JNS 007ER
(ER OROS®Paliperidone)

Summary of a Japanese early phase II study results

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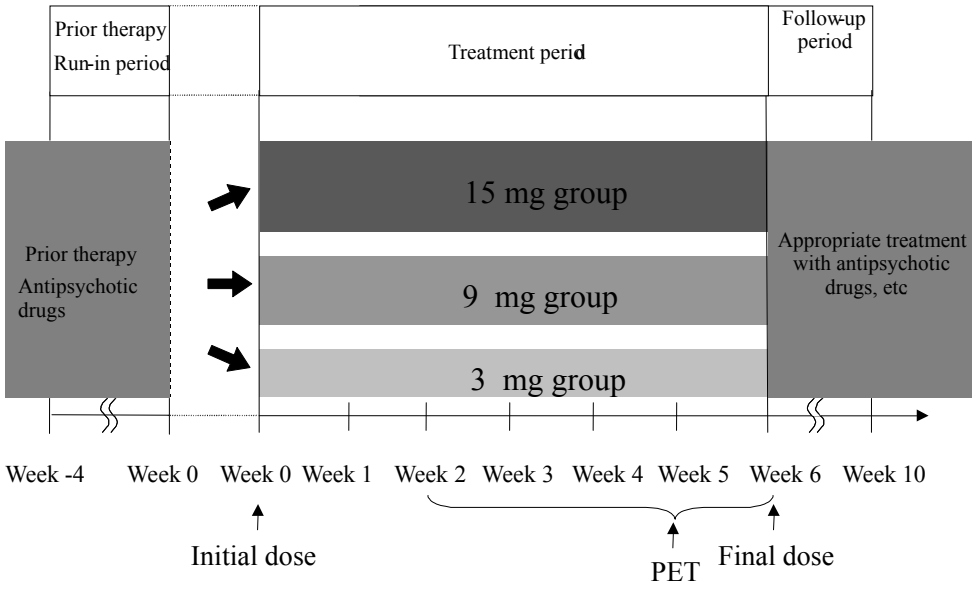
Synopsis of the Study Plan

Title of the study	Exploratory study of JNS007ER to assess the safety and efficacy in subjects with schizophrenia (Protocol No.: JNS007ER-JPN-S21)
Study objectives	The safety, efficacy and plasma concentration of JNS007ER were assessed in subjects with schizophrenia treated with JNS007ER (3, 9, or 15 mg/dose) once daily after breakfast for 6 weeks. In addition, the relationship between dopamine D_2 receptor occupancy and the dose or plasma concentration of JNS007ER were examined in subjects who consent to undergo Positron Emission Tomography (PET) in the medical institutions where PET was to be performed. Primary objective: (1) Safety Safety was assessed using as indices adverse events (subjective symptoms and objective findings), laboratory tests, DIEPSS, physical examination, and electrocardiography (12-lead). Secondary objectives: (1) Efficacy Efficacy was assessed using as indices changes in PANSS total score, changes in PANSS subscale scores (positive symptom scale score, negative symptom scale score, general psychopathology scale score), and CGI-C. (2) Plasma drug concentration Achievement of a steady state was confirmed using the mean plasma concentration ($C_{avg,ss}$) of JNS007 as the index. (3) Dopamine D_2 receptor occupancy (to be examined only in the medication institutions where PET was to be performed) The relationship between dopamine D_2 receptor occupancy and the dose or plasma drug concentration was examined during the steady state with JNS007.
Study design	Multicenter, open-label, parallel-group, fix-dose
Study subjects "Inclusion criteria"	The study was conducted in subjects who meet all the following inclusion criteria. (1) Subjects diagnosed as schizophrenia (295.30, 295.10, 295.20, 295.90, 295.60) on the basis of the DSM-IV diagnostic criteria. (2) Subjects whose PANSS total score at screening are less than 120. (3) Subjects who have been treated with a single oral antipsychotic drug for 28 days before the provision of informed consent, with no changes in the dosage or dosing regimen (except for as-needed use). (4) Subjects aged 20 to 64 years at the provision of informed consent. (5) Subjects able to provide written consent themselves for the participation in the study (Informed consent will be obtained also from the subject's representative, if the investigator or subinvestigator judges it necessary.) (6) No restriction regarding insubject/outsubject status. (7) No restriction regarding sex.
Study subjects "Exclusion criteria"	Subjects who meet any of the following exclusion criteria were excluded. (1) Subjects diagnosed as having psychiatric disorders other than schizophrenia on the basis of DSM-IV diagnostic criteria. (2) Subjects with concurrent Parkinson's disease (except for drug-induced extrapyramidal diseases) (3) Subjects who have or have a history of convulsive disorders such as epilepsy. (4) Subjects with clinically significant gastrointestinal disorders including gastrointestinal stenosis (pathogenic or iatrogenic). (5) Subjects who have or have a history of cerebrovascular disorder. (6) Subjects with a history of malignant syndromes or physical exhaustion accompanied by dehydration, malnutrition, etc. (7) Subjects who have or have a history of diabetes mellitus, or subjects with risk factors of diabetes mellitus, such as hyperglycaemia (random glucose measurement: $\geq$ 200 mg/dL; morning fasting glucose reading: $\geq$ 126 mg/dL; or HbA_{1c}: $\geq$ 5.9%). (8) Subjects with liver disorders [e.g., T-Bil: $\geq$ 3.0 mg/dL; AST (GOT), ALT (GPT), and ALP: at least 2.5-fold higher than the upper limit of reference values of each institution].

	(9) Subjects with renal disorders (e.g., BUN: ≥ 40 mg/dL; creatinine: ≥ 4 mg/dL). (10) Subjects with cardiovascular disorders (e.g., QTc: ≥ 450 msec). (11) Subjects who are pregnant, suspected to be pregnant, or lactating, or who desire to become pregnant during the study period. (12) Subjects who have received electroconvulsive therapy within 90 days prior to the screening test day. (13) Subjects who have received a long-acting injection formulation (depot formulation) of an antipsychotic drug within 60 days before start of the investigational drug. (14) Subjects who are contraindicated for the use of risperidone formulations. a) Subjects with comatose b) Subjects on treatment with epinephrine c) Subjects who are strongly under the influence of central nervous system depressants, such as barbiturate derivatives d) Subjects who have hypersensitivity to risperidone formulations (15) Subjects who have allergy or hypersensitivity to antipsychotic drugs. (16) Subjects who have participated in another clinical study within 90 days before the provision of informed consent. (17) Subjects who are judged ineligible for participation in the study by the investigator or subinvestigator.
Investigational drugs	JNS007ER 3 mg tablets, JNS007ER 9 mg tablets
Administration method (investigational drug)	The prior antipsychotic therapy was discontinued on the day before the start of the investigational drug, and the therapy was switched to JNS007ER from the start day of the investigational drug. JNS007ER was administered as follows. Following the final day of investigational drug treatment, appropriate therapy (including drug therapy) was given in the judgment of the investigator or subinvestigator. (1) Route of administration Oral administration (2) Selection of dosages The investigator or subinvestigator selected one of 3 mg, 9 mg, and 15 mg doses for each subject, in his/her judgment, taking into consideration the dose of the prior antipsychotic medication used in the subject, pharmacokinetic data of JNS007ER, safety of the subject, etc. In each group, when the target number of subjects was reached, no additional subject was registered to the dose group. (3) Dosage and administration In each dose group, the following dose was administered once daily after breakfast for 6 weeks. 3 mg group: JNS007ER 3 mg tablets × 1 9 mg group: JNS007ER 9 mg tablets × 1 15 mg group: JNS007ER 3 mg tablets × 2 and 9 mg tablets × 1
Concomitant therapy	(1) Drug therapy 1) Prohibited concomitant drugs The concomitant use of the following drugs during the treatment period was prohibited. a) Antipsychotic drugs b) Epinephrine c) Other investigational drugs under development 2) Restricted concomitant drugs The concomitant use of the following drugs during the treatment period was restricted. a) Antiparkinson agents The use of an antiparkinson agent, when started after provision of informed consent, were discontinued by the start day of the investigational drug. However, when the use of this agent was judged to be essential by the investigator or subinvestigator due to the development of extrapyramidal symptoms during the treatment period, the concomitant use was allowed. The extrapyramidal symptoms were evaluated using DIEPSS before the use and dose increase of the antiparkinson agent. When the symptoms were alleviated or resolved, the dose was reduced or discontinued. 3) Other concomitant drugs (including hypnotics, anxiolytics, and antidepressants) When these drugs were used concomitantly at the first administration of the investigational

	drug, these drugs were continuously used with no changes in the dosage or dosing regimen. However, when the target symptoms were alleviated or resolved, the doses of the concomitant drugs could be reduced or discontinued. When the investigator or subinvestigator judged it necessary to increase the dose, the dosing regimen could be changed. (2) Antipsychotic therapies other than drug therapy 1) Prohibited concomitant therapies Electroconvulsive therapy were not be administered concomitantly during the period from the screening test day to the completion day of the treatment period. 2) Restricted concomitant therapies When the subject was receiving antipsychotic therapy (e.g., social skills training) other than drug therapy at the first administration of the investigational drug, the therapy were continued with no change in the therapy. However, when the investigator or subinvestigator judged it essential, it was allowed to make changes in the therapy and to discontinue the therapy.
Study period	Treatment period: 6 weeks Follow-up period: 4 weeks Total: 10 weeks
Observation / evaluation items	(1) Subject characteristics (2) Compliance with the investigational drug and concomitant medication, implementation status of concomitant therapies other than drug therapy (3) Safety Subjective symptoms and objective findings, physical examination, laboratory tests, electrocardiography (12-lead), adverse events, and DIEPSS (4) Efficacy PANSS, CGI-S, CGI-C (5) Plasma drug concentration (6) Dopamine D_2 receptor occupancy
Total amount of blood sampling	56 mL in total (5 mL × 4 = 20 mL for plasma drug concentration measurement, 12 mL × 3 = 36 mL for laboratory tests) For subjects undergoing PET, 66 mL in total (5 mL × 6 = 30 mL for plasma drug concentration measurement; 12 mL × 3 = 36 mL for laboratory tests)
Study period	January 2005 to October 2005 (Subject registration period: January 2005 to July 2005)
Target sample size	Sample size: 45 subjects, consisting of 15 subjects per group. This includes 16 subjects undergoing PET (8, 4, and 4 subjects of the 3 mg, 9 mg, and 15 mg groups, respectively)

Study design



Study schedule

Endpoint	Informed consent	Screening	Registration	Treatment period						Follow-up period	At discontinuation	
Week		Weeks - 2-0		Week 0		Week 2	Week 4	Week 5	Week 6	Week 10	At discontinuation	4 weeks after discontinuation
Day		-14d—0d		0d	1d	14d	28d	35d	42d	70d		
Acceptable range of discrepancy in the days of evaluation and hospital visit						±7d	±7d	±7d	±7d	+7d		
Hospital visit[*1]	○	○		○		○	○		○		○	
Acquisition of informed consent	○											
Subject characteristics		○										
Registration			○									
Administration of JNS007ER					←	—	—	—	→			
Antipsychotic drug	←	—	—	→						←	—	→
Height		○										
Blood pressure, pulse rate, body temperature		○		○		○	○		○		○	
Body weight		○		○					○		○	
ECG (12-lead)		○		○		○	○		○		○	
Laboratory test		○				○			○		○	
DIEPSS[*2]				○					○		○	
Adverse event (Subjective symptoms, objective findings)					←	—	—	—	—	→	—	→
PANSS		○				○			○		○	
CGI-S				○								
CGI-C						○	○		○		○	
Plasma drug concentration measurement				○		○	○		○		○	
PET[*3]						←	—	○	→			

*1 Applicable to outsubjects only.

*2 To be evaluated also when an antiparkinson drug was used.

*3 To be conducted in the medical institutions where PET was to be performed. At the time of PET, PET using two ligands ([^{11}C] FLB457 and [^{11}C] raclopride) were performed twice in total, and MRI was also performed. A blood sample for plasma drug concentration measurement was obtained immediately before each PET.

1. Summary of study results and general overview

1.1 Subject disposition and characteristics

In this study, 47 subjects whose eligibility was confirmed by the screening test after providing written informed consent were registered. These subjects received the investigational drug (JNS007ER) at least once. The dose groups consisted of 16 subjects for the 3 mg group, 15 subjects for the 9 mg group, and 16 subjects for the 15 mg group. Of these, 9 subjects (2, 1, and 6 subjects of the 3 mg, 9 mg, and 15 mg groups, respectively) were discontinued the sutdy, and the remaining 38 subjects completed the study. Of these subjects who received the JNS007ER, 14 subjects underwent PET. The reasons for discontinuation were "Adverse events" in 5 subjects, "Requested by the subject or the subject's representative" in 3 subjects, and "Others (judgment of the investigator)" in 1 subject. Regarding subject characteristics, since the treatment group was selected for each subject in the judgment of the investigator, the higher dose groups tended to show more severe psychiatric symptoms and to have received higher amounts of prior antipsychotic medications. In other subject characteristics, no particular bias was observed.

1.2 Safety

The safety analysis population was defined as subjects (47 subjects) who received the JNS007ER at least once. During the treatment period with the JNS007ER, 83 adverse events were observed in 34 subjects (72.3%). There were no deaths and no serious adverse events. The most frequently observed adverse event (AE) was "an increase in blood prolactin level (MedDRA/E term : blood prolactin increased)" (16 events in 16 subjects: 34.0%). By dose, 20 AEs in 11 subjects (68.8%) in the 3 mg group, 29 AEs in 11 subjects (73.3%) in the 9 mg group, and 34 AEs in 12 subjects (75.0%) in the 15 mg group were observed. Thus, adverse events tended to show higher percentages of subjects who received higher dose group compared with subjects who received lower dose group. In general, the safety of multiple doses of JNS007ER up to 15 mg/day in subjects with schizophrenia was confirmed.

1.3 Efficacy

The efficacy analysis population was defined as subjects in whom efficacy was evaluated at least once after administration of the JNS007ER (FAS). The baseline PANSS total score in each group tended to be higher in the higher dose groups. The change from baseline to final evaluation (Mean ± SD) was -1.9 ± 4.8 in the 3 mg group, -4.0 ± 3.9 in the 9 mg group, and -2.9 ± 6.1 in the 15 mg group. No trend of aggravation was observed in any of the dose groups, indicating that the effect was maintained.

1.4 Pharmacokinetics

In the 6-week multiple dose regimen of the JNS007ER, the plasma JNS007 concentration at each hospital visit (Weeks 2, 4, and 6) was measured. The measurement result suggested that the plasma JNS007 concentration at Week 2 of treatment was already in a steady state, and that there was dose proportionality in the dose range from 3 mg to 15 mg.

1.5 Dopamine D_2 receptor occupancy

Of the subjects registered in this study, 14 subjects who provided written consent to undergo PET were subjected to PET. Of these subjects, 1 subject whose data were unavailable for analysis was excluded from the analysis, and the remaining 13 subjects were subjected to the analysis.

The mean of the striatal dopamine D_2 receptor occupancies determined using [^{11}C] raclopride were 57.9%, 77.4% and 80.4% in 3 mg, 9 mg and 15 mg groups respectively whereas the mean of the temporal cortical dopamine D_2 receptor occupancies determined using [^{11}C] FLB457 were 53.1%, 76.2% and 77.7% in 3 mg, 9 mg and 15 mg group respectively. The occupancy ratios in both the sites were comparable. To attain the striatal dopamine D_2 receptor occupancy of 70% to 80%, the JNS007 ER dose required was 5.55 - 9.52 mg/day with the plasma concentration of paliperidone 15.5 - 26.6 ng/mL. To attain the temporal cortical dopamine D_2 receptor occupancy of 70% to 80%, the JNS007 ER dose required was 6.63 - 11.4 mg/day with the plasma concentration of paliperidone 18.0 - 30.9 ng/mL.

1.6 General overview

The safety of multiple doses of JNS007ER at 3 to 15 mg/day in subjects with schizophrenia was confirmed. Regarding efficacy, the effect of JNS007ER was suggested to be similar to that of the prior

medication in all the dose groups. Regarding plasma drug concentration, achievement of a steady state in all the dose groups and dose proportionality were confirmed. The evaluation of dopamine D_2 receptor occupancy by PET showed that the JNS007ER dose required to achieve the striatal dopamine D_2 receptor occupancy of 70% to 80% was 5.55 - 9.52 mg/day with the plasma concentration of paliperidone ranging from 15.5 to 26.6ng/mL. The evaluation of dopamine D_2 receptor occupancy by PET showed that the JNS007ER dose required to achieve the temporal cortical dopamine D_2 receptor occupancy of 70% to 80% was 6.63 - 11.4 mg/day with the plasma concentration of paliperidone ranging from 18.0 to 30.9 ng/mL.

2. Subject disposition and characteristics

2.1 Subject disposition

In this study, of 52 schizophrenic subjects who provided written consent themselves for the participation in the study, 47 subjects whose eligibility was confirmed by the screening test were registered. These subjects received the JNS007ER at least once. The dose groups consisted of 16 subjects for the 3 mg group, 15 subjects for the 9 mg group, and 16 subjects for the 15 mg group. Of these, 9 subjects were discontinued the study, and the remaining 38 subjects completed the study. The 9 subjects consisted of 2 subjects of the 3 mg group, 1 subject of the 9 mg group, and 6 subjects of the 15 mg group. Of the 47 subjects who received the JNS007ER, 14 subjects who consented to undergo PET were subjected to PET. (Figure 1)

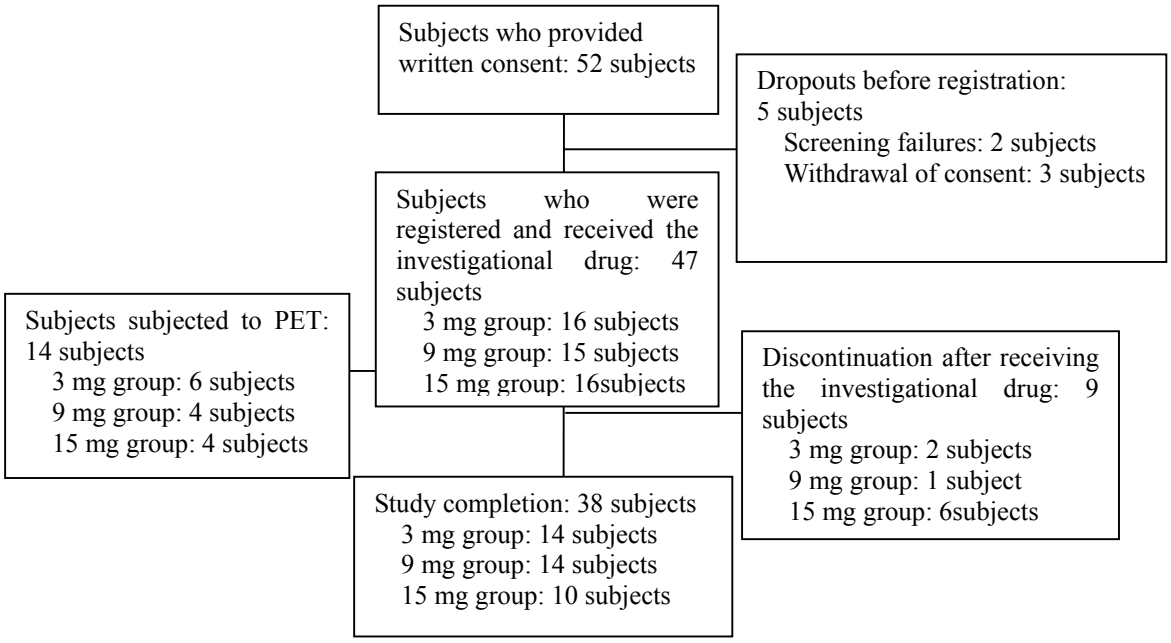


Figure 1. Subject disposition

The safety analysis population was defined as subjects who received the JNS007ER at least once among the subjects registered. The efficacy analysis population was defined as subjects in whom efficacy was evaluated at least once after administration of the JNS007ER (FAS).

2.2 Discontinuation the study

The reasons for discontinuation in the 9 subjects who were discontinued the study after receiving the JNS007ER were “Adverse events” in 5 subjects, “Requested by the subject or the subject’s representative” in 9 subjects, and “Others (judgment of the investigator)” in 1 subject.

The details of AEs that led to discontinuation are shown in “3.4 Deaths, serious adverse events, and adverse events that led to discontinuation”. The details of discontinuations due to other reasons are as follows:

Subject NA-04 (3 mg group), Subject PC-02 (15 mg group) and Subject PC-03 (15 mg group) were discontinued the study on Day 14, Day 32 and Day 30 after the start of the JNS007ER, respectively on their

own willingness. Subject PA-02 (3 mg group) was discontinued the study on Day 9, because the investigator judged it difficult to continue the study due to the subject's noncompliance with the medication, use of a prohibited concomitant drug (antipsychotic drug), and the subject's unwillingness of continuing his/her participation in the study (Table 1) :

Table 1 . Discontinuation Information

Disposition of subjects discontinue the study — Safety analysis population

Treatment period	Disposition	3 mg group	9 mg group	15 mg group	Total
Entire period	Total number of subjects	16	15	16	47
	Number of subjects who completed the study	14 (87.5%)	14 (93.3%)	10 (62.5%)	38 (80.9%)
	Number of subjects discontinuation the study	2 (12.5%)	1 (6.7%)	6 (37.5%)	9 (19.1%)
	AEs	0 (0.0%)	1 (6.7%)	4 (25.0%)	5 (10.6%)
	Request of the subject or subject's representatives	1 (6.3%)	0 (0.0%)	2 (12.5%)	3 (6.4%)
	Others	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Weeks 0 - 2 (1d - 14d)	Total number of subjects	16	15	16	47
	Number of subjects discontinuation the study	2 (12.5%)	1 (6.7%)	3 (18.8%)	6 (12.8%)
	AEs	0 (0.0%)	1 (6.7%)	3 (18.8%)	4 (8.5%)
	Request of the subject or subject's representatives	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
	Others	1 (6.3%)	0 (0.0%)	0 (0.0%)	1 (2.1%)
Weeks 2 - 4 (15d - 28d)	Total number of subjects	14	14	13	41
	Number of subjects discontinuation the study	0 (0.0%)	0 (0.0%)	1 (7.7%)	1 (2.4%)
	AEs	0 (0.0%)	0 (0.0%)	1 (7.7%)	1 (2.4%)
	Request of the subject or subject's representatives	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Others	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Week 4 - (29d -)	Total number of subjects	14	14	12	40
	Number of subjects discontinuation the study	0 (0.0%)	0 (0.0%)	2 (16.7%)	2 (5.0%)
	AEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Request of the subject or subject's representatives	0 (0.0%)	0 (0.0%)	2 (16.7%)	2 (5.0%)
	Others	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

2.3 Demographic and other baseline characteristics

Demographic and other baseline characteristics are shown in Table 2.

Table 2 . Demographic and other baseline characteristics

Demographic and other baseline characteristics — Safety analysis population

Factor		3 mg group	9 mg group	15 mg group	Total
Number of subjects analyzed		16	15	16	47
Gender	Male	10 (62.5%)	11 (73.3%)	12 (75.0%)	33 (70.2%)
	Female	6 (37.5%)	4 (26.7%)	4 (25.0%)	14 (29.8%)
Age	Mean (SD)	33.1 (10.9)	35.4 (10.9)	34.0 (8.2)	34.1 (9.9)
	Median	30.0	33.0	32.5	32.0
	(Min. - Max.)	(21-62)	(22-60)	(22-51)	(21-62)
Height (cm)	Mean (SD)	165.41 (9.43)	168.73 (8.92)	167.99 (8.22)	167.35 (8.79)
	Median	165.35	168.20	169.05	168.20
	(Min. - Max.)	(148.7-179.9)	(148.4-181.6)	(154.1-183.5)	(148.4-183.5)
Body weight (kg)	Mean (SD)	64.39 (8.62)	68.14 (15.86)	67.86 (12.17)	66.77 (12.33)
	Median	62.50	68.90	67.25	66.50
	(Min. - Max.)	(52.5-80.9)	(44.1-88.1)	(44.9-86.9)	(44.1-88.1)
Diagnosis	Schizophrenia	16 (100.0%)	15 (100.0%)	16 (100.0%)	47 (100.0%)
Disease type	295.30 Delusion type	9 (56.3%)	7 (46.7%)	7 (43.8%)	23 (48.9%)
	295.10 Disorganized type (hebephrenic type)	2 (12.5%)	3 (20.0%)	1 (6.3%)	6 (12.8%)
	295.20 Catatonic type	-	3 (20.0%)	2 (12.5%)	5 (10.6%)
	295.90 Undifferentiated type	2 (12.5%)	1 (6.7%)	3 (18.8%)	6 (12.8%)
	295.60 Residual type	3 (18.8%)	1 (6.7%)	3 (18.8%)	7 (14.9%)
History of disease	Initial onset	10 (62.5%)	4 (26.7%)	11 (68.8%)	25 (53.2%)
	Recurrence	6 (37.5%)	11 (73.3%)	5 (31.3%)	22 (46.8%)
Duration of illness (years)	Mean (SD)	8.66 (6.18)	9.75 (7.48)	10.75 (8.19)	9.72 (7.22)
	Median	8.05	7.90	8.85	8.10
	(Min. - Max.)	(0.2-22.3)	(0.7-27.3)	(0.2-28.0)	(0.2-28.0)
Duration (years) from the latest onset to the start of the investigational drug	Mean (SD)	5.46 (6.41)	3.08 (3.22)	7.94 (7.49)	5.54 (6.23)
	Median	2.65	1.80	5.25	2.80
	(Min. - Max.)	(0.2-22.3)	(0.2-11.8)	(0.2-23.8)	(0.2-23.8)
Therapeutic category (before acquisition of informed consent)	Outsubject	16 (100.0%)	15 (100.0%)	16 (100.0%)	47 (100.0%)
CGI-S	Very mild	6 (37.5%)	3 (20.0%)	3 (18.8%)	12 (25.5%)
	Mild	8 (50.0%)	10 (66.7%)	5 (31.3%)	23 (48.9%)
	Moderate	2 (12.5%)	1 (6.7%)	7 (43.8%)	10 (21.3%)
	Slightly severe	-	-	1 (6.3%)	1 (2.1%)
	Severe	-	1 (6.7%)	-	1 (2.1%)
DIEPSS	Mean (SD)	0.7 (1.3)	1.5 (1.7)	1.9 (2.5)	1.3 (1.9)
	Median	0.0	1.0	1.0	1.0
	(Min. - Max.)	(0-4)	(0-5)	(0-9)	(0-9)
PANSS	Mean (SD)	56.3 (11.4)	61.2 (16.7)	65.3 (12.9)	60.9 (14.0)
	Median	57.0	60.0	63.5	60.0
	(Min. - Max.)	(36-77)	(40-99)	(44-88)	(36-99)

The 47 registered subjects consisted of 33 males (70.2%) and 14 females (29.8%). The mean age was 34.1 years, with the age range from 21 to 62 years. The mean height and body weight were 167.35 cm and 66.7 kg, respectively. All the 47 subjects were schizophrenic subjects. Their disease type was delusion type (295.30) in 23 subjects, residual type (295.60) in 7 subjects, disorganized type (hebephrenic type) (295.10) in 6 subjects, undifferentiated type (295.90) in 6 subjects, and catatonic type (295.20) in 5 subjects. The mean baseline DIEPSS total score was 1.3. The assessment in CGI-S was “Very mild” in 12 subjects, “Mild” in 23 subjects, “Moderate” in 10 subjects, “Slightly severe” in 1 subject, and “Severe” in 1 subject. The mean baseline PANSS total score was 56.3 in the 3 mg group, 61.2 in the 9 mg group, and 65.3 in the 15 mg group. There was no bias in these groups with respect to sex, age, body weight, height, disease type, etc. On the other hand, since the treatment group was selected for each subject in the judgment of the

investigator in this study, the higher dose groups tended to show higher scores or higher severity in DIEPSS score, CGI-S, and PANSS total score.

2.4 Type and dose of prior medication

The type of antipsychotic drugs used at the start of the JNS007ER and their risperidone-equivalent doses[1] are shown in Tables 3 and 4, respectively. The most commonly used prior antipsychotic medication was risperidone (35 subjects), followed by olanzapine (6 subjects). The mean of risperidone-equivalent daily doses of prior antipsychotic drugs was calculated in each group, and was 2.16 mg in the 3 mg group, 3.89 mg in the 9 mg group, and 5.44 mg in the 15 mg group. In this study, since the treatment group was selected for each subject in the judgment of the investigator, the higher dose groups tended to have received higher amounts of prior antipsychotic drugs.

Table 3. Type of prior antipsychotic medications

Prior medications (antipsychotic medications) Safety analysis population

Drugs	3 mg group	9 mg group	15 mg group	Total
Number of subjects analyzed	16	15	16	47
Antiparkinson drugs	-	4 (26.7%)	5 (31.3%)	9 (19.1%)
Trihexyphenydyl hydrochloride	-	2 (13.3%)	1 (6.3%)	3 (6.4%)
Biperidene hydrochloride	-	2 (13.3%)	4 (25.0%)	6 (12.8%)
Promethazine hydrochloride	-	1 (6.7%)	1 (6.3%)	2 (4.3%)
Antipsychotics	16 (100.0%)	15 (100.0%)	16 (100.0%)	47 (100.0%)
Olanzapine	3 (18.8%)	3 (20.0%)	-	6 (12.8%)
Haloperidol	-	1 (6.7%)	1 (6.3%)	2 (4.3%)
Quetiapine fumarate	-	1 (6.7%)	1 (6.3%)	2 (4.3%)
Bromperidol	-	-	1 (6.3%)	1 (2.1%)
Risperidone	13 (81.3%)	10 (66.7%)	12 (75.0%)	35 (74.5%)
Perospirone hydrochloride hydrate	-	-	1 (6.3%)	1 (2.1%)
Other medication	11 (68.8%)	13 (86.7%)	15 (93.8%)	39 (83.0%)
Treatment other than medication	3 (18.8%)	5 (33.3%)	6 (37.5%)	14 (29.8%)

Table 4. Dose of prior antipsychotic medications (risperidone equivalent)

Dose of prior antipsychotic medications Safety analysis population

Items		3 mg group	9 mg group	15 mg group	Total
Number of subjects analyzed		16	15	16	47
Mean dose (mg/day)	- 2 mg	12 (75.0%)	2 (13.3%)	-	14 (29.8%)
	2 mg <- 4 mg	4 (25.0%)	12 (80.0%)	3 (18.8%)	19 (40.4%)
	4 mg <- 6 mg	-	-	11 (68.8%)	11 (23.4%)
	6 mg <-	-	1 (6.7%)	2 (12.5%)	3 (6.4%)
	Mean (SD)	2.16 (1.09)	3.89 (2.20)	5.44 (1.79)	3.83 (2.19)
	Median (Min. - Max.)	2.00 (0.5-4.0)	4.00 (2.0-11.4)	5.00 (3.0-10.0)	4.00 (0.5-11.4)

1 The target of the tabulation was antipsychotic drugs used during the period from 8 days to 2 days before the start of the JNS007ER. The dose of these drugs was tabulated after converted into a risperidone equivalent.

2.5 Treatment duration

The duration with the JNS007ER in each group is shown in Table 5. The mean duration of the JNS007ER treatment is 36.9 days in the 3 mg group, 39.3 days in the 9 mg group, and 32.3 days in the 15 mg group. Due to a higher number of subjects discontinued the study, the 15 mg group had a shorter duration of treatment than other groups.

Table 5. Duration of Study Medication

Duration of Study Medication Safety analysis population

Items		3 mg group	9 mg group	15 mg group
Number of subjects analyzed		16	15	16
Treatment duration (day)	Mean (SD)	36.9 (11.2)	39.3 (9.5)	32.3 (14.2)
	Median (Min.-Max.)	42.0 (4-42)	42.0 (5-42)	40.5 (1-42)

3. Safety results

3.1 Safety analysis population

The safety analysis population was defined as subjects who received the JNS007ER among those registered. Adverse events were tabulated separately for the treatment period with the JNS007ER and for the follow-up period.

3.2 Adverse events occurring during the treatment period with the investigational drug

During the treatment period with the JNS007ER, 83 adverse events were observed in 34 (72.3%) of 47 subjects who received in the JNS007ER. Frequently observed adverse events were " an increase in blood prolactin level (MedDRA/E term : blood prolactin increased)"(16 events in 16 subjects: 34.0%), " an increase in blood creatinine phosphokinase level (MedDRA/E term : blood creatinine phosphokinase increased)" (5 events in 5 subjects: 10.6%), "akathisia" (4 events in 4 subjects: 8.5%), "nasopharyngitis" (4 events in 4 subjects: 8.5%), and "hyperprolactinaemia" (4 events in 4 subjects: 8.5%).

By dose, 20 AEs in 11 subjects (68.8%) in the 3 mg group, 29 AEs in 11 subjects (73.3%) in the 9 mg group, and 34 AEs in 12 subjects (75.0%) in the 15 mg group were observed. Thus, the incidence of AEs was higher in the higher dose groups.

Table 6 List of adverse events (during the study period)

Safety analysis population

	3 mg group		9 mg group		15 mg group		Total	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Number of subjects analyzed	16	-	15	-	16	-	47	-
Number of events	11 (68.8)	20	11 (73.3)	29	12 (75.0)	34	34 (72.3)	83
<Infections and infestations>	2 (12.5)	2	3 (20.0)	4	1 (6.3)	1	6 (12.8)	7
Nail tinea	-	-	1 (6.7)	1	-	-	1 (2.1)	1
Nasopharyngitis	2 (12.5)	2	2 (13.3)	2	-	-	4 (8.5)	4
Rhinitis	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Tinea cruris	-	-	1 (6.7)	1	-	-	1 (2.1)	1
<Endocrine disorders>	-	-	2 (13.3)	2	2 (12.5)	2	4 (8.5)	4
Hyperprolactinaemia	-	-	2 (13.3)	2	2 (12.5)	2	4 (8.5)	4
<Metabolism and nutrition disorders>	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Anorexia	-	-	-	-	1 (6.3)	1	1 (2.1)	1
<Psychiatric disorders>	1 (6.3)	1	2 (13.3)	2	2 (12.5)	3	5 (10.6)	6
Anxiety	-	-	-	-	1 (6.3)	2	1 (2.1)	2
Insomnia	1 (6.3)	1	1 (6.7)	1	1 (6.3)	1	3 (6.4)	3
Libido decreased	-	-	1 (6.7)	1	-	-	1 (2.1)	1
<Nervous system disorders>	2 (12.5)	2	2 (13.3)	2	7 (43.8)	8	11 (23.4)	12
Akathisia	-	-	2 (13.3)	2	2 (12.5)	2	4 (8.5)	4
Dizziness postural	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Extrapyramidal disorder	-	-	-	-	2 (12.5)	2	2 (4.3)	2
Headache	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Mental impairment	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Parkinsonism	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Somnolence	1 (6.3)	1	-	-	1 (6.3)	1	2 (4.3)	2
<Eye disorders>	1 (6.3)	2	-	-	-	-	1 (2.1)	2
Conjunctivitis	1 (6.3)	2	-	-	-	-	1 (2.1)	2
<Respiratory, thoracic and mediastinal disorders>	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Rhinitis allergic	-	-	-	-	1 (6.3)	1	1 (2.1)	1
<Gastrointestinal disorders>	2 (12.5)	2	1 (6.7)	1	-	-	3 (6.4)	3
Abdominal pain upper	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Diarrhoea	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Gastritis			1 (6.7)	1	-	-	1 (2.1)	1
<Skin and subcutaneous tissue disorders>	-	-	1 (6.7)	1	-	-	1 (2.1)	1
Dermal cyst	-	-	1 (6.7)	1	-	-	1 (2.1)	1
<Musculoskeletal and connective tissue disorders>	-	-	1 (6.7)	1	-	-	1 (2.1)	1
Pain in extremity	-	-	1 (6.7)	1	-	-	1 (2.1)	1
<General disorders and administration site conditions>	2 (12.5)	4	1 (6.7)	1	1 (6.3)	1	4 (8.5)	6
Discomfort	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Irritability	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Malaise	1 (6.3)	1	1 (6.7)	1	-	-	2 (4.3)	2
Thirst	1 (6.3)	1	-	-	1 (6.3)	1	2 (4.3)	2
<Investigations>	5 (31.3)	7	8 (53.3)	15	8 (50.0)	17	21 (44.7)	39
Alanine aminotransferase increased	-	-	2 (13.3)	2	1 (6.3)	1	3 (6.4)	3
Aspartate aminotransferase increased	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Blood bilirubin increased	1 (6.3)	1	-	-	2 (12.5)	2	3 (6.4)	3
Blood creatine phosphokinase increased	1 (6.3)	1	2 (13.3)	2	2 (12.5)	2	5 (10.6)	5
Blood lactate dehydrogenase increased	-	-	-	-	2 (12.5)	2	2 (4.3)	2
Blood pressure decreased	-	-	1 (6.7)	1	-	-	1 (2.1)	1
Blood pressure increased	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Blood prolactin increased	3 (18.8)	3	7 (46.7)	7	6 (37.5)	6	16 (34.0)	16
Blood triglycerides increased	1 (6.3)	1	1 (6.7)	1	-	-	2 (4.3)	2
Gamma-glutamyltransferase increased	-	-	1 (6.7)	1	-	-	1 (2.1)	1
Glucose urine present	-	-	1 (6.7)	1	-	-	1 (2.1)	1
Weight decreased	-	-	-	-	1 (6.3)	1	1 (2.1)	1
White blood cell count increased	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Protein urine present	-	-	-	-	1 (6.3)	1	1 (2.1)	1

3.3 Adverse events occurring during the follow-up period

During the follow-up period, 13 adverse events were observed in 11 (23.4%) of 47 subjects who received the JNS007ER. In any of the dose groups, no late AE was observed.

Table 7 List of adverse events (during the follow-up period)

Safety analysis population

Events (MedDRA/E V8.1)	3 mg group		9 mg group		15 mg group		Total	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects ((%)	Number of events	Number of subjects (%)	Number of events
Number of subjects analyzed	16	-	15	-	16	-	47	-
Number of events	3 (18.8)	4	3 (20.0)	3	5 (31.3)	6	11 (23.4)	13
<Infections and infestations>	1 (6.3)	1	1 (6.7)	1	4 (25.0)	4	6 (12.8)	6
Bronchitis	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Dental caries	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Furuncle	-	-	1 (6.7)	1	-	-	1 (2.1)	-
Gastroenteritis	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Nasopharyngitis	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Tinea pedis	-	-	-	-	1 (6.3)	1	1 (2.1)	1
<Nervous system disorders>	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Anxiety	-	-	-	-	1 (6.3)	1	1 (2.1)	1
<Nervous system disorders>	-	-	2 (13.3)	2	-	-	2 (4.3)	2
Akathisia	-	-	2 (13.3)	2	-	-	2 (4.3)	2
<Respiratory, thoracic and mediastinal disorders>	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Pharyngolaryngeal pain	1 (6.3)	1	-	-	-	-	1 (2.1)	1
<Gastrointestinal disorders>	-	-	-	-	1 (6.3)	1	1 (2.1)	1
Nausea	-	-	-	-	1 (6.3)	1	1 (2.1)	1
<Musculoskeletal and connective tissue disorders>	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Back pain	1 (6.3)	1	-	-	-	-	1 (2.1)	1
<Investigations>	1 (6.3)	1	-	-	-	-	1 (2.1)	1
Alanine aminotransferase increased	1 (6.3)	1	-	-	-	-	1 (2.1)	1

3.4 Deaths, serious adverse events, and adverse events that led to discontinuation

No deaths or no serious adverse events were observed in this study.

3.4.1 Adverse events that led to discontinue the study

9 subjects of 47 subjects who received the JNS007ER, were discontinued the study. Of these cases of discontinuation, 5 cases were due to the development of AEs during the study period. The details of the AEs that led to discontinuation in the 5 subjects are described below.

Subject NB-11 was registered in the 9 mg group, but was discontinued the study on Day 5 after the start of the JNS007ER due to AEs (akathisia and malaise). The akathisia started on Day 3 after the start of the JNS007ER, and resolved on Day 14 (Day 10 after discontinuation of the JNS007ER) by the treatment with Artane at 2 mg/day. Artane at 2 mg/day was also used before and after the occurrence of the AE to prevent extrapyramidal symptoms. The malaise occurred on Day 2 after the start of the JNS007ER, and resolved on Day 14 (Day 10 after discontinuation of the JNS007ER) without any treatment. The causal relationship of the two AEs to the JNS007ER was judged to be “Probably related”.

Subject NC-05 was registered in the 15 mg group, but was discontinued the study on Day 21 after the start of the JNS007ER due to an AE (sleepiness). The sleepiness started on Day 3 after the start of the JNS007ER, and resolved on Day 24 after the start of the JNS007ER (Day 4 after discontinuation of the JNS007ER) by the dose reduction of Benzalin, which was used for the treatment of the underlying disease, from 10 mg/day to 5 mg/day. The causal relationship of the AE to the JNS007ER was judged to be “Almost definitely related”.

Subject NC-07 was registered in the 15 mg group, but was discontinued the study on Day 3 after the start of the JNS007ER due to AEs (anxiety complex and feeling queasy). The anxiety complex started on Day 2 after the start of the JNS007ER, and resolved on Day 5 after the start of the JNS007ER (Day 3 after discontinuation of the JNS007ER) without any treatment. The feeling queasy started on Day 3 after the

start of the JNS007ER, and resolved on Day 5 after the start of the JNS007ER (Day 3 after discontinuation of the JNS007ER) by the treatment with Gasmotin 3 times daily at 5 mg/dose. Both AEs were considered as withdrawal symptoms of the prior medication, and their causal relationship to the JNS007ER was judged to be “Not related”.

Subject NC-11 was registered in the 15 mg group, but was discontinued the study on Day 14 after the start of the JNS007ER due to an AE (akathisia). The akathisia started on Day 3 after the start of the JNS007ER, and resolved on Day 22 after start of the JNS007ER (Day 9 after discontinuation of the JNS007ER) without any treatment. The causal relationship of the AE to the JNS007ER was judged to be “Probably related”.

Subject NC-12 was registered in the 15 mg group, but was discontinued the study on Day 5 after the start of the JNS007ER due to an AE (insomnia aggravated). The insomnia aggravated started on Day 2 after the start of the JNS007ER, and resolved on Day 6 after the start of the JNS007ER (Day 2 after discontinuation of the JNS007ER) by the treatment with intermittent doses of Dezolam 1 mg. The treatment with intermittent doses of Dezolam 1 mg was given also before and after the occurrence of AE for the treatment of the underlying disease. The causal relationship of the AE to the JNS007ER was judged to be “Almost definitely related”.

3.4.2 Adverse events related to extrapyramidal symptoms

7 AEs related to extrapyramidal symptoms were observed in 7 subjects (14.9%) during the treatment period with the JNS007ER. These AEs were “ akathisia ” (4 events in 4 subjects: 8.5%), “ extrapyramidal symptoms “ (2 events in 2 subject: 4.3%), “ Parkinsonism ” (1 event in 1 subjects: 2.1%). By dose, no AE in the 3 mg group, 2 AEs in 2 subjects (13.3%) in the 9 mg group, and 5 AEs in 5 subjects (31.3%) in the 15 mg group were observed. Thus, the incidence of AEs was higher in the higher dose groups.

During the follow-up period, akathisia (2 events in 2 subjects: 13.3%) in the 9 mg group.

Table 8. List of AEs related to extrapyramidal symptoms (during the treatment period with the investigational drug)

Safety analysis population

Events (MedDRA/E V8.1)	3 mg group		9 mg group		15 mg group		Total	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Number of subjects included in the analysis	16	-	15	-	16	-	47	-
Number of events	-	-	2 (13.3)	2	5 (31.3)	5	7 (14.9)	7
<Nervous system disorders>	-	-	2 (13.3)	2	5 (31.3)	5	7 (14.9)	7
Akathisia	-	-	2 (13.3)	2	2 (12.5)	2	4 (8.5)	4
Extrapyramidal disorder	-	-	-	-	2 (12.5)	2	2 (4.3)	2
Parkinsonism	-	-	-	-	1 (6.3)	1	1 (2.1)	1

3.4.3 Adverse events related to prolactin

During the treatment period, 21 prolactin-related adverse events were observed in 20 subjects (42.6%). Of these events, abnormal laboratory test values included “ Hyperprolactinaemia” (4 events in 4 subjects: 8.5%) and “ an increase in blood prolactin level (MedDRA/E term : blood prolactin increased)”(16 events in 16 subjects: 34%). Clinical symptoms relating to blood prolactin increase included “ Libido decreased ” (1 event in 1 subject :2.1%).

Table 9. List of AEs related to prolactin
(during the treatment period with the investigational drug)

Safety analysis population

Number of events	3 mg group		9 mg group		15 mg group		Total	
	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events	Number of subjects (%)	Number of events
Number of subjects analyzed	16	-	15	-	16	-	47	-
Number of events	3 (18.8)	3	9 (60.0)	10	8 (50.0)	8	20 (42.6)	21
<Endocrine disorders>	-	-	2 (13.3)	2	2 (12.5)	2	4 (8.5)	4
Hyperprolactinaemia	-	-	2 (13.3)	2	2 (12.5)	2	4 (8.5)	4
<Psychiatric disorders>	-	-	1 (6.7)	1	-	-	1 (2.1)	1
Libido decreased	-	-	1 (6.7)	1	-	-	1 (2.1)	1
<Investigations>	3 (18.8)	3	7 (46.7)	7	6 (37.5)	6	16 (34.0)	16
Blood prolactin increased	3 (18.8)	3	7 (46.7)	7	6 (37.5)	6	16 (34.0)	16

The mean changes from the baseline of prolactin in male subjects at Week 2 of the treatment were 2.53ng/mL, 21.16ng/mL and 13.39 ng/mL in 3 mg, 9 mg and 15 mg group, respectively and 12.69 ng/mL as a whole. At Week 6, the changes from the baseline were 1.64ng/mL, 22.16ng/mL and 12.84 ng/mL in 3 mg, 9 mg and 15 mg group, respectively and 12.91 ng/mL as a whole. Although statistically significant increase was observed at Weeks 2 and 6 in the 9mg group and 15 mg group, it was not observed in 3 mg group. Since the change observed at Week 6 was comparable with that observed at Week 2, it was suggested that prolactin increased up to Week 2 and it became stable by Week 6. In female subjects, although prolactin increased at Weeks 2 and 6, it was not statistically significant.

Thus, although prolactin increased after administration of JNS007ER, it was not associated with increase of any clinical findings.

Table 10. Descriptive statistics of laboratory test values (prolactin)

Safety analysis population

Gender	Timepoints		3 mg group	9 mg group	15 mg group	Total
Male	Baseline					
		No. of subjects	10	11	12	33
		Mean（SD）	17.95 (10.63)	23.27 (18.99)	27.88 (18.90)	23.34 (16.86)
		Median (min-max)	15.10 (3.4 - 42.3)	18.90 (2.8 - 66.8)	23.00 (10.2 - 74.0)	17.70 (2.8 - 74.0)
	Week 2					
		No. of subjects	10	11	12	33
		Mean（SD）	20.48 (10.96)	44.44 (22.43)	41.28 (22.50)	36.03 (21.80)
		Median (min-max)	18.30 (4.6 - 43.2)	40.40 (21.2 - 88.1)	40.15 (7.6 - 97.9)	32.90 (4.6 - 97.9)
		Change from baseline				
		No. of subjects	10	11	12	33
		Mean（SD）	2.53 (9.35)	21.16 (23.63)	13.39 (14.31)	12.69 (18.07)
		Median (min-max)	-0.05 (-9.0 - 19.5)	18.90 (-10.1 - 65.4)	10.95 (-4.1 - 36.8)	8.70 (-10.1 - 65.4)
		p-value [a]	p=0.7695	p=0.0137*	p=0.0127*	p=0.0002**
	Week 6					
		No. of subjects	9	11	7	27
		Mean（SD）	19.74 (8.58)	45.44 (20.44)	38.29 (9.23)	35.02 (18.23)
		Median (min-max)	18.90 (6.2 - 36.9)	42.80 (21.3 - 93.6)	38.10 (24.9 - 54.3)	34.60 (6.2 - 93.6)
		Change from baseline				
		No. of subjects	9	11	7	27
		Mean（SD）	1.64 (8.69)	22.16 (16.95)	12.84 (14.70)	12.91 (16.24)
		Median (min-max)	0.60 (-9.3 - 14.7)	20.00 (2.4 - 51.2)	7.20 (-3.2 - 38.2)	7.50 (-9.3 - 51.2)
		p-value [a]	p=0.6523	p=0.0010**	p=0.0313*	p<0.0001**
Female	Baseline					
		No. of subjects	6	4	4	14
		Mean（SD）	82.03 (62.69)	143.58 (51.73)	102.23 (73.41)	105.39 (63.85)
		Median (min-max)	65.10 (7.4 - 185.9)	134.75 (94.8 - 210.0)	109.25 (6.1 - 184.3)	106.95 (6.1 - 210.0)
	Week 2					
		No. of subjects	6	4	4	14
		Mean（SD）	81.48 (36.43)	220.68 (47.67)	119.03 (50.41)	131.98 (72.60)
		Median (min-max)	83.30 (19.1 - 119.5)	228.20 (155.8 - 270.5)	113.45 (66.4 - 182.8)	117.25 (19.1 - 270.5)
		Change from baseline				
		No. of subjects	6	4	4	14
		Mean（SD）	-0.55 (45.07)	77.10 (58.44)	16.80 (30.78)	26.59 (54.25)
		Median (min-max)	7.15 (-66.4 - 64.7)	64.40 (20.6 - 159.0)	7.45 (-8.0 - 60.3)	16.95 (-66.4 - 159.0)
		p-value [a]	p=1.0000	p=0.1250	p=0.6250	p=0.0785
	Week 6					
		No. of subjects	5	3	3	11
		Mean（SD）	92.62 (59.45)	200.20 (62.32)	133.40 (36.91)	133.08 (68.07)
		Median (min-max)	86.00 (36.1 - 191.7)	217.00 (131.2 - 252.4)	150.00 (91.1 - 159.1)	131.20 (36.1 - 252.4)
		Change from baseline				
		No. of subjects	5	3	3	11
		Mean（SD）	-4.34 (16.95)	61.43 (70.37)	-0.87 (30.90)	14.55 (46.96)
		Median (min-max)	5.80 (-29.0 - 9.6)	36.40 (7.0 - 140.9)	-11.30 (-25.2 - 33.9)	7.00 (-29.0 - 140.9)
		p-value [a]	p=0.8125	p=0.2500	p=1.0000	p=0.5625

a: Changes from baseline by Wilcoxon signed rank test.

**：$p \leqq 0.01$, *：$0.01 < p \leqq 0.05$

Unit：ng/mL

3.5 Laboratory test values

Statistically significant changes were sporadically observed in the changes from baseline in each group and in the entire population. In prolactin, significant increases were observed in the 9 mg and 15 mg groups. In the 9 mg group, libido decreased (1 event in 1 subject: 2.1%) was observed as an AE related to prolactin. Other significant laboratory changes had no particular clinical significance.

3.6 DIEPSS

The mean baseline in each dose group was 0.7 in the 3 mg group, 1.5 in the 9 mg group, and 1.9 in the 15 mg group. Thus, the higher dose groups tended to show higher baseline values. The change at Week 6 from baseline was -0.1 in the 3 mg group, -0.1 in the 9 mg group, and 0.6 in the 15 mg group. The difference from the maximum score after start of the JNS007ER was -0.1 in the 3 mg group, -0.0 in the 9 mg group, and 1.8 in the 15 mg group. No increase from baseline was observed in the 3 mg and 9 mg groups, but a trend of slight increase was observed in the 15 mg group.

Table 11 Descriptive statistics of DIEPSS total score

Safety analysis population

		3 mg group	9 mg group	15 mg group	Total
Baseline	Score				
	Number of subjects	16	15	16	47
	Mean value (S.D.)	0.7 (1.3)	1.5 (1.7)	1.9 (2.5)	1.3 (1.9)
	Median (min. - max.)	0.0 (0 - 4)	1.0 (0 - 5)	1.0 (0 - 9)	1.0 (0 - 9)
Week 6	Score				
	Number of subjects	14	14	10	38
	Mean value (S.D.)	0.6 (1.1)	1.1 (1.5)	2.4 (2.6)	1.3 (1.9)
	Median (min. - max.)	0.0 (0 - 3)	0.5 (0 - 4)	1.5 (0 - 8)	0.5 (0 - 8)
	Change from baseline				
	Number of subjects	14	14	10	38
	Mean value (S.D.)	-0.1 (0.7)	-0.1 (0.5)	0.6 (1.3)	0.1 (0.9)
	Median (min. - max.)	0.0 (-2 - 1)	0.0 (-1 - 1)	0.0 (0 - 3)	0.0 (-2 - 3)
	p value[a]	0.4346	0.3356	0.1679	0.7108
Maximum score observed after the start of the measurement	Score				
	Number of subjects	16	15	16	47
	Mean value (S.D.)	0.6 (1.1)	1.5 (1.9)	3.7 (5.5)	1.9 (3.6)
	Median (min. - max.)	0.0 (0 - 3)	1.0 (0 - 6)	1.0 (0 - 17)	1.0 (0 - 17)
	Change from baseline				
	Number of subjects	16	15	16	47
	Mean value (S.D.)	-0.1 (0.7)	-0.1 (0.8)	1.8 (4.2)	0.6 (2.6)
	Median (min. - max.)	0.0 (-2 - 1)	0.0 (-1 - 2)	0.0 (0 - 16)	0.0 (-2 - 16)
	p value[a]	0.7183	1.0000	0.1083	0.1291

a: Changes from baseline by paired t-test

3.7 Physical examination

Statistically significant changes were observed in the changes from the baseline in each group and in the entire population, but were of no particular clinical significance.

3.8 Electrocardiogram

In each group and in the entire population, no particular clinical significance was observed in the change in each parameter from the baseline. QTc was calculated using the ECG parameter values from all the subjects in the assessment of the cardiologist, and showed no particular trend for prolongation of QT.

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