PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: 3098B1-202-WW/EU/FR (B3431058)

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) Sustained-Release Formulation in Subjects With Mild-to-Moderate Alzheimer's Disease

Study Centers: Fifty seven (57) centers in 11 countries (Argentina, Australia, Canada, Finland, France, Italy, Poland, South Africa, Spain, the United Kingdom, and the United States) took part in the study and randomized subjects.

Study Initiation Date and Final Completion Date: January 2006 to March 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 12 evaluations of a previous 3-month double-blind, placebo-controlled study (A 3-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 With Donepezil as Active Control [NCT00151398]).

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, safety, tolerability, and preliminary long-term efficacy study (extension to previous 3-month study) with 3 dose levels of lecozotan SR (2, 5, and 10 mg total daily dose) and donepezil 10-mg total daily dose in outpatients with mild to moderate AD. Subjects who were receiving placebo in the previous 3-month study were re-randomly assigned to receive 1 of the 3 doses of lecozotan SR in the extension study. Other subjects remained in the same treatment dose group. Subjects participated in the study for approximately 42 weeks (9.5 months). This

included a 40-week (or 9 month) double-blind phase and a 2-week follow-up phase. The study visit procedures are presented in Table 1.

Table 1. Study Visit Procedures

Study Procedure[a]	Double-Blind Treatment Period						Follow-Up[b]
Study (Weeks)	**Visit 1 Baseline (Previous Study Week 12 Visit)**	**Visit 2 Week 4**	**Visit 3 Week 8**	**Visit 4 Week 14**	**Visit 5 Week 26**	**Visit 6 Week 40[c]**	**Visit 7 Week 42**
Informed consent	X						
Inclusion/exclusion criteria	X						
MMSE[d]	X[d]			X	X	X	
ADAS-Cog[e]	X			X	X	X	
ADCS-CGIC[f]	X			X	X	X	
CDT-CAT[g]	X			X	X	X	
DAD[h]	X			X	X	X	
NPI[i]	X			X	X	X	
Cornell scale for depression	X			X	X	X	
Health outcome assessments[j]	X			X	X	X	X
Physical examination[k]	X			X	X	X	
Neurological examination	X			X	X	X	
Vital signs[l]	X	X	X	X	X	X	X
Laboratory determinations[m]	X			X	X	X	
12-lead electrocardiogram	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X
Dispense double-blind test article[n]	X			X	X		

PK = pharmacokinetic; SAE = serious adverse event; SR = sustained release; TSH = thyroid stimulating hormone; T3/T4 = triiodothyronine/thyroxine.

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. Follow-up visit, 2 weeks after the last test article administration.
c. Subjects who withdrew before Week 40 should have had all Week 40 evaluations performed on the last day of receiving test article or as soon as possible thereafter.
d. Mini-Mental State Examination ≥12.
e. Alzheimer's Disease Assessment Scale-Cognition.
f. Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. Baseline was to be the assessment performed at the Baseline Visit of the previous 3-month study.
g. Clinical Drug Trial - Cognitive Assessment Tool.
h. Disability Assessment for Dementia.
i. Neuropsychiatric inventory.
j. The subject was to complete subject 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 was 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 3-month study would have been 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.
k. Weight was to be included as part of the physical examinations at Baseline and Week 40 or at Early Termination.

Table 1. Study Visit Procedures

l. Vital signs were to be collected as per the study-specific procedures.
m. Hematology, blood chemistry, coagulation, and urinalysis. Thyroid panel (TSH, FREET3/T4) were to be performed at Baseline and Week 40 or at Early Termination. A blood sample for PK was to be collected at Baseline and if 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 lecozotan plasma level determination.
n. Each subject was to receive lecozotan SR or donepezil once daily for 40 weeks. The first dose of test article was to be administered on the evening of the Baseline Visit.

Number of Subjects (Planned and Analyzed): It was estimated that approximately 250 subjects would be enrolled in this extension study. A total of 229 subjects with AD were randomized in the study, including 64 subjects in each of the 2-mg and 5-mg dose groups, 61 subjects in the 10-mg group, and 40 subjects in the donepezil group.

Diagnosis and Main Criteria for Inclusion: Male and 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 were included in the study. Subjects were required to have completed Week 12 evaluations of the previous 3-month study (with no early completions) and have been compliant, have Mini-Mental State Examination (MMSE) ≥12 and, in the judgment of the Investigator, have had no clinically significant cognitive deterioration since enrollment in the previous 3-month study.

Main Exclusion Criteria: Subjects with significant neurological disease other than AD that might have affected cognition; with any clinically significant abnormality in physical examination, vital signs, adverse events (AEs), electrocardiogram (ECG) or clinical laboratory test results, observed at the Baseline visit (Week 12 of the previous 3-month study), that, in the judgment of the Investigator, was likely to deteriorate or affect the subject's safety or ability to complete the study; and subjects taking medications for cognitive enhancement, including memantine, cholinesterase inhibitors, or other medications prohibited in the previous 3-month study were excluded from the study.

Study Treatment: Test article consisted of lecozotan SR (2 mg and 5 mg tablets), donepezil 5 mg encapsulated tablets, and matching placebo for lecozotan tablets and donepezil capsules. Subjects received 1 of 3 doses of lecozotan SR (2, 5, 10 mg) or donepezil 5 mg, administered orally (Table 2). Subjects remained in the same treatment group as in the previous 3-month study, except the subjects in the placebo group, who were re-randomized to 1 of the 3 lecozotan SR arms.

Each subject was to take the test article once in the morning and once in the evening just before retiring, on Day 1 through Week 40 (Visits 1 through 6). The first intake of test article was to be in the evening of the day of the Baseline visit. Subjects were instructed to swallow the test article whole and never to chew, divide, or crush it.

Table 2. Test Article Administration

Treatment Arm	AM		PM	
	Tablet 1	Tablet 2	Capsule 1	Capsule 2
2.0 mg lecozotan SR QD	2.0 mg lecozotan SR	Lecozotan SR Pbo	Donepezil Pbo	Donepezil Pbo
5.0 mg lecozotan SR QD	5.0 mg lecozotan SR	Lecozotan SR Pbo	Donepezil Pbo	Donepezil Pbo
10.0 mg lecozotan SR QD	5.0 mg lecozotan SR	5.0 mg lecozotan SR	Donepezil Pbo	Donepezil Pbo
10.0 mg donepezil QD	Lecozotan SR Pbo	Lecozotan SR Pbo	5 mg donepezil TIC	5 mg donepezil TIC

Pbo = placebo; SR = sustained release; TIC = tablet in capsule; QD = once daily.

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 Change (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 AEs, scheduled physical findings and neurological examinations, vital signs, 12-lead ECGs, and clinical laboratory test results.

Statistical Methods: Efficacy analyses were performed twice on the modified intent-to-treat (mITT) population, defined as all randomly assigned subjects. Firstly on all available data at each assessment, and secondly applying the Last Observation Carried Forward (LOCF) technique. The change from the previous 3-month study Baseline was computed for the ADAS-Cog and DAD scale using an analysis of covariance (ANCOVA) model.

RESULTS

Subject Disposition and Demography: A total of 229 subjects with AD were randomized in the study. Of the 229 subjects, 226 subjects were included in the safety population and 209 subjects were included in the mITT population.

Of the 226 subjects included in the safety population, 134 (60%) were women and 209 (92%) were White/Caucasian. They ranged in age from 50 to 90 years, with a mean age at Baseline of 74 years. The mean duration of AD at study entry was 3.2 years. A total of 35% of subjects had a MMSE score at Baseline between 12 and 20, 48% of subjects between 21 and 26, and 17% of subjects >26.

Efficacy and Outcomes Research Results: On the ADAS-Cog scale, (ANCOVA) in the mITT population, the least squares means changes from (previous 3-month study) Baseline at Week 40 were 1.99, 2.64, and 0.04 in the lecozotan SR 2-mg, 5-mg, and 10-mg groups, respectively, and 0.98 in the donepezil group.

On the DAD scale (ANCOVA with LOCF data) in the mITT population, the mean changes from Baseline at Week 40 were -6.05, -5.68, and -5.29 in the lecozotan SR 2-mg, 5-mg, and 10-mg groups, respectively, and -3.67 in the donepezil group.

For the efficacy endpoints ADCS-CGIC, NPI, and Cornell Scale for Depression in Dementia, data were not available.

Safety Results: During the study, 176 (77.9%) subjects had treatment-emergent AEs (TEAEs): 45 (71.4%) subjects in the lecozotan SR 2-mg group, 44 (69.8%) subjects in the

lecozotan SR 5-mg group, 56 (91.8%) subjects in the lecozotan SR 10-mg group, and 31 (79.5%) subjects in the donepezil group. The most common TEAEs were headache (32 subjects, 14.2%), accidental injury (21 subjects, 9.3%), infection (19 subjects, 8.4%), urinary tract infection (17 subjects, 7.5%), hypertension (16 subjects, 7.1%), arthralgia (15 subjects, 6.6%), anxiety (14 subjects, 6.2%), insomnia (13 subjects, 5.8%), and dizziness (11 subjects, 4.9%).

Of the 176 subjects who had TEAEs, 123 subjects had TEAEs which were judged by the Investigator to be not related to the test article. Most of these TEAEs were mild or moderate in severity. A total of 34 severe TEAEs were reported in 18 subjects. Some TEAEs were more common with lecozotan SR (hypertension, arthralgia, anxiety, and dizziness) and at increasing dose levels of lecozotan. Some TEAEs were more common with donepezil including urinary incontinence and vomiting. There was a potential lecozotan-dose relation for TEAEs, including the cardiovascular TEAEs.

A total of 19 (8.4%) subjects with AD receiving lecozotan SR or donepezil had serious AEs (SAEs), including 6 (9.5%) subjects in the lecozotan SR 2-mg group, 3 (4.8%) subjects in the lecozotan SR 5-mg group, 8 (13.1%) subjects in the lecozotan SR 10-mg group, and 2 (5.1%) subjects in the donepezil group.

Six (6) subjects had reported SAEs that were considered by the Investigator to be probably drug related, including: (1) pancreatitis (with gastrointestinal carcinoma) and (2) atrial fibrillation with sick sinus syndrome in the lecozotan 2-mg group, (3) coagulopathy in the lecozotan 5-mg group, (4) myocardial infarct and (5) syncope in the lecozotan 10-mg group, and (6) asthma exacerbation in the donepezil group.

A total of 23 (10.2%) subjects discontinued from the study because of an AE including 7 (11.1%) subjects from lecozotan SR 2-mg group, 3 (4.8%) subjects in the lecozotan SR 5-mg group, 10 (16.4%) subjects in the lecozotan SR 10-mg group, and 3 (7.7%) subjects in the donepezil group.

One (1) subject died from pancreatic carcinoma after discharge from the hospital. This death was judged not to be study-drug related by the Investigator and the Sponsor.

Laboratory test evaluations revealed no clinically significant trends. For vital sign measurements, slight declines were noted in systolic supine blood pressure (1 to 4 mm Hg for donepezil and all lecozotan doses) and in diastolic supine blood pressure (1 to 4 mm Hg for donepezil and 0.6 to 2.4 mm Hg for all lecozotan doses). A slight increase was observed in standing pulse with donepezil and 5 and 10 mg of lecozotan, and in supine pulse for donepezil and lecozotan 5 mg. No significant changes in weight were noted.

No clinically significant trends were noted for laboratory, ECG, or vital sign data for lecozotan. A higher rate of AEs, SAEs, and discontinuations because of AEs were noted at the 10 mg lecozotan SR dose versus donepezil.

CONCLUSIONS: Lecozotan SR was safe and generally well tolerated at oral doses of 2, 5, and 10 mg daily during this 40 week study. The safety and tolerability of lecozotan SR was

not better than donepezil. Efficacy results suggested that lecozotan SR 10 mg improved cognition better than donepezil, but showed less improvement of function than donepezil.