SYNOPSIS

Issue Date: 20 NOVEMBER 2012

Name of Sponsor/Company	Janssen Pharmaceutical K. K.
Name of Finished Product	CONCERTA®
Name of Active Ingredient(s)	Methylphenidate HCl

Protocol No.: JNS001-JPN-A01

Title of Study: A Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of JNS001 in Adults with Attention-Deficit/Hyperactivity Disorder at Doses of 18 mg, 36 mg, 54 mg or 72 mg per day.

NCT No.: NCT01323192

Clinical Registry No.: CR017755

Study Center(s): The study was conducted at 39 study sites in Japan.

Publication (Reference): None

Study Period: 22 February 2011 to 19 April 2012, Database lock date: 21 June 2012

Phase of Development: Phase 3

Objectives:

Primary Objective: To evaluate the efficacy of JNS001 titrated to daily dose of 18 to 72 mg in adults with Attention-Deficit/Hyperactivity Disorder (ADHD) relative to placebo, based on the change in Diagnostic And Statistical Manual of Mental Disorders 4th Edition (DSM-IV) Total ADHD Symptoms scores (18 items) of the investigator-rated Conners' Adult ADHD Rating Scale-Observer: Screening Version (CAARS-O:SV) from baseline to the end of the double-blind (DB) phase.

Secondary Objectives: Assessment of overall safety of JNS001, efficacy (based on Clinical Global Impression [CGI], the reduction of ADHD symptoms using the Conners' Adult ADHD Rating Scale-Self Report Screening version [CAARS-S:SV] [Total score, DSM-IV Total ADHD Symptoms scores, DSM-IV Inattentive Symptoms scores, DSM-IV Hyperactive-Impulsive Symptoms scores and ADHD Index], CAARS-O:SV [Total score, DSM-IV Inattentive Symptoms scores, DSM-IV Hyperactive-Impulsive Symptoms scores and ADHD Index], Quality of Life Enjoyment and Satisfaction Questionnaire Short Form [Q-LES-Q-SF] total score), the pharmacokinetics of JNS001 at steady state, and exploratory assessment of the relationship between plasma drug concentration and Corrected QT interval (QTc) change from baseline.

Methodology: This was a randomized, DB, multicenter, placebo-controlled, parallel group, dose-titration study. The study consisted of a 1 to 2-week screening phase (including washout), an 8-week DB phase (4-week titration period and 4-week efficacy assessment period), and a 1-week Post-study phase. Eligible subjects were randomly assigned in a ratio of 1:1 to receive JNS001 or placebo once daily. Subjects were titrated from a starting dose of 18 mg per day at weekly increments of 18 mg per day to an individually-optimized dose at which the CAARS-O:SV score had improved by 30% from baseline and a Clinical Global Impression-Global Change (CGI-C) rating of 1 or 2 (very much improved/much improved) was achieved or to a maximum dose of 72 mg per day. The subjects were to remain on this dose for the remainder of the study, if possible. Safety was evaluated throughout the study and efficacy evaluations were performed at baseline and at designated time points in the DB phase. Pharmacokinetic samples were obtained at Weeks 4 and 8. The Post-study phase was held for all subjects who received study treatment.

Number of Subjects (planned and analyzed): It was planned to enroll a total of 280 subjects (140 subjects per treatment group) to ensure at least 133 evaluable subjects per treatment group to secure a power of 90%. A total of 284 eligible subjects were randomized and receive at least 1 dose of study drug (143 subjects with JNS001, 141 subjects with placebo) (safety analysis set); 283 subjects (143 subjects with JNS001, 140 subjects with placebo) had baseline and at least 1 post-dose efficacy assessment (full analysis set). Pharmacokinetic analyses were based on 142 subjects who had at least 1 plasma concentration of methylphenidate (MP), which was available to the evaluation of pharmacokinetics (pharmacokinetic analysis set).

Diagnosis and Main Criteria for Inclusion: Men and women, between 18 and 64 years old, inclusive, with a diagnosis of ADHD according to the Diagnostic And Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR) criteria (Conners' Adult ADHD Diagnostic Interview for DSM-IV [CAADID] Japanese version) and DSM-IV Total ADHD Symptoms scores of CAARS-O:SV score of ≥24.

Test Product, Dose and Mode of Administration, Batch No.: JNS001 was supplied as oral tablets in 3 dose strengths: 18 mg yellow tablet (Batch No. 16AB), 27 mg gray tablet (Batch No. 17AB), and 36 mg white tablet (Batch No. 18AB).

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo was supplied as 3 tablets matching JNS001 18 mg (Batch No. 16AB), 27 mg (Batch No. 17AB), and 36 mg (Batch No. 18AB), respectively.

Duration of Treatment: JNS001 or placebo was to be administered for 8 weeks during the DB treatment phase.

Criteria for Evaluation:

Pharmacokinetic samples for concentrations of MP and its major metabolite α-phenyl-piperidine-acetic acid (PPAA) were collected at Weeks 4 and 8 (Day 28 and 56) or at early discontinuation in the DB phase.

The primary efficacy outcome measure was the CAARS-O:SV: DSM-IV ADHD Symptom scales. Other efficacy assessments included the CAARS-S:SV: DSM-IV ADHD Symptom scales, Clinical Global Impression-Severity of Illness (CGI-S) score, CGI-C score, and Q-LES-Q-SF total score.

Safety assessment was based on reported adverse events (AEs), clinical laboratory tests, vital sign and body weight measurements, electrocardiograms (ECG), evaluations of sleep, appetite, and abuse potential, and the Columbia-Suicide Severity Rating Scale (C-SSRS).

Statistical Methods:

Pharmacokinetic Analyses: The pharmacokinetic analysis was performed on the pharmacokinetic dataset, which included all randomized subjects who received study treatment and had at least 1 plasma concentration of MP, which was available to the evaluation of pharmacokinetics. For each dose, descriptive statistics were calculated for the plasma concentrations of MP and PPAA at each sampling time.

Efficacy Analyses: All subjects who received at least 1 dose of study drug and had baseline and at least 1 postdose efficacy assessment were included in efficacy analyses as full analysis set. For efficacy analyses, the last-observation-carried-forward (LOCF) method was used for imputation of missing data. The analysis of observed data available at each visit was also performed. All statistical tests were performed at the 5% level of significance (2-sided). For calculation of confidence intervals, two-tailed 95% confidence intervals were used. No adjustments will be made for multiple comparisons.

Primary endpoint was the change from baseline in DSM-IV Total ADHD Symptoms scores (18 items) of CAARS-O:SV. As the primary analysis, the change from baseline score at the end point (ie, Week 8 or

early discontinuation in the DB phase) was analyzed using an analysis of covariance (ANCOVA) model including treatment and sex as factors and baseline score as a covariate. The LOCF method was used for imputation of missing data. Treatment effect was based on the difference in least-squares (LS) mean change from baseline. Comparisons between JNS001 and placebo were performed at the 5% level of significance (2-sided). As the secondary analysis, changes from baseline score at each visit were analyzed using the same method stated above for primary analysis. An analysis of actual scores available at each visit was also performed.

Secondary endpoints included CAARS-O:SV total score and subscale scores other than DSM-IV Total ADHD Symptoms scores, CAARS-S:SV total score and subscale scores, CGI-S, CGI-C, and Q-LES-Q-SF total score. The changes from baseline in CAARS-O:SV total score, CAARS-S:SV total score, CAARS-O:SV subscale scores other than DSM-IV Total ADHD Symptoms scores, CAARS-S:SV subscale scores, and Q-LES-Q-SF total score were analyzed using an ANCOVA model with treatment and sex as factors and baseline score as a covariate. The CGI-S score was analyzed using an ANCOVA model on the ranks of change from baseline with treatment as a factor and the baseline score as a covariate. The CGI-C score was analyzed using an analysis of variance (ANOVA) model on the ranks of actual values with treatment as a factor.

Safety Analyses: Subjects who received at least 1 dose of study drug were included in safety analyses. The reported terms used in the electronic case report forms (eCRFs) by investigator or coinvestigator to identify AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 15.0. All reported AEs with onset during the treatment phase (ie, treatment-emergent AEs) were included in the analysis. For each AE, the percentage of subjects who experienced at least 1 occurrence of the given event was summarized by treatment group. The AEs by severity, serious adverse events (SAEs) and AEs leading to study discontinuation were also summarized. Descriptive statistics were calculated for the change from baseline to each scheduled visit in clinical laboratory test results, vital sign measurements, ECG parameters, and weight. For C-SSRS, the percentage of subjects with a suicide related outcome was summarized.

RESULTS:

STUDY POPULATION:

Eligible subjects (N=284) were enrolled in the study and randomly assigned to receive JNS001 or placebo. All of the 284 subjects (143 for JNS001, 141 for placebo) received at least 1 dose of the study drug (safety analysis set), of which 283 subjects (143 for JNS001, 140 for placebo) had both baseline and postbaseline efficacy data (full analysis set). Pharmacokinetic analyses were based on 142 subjects who had at least 1 plasma MP concentration available for the evaluation of pharmacokinetics (pharmacokinetic analysis set).

Of the 284 randomized and treated subjects (143 for JNS001, 141 for placebo), 134 subjects (93.7%) in the JNS001 group and 135 subjects (95.7%) in the placebo group completed the DB phase. Nine subjects (6.3%) in the JNS001 group and 6 subjects (4.3%) in the placebo group discontinued study treatment in the DB phase. The most common reasons for discontinuation were adverse events (6 subjects) in the JNS001 group and noncompliance with study drug (3 subjects) in the placebo group.

All of the demographic and baseline characteristics were well balanced between the 2 treatment groups. The subjects' age ranged from 18 to 59 years, with a mean age of 33.4 and 34.1 years in the JNS001 and placebo groups, respectively. Overall, the age at initial ADHD diagnosis ranged from 1 to 58 years, with a mean age of 31.4 and 32.4 years in the JNS001 and placebo groups, respectively. All subjects in both groups met the diagnostic criteria for ADHD according to DSM-IV-TR at present and in childhood based on CAADID.

Within 3 months prior to screening, 14.7% subjects in the JNS001 group and 12.1% subjects in the placebo group received 1 or more psychotropic agents for ADHD. The most commonly used psychotropic

agents for ADHD were atomoxetine hydrochloride and pemoline. More subjects in the placebo group (14.2%) than in the JNS001 group (9.1%) received hypnotics during the DB phase. The frequency of use of antianxiety drugs during the DB phase was generally similar in both groups.

The mean duration of exposure to study drug (including days with missed intakes) was 54.0 days in the JNS001 group and 55.1 days in the placebo group. The majority of subjects (93% or greater) in both groups received the study drug for at least 50 days.

PHARMACOKINETIC RESULTS:

From 142 subjects included in the pharmacokinetic analysis set, 277 plasma MP concentrations and 277 plasma PPAA concentrations (a total of 554 concentrations) were included in the pharmacokinetic analysis.

Individual plasma concentrations of MP and PPAA at Week 8 (the end of the DB phase) were generally similar to those at Week 4 (the end of the titration period). This indicates that plasma concentrations of MP and PPAA reached steady state by Week 4 and were maintained thereafter till the end of the DB phase with subject's individualized doses. Mean plasma concentrations of MP and PPAA at Week 4 and 8 increased with dose, within a dose range of 18 to 72 mg.

EFFICACY RESULTS:

The primary objective of this study was to evaluate the efficacy of JNS001 titrated to a daily dose of 18 to 72 mg in adults with ADHD relative to placebo. The primary endpoint was the change from baseline in DSM-IV Total ADHD Symptoms scores (18 items), 1 of the subscale scores of CAARS-O:SV. The secondary endpoints included CAARS-O:SV total score and other subscale scores, CAARS-S:SV total score and subscale scores, CGI-S, CGI-C, and Q-LES-Q-SF total score.

The baseline mean (SD) total ADHD Symptoms scores were similar between the treatment groups: 31.8 (5.96) in the JNS001 group and 31.5 (6.44) in the placebo group. Based on the ANCOVA model, the LS mean change from baseline to the end point in the total scores was -12.5 (95% Confidence interval [CI]: -14.0 to -11.0) in the JNS001 group and -7.9 [95% CI: -9.5 to -6.4] in the placebo group. The LS mean difference (SE) from placebo was -4.5 (1.10) for the JNS001 group at end point (LOCF). The magnitude of improvement in the total ADHD Symptoms scores was statistically significantly larger in the JNS001 group than in the placebo group ($p<0.0001$, ANCOVA). Sensitivity analyses confirmed the robustness of the results of the primary analysis. The statistical superiority of JNS001 over placebo in reducing the total ADHD symptoms scores was initially observed at Week 2, and was maintained thereafter through the end of the DB phase. Primary endpoint results indicated that JNS001 titrated to a daily dose of 18 to 72 mg significantly improved ADHD symptoms with onset of efficacy at 2 weeks after treatment initiation.

The results of secondary endpoints consistently supported the superior efficacy of JNS001 over placebo in adult subjects with ADHD. JNS001 also reduced the severity of both inattentive symptoms and hyperactivity-impulsivity symptoms, as shown by the statistically significantly greater improvement compared to placebo in the CAARS-O:SV "Inattentive symptoms" and "Hyperactive-Impulsive symptoms" subscales. The LS mean difference (SE) from placebo for JNS001 in these subscale scores was -3.1 (0.72) for "Inattentive symptoms" and -1.4 (0.51) for "Hyperactive-Impulsive symptoms" at end point (LOCF).

In addition, the subject self-reported CAARS-S:SV scale and the investigator-rated CGI-S and CGI-C scales demonstrated a significantly greater effect of JNS001 relative to placebo in reducing the severity of ADHD symptoms. The LS mean difference (SE) from placebo for JNS001 in CAARS-S:SV total ADHD symptoms scores and total score was -4.1 (1.11) and -6.9 (1.86), respectively, at end point (LOCF). At end point, the improvement in CGI-S and CGI-C score was statistically significantly greater in the JNS001 group than in the placebo group (CGI-S, $p<0.0001$ [ANCOVA]; CGI-C, $p<0.0001$ [ANOVA]). For the CGI-S scale, the percentage of subjects assessed as "moderately ill" or worse decreased from

97.2% at baseline to 43.4% at end point in the JNS001 group, and from 92.9% to 62.1% in the placebo group. For the CGI-C scale, the percentage of subjects assessed as "much improved" or "very much improved" was 48.3% in the JNS001 group and 27.9% in the placebo group at end point.

These efficacy results demonstrated that daily dosing of JNS001 for 8 weeks at individualized doses titrated from 18 to 72 mg is superior to placebo in the treatment of ADHD in adult patients in Japan.

SAFETY RESULTS:

AEs were reported in 81.8% and 53.9% of subjects in the JNS001 and placebo groups, respectively, during the DB phase. More subjects in the JNS001 group than in the placebo group experienced drug-related AEs (65.0% versus 25.5%). All of the AEs, except 2 SAEs were mild or moderate in severity. The most commonly reported drug-related AEs (≥5% of subjects) in the JNS001 group were decreased appetite (37.1%), palpitations (18.2%), nausea (14.7%), thirst (13.3%), insomnia (8.4%), headache (7.0%), weight decreased (7.0%), and tachycardia (5.6%).

Among the commonly reported AEs, a larger percentage of subjects in the JNS001 group compared to the placebo group experienced (≥5% difference between the treatment groups) decreased appetite (39.9% versus 7.1%), palpitations (18.2% versus 1.4%), nausea (14.7% versus 2.8%), thirst (14.0% versus 4.3%), weight decreased (7.0% versus 0%), and tachycardia (5.6% versus 0%). In the JNS001 group, more subjects experienced AEs during the titration period. The type and frequency of AEs that occurred during the DB phase were generally similar for male and female subjects.

No deaths occurred in this study. Two subjects in the JNS001 group experienced 1 SAE each. A [redacted] subject developed a severe psychotic disorder during the DB phase. The subject permanently discontinued study treatment due to the SAE. The causal relationship to the study drug could not be ruled out by the investigator. The other [redacted] subject experienced severe pneumothorax spontaneous tension, which was judged by the investigator to be not related to the study drug. The subject recovered from the SAE during the DB phase.

During the DB phase, 6 subjects (4.2%) in the JNS001 group and 1 subject (0.7%) in the placebo group permanently discontinued study treatment due to at least 1 AE. Each event was observed in a single subject, except for decreased appetite in 2 subjects in the JNS001 group.

Analysis of selected AEs of special interest showed that AEs related to decreased appetite, weight decrease and growth (40.6% in the JNS001 versus 7.1% in the placebo) and AEs related to cardiovascular disorders (21.0% in the JNS001 versus 1.4% in the placebo) were more common in the JNS001 group than in the placebo group. The incidence of AEs related to initiating or maintaining sleep (11.9% in the JNS001 versus 10.6% in the placebo) and AEs related to psychiatric disorders (6.3% versus 4.3%) was generally similar between the treatment groups. No AEs related to drug abuse or misuse were reported during the DB phase.

The adverse events during the Post-study phase were evaluated for possible symptoms of withdrawal. None of the adverse events was reported by more than 1 subject in the JNS001 group except nasopharyngitis (3 subjects), which suggests that after discontinuation of treatment there were no dominant adverse events that would be indicative of a withdrawal phenomenon.

A few subjects (3 subjects or less) in both groups experienced laboratory-related AEs. In general, no clinically significant trend in vital signs, body weight, laboratory values, or ECG parameters were observed in either group. However, 10 subjects in the JNS001 group and none in the placebo group experienced AEs of weight decreased (7.0% versus 0%). Additionally, a transient increase in mean pulse rate from baseline was observed in the JNS001 group compared to the placebo group (change: 9.2 bpm versus 1.3 bpm) at the end point, but nearly returned to baseline by the end of the Post-study phase. Abnormal ECG findings in 2 subjects in the JNS001 group at Week 4 were considered clinically significant.

Based on questionnaires on sleep, the percentage of sleep conditions rated “poor” decreased from baseline at each postbaseline assessment point in both treatment groups. Based on questionnaires on appetite, the percentage rated their appetite as “less than usual amount” increased to 37.8% in the JNS001 group and 12.1% in the placebo group at the end point, but returned to 6.3% and 5.7%, respectively, at the end of the Post-study phase. Based on questionnaires on abuse potential, no apparent drug abuse potential was found in the JNS001 group compared to the placebo group. Based on the C-SSRS, a few subjects (4.2% in the JNS001 group, 2.9% in the placebo group) experienced treatment-emergent suicidal ideation, while none experienced any treatment-emergent suicidal behavior, compared to all prior history.

No apparent relationship was observed between steady-state plasma concentration of MP or PPAA and the change in QTc from baseline after multiple dosing.

Although several AEs such as decreased appetite, palpitations, and weight decreased were more frequently reported with JNS001 than placebo, as expected, no other safety signals or concerns were identified. JNS001 (titrated at weekly intervals in 18 mg increments up to a maximum of 72 mg/day) was generally safe and well tolerated by Japanese adult subjects with ADHD.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSION(S):

The results of this study indicate that JNS001 in a dose range of 18 to 72 mg per day was effective and well-tolerated in the treatment of ADHD in Japanese adult subjects. No clinically important safety signals were observed for JNS001 compared with placebo.