CLINICAL STUDY SYNOPSIS

Title: A Preliminary, Multicenter, Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of E2020 in Patients With Alzheimer's Disease

Investigators: Multicenter, 10 investigators in the U.S.

Objectives: The objectives of this study were to evaluate the safety and efficacy of three dose levels of E2020, versus Placebo, in patients with Alzheimer's disease. The study objectives were to be met by measuring defined safety and efficacy parameters prior to, during, and after the study.

Study Design: This was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study. The treatment phase was twelve weeks in duration with a subsequent two-week washout. The test drug was administered, in a double-blind manner, once daily during the treatment phase. A Placebo was administered, in a single-blind manner, during the washout period. Patients were randomized to either 1, 3, or 5 mg/day of E2020, or Placebo at the start of the treatment phase. A central randomization schedule was used.

Test Materials: E2020 tablets: 7.2-mm, film-coated tablets of identical appearance in doses of 1, 2, and 5 mg.

Placebo tablets: Tablets containing inert materials that were identical in appearance to the E2020 tablets.

Dose Administration: After Baseline evaluations were completed, patients received their first dose of test medication. Beginning the following day, subsequent doses were administered on each successive evening, just prior to bedtime, through the completion of the study.

Patients: A total of 161 patients were randomized and enrolled into the study: 40 to the placebo group, and 42, 40, and 39 to the E2020 1, 3, and 5 mg/day groups, respectively. A total of 141 (88%) patients completed the study. Twenty patients (12%) discontinued from the study: 5 (13%) in the placebo group, 8 (19%) in the E2020 1 mg/day group, 2 (5%) in the E2020 3 mg/day group, and 5 (13%) in the E2020 5 mg/day group.

Study Variables:

Efficacy: The primary efficacy parameters included Alzheimer's Disease Assessment, cognitive subscale (ADAS-cog), and Clinical Global Impression of Change (CGIC). The secondary efficacy parameters included Activities of Daily Living (ADL), Mini-Mental State Examination (MMSE), Quality of Life, patient and caregiver (QOL-P and QOL-C), and Clinical Dementia Rating - Sum of the Boxes (CDR-SB).

Safety: Adverse events were recorded throughout the study. Laboratory safety assessments were conducted at Screening, each scheduled visit, and Study Discharge. These included hematology, blood chemistries and urinalyses. Physical examination and vital sign assessments were performed at Screening, at each scheduled visit, and at Study Discharge. Safety criteria assessed at Screening included B_{12} and folate measurements, thyroid function, hepatitis screen, electrocardiogram (ECG) and CT scan or MRI. ECGs were repeated at the end of the study.

Statistical Methods: The last assessment obtained from each patient after the Baseline visit (Week 0) but prior to the placebo washout (Week 14) was defined as Endpoint and was used as the primary visit in the analysis. The analyses of efficacy and safety were performed on three patient populations:

1) the intent-to-treat population (ITT analysis) that was defined as all patients who were randomized to treatment, received at least the first dose of study drug, and provided at least some post-Baseline assessment data,

2) the population of fully evaluable patients (EP analysis) who had completed the study in compliance with the protocol and

3) the last-observation-carried-forward population (LOCF analysis) which included those patients who either discontinued from the study prior to completion of the protocol or who had unevaluable visits at Week 12 (due to protocol violations).

For the EP analysis, the Week 12 visit (if evaluable), was the Endpoint or the observations from their last evaluable clinic visit were carried forward and used as the Endpoint.

Changes from Baseline values were compared for all efficacy measures (except the CGIC assessment) to determine if differences existed among the four specified treatment groups. This analysis was performed at each scheduled visit and at Endpoint visit.

All continuous efficacy variables (i.e., ADAS-cog, ADL, MMSE, CDR, and QOL) were analyzed using analysis of covariance techniques (ANOCOVA)[10]. Pairwise comparisons were performed using a Fisher's two-tailed least significant difference procedure[10]. The Clinical Global Impression of Change was analyzed using Cochran-Mantel-Haenszel methods[12] adjusting for site. Continuous demographic variables (i.e., age, height, weight) were analyzed using an analysis of variance model[10]. Categorical demographic variables (i.e., sex, race, etc.) were analyzed using Cochran-Mantel-Haenszel methods, or in the case where sample size was too small, a Fisher's Exact test[11]. A Fisher's Exact test was employed to test for treatment differences for the incidence of treatment emergent signs and symptoms (TESS) and clinically significant treatment emergent abnormal laboratory values (TEAV).

Results:

Efficacy: A summary of the primary and secondary Endpoints is summarized in the following table.

Efficacy Variables at the Baseline and Endpoint (S.E.) Visits - Evaluable Population

Assessment	Placebo	E2020 1 mg/day	E2020 3 mg/day	E2020 5 mg/day
Primary Variables				
ADAS-cog Baseline	27.03	26.15	29.18	29.43
Change at Endpoint Visit	0.47	-0.92	-1.33	-2.32**
	(0.80)	(0.70)	(0.72)	(0.63)
CGIC Baseline Mean	3.97	3.79	4.05	4.00
Endpoint Visit Mean	3.84	3.85	3.93	3.69
	(0.16)	(0.12)	(0.11)	(0.11)
Secondary Variables				
CGIC				
Success at Endpoint (%)	78	82	83	92
Failure at Endpoint (%)	22	18	18	8
Proportion of Failed Visits	0.133	0.119	0.086	0.061*
ADL Baseline	93.84	93.08	98.75	104.09
Change at Endpoint Visit	1.43	3.76	0.43	-3.47
	(2.51)	(3.26)	(1.56)	(1.75)
MMSE Baseline	18.30	19.77	18.55	17.81
Change at Endpoint Visit	1.05	0.33	0.83	2.11
	(0.47)	(0.42)	(0.42)	(0.34)
QOL (Patient) Baseline	297.27	292.41	270.29	284.20
Change at Endpoint Visit	-6.73	-4.03	7.00	9.69
	(5.57)	(5.00)	(7.24)	(7.39)
QOL (Caregiver) Baseline	249.97	249.00	250.95	253.61
Change at Endpoint Visit	5.73	-3.05	0.28	1.94
	(6.57)	(6.20)	(5.82)	(6.59)
CDR-SB Baseline	6.59	6.59	6.91	7.32
Change at Endpoint Visit	0.11	0.12	0.21	-0.18
	(0.18)	(0.21)	(0.21)	(0.15)

*Significant at the 0.05 level vs. Placebo, **Significant at the 0.01 level vs. Placebo.
p values based on comparison of adjusted means in the analysis of covariance.

Primary Variables: Patients in all three E2020 groups showed decreases from Baseline in ADAS-cog assessments throughout the course of the 12-week treatment period. Pairwise comparisons of adjusted means in the evaluable population revealed that the 5 mg/day group was superior in decreasing ADAS-cog scores when compared to the placebo group at Weeks 3, 9, 12 and 14 ($p \leq 0.01$), when compared to the 1 mg/day group at Week 14 ($p<0.01$) and also when compared to the 3 mg/day group at Week 14 ($p=0.019$). At the Endpoint visit, the E2020, 5 mg group was superior in decreasing ADAS-cog scores compared to the placebo group ($p=0.006$). Overall treatment effects were statistically significant at Weeks 3 ($p<0.05$), 12 ($p=0.01$), 14 ($p<0.01$) and Endpoint ($p=0.05$). Analysis of the intent-to-treat population revealed similar results.

The results of the CGIC assessments showed that for every post-Baseline visit, the majority of the patients were assessed a score of "no change" (at least 50% for most of each treatment groups at every visit). There were no statistically significant overall treatment differences found in the distribution of the CGIC assessments at any scheduled visit or Endpoint visit.

Secondary Variables: A secondary analysis of the CGIC assessments was conducted by calculating the number of treatment successes and failures where success was defined as a score of 1-4 (very much improved to no change) and failure was defined as a score of 5-7 (minimally worse to very much worse). There was a statistically significant treatment difference found among the four treatment groups in the proportion of patients termed a success at Week 9 ($p=0.048$). The proportion of subjects described as treatment failures was lower for the 5 mg/day group at Week 12 and Endpoint (9% and 8%, respectively) compared with other groups, and was less than half that of the placebo group (20% and 22%, respectively), but there was no overall statistically significant treatment effect. The E2020, 5 mg group had a statistically significant ($p<0.05$) lower proportion of total failed visits per patient (0.061) compared to the placebo group (0.133).

Patients in the 5 mg/day group demonstrated decreases from Baseline (improvement) in ADL assessments at every post-Baseline visit and Endpoint while patients in the remaining three groups showed increases from Baseline at almost every post-Baseline visit, including all those from Week 6-12. Statistically significant differences were found for the adjusted means in ADL assessments between the 5 mg and 1 mg groups at Weeks 9, 12 and 14 visit as well as at the Endpoint visit ($p=0.020$ to 0.037).

All four treatment groups demonstrated increases (improvement) from Baseline for the MMSE assessments to every post-Baseline visit and Endpoint visit. Pairwise comparisons of adjusted means revealed the 5 mg/day group was superior in increasing MMSE scores when individually compared to each of the three other groups ($p \leq 0.01$) at Week 9. The 5 mg/day group was statistically superior to the 1 mg/day and 3 mg/day groups at the Endpoint visit ($p<0.01$ and <0.05, respectively). There was significant treatment-by-site interaction, however results for the 5 mg group were more consistent than that of other groups.

There was a trend toward greater increases (improvement) in patient-rated QOL scores starting at Week 6 in the 3 mg/day and the 5 mg/day groups, compared with the placebo and 1 mg/day groups, although the differences did not achieve statistical significance. There were no statistically significant differences or dose-related trends found for the change from Baseline in the caregiver-rated QOL assessments at any scheduled visit or at Endpoint.

CDR-SB scores were lower, compared with Baseline, for the 5 mg/day group at each post-Baseline visit, while other groups demonstrated more variable results. None of the pairwise comparisons were statistically significant.

Safety: There were 26 (65%) patients in the placebo group, 27 (64%) patients in the 1 mg/day group, 27 (68%) patients in the 3 mg/day group, and 26 (67%) patients in the 5 mg/day group who experienced at least one TESS during the

course of the study. The most prevalent body system for which a TESS was reported was Body as a Whole, where 10 (25%), 15 (36%), 8 (20%), and 12 (31%) of the patients in the placebo and 1, 3, and, 5 mg/day groups, respectively, had reported at least one TESS. There were 30 (19%) patients who experienced at least one digestive system adverse event and 34 (21%) patients who experienced at least one nervous system adverse event. In these two latter body systems, the most commonly reported adverse events were nausea/vomiting and dizziness, for the digestive and nervous system, respectively. No statistically significant overall treatment differences were found in the proportion of patients reporting TESS.

No statistically significant overall treatment differences were found in the proportion of patients that had clinically significant TEAVs. In fact, the smallest proportion of patients with clinically significant TEAVs was associated with the highest dose of E2020 (5 mg/day). Statistically significant treatment differences were found for the proportion of patients having at least one treatment emergent abnormal hematocrit value for the males only ($p=0.028$), eosinophils ($p=0.042$), platelet count ($p=0.007$) and phosphorus ($p=0.041$). Treatment emergent abnormal hematocrit levels occurred in 3 of 13 (23%) male patients receiving 1 mg/day, 1 of 18 (6%) male patients receiving 3 mg/day and in 4 of 14 (29%) receiving 5 mg/day. The occurrence of high and low abnormalities was equal. Abnormal eosinophil counts occurred only in the 3 mg/day group (8%) and abnormal platelet counts only in the 1 and 3 mg/day groups. Only one abnormally low platelet count was noted and it was not considered clinically significant. The statistical difference in incidence of TEAV for phosphorus were due to the higher incidence in the placebo group.

Conclusions: The results of this study demonstrated that a 5 mg/day dose of E2020 produced improvement in cognitive test performance, activities of daily living, quality of patient life and global success/failure. There was also a consistent trend in the level of improvement observed. The safety profile of this study shows only two statistically significant differences between the E2020 treatment groups and Placebo. These differences were seen in the incidence of male patients who have at least one abnormal hematocrit value, and the number of patients having at least one abnormal platelet count. In neither case were these abnormalities considered clinically significant.