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GENERIC NAME / COMPOUND NUMBER: Lecozotan (SRA-333) / WAY-161333

PROTOCOL NO.: 3098B1-201-WW/EU/FR (B3431057)

PROTOCOL TITLE: A 3-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 With Donepezil as Active Control

Study Centers: In total 64 centers in 11 countries took part in the study and randomized subjects including centers in Argentina, Australia, Canada, Europe (including Finland, France, Italy, Poland, Spain, and the United Kingdom), South Africa, and the United States.

Study Initiation and Final Completion Dates: April 2005 to June 2007

Phase of Development: Phase 2b

Study Objectives:

Primary objective: To determine the safety, tolerability, and efficacy of 3 doses of lecozotan sustained-release (SR) formulation in subjects with mild to moderate Alzheimer's disease (AD).

Secondary objectives: To estimate comparative safety, tolerability, and efficacy versus donepezil over a 12-week period in subjects with AD and to measure the responsiveness of subject- and caregiver-reported outcomes instruments.

METHODS

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, comparator study. After a 2- to 30-day screening period, eligible subjects received the test article (lecozotan SR 2 mg once daily (OD), 5 mg OD or 10 mg OD, placebo or donepezil) for up to 12 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. Subject enrollment was completed in approximately 18 months. The clinical portion of the study was completed in 22 months. Each subject participated in the study for up to 19 weeks. An external data safety monitoring board continuously monitored the study.

Number of Subjects (Planned and Analyzed): A total of 378 subjects with AD enrolled; 372 subjects in the safety population; 360 subjects in the modified intent-to-treat (mITT) population; and 266 subjects in the per-protocol population.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Diagnosis of probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria;
- Men and postmenopausal or surgically sterile women aged ≥50 years;
- Mini-Mental State Examination score of 12 to 26;
- Rosen Modified Hachinski Ischemic score ≤4;
- Living at home with appropriate caregiver or in a community dwelling with caregiver capable of accompanying the subject on all clinic visits and visiting the subject at least daily for the duration of the study.

Exclusion Criteria:

- Use of medications for cognitive enhancement within 3 months of baseline;
- Significant neurologic disease other than AD that might affect cognition.

Study Treatment: Subjects with AD were randomly assigned to receive 1 of 3 fixed doses of lecozotan SR, placebo, or donepezil. Oral doses of lecozotan SR 2 mg OD, 5 mg OD, or 10 mg OD were evaluated. Lecozotan SR was supplied in 2- and 5-mg strength tablets. Matching placebo to lecozotan tablets, donepezil 5 mg tablet in capsules and placebo to donepezil tablet in capsules were also provided. Each subject took the test article twice daily (once in the morning and once in the evening) before retiring on Days 1 through 84.

Efficacy and Outcomes Research 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 Change (ADCS-CGIC); Functional: Disability Assessment for Dementia (DAD); and Behavioral: Neuropsychiatric Inventory (NPI). The primary efficacy variables were the ADAS-Cog total score and ADCS-CGIC total score.

Other Analyses:

- Health Outcome Assessments were performed during the study; no further information regarding these assessments is available.

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

Statistical Methods: Statistical methods for comparisons between groups were not specified.

RESULTS

Subject Disposition and Demography: In total, 378 subjects were enrolled, 375 subjects were entered, out of which 292 completed the study. Of the 372 subjects included in the safety population, 127 were male and 245 were female.

No other demography data available.

Efficacy and Outcomes Research Results:

The primary endpoints were the change from Baseline in ADAS-Cog and ADCS-CGIC at Week 12. Key secondary endpoints were the DAD and NPI scores.

On the ADAS-Cog scale (analysis of covariance [ANCOVA] with last observation carried forward [LOCF] data) in the mITT population, the adjusted mean change for subjects taking placebo showed a decline in cognitive function from Baseline to Week 12 (+1.64). In contrast, lecozotan SR 10 mg-treated subjects and donepezil-treated subjects showed a slight improvement from Baseline to Week 12 (-0.33 and -0.53, respectively). In both the lecozotan SR 10 mg and donepezil groups, the adjusted mean difference from placebo at Week 12 was statistically significant (p=0.019 and p=0.009, respectively). The magnitude of effect on the ADAS-Cog total score for lecozotan 10 mg was 1.97 (95% confidence limit [CL], 0.32 to 3.63) for the ANCOVA (LOCF). Subjects treated with lecozotan SR 2 or 5 mg tended to show less decline in cognition from Baseline to Week 12 compared with placebo (adjusted mean change from Baseline of 0.23 and 0.24, respectively); this decline was not statistically different from placebo (p=0.090 and p=0.087, respectively).

On the ADCS-CGIC (co-primary; balanced 7-point 'improvement' scale, ranging from 'marked worsening' to 'marked improvemen'), neither the donepezil nor any of the lecozotan SR groups showed a significant difference from placebo. In each treatment group, "no change" was the most common reported outcome at Week 12. No clear trends were evident. The reason for the failure of donepezil to separate from placebo on this scale is unclear but may be related to the relatively low level of symptom severity at Baseline. Neither donepezil nor any of the lecozotan SR doses showed a significant difference from placebo on any of the secondary variables (i.e., DAD, NPI, and CSDD scores) except CDT-CAT, and no trends were evident. On the DAD scale (key secondary, functional), placebo-treated subjects showed decline in function from Baseline to Week 12 in the adjusted mean change (-2.97). Compared with placebo, donepezil-treated subjects tended to show less decline in function from Baseline to Week 12 (-0.11); this difference from placebo did not reach statistical significance (p=0.085). Results for lecozotan SR-treated subjects tended toward a lesser decline in function than those taking placebo, with a smaller effect size than donepezil. No

dose response was evident with lecozotan SR (-1.01, -0.58, and -1.97 for lecozotan SR 2, 5, and 10 mg, respectively).

No change from Baseline was observed in any health outcome assessment differentiating either lecozotan at any dose or donepezil from placebo, arising from insufficiency of sample size, length of exposure, or both. The phenomenon of assay sensitivity may have also occurred with several health outcome variables. A bi-variate regression analysis was also performed to explore the predictive power of baseline factors and co-variates on change from Baseline dependent health outcome variables. The baseline dependent variable value was found to consistently predict change from Baseline in the final bi-variate model. Baseline clinical or demographic variables of the subjects with AD were rarely found to significantly predict change from Baseline in health outcome dependent variables in the final models.

Safety Results: Of the 372 subjects included in the safety population, 234 (63%) subjects reported at least 1 treatment-emergent AE (TEAE), including 39 (52%) subjects in the placebo group, 40 (53%) subjects in the lecozotan SR 2 mg group, 47 (63%) subjects in the lecozotan SR 5 mg group, 54 (73%) subjects in the lecozotan SR 10 mg group, and 54 (75%) subjects in the donepezil group. Common TEAEs included headache, urinary tract infection, diarrhea, insomnia, accidental injury, dizziness, nausea, hypertension, anxiety, and asthenia.

No deaths occurred in this study.

A total of 23 serious AEs (SAEs) were reported by 15 subjects with AD in the study. Except for 1 SAE (hypotension) in the lecozotan 5 mg group, all SAEs were judged by the Investigator and Medical monitor to be not related to the test article.

Of the 372 subjects included in the safety population, 30 subjects discontinued from the study because of an AE. The rate of discontinuation was relatively low and was similar across all treatment groups (11% for subjects taking placebo; 14% for donepezil-treated subjects; and 17%, 16%, and 15% for 2, 5, and 10 mg lecozotan SR‑treated subjects, respectively). Reasons for discontinuation were also similar across the treatment groups. For all treatment groups except the donepezil group, more subjects discontinued from the study because of AEs than for any other reason. For the donepezil-treated subjects, the main reasons for discontinuation were AEs and unsatisfactory response-efficacy (6% each). Lecozotan SR was well tolerated and no clinically significant trends in mean or potentially clinically important (PCI) laboratory values, vital signs, or ECG results were noted in the lecozotan SR groups. Trends were noted in the donepezil group for decreased postural blood pressure (8% subjects had PCI values), decreased mean heart rate (about 4 beats/min), and slightly increased Fridericia-corrected QTc (about 3 msec).

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 values, vital signs, or ECG results were noted in the lecozotan SR groups. Lecozotan SR also showed strong signals for efficacy in this 12-week study, with lecozotan SR 10 mg showing a better efficacy than placebo (p=0.009) on the ADAS-Cog scale (cognition).