SYNOPSIS

Issue Date: 4 January 2011

Name of Sponsor/Company	Ortho-McNeil Janssen Scientific Affairs, LLC
Name of Finished Product	INVEGA® SUSTENNA™
Name of Active Ingredient(s)	R092670 (paliperidone palmitate)

Protocol No.: R092670-SCH-3004

Title of Study: A Prospective, Randomized, Active-controlled, Rater-blinded Study of the Prevention of Relapse Comparing Paliperidone Palmitate with Oral Risperidone in Adults with Recently-Diagnosed Schizophrenia who are at High Risk of Relapse

Study Name: ROAR

EudraCT Number: 2008-007800-27

Publication (Reference): None

Study Period: 30 June 2009 to 17 March 2010

Phase of Development: 3b

Objectives: The primary objective of this study was to assess the efficacy of paliperidone palmitate compared with oral risperidone in delaying time to relapse in subjects recently diagnosed with schizophrenia who were at high risk of relapse.

Secondary objectives of this study were: Evaluation of the impact of paliperidone palmitate compared with oral risperidone with respect to personal and social functioning (Personal and Social Performance Scale [PSP]); and assessment of the safety and tolerability of paliperidone palmitate in this study population by monitoring of adverse events, laboratory tests, vital signs recordings including weight, physical examination, assessment for movement disorders (Extrapyramidal Symptom Rating Scale-abbreviated, [ESRS-A]), sexual functioning (Arizona Sexual Experiences Scale [ASEX] and Sexual Side Effects Questionnaire [SSEQ]), and suicidality (InterSePT Scale for Suicidal Thinking-Plus [ISST-Plus]).

Methods: The study was a randomized, rater-blinded, active-controlled, parallel-group, multicenter study in subjects with a recent DSM-IV diagnosis of schizophrenia. Participation in the pharmacogenomic portion of the study was optional. The study consisted of 3 phases: Screening (up to 2 weeks), Stabilization Phase (up to 25 weeks), and Relapse Prevention Phase (24 months). A Relapse Monitoring Board (RMB), composed of experts in the diagnostic, clinical, and therapeutic management of schizophrenia, was to be commissioned.

Number of Subjects (planned and analyzed): The plan was to enroll 936 subjects in the Stabilization Phase with the goal of randomly assigning 748 subjects in a 1:1 ratio to treatment with either paliperidone palmitate (374 subjects) or risperidone (374 subjects) in the Relapse Prevention Phase. One hundred sixty-two subjects were enrolled, 2 subjects completed the Stabilization Phase and were randomly assigned to treatment in the Relapse Prevention Phase, and no subject completed the study.

	Stabilization	Randomization		Relapse Prevention				
	Paliperidone Palmitate			Risperidone		Paliperidone Palmitate		Total
	N	N	N	(%)	N	(%)	N	(%)
Planned								
Enrolled in Stabilization (all treated subjects[a])	936							
Entered Relapse Prevention		748	374	(50)	374	(50)	748	
Final analysis								
All treated subjects	162	2	2	(100)	0	(0)	0	0.0
Safety	162	2						

[a] All treated subjects are those who received at least one dose of study drug

Diagnosis and Main Criteria for Inclusion: Subjects were men and women, aged 18 to 35 years of age (inclusive), who had a current diagnosis of schizophrenia [paranoid type (295.30), disorganized type (295.10), undifferentiated type (295.90), or residual type (295.60)] based upon the SCID CV-1 according to DSM-IV criteria. The initial diagnosis of any psychotic disorder must have been made within 5 years of screening. Subjects must have been at high-risk of relapse defined as having had 3 periods of breakthrough symptoms within the previous 24 months, including 1 such period within the previous 6 months.

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone palmitate was provided in prefilled syringes containing doses of 50, 75, 100, or 150 mg eq.

Reference Therapy, Dose and Mode of Administration, Batch No.: Oral risperidone was provided as 2 and 4 mg tablets for 2, 4, 6, and 8 mg doses.

Duration of Treatment: The mean number of days (±SD) of exposure to paliperidone palmitate for all treated subjects was 67.1 (±28.77). The mean first injection dose was 150.0 mg, the mean last injection dose was 93.2 mg (±23.97), and the mean total injection dose was 333.2 mg (±103.8).

Criteria for Evaluation: The primary efficacy variable was the time from randomization to the first relapse event (as defined based on the relapse criteria specified in the independent RMB charter) during the 24-month Relapse Prevention Phase. Secondary efficacy variables included change from baseline in PANSS (total score and Marder factor scores), CGI-S, NSA-4, Covi, and PSP and the time to first decrease from baseline of at least 10 points in PSP score.

Safety was assessed by monitoring adverse events, clinical laboratory testing (hematology; serum chemistry, including lipids and prolactin levels; and urinalysis), vital signs measurements (blood pressure, pulse rate, weight), physical examination, 12-lead ECG, movement disorder evaluation, and sexual functioning and suicidality assessments.

Statistical Methods:

The primary analysis set for efficacy was to be the intent-to-treat (ITT) analysis set, which included the time to relapse or time to censoring for any randomly assigned subject who received at least 1 dose of study medication in the Relapse Prevention Phase.

The primary efficacy analysis was to be a comparison between treatments of distributions of time to relapse based on a log-rank test conducted at the 2-sided 0.025 significance level. The probability of relapse at 12, 24, 52, 76, and 104 weeks were to be estimated. An estimate of the hazards ratio and its 95% confidence interval were to be determined using a Cox proportional hazards model with treatment as the covariate.

An interim analysis was to be performed when 178 relapses had occurred, however, because the study was terminated, this was not done.

RESULTS:

It was planned to randomly assign 748 subjects to treatment group in this study. However, because of difficulty in study enrollment, the sponsor terminated the study after only 2 subjects were randomly assigned to treatment. As a result, all planned efficacy analyses as specified in the protocol were not performed. This abbreviated clinical study report focuses only on the analysis of safety data collected on all enrolled subjects.

Subjects were 162 men and women aged 18 to 35 years. There were about twice as many men as women (66.7% men and 33.3% women). Age distribution was approximately equal across each of the age groups of 18 to 23 years (28.4%), 24 to 29 years (38.3%), and 30 to 35 years (33.3%). The majority of subjects were Caucasian (62.3%), 22.8% were Asian, 14.2% were Black or African-American, and 0.6% were Other.

SAFETY RESULTS:

Paliperidone palmitate IM injections were generally well tolerated. There were no deaths , and for all treated subjects (N=162), 72 (44.4%) reported a treatment-emergent adverse event. The most frequently reported events were psychiatric (29 subjects [17.9%]), nervous system disorders (25 subjects [15.4%]), and general disorders and administration site conditions (17 subjects [10.5%]). Four subjects discontinued from the study because of a treatment emergent adverse event (TEAE). All 4 experienced psychiatric disorders. Six subjects had 8 serious TEAEs: 1 hand fracture, 1 incident of aggression, 1 of depression, 4 of exacerbation of schizophrenia, and 1 of self injurious behavior. There was no change in the occurrence of suicidal ideation as measured by the InterSePT Scale for Suicidal Thinking Plus and no effect on sexual experience as measured by the ASEX.

EPS related adverse events were infrequent in this study, all were mild or moderate in severity and none resulted in discontinuation of study treatment. Thirty of 162 subjects (18.5%) showed at least 1 clinically notable vital sign at any time. The most frequently recorded was change in weight, ie, losses of $\geq$7%. No subject had a serious adverse event that was associated with markedly abnormal vital sign measurements and no subject was discontinued as a result of an abnormal vital sign value.

STUDY LIMITATIONS: Enrollment of subjects was insufficient for a reasonably timely completion of the study.

CONCLUSION: Because of lack of data, no conclusion can be drawn from this study concerning efficacy of paliperidone palmitate. The study drug was well tolerated and no safety data contrary to previous studies was seen.

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