CLINICAL STUDY SYNOPSIS

Title: A 15-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of E2020 in Patients With Alzheimer's Disease

Investigators:

Multicenter, 23 Investigators in the United States.

Objectives: The objectives of this study were to evaluate the safety and efficacy of two oral dose levels of E2020, 5 mg/day and 10 mg/day, versus placebo, in patients with Alzheimer's disease.

Study Design:

This was a randomized, multicenter, double-blind, placebo-controlled, parallel group study, with a single-blind placebo washout before Termination. The treatment phase was 12 weeks in duration, followed by a three-Week washout. Treatment groups received either placebo, E2020 5 mg/day, or E2020 10 mg/day. Study medication was administered orally once daily during the treatment phase. Placebo was administered once daily in a single-blind manner during the washout period. Efficacy and safety evaluations were performed every three weeks for the 12 weeks of the double-blind portion of the study. Follow-up examinations were conducted at 15 weeks, after the three-Week placebo washout. Blood samples were obtained throughout the study for analysis of plasma E2020 concentrations and inhibition of acetylcholinesterase activity for pharmacokinetic/pharmacodynamic analyses.

Test Materials:

Identical appearing, 7.2 mm, film-coated tablets:

Study Medication

	Dose	
	Placebo	5 mg
Lot Numbers	K28005ZZB	K3Y002ZZZ
	K37007ZZA	K3Y004ZZZ
	K42008ZZZ	K3X015ZZZ
	K3X010ZZZ	K37015ZZA
	K3X016ZZZ	K42009ZZZ
	K3X019ZZZ	K42010ZZZ
		K42011ZZZ

Dose Administration:

Patients were screened for entry into the study by completing physical, laboratory, and psychometric/neurologic examinations within two weeks prior to Baseline. Tests were repeated at Baseline prior to the first dose of study medication. Subsequent doses were administered on each successive evening, just prior to bedtime.

Patients: Patient disposition is summarized in the table below. Exclusive of Site 53 (Dr. Hartford, 13 patients: four each receiving placebo and E2020 5 mg/day and five receiving E2020 10 mg/day), a total of 468 patients was enrolled in the study: One hundred fifty-three were randomized to receive placebo, 157 to receive E2020 5 mg/day, and 158 to receive E2020 10 mg/day. A total of 412 patients (88%) completed the study. The overall incidence of discontinuations, as well as the incidence of discontinuations because of non-serious signs and symptoms, appeared to be dose-related.

Patient Disposition

	Treatment			
	Placebo	E2020 5 mg/day	E2020 10 mg/day	Total
Patients Enrolled	153	157	158	468
Patients Completing Study	142 (93)	141 (90)	129 (82)	412 (88)
Patients Discontinued from Study	11 (7)	16 (10)	29 (18)	56 (12)
Reasons for Discontinuation				
Non-serious Signs and Symptoms	2 (1)	7 (4)	14 (9)	23 (5)
Serious Adverse Events	1 (<1)	0	2 (1)	3 (2)
Intercurrent Illness	0	0	0	0
Request of Patient /Investigator	3 (2)	4 (3)	6 (4)	13 (3)
Medication Non-compliance	1 (<1)	0	0	1 (<1)
Protocol Violation	2 (1)	3 (2)	4 (3)	9 (2)
Other	2 (1)	2 (1)	3 (2)	7 (1)

Data source: Table 2.0

Study Variables:

Efficacy: The primary efficacy parameters included Alzheimer's Disease Assessment, cognitive subscale (ADAS-cog), and Clinician's Interview-Based Impression of Change-Plus Version (CIBI-C Plus). The secondary efficacy parameters included individual items from ADAS-cog, Mini-Mental State Examination (MMSE), Quality of Life (QOL), and Clinical Dementia Rating - Sum of the Boxes (CDR-SB).

Safety: Signs and symptoms were recorded throughout the study. Laboratory safety assessments were conducted at Screening, each study visit and study Termination. These included hematology, blood chemistry and urinalysis assessments. Physical examination and vital sign assessments were performed at Screening, at each scheduled visit and at Termination. Additional measurements performed at

Screening included Vitamin B_{12} and folate, thyroid function, hepatitis B screen, electrocardiogram (ECG) and computed tomography (CT) scan or magnetic resonance imaging (MRI). ECGs were repeated at Week 12 or at Termination, if prior to Week 12.

Pharmacokinetic/Pharmacodynamic:

Plasma concentrations of E2020 and percent inhibition of acetylcholinesterase activity in red blood cells were measured at Baseline and at Weeks 3, 6, 9, 12, and 15 (Termination).

Statistical Methods:

The analyses of efficacy were performed on two patient populations: the Intent-To-Treat (ITT) population and the Fully Evaluable (FE) population. The ITT population was defined as all patients who were randomized to treatment, received at least one dose of study medication, and provided complete Baseline and at least some post-Baseline assessment data. The ITT population was further stratified as follows:

Observed Cases (OC): All ITT patients who provided complete data for an on-double-blind assessment of Week 12 Endpoint, irrespective of compliance and protocol violation. The associated data were analyzed in the Week 12 analysis.

Division of Neuropharmacologic Drug Products (DNDP) Last Observation Carried Forward (LOCF): The last observation on double-blind treatment was carried forward as the Endpoint evaluation for ITT patients for each measure. The associated data were analyzed in the Endpoint analysis.

Classical Intent-To-Treat (Retrieved Dropout-RDO): For ITT patients who lacked a Week 12 value on double-blind treatment, the RDO (Retrieved Dropout visit, an off-treatment Week 12 evaluation) was used as the Endpoint value, and labeled Endpoint $^{(R)}$. For ITT patients who lacked any Week 12 value, the Endpoint value was imputed using the LOCF method defined above. The associated data were analyzed in the Endpoint $^{(R)}$ analysis.

The Fully Evaluable Population (FE analysis) was defined as all patients who completed the study in compliance with the protocol. Furthermore, Week 12 (the Endpoint visit) had to fall within the defined Visit Window; have complete data for the scores of primary efficacy assessments (ADAS-cog and CIBI-C Plus) and for the

change scores (from Baseline) of these two assessments; and occur no more than three days after the last double-blind date.

The primary analysis was to be conducted on the FE population. However, since the results from both the ITT and FE populations are similar, the larger population (ITT) is presented in the text with supportive discussion of the FE population.

For both populations, the mean change (from Baseline value) of continuous measures and frequency distribution of CIBI-C scores were compared at each scheduled visit, Endpoint Visit, and Endpoint [(R)] Visit to determine if differences existed among the three treatment groups (placebo, E2020 5 mg/day, and E2020 10 mg/day).

All continuous efficacy variables (ADAS-cog, MMSE, QOL, and CDR-SB) were analyzed using analysis of covariance techniques (ANACOVA) with Baseline as the covariate. Pairwise comparisons were performed using a Fisher's two-tailed least significant difference procedure. The CIBI-C score, a categorical variable, was analyzed using Cochran-Mantel-Haenszel tests, adjusting for site. The proportion of failed visits (CIBI-C score > 4 was defined as a failure) was analyzed using an analysis of variance model (ANOVA) on ranks of proportion. Continuous demographic variables (age, weight, height, etc.) were analyzed using an ANOVA model. Categorical demographic variables (sex, race, etc.) were analyzed using Cochran-Mantel-Haenszel methods, adjusting for site. 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:

Results from the analysis of both primary parameters demonstrated the effectiveness of E2020 in a statistically significant manner. Results from the analysis of the secondary parameters were generally consistent with the primary parameter results. Results for the Intent-To-Treat and fully evaluable populations were similar.

Primary Parameters:

Patients in the two active treatment groups showed statistically significant improvements from Baseline in ADAS-cog scores at every post-Baseline on-treatment visit and at the Week 15 visit, while patients in the placebo group showed small improvements at Weeks 3, 6 and 9, and deterioration at Week 12, Endpoint and

Week 15. All patients demonstrated a deterioration in their scores during the washout phase (from Week 12 to Week 15), and although the changes in the active treatment groups who had been switched to placebo were larger than in the group who had received placebo throughout the study, the changes were not statistically significantly different among the treatment groups. Comparisons of the changes from Baseline among the treatment groups from Week 3 through Endpoint, and at Week 15, showed overall treatment group differences ($p \leq 0.0013$), differences between each active treatment and placebo ($p \leq 0.0149$), and differences between a combination of the active treatments and placebo ($p \leq 0.0003$).

Both active treatment groups had lower CIBI-C Plus scores at all post-Baseline on-treatment visits than did the placebo group. At Week 3, the percentages of patients who showed an improvement in their CIBI-C Plus scores were higher in the 10 mg/day group as compared to the 5 mg/day and placebo groups; at Weeks 6 and 9, the percentages of patients who showed an improvement in their CIBI-C Plus scores were higher in the active treatment groups as compared to the placebo groups. At Weeks 12 and at Endpoint, the percentages of patients showing an improvement in the active treatment groups were approximately twice that in the placebo group. Overall treatment differences ($p \leq 0.0142$), as well as pairwise differences between each active treatment and placebo ($p \leq 0.0088$) in the distribution of the CIBI-C scores were statistically significant from Week 9 through Endpoint (with the exception of the comparison between the 10 mg/day and placebo groups at Week 9). Scores worsened for all groups at Week 15, compared to both Baseline and Week 12, although the changes were not statistically significant.

Results for the primary efficacy parameters are summarized in the following table:

Summary of Primary Efficacy Parameters: ADAS-cog and CIBI-C Plus
ITT Population

Visit	Placebo n	Placebo Mean (SE)	E2020 5mg/day n	E2020 5mg/day Mean (SE)	E2020 10mg/day n	E2020 10mg/day Mean (SE)	Overall Treatment Effect
ADAS-cog[1]							
Baseline	150	25.28	156	26.39	155	26.41	p=0.4916
S.E. of Mean		(0.87)		(0.92)		(0.89)	
Mean Change from Baseline at Endpoint	150	0.39	154	-2.09	153	-2.73	
LS Mean Change at Endpoint		0.36		-2.08		-2.71	p<0.0001
S.E. of LS Mean		(0.43)		(0.43)		(0.43)	
p-value vs. Placebo			p<0.0001		p<0.0001		
CIBI-C Plus[2]							
Mean at Endpoint	150	4.19	153	3.90	152	3.85	p=0.0058
S.E.		(0.07)		(0.08)		(0.08)	
p-value vs. Placebo			p=0.0026		p<0.0082		

1 p-values based on an ANACOVA using Fisher's two-tailed least significant difference procedure for the pairwise comparisons
2 CIBI-C Plus: 0=Not Assessed; 1=Marked Improvement; 2=Moderate Improvement; 3=Minimal Improvement; 4=No Change; 5=Minimal Worsening; 6=Moderate Worsening; 7=Marked Worsening
p-values from a Cochran-Mantel-Haenszel test excluding not assessed.

Data Source: Tables 4.0 and 5.0

Secondary Parameters:

For the MMSE scores the two active treatment groups demonstrated improvements from Baseline at every post-Baseline on-treatment visit. Overall treatment effects were statistically significant at Week 3, then at Week 12, Endpoint and Week 15. Compared with placebo, the changes were statistically significantly better in both the 5 mg/day group ($p \leq 0.0342$) and the 10 mg/day group ($p \leq 0.0160$) at these assessments. Changes from Week 12 to 15 did not achieve statistical significance.

For the CDR-SB scores the two active treatment groups demonstrated improvements from Baseline at every post-Baseline on-treatment visit (with the exception of the 5 mg/day group at Week 6). The mean changes from Baseline were not significantly different among the treatment groups (except at Week 6, p=0.0075), and no pairwise comparisons were significant.

There was a statistically significant difference in the distribution of the proportion of failed visits, as assessed by the CIBI-C Plus score among treatment groups (p=0.0339). Pairwise comparisons showed a significant difference between the 5 mg/day group and placebo and also between a combination of the active treatments and placebo (p=0.0094 and p=0.0299, respectively).

For the QOL scores, the results were highly variable both within and between patients and thus are considered unreliable. Nonetheless, scores for the 10 mg/day dose group were statistically significantly lower than those of the placebo group at Endpoint and at Week 15 (p=0.0253 and p=0.0179, respectively).

Safety:

There was no clinically meaningful difference between treatment groups with respect to vital signs or physical examination results. There were no statistically significant differences in changes from Baseline in temperature or respiratory rate, but changes in heart rate were decreased in the 5 mg/day (-2.65±0.67 beats per minute (bpm), p=0.0001) and 10 mg/day groups (-2.26±0.74 bpm, p=0.0028). These latter decreases were significantly different from the decreases in the placebo group (-0.09±0.22 bpm, p≤0.03), although the magnitude of changes was not clinically significant. Systolic blood pressure was decreased (p=0.0449) in the 10 mg/day group and diastolic blood pressure was decreased in both E2020 groups (p≤0.016), compared to Baseline values; however, these changes were not different from those of the placebo group in a statistically significant manner. Normal-to-abnormal shifts in ECG results were observed in 15% of patients in each active treatment group, compared to 7% of patients receiving placebo. However, only four shifts were judged clinically significant, two each in the placebo and 5 mg/day groups.

An overall summary of signs and symptoms (SS) is presented in the table below. The incidence of signs and symptoms leading to withdrawal was dose-related. Patients in the 10 mg/day group had a higher incidence of specific treatment emergent signs and symptoms (TESS) and SS leading to withdrawal than the other two treatment groups. Nausea, vomiting, diarrhea, and insomnia occurred at a statistically significantly higher rate in the 10 mg/day group. Most of these TESS

were mild, episodic (lasting one to two days), and resolved while patients remained on treatment.

Signs and Symptoms and Study Withdrawals

	Placebo	E2020 5 mg/day	E2020 10 mg/day	Total
Number of patients at risk	**153**	**157**	**158**	**468**
Patients with any TESS	106 (69)	106 (68)	124 (78)	336 (72)
Patients with SAEs*	7 (5)	6 (4)	6 (4)	19 (4)
Patients with any SAEs or SS leading to withdrawal*	3 (2)	7 (4)	16 (10)	26 (6)

*Note: SAEs and SS leading to withdrawal were not necessarily treatment emergent

There were no clinically meaningful differences between treatment groups for any of the clinical laboratory measurements.

Pharmacokinetic/Pharmacodynamic:

The relationship between E2020 plasma concentrations and inhibition of red blood cell acetylcholinesterase (AChEI) collected over the 15-week study period was evaluated graphically and by nonlinear regression. A predictive relationship between AChEI and plasma concentrations was established. The relationship between clinical response (ADAS-cog and CIBI-C Plus) and drug exposure (E2020 plasma concentrations or AChEI) was explored graphically and by linear regression. The trend in ADAS-cog as a function of either plasma E2020 concentrations or AChEI was most notable when placebo patients were compared to active treatments. The sensitivity to differentiate between the 5 mg/day and 10 mg/day dose groups was diminished by the relatively small range of observed values.

Conclusions:

Efficacy:

E2020, in doses of both 5 mg/day and 10 mg/day, was more effective than placebo in improving the disease state of patients with Alzheimer's disease as measured by the primary efficacy variables, Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog), and the Clinician's Interview-Based Impression of Change (CIBI-C Plus). This was supported by the secondary variables, the proportion of failed visits as assessed by the CIBI-C Plus score and the Mini-Mental State

Examination (MMSE). A trend for improvement in the 10 mg/day group compared to placebo was observed at Endpoint on the Clinical Dementia Rating - Sum of the Boxes (CDR-SB). The Quality of Life (QOL) Scale as assessed by patients was highly variable and thus not easily interpretable.

Safety:

Placebo and E2020 at the 5 mg/day dose were equally well tolerated. The incidence of specific TESS and non-serious SS leading to discontinuation indicate that E2020 was slightly less well tolerated at 10 mg/day particularly with respect to digestive and nervous system SS. Most of SS were mild, episodic (lasting one to two days), resolved with continuation of E2020 treatment, and are considered to be related to the cholinergic activity of E2020. Neither dose of E2020 had clinically meaningful effects on vital signs, cardiac function, physical examination results, or clinical laboratory parameters.