SYNOPSIS

Issue Date: 19 August 2013

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

Protocol No.: JNS001-JPN-A02

Title of Study: An Open-Label, Dose-Titration, Long-Term Study to Evaluate the Safety of JNS001 in Adults with Attention-Deficit/Hyperactivity Disorder at Doses of 18 mg, 27 mg, 36 mg, 45 mg, 54 mg, 63 mg or 72 mg per day.

NCT No.: NCT01357993

Clinical Registry No.: CR017758

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

Publication (Reference): None

Study Period: 2 May 2011 (first subject informed consent date) to 28 March 2013 (last observation date of last subject), Database lock date: 7 May 2013

Phase of Development: Phase 3

Objectives:

Primary Objective:

The primary objective of this study was to evaluate the long-term safety and tolerability of JNS001 titrated to daily doses of 18 to 72 mg in adults with Attention-Deficit/Hyperactivity Disorder (ADHD). Safety was to be evaluated based on adverse events (AEs) reporting, vital signs, and clinical laboratory tests.

Secondary Objectives:

The secondary objectives of this study were as follows:

- Assessment of long-term maintenance of efficacy of JNS001 titrated to daily doses of 18 to 72 mg based on the change in DSM-IV Total ADHD Symptoms scores (18 items) of the investigator-rated Conners' Adult ADHD Rating Scale-Observer:Screening Version (CAARS-O:SV);
- Assessment of long-term maintenance of efficacy on ADHD symptoms based on changes in the investigator-rated CAARS-O:SV (Total score, DSM-IV Inattentive Symptoms scores, DSM-IV Hyperactive-Impulsive Symptoms scores, and ADHD Index);
- Assessment of long-term maintenance of efficacy as measured by the Clinical Global Impression scale and 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), and its impact on overall functioning, work, family, and social functioning using quality-of-life parameters.

Methodology: This was a multicenter, open-label, dose-titration, long-term safety study in adult subject with a diagnosis of ADHD based on Diagnostic And Statistical Manual of Mental Disorders 4th Edition Text Revision (DSM-IV-TR). The study consisted of a 48-week Long-term phase (4-week titration period

and 44-week maintenance period) and a 1-week Post-study phase. Subjects who had completed the preceding study (JNS001-JPN-A01, which consisted of an 8-week double-blind placebo-controlled phase and a 1-week Post-study phase) were eligible for this extension study to continue JNS001 treatment. Subjects were titrated from a starting dose of 18 mg per day for 7 days, and continued with weekly increments (+/- 2 days) of 9 or 18 mg per day until an individualized dose was achieved. During the maintenance period, the dose was adjusted between 18 to 72 mg per day depending on the subjects' symptoms. Safety was evaluated throughout the study and efficacy evaluations were performed at baseline and at designated time points in the Long-term phase. The Post-study phase was held for all subjects who received study treatment including those discontinued from the study.

Number of Subjects (planned and analyzed): It was planned to enroll at least 160 subjects to ensure 100 subjects completed for 1 year. A total of 253 subjects received at least 1 dose of study drug (safety analysis set) as of the interim cutoff date; the 253 subjects had baseline and at least 1 post-dose efficacy assessment (full analysis set).

Diagnosis and Main Criteria for Inclusion: Adult subject with a diagnosis of ADHD according to the DSM-IV-TR criteria (Conners' Adult ADHD Diagnostic Interview for DSM-IV [CAADID] Japanese version) who had completed the preceding study (JNS001-JPN-A01).

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. 19AB, 22AF, 25AF, 31AL, 34AL), 27 mg gray tablet (Batch No. 20AB, 23AF, 26AF, 32AL, 35AL), and 36 mg white tablet (Batch No. 21AB, 24AF, 27AF, 33AL, 36AL).

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: JNS001 was to be administered for 48 weeks (1-year) during the long-term treatment phase.

Criteria for Evaluation:

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

Safety assessment was based on reported 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:

Efficacy Analyses: The efficacy analyses were based on the full analysis set population, which included all subjects who received at least 1 dose of study drug and had baseline and at least 1 post-dose efficacy assessment. 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. The baseline for analysis of the data in this study was defined as baseline of the preceding JNS001-JPN-A01 study.

The primary parameter was DSM-IV Total ADHD Symptoms scores of CAARS-O: SV. At each assessment time point and end point, descriptive statistics of actual score and change from baseline in the DSM-IV Total ADHD symptoms score were presented for both the observed case and LOCF data.

The other parameters 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. At each assessment time point and end point, descriptive statistics of actual scores and

changes from baseline in 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 score and Q-LES-Q-SF total score, and descriptive statistics of actual scores for CGI-C score were presented for both the observed case and LOCF data. For the CGI-S and CGI-C scores, frequency distribution of scores was presented for both the observed case and LOCF data at each assessment time point and end point.

Safety Analyses: All safety analyses were performed on the safety analysis set, which included all subjects who received at least 1 dose of study drug. 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 that newly occurred or worsened in severity 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. 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 body weight. For C-SSRS, the percentage of subjects with a suicide related outcome was summarized.

RESULTS:

This Final Clinical Study Report is based on the final dataset that was produced after completion of the study.

STUDY POPULATION:

Of 254 eligible subjects who were enrolled in the study, 253 received at least 1 dose of study drug and had both baseline and post-dose efficacy data. These subjects were included in the full analysis set and the safety analysis set.

Of the 253 treated subjects, 205 subjects (81.0%) completed the Long-term phase, and 48 subjects (19.0%) discontinued study treatment in the Long-term phase. The most common reasons for discontinuation were adverse event (22 subjects) and withdrawal of consent (11 subjects).

At the entry of the preceding JNS001-JPN-A01 study, the subjects' age ranged from 18 to 58 years, with a mean age of 33.9 years. The age of subjects at initial ADHD diagnosis ranged from 1 to 58 years, with a mean age of 32.1 years. All of the subjects 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 in the preceding JNS001-JPN-A01 study, 14.2% of the subjects (36/253) received 1 or more psychotropic agents for ADHD. The most commonly used psychotropic agents for ADHD were atomoxetine hydrochloride (12 subjects) and pemoline (10 subjects). During the Long-term phase, 22.1% of the subjects (56/253) received hypnotics or antianxiety drugs, and 7.9% of the subjects (20/253) psychotropic agents.

The mean duration of exposure to JNS001 (including days with missed intakes) was 296.6 days. Most of the subjects received JNS001 for at least 253 days. The dose distributions remained similar on any study visit day after Week 8, and the doses did not increase with extended treatment durations.

EFFICACY RESULTS:

The secondary objective of this study was to evaluate the long-term maintenance of efficacy of JNS001 titrated to daily doses of 18 to 72 mg in adults with ADHD. The primary efficacy parameter was DSM-IV Total ADHD Symptoms scores, 1 of the subscale scores of CAARS-O:SV. The other efficacy parameters 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 baseline mean (SD) DSM-IV Total ADHD Symptoms scores of CAARS-O:SV were 31.8 (6.32). The mean DSM-IV Total ADHD Symptoms scores had decreased from baseline at Week 4, Week 12, Week 24, Week 36, and end point (LOCF), with a mean change (SD) of -14.6 (8.72), -15.5 (9.37), -16.1 (9.83), -16.7 (9.81), and -17.2 (9.91), respectively. A rapid decrease from baseline in the mean DSM-IV Total ADHD symptoms scores was observed during the 4-week titration period and then the decrease was generally maintained throughout the Long-term phase. This indicates that the efficacy of JNS001 for improvement of ADHD symptoms was maintained over a long period. Similar improvement in DSM-IV Total ADHD Symptoms scores of CAARS-O:SV was achieved regardless of whether subjects received placebo or JNS001 in the preceding JNS001-JPN-A01 study.

The results of the other efficacy parameters consistently supported the long-term maintenance of efficacy of JNS001 in adult subjects with ADHD. JNS001 also reduced the severity of both inattentive symptoms and hyperactive-impulsive symptoms, as shown by a consistent marked improvement in the CAARS-O:SV "Inattentive symptoms" and "Hyperactive-Impulsive symptoms" subscales. The mean change (SD) from baseline in CAARS-O:SV other subscale scores at end point (LOCF) was -11.1 (6.24) for "Inattentive symptoms" and -6.1 (5.23) for "Hyperactive-Impulsive symptoms".

In addition, the subject-rated CAARS-S:SV scale and the investigator-rated CGI-S and CGI-C scales also revealed a long-term effect of JNS001 in reducing the severity of ADHD symptoms. The mean change (SD) from baseline in CAARS-S:SV DSM-IV Total ADHD symptoms scores and Total score was -14.6 (11.56) and -24.5 (19.24), respectively, at end point (LOCF). For the CGI-S scale, the percentage of subjects assessed as "moderately ill" or worse had decreased from 95.3% (241/253) at baseline to 26.5% (67/253) at end point (LOCF). For the CGI-C scale, the percentage of subjects who were assessed as "much improved" or "very much improved" was 64.8% (164/253) at end point (LOCF). There was a slight improvement in daily functioning based on Q-LES-Q-SF total scores, from baseline to end point (mean change: 2.5).

The dose distributions remained similar on any study visit day after Week 8. The doses did not tend to increase with extended treatment durations, and the effects based on the scales including CAARS-O:SV did not decrease. Therefore, there was no indication of tolerance to the therapeutic effects of the study drug for up to 48 weeks.

These efficacy results indicate that the therapeutic effect of JNS001 at a dose range of 18 to 72 mg per day was maintained during long-term treatment of ADHD in Japanese adult subjects.

SAFETY RESULTS:

During the Long-term phase, 239 subjects (94.5%) experienced at least 1 AE. Drug-related AEs were reported in 179 subjects (70.8%). All of the AEs were mild or moderate in severity except 1 severe psychotic disorder (SAE), 1 severe deafness neurosensory (non-SAE), and 1 severe diverticulum intestinal (SAE). The most commonly reported drug-related AEs (≥5% of subjects) were decreased appetite (30.0%), weight decreased (19.4%), palpitations (15.8%), nausea (13.8%), insomnia (13.0%), thirst (10.3%), headache (9.1%), and tachycardia (7.1%). More subjects experienced AEs during the first 12-week period (including 4-week titration period) in this study. During Weeks 1 to 12, decreased appetite, insomnia, thirst, weight decreased, and palpitations were observed more frequently (difference of ≥5%) in subjects who were assigned to the placebo group in the preceding study than in those who were assigned to the JNS001 group in the preceding study. During the Long-term phase, adverse events were reported in 91.1% of male subjects and 97.7% of female subjects. AEs that occurred more frequently in females than males (difference of ≥5%) were decreased appetite, insomnia, nausea, weight decreased, musculoskeletal stiffness, headache, nasopharyngitis, thirst, palpitations, and abdominal pain upper.

No deaths occurred in this study. Four other SAEs were reported during the study. During the Long-term phase, 3 SAEs occurred: psychotic disorder in 2 subjects and diverticulum intestinal in 1 subject. Psychotic disorder was considered by the investigator to be probably or possibly related to the study drug,

while diverticulum intestinal was considered not related to the study drug. During the Post-study phase, 1 SAE (pyrexia) was reported in 1 subject who permanently discontinued study treatment due to a non-serious AE (headache) during the Long-term phase. The event was considered not related to the study drug by the investigator.

During the Long-term phase, 22 subjects (8.7%) permanently discontinued the study drug due to at least 1 AE. The most commonly reported AE leading to study drug discontinuation was palpitations, which was observed in 4 subjects (1.6%). Other AEs leading to study drug discontinuation were observed in 1 or 2 subjects, except for nausea (3 subjects).

Analysis of selected AEs of special interest showed that AEs related to decreased appetite, weight decreased, and growth (41.1%), AEs related to cardiovascular disorders (21.7%), and AEs related to initiating or maintaining sleep (19.4%) had been commonly observed. The AEs related to psychiatric disorders (7.1%) were relatively infrequent. No AEs related to drug abuse or misuse were reported during the study.

During the Post-study phase, 16 subjects (6.3%) experienced at least 1 AE. Two subjects (0.8%) experienced drug-related AEs. Delirium, headache, hypoesthesia, and oropharyngeal pain were observed in the same subject mentioned above who experienced 1 SAE of pyrexia during the Post-study phase. All AEs reported in the Post-study phase were observed in 1 subject, except for nasopharyngitis (3 subjects), malaise (2 subjects), and weight increased (2 subjects). The adverse events during the Post-study phase were evaluated for possible symptoms of withdrawal. None of the adverse events were reported in 3 or more subjects except nasopharyngitis, which suggests that after discontinuation of treatment there were no adverse events that would be indicative of a withdrawal phenomenon.

During the Long-term phase, 6 or fewer ($\leq$ 2.4%) subjects experienced laboratory-related AEs. In general, no clinically significant trends in vital sign and body weight measurements, laboratory values, and ECG parameters were observed. Weight decreased was reported as an AE in 20.6% of the subjects during the Long-term phase, but none were reported during the Post-study phase. An increase in mean pulse rate from baseline was observed at end point (change: 7.3 bpm). The change from baseline tended to decrease, and the mean increase in pulse rate was 3.4 bpm at the end of the Post-study phase. No ECG findings were reported as an AE except 3 abnormalities (electrocardiogram QT prolonged, tachycardia, and palpitations).

Based on questionnaires on sleep, the percentage of sleep conditions rated “poor” decreased from baseline at each post-dose assessment point. Based on questionnaires on appetite, the percentage of subjects that rated their appetite as “less than usual amount” increased from 4.7% (12 subjects) at baseline to 19.8% (50 subjects) at end point, but returned to near baseline, 6.4% (16 subjects), at the end of the Post-study phase. Based on questionnaires on abuse potential, no apparent drug abuse potential was found in the JNS001 treatment. Based on the C-SSRS, a minority of subjects (12 subjects, 4.8%) experienced treatment-emergent suicidal ideation during the Long-term phase, compared to all prior history. No subjects experienced any treatment-emergent suicidal behavior during the Long-term phase.

Although several AEs such as decreased appetite, weight decreased, and palpitations were frequently reported in JNS001 treatment as expected, no other safety signals or concerns were identified. In this study, there were no adverse findings that were unexpected from the findings in other pediatric or adult ADHD studies of MPH. Long-term treatment with JNS001 (titrated at weekly intervals in 9 or 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.

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