Paliperidone: Clinical Protocol R076477SCH4012, CR013771 – Amendment INT-1

A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of a Fixed Dosage of 1.5 mg/day of Paliperidone Extended Release (ER) in the Treatment of Subjects With Schizophrenia*

SYNOPSIS

Paliperidone is a new atypical antipsychotic agent that has recently been approved by the FDA for the treatment of schizophrenia in adults.

OBJECTIVES*:

The primary objective of this study is to evaluate the efficacy and safety of a fixed dosage of paliperidone Extended Release (ER) (1.5 mg/day) compared with placebo in subjects with schizophrenia. The efficacy response will be measured by the change in the Positive and Negative Syndrome Scale (PANSS) total score from start of treatment to the end of the double-blind treatment phase.

The secondary objectives of this study are:

- Assessment of the global improvement in severity of illness associated with the use of paliperidone ER compared with placebo
- Assessment of the benefits to personal and social functioning associated with the use of paliperidone ER compared with placebo
- Evaluation, using a population pharmacokinetic (PK) approach, of the pharmacokinetics of paliperidone released from paliperidone ER in this study population
- Assessment of improvement in patient reported health status associated with the use of paliperidone ER compared with placebo as measured by the Medical Outcomes Study Short Form Health Survey (MOS SF-36)

Hypothesis

Paliperidone ER at 1.5 mg per day will be effective in the treatment of schizophrenia as measured by the change in total PANSS score between baseline and endpoint in comparison with placebo.

OVERVIEW OF STUDY DESIGN*:

This is a multicenter, double-blind, randomized, placebo-controlled, parallel group study. It starts with an up-to-5-day screening phase that includes a 3- to 5-day washout of disallowed medications, if necessary. A 6-week double-blind treatment phase follows and concludes with an end-of-study visit (Visit 10). A post-study visit (Visit 11) for collection of additional safety data will be scheduled 1 week after a subject receives his or her final dose of study drug. For all subjects exiting the study, the investigator should make every effort to see that they receive adequate continuity of care.

At baseline (Day -1), subjects will be randomly assigned to 1 of 3 treatment groups to receive oral paliperidone ER 1.5 mg, paliperidone ER 6 mg, or placebo once daily for 6 weeks. At the time of randomization subjects must be voluntary inpatients, and they must remain in the hospital for a minimum of 8 days.

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SYNOPSIS (CONTINUED)

Efficacy will be evaluated at the time points indicated in the Time and Events Schedule. Subject safety will be assessed throughout the study, which will last approximately 8 weeks. The pharmacokinetics of paliperidone ER in this study population will be evaluated using a population PK approach.

A blood sample for pharmacogenomic research will be collected from subjects who consent (where local regulations permit). Participation in pharmacogenomic research is optional.

STUDY POPULATION:

Two hundred one (67 per study treatment group) men and women, 18 years of age or older, who were diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (295.10, 295.20, 295.30, 295.60, 295.90) at least 1 year before screening, who are experiencing an acute episode with a total PANSS score at screening of between 70 and 120, who are otherwise physically healthy, and who agree to at least 8 days of voluntary hospitalization will be enrolled in the study.

DOSAGE AND ADMINISTRATION:

During the 6-week double-blind treatment phase, subjects will take 1 dose of study drug each morning (1.5 mg paliperidone ER, 6.0 mg paliperidone ER, or placebo), preferably before 10:00 a.m., if possible. When a subject is hospitalized, site personnel will administer the study drug. Once a subject has been discharged from the hospital, it will be the subject's responsibility to take his or her medication.

PHARMACOKINETIC EVALUATIONS:

A sparse sampling procedure will be followed. The procedure combines the PK information gathered from a few blood samples collected in this study with knowledge of the population PK analysis of paliperidone obtained in previous studies. The plasma concentration-time data collected will be included in a population PK analysis.

EFFICACY EVALUATIONS/CRITERIA:

Efficacy will be measured using the following rating scales: PANSS, Clinical Global Impression Scale Severity (CGI-S), Personal and Social Performance Scale (PSP), and the MOS SF-36.

SAFETY EVALUATIONS:

Safety will be evaluated using physical examinations, electrocardiograms (ECGs), clinical laboratory testing (hematology, serum chemistry, and urinalysis), testings for pregnancy, and monitoring for adverse events, including extrapyramidal symptoms (EPS) using the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson-Angus Rating Scale (SAS).

STATISTICAL METHODS*:

Sample Size Determination

For sample size evaluation the following assumptions were made: the difference between the 1.5-mg dose group and placebo group in the mean change of total PANSS from baseline to Week 6 (Last Observation Carried Forward [LOCF]/endpoint) is 11 points and the within-group standard deviation is 20 points. Based on the pooled analysis of the 3- and 6-mg dose groups in studies R076477-SCH-303, R076477-SCH-304 and R076477-SCH-305, it was observed that the mean change of total PANSS from baseline was 11 points for the 3-mg and the 6-mg dose groups. Since there were no prior studies that tested the 1.5 mg paliperidone ER dose group, the difference of 11 points for this group was assumed to be the same as the difference for the previously tested 3-mg and 6-mg dose groups. Mean

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SYNOPSIS (CONTINUED)

change of total PANSS from baseline to Week 6 (LOCF/endpoint) will be assessed within an ANCOVA framework. Since the 6-mg dose group will be used for assay sensitivity only, adjustment for multiple comparisons will not be made.

Given the above assumptions, a sample size of 65 subjects per treatment group will be enough to detect a significant treatment difference between the 1.5-mg dose group and placebo group with a power of 87.5%. With an estimate of approximately 3% of randomized subjects who will discontinue before providing postbaseline total PANSS measurements, the number of randomized subjects was adjusted to 67 in each of the 3 treatment groups. Therefore, a total of approximately 201 subjects will be randomly assigned to treatment groups in this study.

Efficacy Analyses[*]

Primary Endpoint: The primary efficacy endpoint is the change from baseline in total PANSS score from baseline to the end of the double-blind treatment phase (Week 6 or last post-baseline assessment). The change from baseline score to end point will be analyzed using an analysis of covariance (ANCOVA) model. The last-observation-carried-forward (LOCF) method will be used. The model will include treatment and country as factors and baseline total PANSS score as a covariate. Treatment effects will be estimated based on least-squares means of the difference. A test of significance between the 1.5 mg paliperidone dose group and placebo will be carried out at a 5% level (two-tailed). Since the 6-mg dose group will be used for assay sensitivity only, adjustment for multiplicity will not be made. A two-sided 95% confidence interval will be presented for the least-squares means of the difference between **the 1.5-mg** paliperidone group and the placebo group.

Secondary Endpoints: In the analysis of all other efficacy variables, the end point will be the last available post-baseline assessment.

Between-group comparisons of CGI-S will be analyzed by means of an ANCOVA on the ranks of change from baseline, with treatment and country as factors and the baseline CGI-S score as a covariate at each assessment time point and at end point.

Between-group comparisons of PSP change from baseline to end point will be analyzed using an ANCOVA model, with treatment and country as factors and the baseline score as covariate.

The between-group comparison of the change from baseline score at each visit and at endpoint in the 2 summary scales of the MOS SF-36 as well as the 8 domain subscales will be analyzed by means of an ANCOVA model with treatment and country as factors and baseline score as a covariate.

Other End Points:

Onset of therapeutic effect is defined as the first time point at which the treatment groups (1.5 mg paliperidone dosage vs. placebo) are different (at the 2-sided 5% level of significance) and remain different thereafter until endpoint based on the change from baseline in the total PANSS score (LOCF).

Responder Rate. Responders are defined as those who show a 30% or more reduction from baseline in the total PANSS score at the end of 6 weeks or at the last post-baseline assessment in the double-blind phase. This binary variable will be analyzed using the Cochran-Mantel-Haenszel test, controlling for country. Cumulative response rate, defined as the percentage of subjects experiencing at least a given value of percent reduction from baseline in total PANSS score, will also be presented graphically.

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SYNOPSIS (CONTINUED)

PANSS Subscales. Between-group comparisons of the change from baseline score of the PANSS at each visit and at end point in the double-blind phase will be analyzed using an ANCOVA model, controlling for country and baseline score.

Safety Analyses

Adverse events including EPS, clinical laboratory tests, ECG data, results of vital signs measurements, and changes in weight or BMI will be summarized using descriptive statistics or frequency tables, where applicable.

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