2. SYNOPSIS

Name of Sponsor Company: Eisai Inc./Pfizer, Inc., US **Name of Finished Product**: Aricept® 5 mg tablets **Name of Active Ingredient**: donepezil hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)

Title of Study:	A 24-week, multicenter, randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of donepezil hydrochloride (E2020) in patients with severe Alzheimer's disease followed by a 12-week open-label extension period (report of the open-label period)	
Investigators:	98 investigators, including 77 in the US, 5 in Canada, 4 in France, 8 in the UK, and 4 in Australia; see Appendix 10.1.4 for a complete list.	
Study Center:	98 centers, including 77 in the US, 5 in Canada, 4 in France, 8 in the UK, and 4 in Australia; see Appendix 10.1.4 for a complete list.	
Publication (reference):	To date, there are no publications based on this research.	
Study Period	From: 04 January 2001 (double-blind phase) To: 22 September 2005 (open-label phase)	**Phase of Development**: III
Study Design	All patients who entered the open-label extension period were eligible to be switched directly from double-blind treatment to 5 mg/day donepezil for 6 weeks. After 6 weeks, patients were dose-escalated to 10 mg/day, based on clinician's judgment. This allowed the blind that was assigned in the double-blind period of the study to be maintained.	
Number of Patients:	A total of 229 patients who had completed the double-blind portion of the study were enrolled in the open-label period (111 who had received donepezil during the double-blind period [DON-DON group] and 118 who had received placebo during the double-blind period [PLA-DON group]).	
Criteria for Inclusion:	Patients were eligible to be enrolled in the open-label treatment period if they had completed the double-blind period and the week 24 assessments.	

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Test Drug (Lot No.):	5 mg donepezil hydrochloride tablets (Lot Numbers: 002442, 800038, 800043, and 05AR0145)	
Dosage/Route	Dosage:	5 mg (one 5 mg tablet) daily for the first 6 weeks of the open-label treatment period, then 10 mg (two 5 mg tablets) once daily for the remainder of the study. The investigator had the option to reduce the study drug dosage from 10 mg daily to 5 mg daily based on clinical judgment of tolerability.
	Route:	Oral
Reference Therapy (Lot No.):	Not applicable	
Duration of Treatment:	Up to 36 consecutive weeks (24-week double-blind phase, 12-week open-label phase)	

Criteria for Evaluation

Efficacy Parameters: The efficacy measures assessed in the double-blind period and continued in the open-label extension period were the SIB, MMSE, ADCS-ADL-sev, NPI, CBQ, and RUSP.

Safety Parameters: Safety was assessed by recording adverse events (AEs) and serious adverse events (SAEs), vital signs, physical examinations, concomitant medications and the Unified Parkinson's Disease Rating Scale (UPDRS).

Results

Statistical Methods: The efficacy analyses were conducted on datasets for the Intent-to-Treat (ITT) population identified in the double-blind phase of the study. Analyses of change from baseline in the week 36/endpoint evaluations were done using both the baseline of the double-blind period and the week 24/endpoint of the double-blind period. Summary statistics by visit for continuous variables included the number of observations (N), mean, standard error, median, minimum, maximum, and 95% confidence interval.

For safety analysis, individual vital signs were descriptively summarized by treatment group and visit. The baseline used for safety parameters was the last week (week 24) of the double-blind treatment period. Changes from baseline to the week 30 and 36 visits were calculated. Incidence rates for AEs by body system, preferred term, severity, and relationship to study medication were calculated.

Data on other medications used by patients during the study were collected and summarized by therapeutic class and generic components

Efficacy: Among those patients who were enrolled in the open-label treatment period, the

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mean SIB scores at baseline in the DON-DON (N=98) and PLA-DON groups (N=105) were 65.8 and 68.7, respectively. The mean SIB score in the DON-DON group during the double-blind treatment period increased at week 24 by 2.35 points and the mean SIB score in the PLA-DON group decreased by 4.68 points. At week 36, after 12 weeks of open-label treatment with donepezil, the SIB scores in the group previously treated with donepezil had decreased slightly from baseline by 1.52 points and had decreased by 3.94 points relative to the week 24 value. At week 36, after 12 weeks of open-label treatment with donepezil, the SIB scores in the group previously treated with placebo were similar to the scores observed in this group at week 24, the mean having increased by 0.37 points relative to the week 24 value (mean score 64.0). There was minimal overlap of the 95% confidence intervals for the week 24 to week 36 mean change in SIB, suggesting that there may be a difference in the group treated previously with donepezil compared to the group previously treated with placebo.

There were no clinically significant differences between the two groups of patients in any of the other efficacy parameters during the open-label treatment period. At week 36, small improvements were noted in both groups in mean MMSE scores relative to baseline. Scores on the ADCS-ADL-sev and the NPI both worsened slightly in both groups during the open-label treatment period. There were no consistent or clinically important differences observed in either the CBQ or RUSP during the open-label period.

Safety: A total of 296 AEs were reported by 126 patients (55.0%) during the open-label period. Patients previously treated with placebo were more likely to experience AEs than patients with prior donepezil exposure (61.0% vs. 48.6%), and reported a higher total number of AEs (170 vs. 126). Patients who had previously been assigned to the placebo group were more likely to experience AEs that were considered by the investigator to be related to donepezil treatment; the most common of these being diarrhea, agitation, and vomiting. One patient in the DON-DON group experienced an AE that led to death during the open-label period. Another patient in the DON-DON group experienced an AE 28 days after completing the open-label period that led to death. Both deaths were considered not related to donepezil treatment by the investigator. Fourteen patients experienced SAEs; 5 patients (4.5%) from the DON-DON group and 9 (7.6%) from the PLA-DON group. Sixteen patients reported AEs that led to discontinuation of open-label donepezil therapy; 4 (3.6%) from the DON-DON group and 12 (10.2%) from the PLA-DON group.

There was no clinically significant mean change in vital signs, physical examinations, or UPDRS observed in either group over the course of treatment in the open-label phase of the study.

Conclusions

In the DON-DON group there was significant improvement observed in SIB during the double-blind period (at week 24). Among patients previously treated with donepezil, SIB scores in 2 patients declined by 44 and 66 points from baseline to week 36, thus skewing the mean change data. Nevertheless, the over all mean SIB value in the DON-DON group

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remained near baseline level after 36 weeks of donepezil treatment, suggesting that these patients maintained their cognitive function relative to baseline. Among patients in the PLA-DON group, the decline in mean SIB observed during the double-blind period did not continue, and when donepezil treatment was initiated the mean SIB score was maintained from weeks 24 to 36. Thus, patients who had a 6-month delayed start of donepezil treatment showed no further decline in their SIB scores and appeared to benefit from donepezil therapy. The pattern of results observed on the SIB during the open-label period was similar to that observed on the MMSE.

There was no consistent or clinically significant improvement or worsening observed in any of the secondary efficacy variables during the open-label treatment period.

A higher proportion of patients in the PLA-DON group reported AEs during the open-label treatment period than those in the DON-DON group. Patients in the PLA-DON group also had a higher percentage of serious AEs and AEs considered related to donepezil therapy.

There were no clinically significant mean changes in vital signs, physical examinations, or UPDRS in either group.

In general, 10 mg/d donepezil therapy was well tolerated over 12 weeks of the open-label treatment.