Efficacy and Safety of Donepezil 23 mg/d in Patients With Moderate to Severe Alzheimer's Disease With Concomitant Memantine Use

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STUDY OVERVIEW

INTRODUCTION

- A new dose of the acetylcholinesterase inhibitor (AChEI) donepezil, a 23-mg tablet, was recently approved by the US Food and Drug Administration for the treatment of moderate and severe Alzheimer's disease (AD)
- Approval was based on results from a 24-week, double-blind trial of patients with moderate and severe AD who were stable on donepezil 10 mg/d and who were randomized to either increase their donepezil dose to 23 mg/d or to continue on their existing donepezil 10 mg/d dose[1]
- In this study approximately one third of the patients were receiving ≤ 20 mg/d memantine for ≥ 3 months prior to screening and continued to receive memantine during the subsequent 24-week treatment period
- Memantine was not considered a study medication and its compliance was not monitored
- Prior studies have indicated differential efficacy and safety profiles among patients receiving an AChEI alone versus patients receiving combined AChEI and memantine therapy[2,3]

OBJECTIVE

- To compare the efficacy and safety of donepezil 23 mg/d with and without background memantine to donepezil 10 mg/d with and without memantine

METHODS

Study Design

- A 24-week, randomized, double-blind, global study in patients with moderate to severe AD
- 1467 patients were randomized 2:1 to increase their daily dose to donepezil 23 mg/d or to continue taking their existing 10 mg/d dose
- Memantine use was allowed if ≤ 20 mg/d for ≥ 3 months prior to screening
- Patients were randomized to donepezil doses (23 mg/d vs 10 mg/d) and stratified by concomitant memantine use (yes/no)
- Efficacy assessments were performed at screening, baseline, and Weeks 6, 12, 18, and 24
- Safety and tolerability were evaluated throughout via adverse event (AE) monitoring

Patient Population

- Diagnosis of probable AD by National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria
- Aged 45-90
- Mini-Mental State Examination (MMSE) score 0-20 (inclusive) at screening and baseline
- Severe Impairment Battery (SIB) scores ≤ 90 at screening and baseline
- Receiving donepezil 10 mg/d for ≥ 3 months prior to screening

Co-primary End Points

- SIB (cognition): Least squares (LS) mean change from baseline to Week 24 in total score
- Clinician's Interview-Based Impression of Change-plus caregiver input (CIBIC-plus; global function): Mean overall change score at Week 24

Statistical Analyses

- The intent-to-treat (ITT) population was used for statistical analysis of efficacy, with missing values imputed by the last observation carried forward (LOCF) method; the observed cases (OC) population was also analyzed
- For the SIB (higher scores are better), an analysis of covariance (ANCOVA) model with terms for baseline, country, and treatment was the primary model for analyzing treatment differences of change from baseline
- For CIBIC-plus scores (lower scores are better), a nonparametric ANCOVA method with a Cochran-Mantel-Haenszel component embedded was performed with adjustment for baseline severity and stratification by country

RESULTS

Patient Characteristics

- Demographics and baseline information for the patient populations taking concomitant memantine or not taking memantine were generally similar (Table 1), with the following notable exceptions:
  - There were more white and fewer Asian/Pacific patients among the groups taking concomitant memantine
  - Prior donepezil use was longer among the groups taking concomitant memantine
  - Mean SIB and MMSE scores were lower and Clinician's Interview-Based Impression of Severity-plus caregiver input (CIBIS-plus) scores higher at baseline among the groups taking concomitant memantine, indicating more advanced disease

Table 1. Patient demographics and baseline information

	Concomitant Memantine		No Concomitant Memantine	
	Donepezil 23 mg	Donepezil 10 mg	Donepezil 23 mg	Donepezil 10 mg
Safety population, n	352	168	611	303
Age, y, mean (SD)	74 (9)	73 (8)	74 (8)	74 (9)
Female, %	60.8	63.1	64.3	62.0
Race, %				
Black	4.0	2.4	1.3	1.7
White	83.8	82.7	67.6	68.3
Hispanic	4.8	3.6	8.2	8.0
Asian/Pacific	7.1	11.3	22.3	19.7
Duration of prior donepezil treatment, weeks, mean (SD)	157 (123)	150 (119)	87 (89)	80 (75)
SIB mean (SD)	72.0 (20.3)	74.2 (18.1)	75.6 (15.6)	76.1 (15.5)
CIBIS-plus mean (SD)	4.58 (0.88)	4.62 (0.85)	4.31 (0.81)	4.27 (0.89)
MMSE mean (SD)	11.9 (5.3)	11.9 (4.9)	13.8 (4.7)	13.7 (4.6)

SD = standard deviation.

Efficacy

- The time course for the change from baseline in SIB scores for the groups taking or not taking concomitant memantine is shown in Figure 1
  - Donepezil 23 mg/d showed significant cognitive benefits over 10 mg/d in both memantine users and nonusers
- On the CIBIC-plus, donepezil 23 mg/d provided no significant incremental benefit over 10 mg/d, irrespective of memantine use (Table 2)

Figure 1. SIB score change by visit (OC) and at end point (ITT-LOCF): (A) no concomitant memantine; (B) concomitant memantine

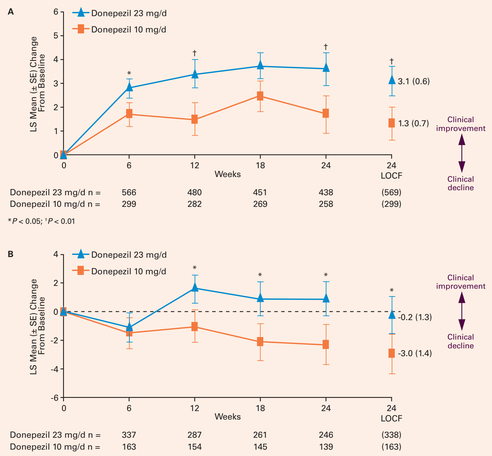

Table 2. Summary of CIBIC-plus scores at Week 24 by concomitant memantine use (ITT-LOCF)

	Concomitant Memantine			No Concomitant Memantine		
	Donepezil 23 mg	Donepezil 10 mg	*P*	Donepezil 23 mg	Donepezil 10 mg	*P*
n	338	161		570	298	
CIBIC-plus, LS mean (SE)	4.40 (1.02)	4.52 (0.94)	0.14	4.12 (1.09)	4.16 (1.12)	0.38

Safety

- The incidence of AEs was higher with donepezil 23 mg/d than with 10 mg/d in both the populations taking and not taking concomitant memantine (Table 3)
- The incidence of gastrointestinal AEs was greater with donepezil 23 mg/d than 10 mg/d, but was not consistently greater (or less) with concomitant memantine use
- Incidence of serious AEs (SAEs) was slightly higher in the groups taking concomitant memantine
  - The incidence of individual SAEs was very low (< 1.0%) across all groups

Table 3. Summary of AEs by concomitant memantine use

	Concomitant Memantine		No Concomitant Memantine	
	Donepezil 23 mg n = 352	Donepezil 10 mg n = 168	Donepezil 23 mg n = 611	Donepezil 10 mg n = 303
Patients with ≥ 1 TEAE, %	80.7	66.7	69.7	62.0
Mild, %	32.4	31.0	30.0	31.4
Moderate, %	39.5	27.4	31.6	24.1
TEAEs*				
Diarrhea	11.4	10.1	6.5	2.6
Nausea	9.9	2.4	12.9	4.0
Urinary tract infection	7.7	4.8	2.5	3.6
Vomiting	7.1	1.2	10.5	3.3
Agitation	6.5	7.1	2.5	2.0
Fall	5.7	6.5	3.1	2.3
Anorexia	5.4	0.6	5.2	2.3
Weight decreased	4.8	2.4	4.6	2.6
Dizziness	4.8	6.0	4.9	2.0
Urinary incontinence	4.5	1.2	1.3	1.3
Headache	4.3	3.6	4.3	3.0
Fatigue	3.4	1.8	1.8	0.3
Insomnia	3.4	3.6	3.4	1.7
Patients with ≥ 1 SAE, %	9.7	10.7	7.5	8.9

*TEAEs occurring in ≥ 3% of patients and at higher frequency with donepezil 23 mg than donepezil 10 mg.
TEAE = treatment-emergent adverse event.

CONCLUSIONS

- In patients with moderate and severe AD, donepezil 23 mg/d provided significant cognitive benefits over 10 mg/d, regardless of background memantine use
- Donepezil 23 mg/d was generally safe and well tolerated among both patients receiving donepezil alone and patients receiving a combination of donepezil and memantine therapy
- Gastrointestinal AEs were greater with donepezil 23 mg/d than 10 mg/d but did not appear to be influenced by concomitant memantine use

References

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