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GENERIC DRUG NAME / COMPOUND NUMBER: Lecozotan / SRA-333

PROTOCOL NO.: 3098B1-204-WW/EU/FR (B3431060)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Long-Term Extension Study to Determine the Safety, Tolerability, and Preliminary Long Term Efficacy of Lecozotan (SRA-333) SR in Patients With Mild to Moderate Alzheimer's Disease Treated With Cholinesterase Inhibitor

Study Centers: This study was conducted at 54 centers in Argentina, Australia, Canada, Europe (France, Spain, Poland, Italy, Finland, and the United Kingdom), South Africa, and the United States.

Study Initiation Date and Final Completion Date: February 2007 to 11 June 2008

Phase of Development: Phase 2b

Study Objectives:

The primary objective was to evaluate the safety and tolerability of long-term therapy with 3 total daily dose levels of lecozotan sustained release ([SR],2, 5, 10 mg) administered to subjects with mild to moderate Alzheimer's disease (AD) who had completed Week 24 evaluations of a previous study, NCT00277810, A 6-Month, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Safety, Tolerability, and Efficacy Study of 3 Doses of Lecozotan (SRA-333) SR in Outpatients With Mild to Moderate Alzheimer's Disease Treated With a Cholinesterase Inhibitor.

Secondary objectives were to evaluate the preliminary efficacy of long-term treatment with lecozotan SR and to measure quality of life in subjects with mild to moderate AD and effort levels of care providers.

METHODS

Study Design: This was a multicenter, randomized, double-blind, long-term extension study with 3 dose levels of lecozotan SR (2, 5, and 10 mg total daily dose). Subjects who met the eligibility criteria at Baseline received 1 of 3 doses of lecozotan SR. Each subject was to be in the study for approximately 30 weeks including 28 weeks of double-blind active phase and 2 weeks of follow-up. The duration of the study was approximately 16 months. The study visit procedures are presented in Table 1.

Table 1. Study Visit Procedure

Study Procedure[a]	Double-Blind Treatment Period					Follow-Up[b,c]
	Visit 1 Baseline (Previous Study Week 24 Visit)	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 14	Visit 5 Week 28[b,d]	Visit 6 Week 30
Informed consent	X					
Inclusion/exclusion criteria	X					
MMSE[e]	X			X	X	
ADAS-Cog[f]	X			X	X	
ADCS-CGIC[g]	X			X	X	
CDT-CAT[h]	X			X	X	
DAD[i]	X			X	X	
NPI[j]	X			X	X	
Cornell Scale for Depression in dementia	X			X	X	
Health outcome assessments[k]	X			X	X	X
Physical examination[l]	X			X	X	
Neurological examination	X			X	X	
Vital signs[m]	X	X	X	X	X	X
Laboratory determinations[n]	X			X	X	
12-lead electrocardiogram	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X
Dispense double-blind test article[o]	X			X		

PK = pharmacokinetic; SAE = serious adverse event; SR = sustained release.

a. Every effort was to be made to bring the subject back on the designated study days (with a ±7-day visit window) for slight variations in schedules.
b. Subjects who no longer wanted to take test article for whatever reason, was to be asked to return for all the remaining scheduled evaluations ending with the post study visit. These visits, after termination of dosing were termed retrieval visits and the subjects were termed retrieval subjects.
c. Follow-up visit 2 weeks after the last test article administration.
d. Subjects who discontinued early the safety and efficacy determinations designated for Week 28 were to be obtained on the last day the subject took a full dose of test article or as soon as possible thereafter.
e. Mini-Mental State Examination (MMSE) ≥12.
f. Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog).
g. Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). Baseline was the assessment performed at the Baseline visit of the previous study. Severity assessments were made at Baseline and at the Week 28 Visit. Each interim visit subsequent to baseline, as well as at Week 28, were to include a rating of the global impression of change.
h. Clinical Drug Trial - Cognitive Assessment Tool (CDT-CAT).

Table 1. Study Visit Procedure

i. Disability Assessment for Dementia (DAD).
j. Neuropsychiatric Inventory (NPI).
k. The subject was to complete subject quality of life instruments. Data collected from the primary significant other person (caregiver) in the subject's life would follow the signature of the subject's own informed consent form. Data collection from the caregiver were to cease if, after randomization, the subject or caregiver reported that they were no longer the caregiver in the subject's life for any reason. Thus, the caregiver who participated throughout the previous study was to be eligible to complete at least the first assessment in this study if there was no change in his or her status as the primary care provider of the subject.
l. Weight was to be included as part of the physical examinations at Baseline and Week 28 or at Early Termination.
m. Vital signs were to be collected by the procedure defined in the study.
n. Hematology, blood chemistry, coagulation, and urinalysis. Thyroid panel were to be performed at Baseline and Week 28 or at Early Termination. A blood sample for PK was to be collected at Baseline, if an overdose or an SAE occurred that was determined to be drug related by the Investigator or the Medical Monitor, another sample was to be drawn at the time of the SAE for plasma level determination.
o. Each subject was to receive lecozotan SR once daily in the morning for 28 weeks. The first dose of test article was to be administered on the morning following the baseline visit.

Number of Subjects (Planned and Analyzed): A total of 200 subjects were planned to be enrolled in the study. Two hundred and forty-one (241) subjects were randomized to the study treatment.

Diagnosis and Main Criteria for Inclusion: Subjects should have completed Week 24 evaluations of the previous study and had been compliant; they should have had Mini-Mental State Examination (MMSE) Scores ≥12, and no clinically significant cognitive deterioration since enrollment in the previous study, in the judgement of the Investigator. The subjects should have been concurrently using a cholinesterase inhibitor (ChI) administered at a stable dose during the subject's participation in the previous study.

Study Treatment: Subjects received 1 of the 3 doses of lecozotan SR (2, 5, or 10 mg total daily dose). The crossover subjects remained in the same treatment groups as in the previous study, except subjects who were previously taking placebo; they were rerandomized to 1 of the 3 lecozotan SR arms (2, 5, or 10 mg/day). Oral doses of lecozotan SR 2 mg once daily (OD), 5 mg OD or 10 mg OD were evaluated. Lecozotan SR tablets were supplied in 2 and 5 mg strengths. The first intake of test article was to be taken in the morning following the baseline visit. Subjects were instructed to swallow the test article whole and never to chew, divide, or crush it.

Efficacy Endpoints: The following core domains were evaluated with the chosen scale:

- Cognitive: Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) and Clinical Drug Trial - Cognitive Assessment Tool (CDT-CAT)
- Global: Alzheimer's Disease Cooperative Study-Clinical Global Impression of Changes (ADCS-CGIC)
- Functional: Disability Assessment for Dementia (DAD)
- Behavioral: Neuropsychiatric Inventory (NPI).

Depression was assessed on the Cornell Scale for Depression in Dementia.

Safety Evaluations: Safety was evaluated from spontaneously reported adverse events (AEs), scheduled physical findings and neurological examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory test results.

Statistical Methods: The population sets used were:

- Modified Intent-To-Treat (mITT) Population: This population was defined as all randomized subjects who had taken at least 1 dose of study medication and had at least 1 on-treatment post-baseline evaluation of ADAS-Cog or ADCS-CGIC.
- Safety Population: The safety population consisted of all subjects who had taken at least 1 dose of test article.

Efficacy Analysis: Statistical analysis for efficacy were exploratory in nature. Except for ADCS-CGIC, the mean changes from baseline evaluations along with their 95% confidence intervals (CIs) were computed for each treatment group at each visit and were analyzed using analysis of covariance (ANCOVA) model, with all the treatment groups and region as factors, and baseline evaluation and baseline categorized MMSE in the previous study as covariates, to study treatment effects at Weeks 14 and 28. Additional similar analyses for changes from Week 24 evaluations in previous study, with Week 24 evaluations in previous study as covariate were also to be performed.

The ADCS-CGIC were analyzed with the generalized Cochran-Mantel-Haenszel (CMH) mean score statistic, controlling for baseline MMSE category in previous study and region, to study the treatment effect at Weeks 14 and 28. For the CMH tests, integer scores were used for the ADCS-CGIC.

Safety Analysis: AEs were classified by body system and preferred term. Mean changes from baseline evaluations from the previous study were computed for vital signs, weight, laboratory evaluations (hematology, blood chemistry, coagulation, and urinalysis), and 12-lead ECGs by treatment group. In addition, 95% CI for these mean changes were also provided. The mean changes were analyzed using paired t-tests in each group. The nominal 5% significance level without adjustment for multiple testing was used. The paired t-test (versus baseline) was used to test for significant changes over time in these measures. Between-group comparisons were performed on continuous and categorical variables using appropriate statistical methodology at the α=0.05 level of significance.

RESULTS

Subject Disposition and Demography: A total of 241 subjects were randomized of which 240 subjects received at least 1 dose of lecozotan SR and were included in the safety population; 234 subjects were included in the mITT population.

Efficacy Results: On the ADAS-Cog scale (ANCOVA with last observation carried forward [LOCF] data) for all the subjects in the mITT population who did not receive placebo in the previous study, the adjusted mean change from baseline to Week 28 in the current study (ie Week 52 in the pooled previous and current studies) were 2.32, 2.85, and 1.60 in the lecozotan SR 2-mg, 5-mg, and 10-mg groups, respectively.

On the DAD scale (ANCOVA with LOCF data) for all the subjects in the mITT population who did not receive placebo in the previous study, the adjusted mean change from baseline (baseline from the previous study) to Week 28 in the current study (ie Week 52 in the pooled studies) were -5.01, -4.86, and -1.71 in the lecozotan SR 2-mg, 5-mg, and 10-mg groups, respectively.

These results suggested a better long-term efficacy in improving both cognition and function with lecozotan SR 10 mg than with lower lecozotan SR doses.

Data were not available for global, behavioral and depression assessments.

Safety Results:

- A total of 173 (72.1%) subjects had treatment-emergent AEs (TEAEs): 81.3% subjects in the lecozotan SR 10-mg group, 76.2% subjects in the lecozotan SR 2-mg group, 71.4% subjects in the placebo/lecozotan SR 10-mg group, 68.2% in the placebo/lecozotan SR 5-mg group, 67.2% in the lecozotan SR 5-mg group, and 59.1% subjects in the placebo/lecozotan SR 2-mg group

- The most common TEAEs were headache, accidental injury, infection, anxiety, pain, arthralgia, dizziness, and urinary tract infection

- Life-threatening TEAEs were reported in 2 subjects, of which 1 was considered related to test article by Investigator (meningitis). There was no lecozotan-dose relationship noticed for TEAEs, including the cardiovascular TEAEs

- Twenty-seven (27 [11.3%]) subjects with AD receiving test article had serious AEs (SAEs), and the percentage of subjects reporting SAEs (19.0%) was highest with the placebo/lecozotan SR 10-mg group. No clear dose-response relationship for SAEs was observed

- Three (3) deaths were reported during this study or the follow-up period, of which 1 case of acute meningitis, followed by sudden death from the 10-mg lecozotan SR group was considered to be possibly related to the study drug by the Medical Monitor

- Fourteen (14, [5.8%]) subjects discontinued from the study because of safety-related AEs

- Laboratory data evaluation revealed no clinically significant trends. No dose response was observed

- No clinically significant changes or trends were observed in standing or supine diastolic or systolic blood pressure measures

- Electrocardiogram showed slight trend for increased heart rate (multiple weeks) for lecozotan SR 5-mg and 10-mg dose group (~1 to 3 bpm). PR intervals showed slight increases for lecozotan SR 10-mg dose (1.3 msec; not clinically significant). Corrected QT factor intervals showed small (3.3-6.4 msecs) increases for only the placebo/5 mg lecozotan SR dose group.

CONCLUSIONS: In summary, in this phase 2b study, the adjunctive use of lecozotan SR with ChIs was found to be safe and generally well tolerated at oral doses of 2-mg, 5-mg, and 10-mg daily during 28 weeks (following an initial 24-week treatment period at the same daily dose). No clinically significant trends in laboratory values, vital signs, or ECG results were noted in the lecozotan SR groups. Higher rates of discontinuations, TEAEs, and SAEs were noted for the placebo/lecozotan SR 10 mg and the lecozotan SR 10-mg groups in comparison to the other treatment groups. Preliminary efficacy results suggested the presence of a dose-related effect with lesser declines in both the ADAS-Cog and DAD scales at Week 52 for the highest adjunctive (10 mg) dose of lecozotan SR.