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

PROTOCOL NO.: 3098B1-203

PROTOCOL TITLE: A 6-Month, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Safety, Tolerability, and Efficacy Study of 3 Doses of Lecozotan (SRA-333) Sustained-Release Formulation in Outpatients With Mild to Moderate Alzheimer's Disease Treated With a Cholinesterase Inhibitor

Study Centers: The study was conducted at 67 investigational sites and 62 sites enrolled subjects, including 21 centers in the United States, 7 centers in Poland, 6 centers in Spain, 5 centers in Argentina, 5 centers in Canada, 4 centers in Australia, 4 centers in the United Kingdom, 3 centers in Finland, 3 centers in France, 2 centers in Italy and 2 centers in South Africa.

Study Initiation and Final Completion Dates: January 2006 to 22 November 2007

Phase of Development: Phase 2b

Study Objectives:

Primary Objective: The primary objective was to determine the safety, tolerability, and efficacy of 3 doses of lecozotan sustained-release (SR) formulation (2, 5, 10 mg) in combination with a cholinesterase inhibitor in subjects with mild to moderate Alzheimer's disease (AD).

Secondary Objective: The secondary objective was to measure the responsiveness of subject-reported and caregiver-reported outcomes instruments.

METHODS

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled study in subjects with mild to moderate AD. Oral doses of lecozotan SR 2 mg once daily (OD), 5 mg OD, 10 mg OD, or placebo were evaluated. After a 2- to 30-day Screening Period, eligible subjects received the test article for up to 24 weeks in a double-blind manner followed by a Poststudy Visit, 2 to 3 weeks after the last dose of test article was administered or by entrance into the double-blind extension study (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 Subjects With Mild to Moderate Alzheimer's Disease Treated With Cholinesterase Inhibitor [NCT00277810]). Each subject participated in the study for up to 31 weeks. An external Data Safety

Monitoring Board continuously monitored the study. The schedule of activities is presented in Table 1.

Table 1. Study Flow Chart

Procedures[a]	Screen	Baseline	Double-Blind Treatment Period (±3 days)									Post Study
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
Study Day/Week	Days -30 to –2	Baseline (Day –1)	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24[b,c,d]	Week 26-27[c,d]
Informed consent	X											
Medical and psychiatric history/prior	X											
Inclusion/exclusion criteria	X	X										
NINCDS-ADRDA criteria review	X											
DSM-IV-TR review	X											
Hamilton Depression Scale, 21-item	X											
Rosen Modified Hachinski Ischemic Scale	X											
MMSE	X					X		X			X	
ADAS-Cog		X				X		X			X	
ADCS-CGIC[e]		X				X		X			X	
CDT-CAT		X				X		X			X	
DAD		X				X		X			X	
NPI		X				X		X			X	
Cornell Scale for Depression in Dementia		X				X		X			X	
Health outcomes assessments[f]	X			X			X		X		X	X
Physical examination[g]	X	X			X	X		X			X	
Neurologic examination	X	X			X	X		X			X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory determinations[i]	X				X		X	X			X	
12-lead electrocardiogram	X	X			X		X	X			X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X
Blood sample collection for PK analysis[j]					X			X			X	
Dispense double-blind test article[k]		X	X	X	X	X	X	X	X	X		

Table 1. Study Flow Chart

An MRI or CT scan must have been performed within 2 years before Screening. If an MRI or CT had not been performed, an MRI or CT scan was to be obtained for review at Visit 2 Baseline (Day -1).
ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognition, ADCS-CGIC = Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change, CDT-CAT = Clinical Drug Trial - Cognitive Assessment Tool, CT = computed tomography, DAD = Disability Assessment for Dementia, DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders; Fourth Edition Test Revision, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria, NPI = Neuropsychiatric Inventory, PK = pharmacokinetics, SR = sustained release.

a. Every effort was made to bring the subject back on the designated study days (with a ±3-day visit window for slight variations in schedules).
b. For subjects who discontinued early, the safety and efficacy determinations designated for Week 24 were obtained on the last day the subject took a full dose of test article or as soon as possible thereafter.
c. Subjects who no longer wanted to take test article for whatever reason, were asked to return for all the remaining scheduled evaluations ending with the poststudy visit. These visits, after termination of dosing were termed retrieval visits and the subjects were termed retrieval subjects.
d. Subjects, who did not transition to the double-blind extension study, came back in 2 to 3 weeks after last test article administration for a poststudy visit. For subjects who transitioned into the long-term extension study, the Week 24 visit was their Baseline Visit in the extension study, except for the ADCS-CGIC assessment. The ADCS-CGIC baseline assessment in this study was the baseline assessment in the long-term extension study.
e. Severity assessments were made at Baseline and at the Week 24 visit. Each interim visit subsequent to Baseline, as well as the Week 24 visit, included a rating of the global impression of change.
f. The subject completed patient quality of life instruments. Data collected from the primary significant other person (caregiver) in the subject's life followed the signature of the subject's own informed consent form. Data collection from the caregiver ceased if, after randomization, the subject or caregiver reported that they were no longer the caregiver in the subject's life for any reason.
g. Weight was included as part of the physical examinations at Screening and Week 24 or early withdrawal. Height was recorded at Screening.
h. Vital signs were collected by the study-defined procedure.
i. Hematology, blood chemistry, coagulation and urinalysis. Vitamin B12 and folate were included in screening tests. Thyroid panel was performed at Screening and Week 24 or early withdrawal. A urine drug screen was done at Screening for all antidepressants and buspirone.
j. Blood samples for PK (lecozotan SR plasma concentration) analysis were collected at Week 4 (predose) and Weeks 12 and 24 or at early withdrawal. The blood sample collected at Week 4 was collected before test article administration. The subject was called the day before the visit and reminded to withhold dosing on the morning of the next day's (Week 4) visit and they took their dose in the clinic after blood collection.
k. Subjects began test article dose administration on the morning of the day following the Baseline Visit (Day 1).

Number of Subjects (Planned and Analyzed): Approximately 284 subjects (71 per treatment group) were planned to be randomly assigned into the double-blind portion of the study. A total of 343 subjects with AD were enrolled in the study and 340 subjects (85 subjects randomly assigned to each of the 4 treatment groups) received at least 1 dose of test article.

Diagnosis and Main Criteria for Inclusion: Male and postmenopausal or surgically sterile female subjects aged ≥50 years with diagnosis of probable AD according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria, who were taking a cholinesterase inhibitor, were able to give signed and dated informed consent and were living with an appropriate caregiver at home or were community dwelling with a caregiver capable of accompanying the subject to all clinic visits and visiting the subject at least daily for the duration of the study were included in the study.

Main Exclusion Criteria: Subjects with significant neurologic disease other than AD, diagnosis of major depression, or history of stroke or other heart disease were excluded from the study.

Study Treatment:

On Study Day 1, subjects were randomly assigned to receive 1 of 3 fixed doses of lecozotan SR (2 mg, 5 mg or 10 mg), or placebo OD. Lecozotan SR tablets were supplied in 2- and 5-mg strengths. Each subject took the test article orally once in the morning on Day 1 through Week 24.

Efficacy Endpoints:

Primary Efficacy Endpoints:

- Cognitive: Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) total score;
- Global: Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) score.

Secondary Efficacy Endpoints:

- Cognitive: Clinical Drug Trial Cognitive Assessment Tool (CDT-CAT);
- Functional: Disability Assessment for Dementia (DAD);
- Behavioral: Neuropsychiatric Inventory (NPI) and Mini-Mental State Examination (MMSE).

Safety Evaluations:

Safety was evaluated from spontaneously reported adverse events (AEs), scheduled physical examination findings and neurological examinations, vital sign measurements, 12-lead electrocardiogram (ECG) findings, and clinical laboratory test results.

Statistical Methods:

Primary Efficacy Analysis: The ADAS-Cog and ADCS-CGIC were co-primary efficacy variables. No lecozotan SR dose could be claimed effective if it had not been shown to be statistically significantly different from placebo in both change from Baseline to Week 24 in ADAS-Cog total score and the ADCS-CGIC score at Week 24.

The change from Baseline in ADAS-Cog total score was analyzed using an analysis of covariance (ANCOVA) model, with treatment (all 4 treatment groups) and region as factors, and baseline ADAS-Cog and baseline categorized MMSE (12-20, 21-26) as covariates. For the comparisons between the 3 lecozotan SR groups and the placebo group, the Hochberg's step- up approach was used to adjust for multiple comparisons. If the least significant comparison (largest p-value) was significant at α=0.05 level, then all 3 lecozotan SR groups were declared significantly different from placebo. Otherwise, the second least significant p-value was compared to 0.025. If it was significant, then both this group and the remaining group were declared significantly different from placebo. If statistical significance was not attained for both of these groups, the p-value of the remaining group versus placebo was compared to 0.0167l. If it was significant, then this group was declared significantly different from the placebo group. Otherwise, none of the 3 lecozotan SR groups were declared significantly different from the placebo group.

The ADCS-CGIC was analyzed with the generalized Cochran-Mantel-Haenszel (CMH) mean score statistic, controlling for baseline MMSE category and region, for comparison between each of the 3 lecozotan SR groups and the placebo group. For the CMH tests, integer scores were used for the ADCS-CGIC. Hochberg's step-up approach was used to adjust for multiple comparisons as described for ADAS-Cog total score.

Secondary Efficacy Analysis: The changes from Baseline in secondary efficacy variables were analyzed using an ANCOVA model as for the ADAS-Cog, but there were no adjustments for multiple comparisons.

RESULTS

Subject Disposition and Demography:

A total of 343 subjects with AD were enrolled in the study and 340 subjects (85 in each treatment group) received test article and were included in the safety population. A total of 332 subjects were included in the modified intent-to-treat (mITT) population. Two hundred and ninety (290) subjects completed the study. Data were not available for the number of subjects who discontinued and reasons for discontinuation.

Of the 340 subjects in the safety population, 176 (52%) were women and 334 (98%) were white/Caucasian. They ranged from 52 to 95 years in age, with a mean age at Baseline of 75 years. The mean duration of AD at study entry was 3.5 years. At study entry, 46% of the subjects suffered from a mild AD and 54% from a moderate AD. A total of 54% of subjects had a MMSE score at Baseline between 12 and 20, and 46% of subjects between 21 and 26.

Efficacy Results:

Primary Efficacy Results:

On the ADAS-Cog scale (ANCOVA with last observation carried forward data) in the mITT population, the adjusted mean change for all treatment groups showed a decline in cognitive function from Baseline to Week 24 (between +0.76 and +1.89). There was no statistically significant difference in ADAS-Cog score between the 3 lecozotan SR dose groups and placebo at Week 24.

There was no statistically significant difference in ADCS-CGIC score between the 3 lecozotan SR dose groups and placebo at Week 24.

Secondary Efficacy Results:

Subjects in the placebo and the lecozotan SR 2- and 5-mg groups had a worsening of their ability to accomplish daily activities (adjusted mean decrease of DAD score of -2.06, -3.01, -1.87, respectively) at Week 24. In the lecozotan SR 10-mg group, there was a small improvement of 0.31 point score between Baseline and Week 24, but this was not statistically significantly different from the placebo group.

Data not available for CDT-CAT, NPI and MMSE.

Safety Results:

During the study, 266 (78.2%) subjects had treatment-emergent AEs (TEAEs): 63 (74.1%) subjects in the placebo group, 64 (75.3%) subjects in the lecozotan SR 2-mg group, 65 (76.5%) subjects in the lecozotan SR 5-mg group, and 74 (87.1%) subjects in the lecozotan SR 10-mg group. The most common TEAEs included were headache (48 subjects, 14.1%), infection (31 subjects, 9.1%), accidental injury (29 subjects, 8.5%), nausea (27 subjects, 7.9%), diarrhea (23 subjects, 6.8%), back pain (22 subjects, 6.5%), urinary tract infection (20 subjects, 5.9%), and pain and anxiety (18 subjects, 5.3% each). Of the 266 (78.2%) subjects who had TEAEs, 89 (26.2%) subjects had TEAEs which were related to the test article and 177 (52.1%) subjects had TEAEs which were not related to the test article. Of the 89 (26.2%) subjects who had drug related TEAEs, the intensity of TEAEs was mild in 48 (14.1%), moderate in 36 (10.6%), and severe in 5 (1.5%) subjects.

A total of 32 (9.4%) subjects with AD receiving lecozotan SR or placebo had serious adverse events (SAEs), including 5 (5.9%) subjects in the placebo group, 6 (7.1%) subjects in the lecozotan SR 2-mg group, 9 (10.6%) subjects in the lecozotan SR 5-mg group, and 12 (14.1%) subjects in lecozotan SR 10-mg group. A total of 11 (3.2%) subjects had SAEs related to the cardiovascular system, which were syncope (4 cases), atrial fibrillation

(2 cases), and congestive heart failure, coronary occlusion, heart arrest, hypotension, myocardial infarction, and sick sinus syndrome (1 case each). Ten (10) of these subjects received lecozotan SR. Five (5) subjects reported SAEs that were considered by the Investigator to be probably drug related, including sick sinus syndrome in the lecozotan 2-mg group, colitis, altered mental status, and vertigo in the lecozotan 5-mg group, and psychosis in the lecozotan 10-mg group.

Two (2) deaths were reported during the follow-up period (21 days after the last dose of test article) study and 1 death was reported after the follow-up period. These 3 deaths were judged to be not related to the test article by the Investigator or the Sponsor.

Of the 340 subjects included in the safety population, 20 (5.9%) subjects discontinued from the study because of an AE, including 3 (3.5%) subjects in the placebo group, 4 (4.7%) subjects in the lecozotan SR 2-mg group, 3 (3.5%) subjects in the lecozotan SR 5-mg group, and 10 (11.8%) subjects in lecozotan SR 10-mg group.

Review of the laboratory data by the Sponsor revealed slight increases (not clinically significant and within normal laboratory ranges) of potassium and blood urea nitrogen values in subjects receiving the 10-mg lecozotan dose, over the 24 week duration of this study. Overall, no clinically important laboratory trends were present.

Mild reductions in diastolic and systolic blood pressure readings were seen, but were not associated with any dose relationship, and were not felt to be clinically significant. No clinically significant weight changes were noted.

Review of electrocardiographic data revealed slight decreases (approximately 3 beats per minute) in heart rate at Week 24 in subjects on the 10-mg lecozotan dose, and slight increases in the PR interval (2 to 5 msec), neither of which were clinically significant.

In summary, review of laboratory data, vital sign measurements, and ECG data revealed no clinically important trends.

CONCLUSIONS:

In this phase 2b study, lecozotan SR was shown to be well tolerated in subjects with mild to moderate AD. No clinically significant trends in laboratory test values, vital sign measurements, or ECG results were noted in the lecozotan SR groups. Higher rates of discontinuations, TEAEs, and SAEs were noted for all 3 lecozotan groups. Efficacy analyses showed no statistically significant differences between the 3 lecozotan dose groups and placebo on the ADAS-Cog, DAD, or CGIC scales at Week 24.