SYNOPSIS ESCITALDEP4001

Name of Sponsor/Company	Xian-Janssen Research & Development
Name of Finished Product	LEXAPRO®
Name of Active Ingredient(s)	JNJ-40518855-AFY (escitalopram)

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Prepared by: Xian-Janssen Research & Development

Protocol No.: ESCITALDEP4001 (LEX-CHN-IV-03)

Title of Study: A Single-arm, Open-label, Multicenter Study to Investigate Efficacy and Safety of LEXAPRO on Acute Treatment of Severe Depression

NCT No.: NCT01814085

Clinical Registry No.: CR016300

Principal Investigator: Tianmei Si, MD - Peking University Institute of Mental Health, Beijing, China.

Study Centers: The study was conducted at 8 sites in China.

Publication (Reference): None

Study Period: This study was conducted from 12 February 2010 (first subject enrolled) to 01 March 2012 (last subject out). The database lock was performed on 12 July 2013.

Phase of Development: 4

Objectives: To evaluate the efficacy and safety of escitalopram treatment in severe major depressive disorder (MDD) subjects, to determine the extent to which serum brain-derived neurotrophic factor (BDNF) levels may serve as biological predictors or correlates of antidepressant response, and to evaluate structural magnetic resonance imaging (MRI) and functional MRI (fMRI) data as predictors of symptom change in subjects with depression.

Methodology: This was an 8-week, single-arm, open-label, multicenter, prospective, post-marketing study designed to evaluate the efficacy and safety of escitalopram (LEXAPRO) in subjects with a diagnosis of MDD.

The initial dosage of LEXAPRO for all subjects was 10 mg/day with the dose adjusted at the investigators' discretion according to subject's response. The maximum dosage was 20 mg/day.

The study included 2 phases: Screening Phase, which included the screening visit (Day –5 to 0) and Treatment Phase, which included a baseline visit (immediately prior to dosing), Visit 1 (Week 1), Visit 2 (Week 2), Visit 3 (Week 4), and Visit 4 (Week 8) (the last post-baseline measurement).

At the screening visit, investigators were to check the inclusion and exclusion criteria and obtain signed informed consent; collect demographic data, medical history information, to assess Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Rating Scale for depression (HAM-D-17), Hamilton Rating Scale for anxiety (HAM-A). In the Treatment Phase, vital signs and MADRS, HAM-D-17, and HAM-A were to be assessed at each visit.

Blood test evaluation and electrocardiogram (ECG) were to be done at screening visit and Visit 4 (Week 8). Physical examination, Short-form-12 (SF-12), BDNF, and fMRI (in 20 first-episode subjects only) were to be assessed at baseline and Week 8. Serum drug level was to be measured at baseline,

Visit 1 (Week 1), and Visit 4 (Week 8). Concomitant therapy and adverse events (AEs) were to be recorded throughout the study.

Number of Subjects (planned and analyzed):

Planned: Approximately 240 subjects with MDD were planned to be enrolled in this study.

Analyzed: A total of 225 subjects were enrolled in the study of which 222 subjects were included in the safety set (SS), 207 (92.0%) subjects were included in the full analysis set (FAS), and 158 (70.22%) subjects were included in the per protocol set (PPS).

Diagnosis and Main Criteria for Inclusion: Male or female subjects; age 18-65 years inclusive with a diagnosis of MDD according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text-revision (DSM-IV-TR) criteria with a minimum baseline MADRS score of 30 were considered to be enrolled in this study.

Test Product, Dose and Mode of Administration, Batch No.: Subjects were administered escitalopram 10 mg tablets in 2 batches (2178355 [expiry date January 2012] and 2182918 [expiry date February 2012]).

Duration of Treatment: The duration of the treatment phase in this study was 8 weeks.

Criteria for Evaluation: Efficacy: The primary efficacy measurement was the MADRS. Other efficacy measurements included HAM-D-17, HAM-A, BDNF, MRI, and SF-12 scales.

Safety: Safety and tolerability were evaluated throughout the study based on AE monitoring, vital signs (pulse rate, and blood pressure), physical examination, ECG, and clinical laboratory tests (hematology, chemistry, and urinalysis).

Statistical Methods: Sample size determination: Based on the previous domestic research data, and with an assumption of remission rate of 56% for those treated with escitalopram oxalate for 8 weeks and expecting the width of the 95% confidence interval (CI) to be 14%, a sample size of 194 subjects was required. Assuming a 20% withdrawal rate, 240 subjects were planned to be enrolled in the study.

Efficacy analysis: The endpoints were summarized using descriptive statistics, 95% CI, and the changes before and after treatment with paired t-test or signed-rank test according to data distribution characteristics.

Subjects who received at least 1 dose of study drug with at least 1 efficacy evaluation were included in the FAS and all subjects in FAS who had good compliance (based on completion of 8-week study treatment) and completed all efficacy endpoint evaluations were included in the PPS. The efficacy endpoints were analyzed for subjects in FAS and PPS. Full analysis set was the primary population of efficacy analysis and PPS was the secondary population of efficacy analysis.

Safety analysis: Safety set (SS) composed of subjects who received at least 1 dose of the study drug and had at least 1 safety assessment. Safety set was the primary population of safety analysis. All AEs were coded using the Medical Dictionary for Regulatory Activities, Version 13.1. All AEs were to be analyzed. The percentage of subjects who had at least 1 recorded AE was to be calculated. Safety data was analyzed using only descriptive statistics and changes before and after treatment without analysis of 95% CI. Changes in the laboratory test results from the baseline were to be analyzed with pre-treatment and post-treatment shift tables. Laboratory test results outside the reference range were to be listed and analyzed and abnormal clinically significant laboratory test results were to be listed.

No subgroup analysis was done; however, subjects who used concomitant medications or not, and sedatives and/or hypnotics were analyzed separately. The change from baseline in serum BDNF level was analyzed between effective and ineffective subjects using analysis of covariance model.

RESULTS:

STUDY POPULATION:

Of the total 225 subjects enrolled in the study, 168 (74.7%) subjects completed the 8-week treatment period. The most common reason for withdrawal was withdrawal of consent (11.1%), followed by lost to follow-up (5.3%) and other reasons (4.9%).

The approximate mean age and mean body weight of subjects in FAS, SS, and PPS was 40.5 years and 62 kg, respectively. A greater percentage of the population in the study was female. Approximately 73% and 70% of the subjects in FAS, SS, and PPS were married and stayed with their spouse, respectively. The MADRS, HAM-D-17, and HAM-A total scores at baseline were approximately 36, 30, and 26.6, respectively with no major difference among the FAS, SS, and PPS.

In the FAS, SS, and PPS, the majority (approximately 83%) of the subjects had no family history of depression. Nearly 50% of the total subjects had psychiatric-social pressure as the reason of induction of depression; however, approximately 35% had no reason and 7% had an unknown cause of depression, respectively. The majority of the percentage of subjects (approximately 55%) were first-episode cases of depression followed by relapse of previous depression (approximately 38%), and only a few (approximately 7%) had chronic depression. Approximately, the mean age of first depression episode was 37 years and the mean duration of current episode was 7 months. A total of 62 (29.95%) subjects used sedatives and/or hypnotics during the study.

EFFICACY RESULTS:

Primary Efficacy Analysis

For the primary efficacy endpoint analysis, the remission rate at Week 8 based on MADRS total scores was 72.9% and 84.2% for the FAS and PPS, respectively. The percentage of subjects who used sedatives and/or hypnotics achieved a lower remission rate compared to the total subjects in FAS.

Secondary Efficacy Analysis

The percentage of subjects in FAS and PPS that achieved a clinically effective response rate (more than or equal to 50% decrease in MADRS total score at Week 8 compared to baseline) was 83.6% and 96.2%, respectively. The percentage of subjects in FAS and PPS that achieved an onset of effect (more than or equal to 20% decrease in MADRS total score at Week 8 compared to baseline) was 88.9% and 98.1%, respectively. Approximately 80% and 90% of the subjects achieved an onset of effect within 2 weeks and 8 weeks of treatment, respectively.

In the FAS, the mean percentage reduction of MADRS total score at Week 1, Week 2, Week 4, and Week 8 compared to the baseline was 19.97%, 39.85%, 58.76%, and 73.81%, respectively, which was statistically significant ($p<0.05$).

In the FAS, the mean percentage reduction of HAM-D-17 total scores at Week 1, Week 2, Week 4, and Week 8 was 19.57%, 38%, 54.31%, and 68.59%, respectively, which was statistically significant ($p<0.05$).

In the FAS, the mean percentage reduction of HAM-D 17 factor scores at Week 8 were higher in sleep disorders (75.60%) followed by anxiety/somatization (70.37%) and functional impairment (65.93%). The highest mean reduction in HAM-D-17 individual item scores was seen in depressed mood (−2.2) and the lowest mean reduction was seen in gastrointestinal symptom (-0.8). Overall, each HAM-D-17 item scores observed at Week 8 compared to baseline were statistically significant ($p=0.0000$).

In the FAS, the mean percentage reduction of HAM-A total scores at Week 1, Week 2, Week 4, and Week 8 was 20.10%, 40.10%, 56.97%, and 71.39%, respectively, which was statistically significant ($p<0.05$).

The mean (±SD) serum BDNF level at baseline was 5.852 (±3.02). The change in mean (±SD) BDNF level at Week 1 and Week 8 compared to baseline was 0.324 (±2.66) and –0.245 (±2.87).

The mean (±SD) SF-12 score at baseline was -20.897 (±6.89) that changed to –10.185 (±7.10), which indicated an improvement in subject's condition. The change in SF-12 score at Week 8 compared to baseline was statistically significant (p=0.0000).

In the FAS, the mean (±SD) serum drug concentration of effective and ineffective subjects was similar at Week 1 (52.49 [±40.93] compared to 54.54 [±44.18]) and greater in effective subjects compared to ineffective subjects at Week 8 (68.88 [±55.41] compared to 56.31 [±49.77]).

Based on the ROC curve, the serum concentration values at Week 1 were not specific or sensitive in predicting whether the subject would be effective or ineffective based on the MADRS total scores at Week 2 and Week 8.

The results of a monofactorial regression analysis showed that there was no statistically significant relationship between the remission rate, responder rate, and onset of effect based on MADRS scores with the change in serum drug concentration.

Exploratory Efficacy Analysis

The results of a monofactorial regression analysis showed that there was no statistically significant relationship between the subject's demographic variables (age and gender), chronicity of depression, age of onset, and comorbid anxiety with serum BDNF values.

No meaningful conclusions could be derived to predict the association between subjects' symptom change based on the structural and/or functional MRI changes after escitalopram treatment.

SAFETY RESULTS: Of the 225 subjects who were enrolled, 222 (98.66%) subjects were included in the SS and 3 (1.34%) subjects did not receive study drug therapy due to the withdrawal of consent.

Of the 73 (32.9%) subjects who reported at least 1 AE during the 8 weeks of treatment duration, 63 (28.38%) subjects experienced AEs that were considered to be drug-related. There were no deaths or serious adverse events (SAEs).

The most common AEs by SOC (observed in ≥5% of the total subjects) were Gastrointestinal disorders (14.9%), Nervous system disorders (14.0%), and Skin and subcutaneous tissue disorders (5.4%). The most frequently reported (observed in ≥2% of the total subjects) AEs by preferred term included somnolence (9.0%), nausea (7.7%), hyperhidrosis (4.5%), dry mouth, dizziness, (4.1%, each), and palpitation (2.3%).

Of the 222 subjects in the SS, 62 (27.9%) subjects experienced at least 1 AE that was considered to be drug-related by the investigator during the 8-week treatment period. The most frequently reported (observed in ≥2% of total subjects) drug-related AEs included somnolence (9.0%), nausea (7.7%), hyperhidrosis (4.5%), and dry mouth and dizziness (4.1% each).

There were only 4 (1.8%) subjects who experienced AEs that led to study drug discontinuation. The incidence of any AE that led to study drug discontinuation was less than 1% and none was severe in intensity.

The AE page on the case report form indicated only treatment-emergent AEs would be collected, thus all the collected AEs were summarized as TEAEs. Among these TEAEs, 7 AEs occurred before the first dosing date of the study drug. Five of these 7 AEs were considered by investigator to be related (possibly or probably related) to the study drug and the 2 AEs of hyperlipidemia were considered by investigator as not related to the study drug that persisted throughout the study.

No major difference was observed in the percentage of total and drug-related AEs that occurred between Week 4 and Week 10. The mean (±SD) interval between AE onset date and the date of first administration of study drug was 11.9 (±17.97) days. The mean (±SD) duration of AEs was 14.7 (±12.58) days.

The percentage of subjects who were more than 45 years of age showed lower incidence of drug-related AEs (24.73%) compared to subjects ≤45 years of age (31.01%). Subjects who received nonbenzodiazepine sedation and hypnotics had lower incidence of drug-related AEs (30.19%) compared to benzodiazepines and other concomitant medications (35.71% and 35.29%, respectively). The subjects who had the lowest baseline MADRS and HAM-D-17 total scores had the highest incidence of drug-related AEs and vice versa.

A total of 10 (4.5%) subjects had clinically abnormal blood pressure (systolic pressure <90 or >140 mm Hg, diastolic pressure <50 or >90 mm Hg, or both) and 19 (8.56%) subjects had abnormal heart rate (HR) (HR <60 or >100 beats/minute). Overall, no major difference in the mean systolic and diastolic blood pressure and heart rate (HR) was observed at Week 8 compared with baseline.

The increase in the body weight observed at Week 4 and Week 8 using a paired t-test was considered to be statistically significant (p=0.0000 and p=0.0001, respectively). At Week 8, 9 (4.1%) subjects gained ≥**7**% of their baseline body weight.

STUDY LIMITATIONS: Subjects with comorbid psychiatric disorders and those with high-risk tendency of suicide were excluded; hence, the population in this study may not be fully representative of patients with MDD. The sample size of fMRI test was relatively small, which may have had limitations to prove the correlation between structural and functional changes in the brain and illness severity, and the treatment effects of antidepressant.

CONCLUSIONS: High remission rates were achieved and significant improvement in the symptoms of depression and overall quality of life of the subjects was observed in the study as assessed on the MADRS, HAM-D-17, HAM-A, and SF-12 scales.

The change in BDNF in response to the escitalopram therapy and fMRI test to predict subject's treatment effect and outcome is unclear. Further genetic marker and biochemical mechanism studies may be required to understand the correlation better.

Overall, escitalopram was effective and well-tolerated in the treatment of severe depression in Chinese study population. The results of this study support findings of previous studies with escitalopram.

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