrome occurred in 58 of 74 patients (78.4%), and the causal relationship with JNS002 could not be ruled out in all the patients with this event.
Stomatitis occurred in 57 of 74 patients (77.0%), and the causal relationship with the investigational drug could not be ruled out in all the patients.

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<table>
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<tr><td>Investigational drug: JNS002</td></tr>
<tr><td>Active ingredient:
doxorubicin hydrochloride</td></tr>
<tr><td colspan="3">Both palmar-plantar erythrodysaesthesia syndrome and stomatitis tended to be relieved or recovered relatively early by taken measures including concomitant medications, reduction of the dose of JNS002 (dose reduction), and postponed treatment, etc., and were considered to be manageable toxicities.

Conclusion:
The above results indicated that JNS002 was expected to have antitumor effects in Müllerian carcinoma (epithelial ovarian carcinoma, primary carcinoma of fallopian tube, peritoneal carcinoma) patients with a history of platinum-based chemotherapy, and the safety was shown to be clinically manageable.</td></tr>
<tr><td colspan="3">Date of report: August 14, 2007</td></tr>
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