TABLE 2 (Continued)

Variable	Group	Baseline			Change				
		Patients	Mean (SD)	*p*, ANOVA	Patients	Mean (SD)	Difference, 95% CI	*p*, *t* test[a,b]	*p*, ANCOVA[a,b]
NPI-10	Placebo	32	18.3 (8.9)	0.079	32	0.3 (17.5)			
	3mg	35	20.7 (12.8)		35	−3.9 (22.0)	−4.2 (−13.9 to 5.6)	0.396	0.602
	5mg	32	14.0 (8.3)		32	−5.5 (6.7)	−5.8 (−12.4 to 0.8)	0.086	0.047
	10mg	36	19.5 (12.8)		35	−8.0 (12.8)	−8.3 (−15.8 to −0.9)	0.029	0.019
NPI-2	Placebo	32	6.3 (4.0)	0.443	32	1.1 (5.7)			
	3mg	35	7.1 (4.1)		35	−2.1 (6.3)	−3.2 (−6.1 to −0.3)	0.032	0.025
	5mg	32	6.3 (4.8)		32	−3.3 (3.8)	−4.4 (−6.8 to −2.0)	<0.001	<0.001
	10mg	36	7.9 (5.4)		35	−4.6 (4.5)	−5.8 (−8.2 to −3.3)	<0.001	<0.001
NPI-4	Placebo	32	12.1 (6.3)	0.269	32	−0.3 (8.5)			
	3mg	35	11.5 (7.0)		35	−2.4 (10.8)	−2.1 (−6.9 to 2.6)	0.377	0.261
	5mg	32	9.0 (5.3)		32	−4.2 (4.9)	−3.9 (−7.3 to −0.4)	0.028	0.008
	10mg	36	11.9 (8.8)		35	−5.1 (7.4)	−4.8 (−8.7 to −1.0)	0.015	0.006
ZBI	Placebo	32	21.8 (10.1)	0.197	31	4.2 (10.4)			
	3mg	35	27.9 (13.9)		33	−1.3 (13.2)	−5.5 (−11.5 to 0.5)	0.069	0.301
	5mg	32	22.9 (11.5)		31	−0.7 (15.7)	−4.9 (−11.7 to 1.8)	0.149	0.172
	10mg	36	26.5 (16.1)		31	−5.0 (13.6)	−9.2 (−15.3 to −3.0)	0.004	0.035
UPDRS part III	Placebo	33	20.8 (10.6)	0.702	31	0.7 (3.8)			
	3mg	35	17.9 (9.0)		34	−0.5 (7.4)	−1.3 (−4.2 to 1.7)	0.393	0.397
	5mg	33	19.1 (10.7)		32	−0.5 (5.4)	−1.3 (−3.6 to 1.1)	0.281	0.358
	10mg	37	18.9 (11.6)		33	−1.0 (6.7)	−1.8 (−4.5 to 1.0)	0.200	0.258

The significant differences in the analyses using mixed-effect model for repeated measures were consistent with those based on last observation carried forward for MMSE, NPI-10, and NPI-2: MMSE (3mg, $p = 0.010$; 5mg, $p < 0.001$; 10mg, $p = 0.003$), NPI-10 (3mg, $p = 0.115$; 5mg, $p = 0.160$; 10mg, $p = 0.028$), NPI-2 (3mg, $p = 0.003$; 5mg, $p < 0.001$; 10mg, $p < 0.001$).

[a]Probability values are for the comparison between placebo and each active group.

[b]Significance level, $p < 0.0167$ (= 0.05/3 with Bonferroni correction).

ANCOVA = analysis of covariance; ANOVA = analysis of variance; CI = confidence interval; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory (NPI-10 = delusions + hallucinations + agitation/aggression + dysphoria + anxiety + euphoria + apathy + disinhibition + irritability/lability + aberrant motor behavior; NPI-2 = hallucinations + cognitive fluctuation; NPI-4 = delusions + hallucinations + dysphoria + apathy); SD = standard deviation; UPDRS =Unified Parkinson's Disease Rating Scale; VPTA = Visual Perception Test for Agnosia; WAIS-III = Wechsler Adult Intelligence Scale; WMS-R = Wechsler Memory Scale-Revised; ZBI = Zarit Caregiver Burden Interview.

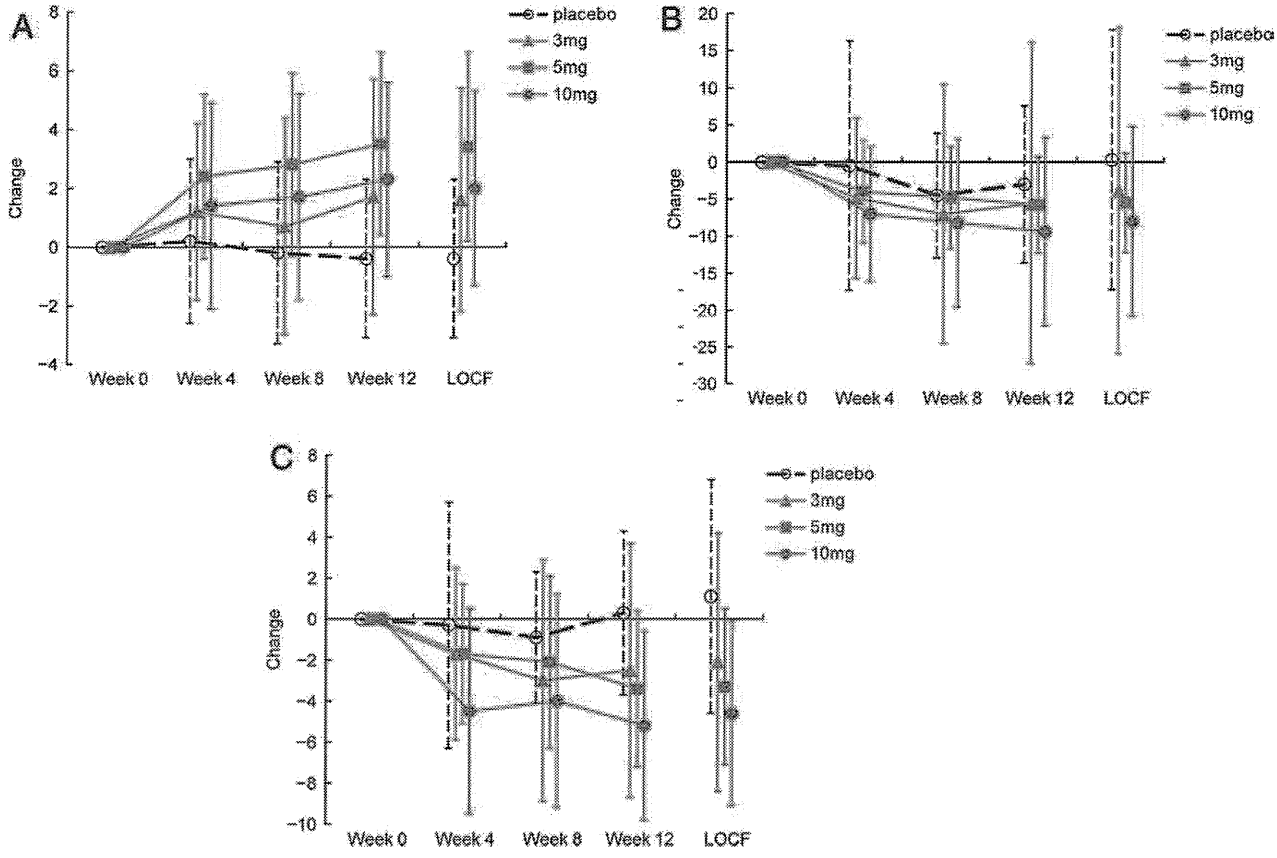

FIGURE 2: Mean changes from baseline in the (A) Mini-Mental State Examination and (B, C) Neuropsychiatric Inventory (B, NPI-10; C, NPI-2). Error bars represent standard deviation of the mean. LOCF = last observation carried forward.

did not reach the significance level. The results of the mixed-effect model analyses were consistent with those of LOCF analyses. The trend analyses demonstrated a linear dose-dependent improvement for NPI-2 (linear, $p = 0.036$; 5mg saturation, $p = 0.076$) but not for NPI-4 and NPI-10.

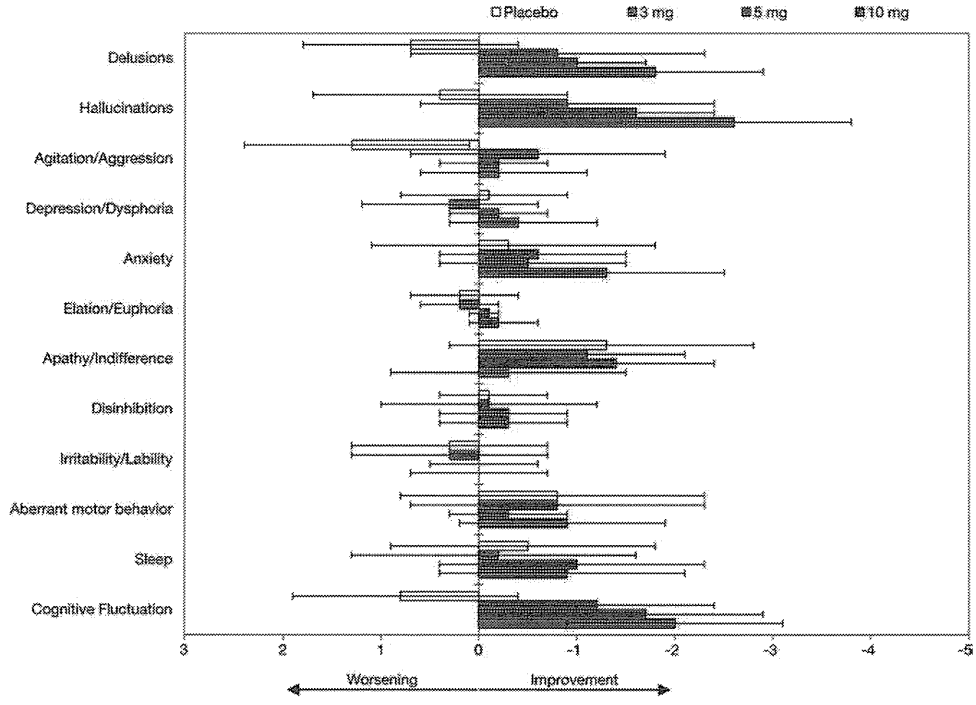

FIGURE 3: Mean changes (95% confidence intervals) of individual Neuropsychiatric Inventory items.

TABLE 3: Distribution of the Clinician's Interview-Based Impression of Change plus Caregiver Input at Week 12 (Last Observation Carried Forward)

Treatment Group	Total	Marked Improvement	Moderate Improvement	Minimal Improvement	No Change	Minimal Worsening	Moderate Worsening	Marked Worsening	Not Evaluable	*p*, Wilcoxon Rank Sum Test
Placebo	30	0 (0.0%)	1 (3.3%)	9 (30.0%)	5 (16.7%)	11 (36.7%)	4 (13.3%)	0 (0.0%)	0	
3mg	32	1 (3.1%)	6 (18.8%)	15 (46.9%)	8 (25.0%)	1 (3.1%)	0 (0.0%)	1 (3.1%)	0	<0.001
5mg	31	5 (16.1%)	7 (22.6%)	10 (32.3%)	4 (12.9%)	3 (9.7%)	2 (6.5%)	0 (0.0%)	0	<0.001
10mg	28	2 (7.1%)	3 (10.7%)	13 (46.4%)	9 (32.1%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	1	<0.001

Percentages are based on the total number of evaluable patients in relevant treatment group. Probability values are for the comparison between placebo and each active group.

The NPI-plus domains Delusion, Hallucination, and Cognitive Fluctuation improved in all active groups, whereas they deteriorated in the placebo group (Fig 3). The differences between the placebo and both the 5 and 10mg groups were significant (5mg, $p = 0.012$, 0.014, and 0.004; 10mg, $p = 0.002$, <0.001, and <0.001 for each symptom, respectively).

Global Function

The distributions of CIBIC-plus at the final evaluation (LOCF) in all active groups were significantly superior to that of placebo ($p < 0.001$ for each group; Table 3). The responder rates were 33.3%, 68.8%, 71.0%, and 64.3% in the placebo, 3mg, 5mg, and 10mg groups, respectively. The differences from placebo were significant in the 3 and 5mg groups (3mg, $p = 0.010$; 5mg, $p = 0.004$; 10mg, $p = 0.034$). No dose dependency was demonstrated on trend analysis.

Caregiver Burden

ZBI score was reduced significantly more in the 10mg group than in placebo at the final evaluation (LOCF; $p = 0.004$), although the difference did not reach the significance level after baseline value adjustment (see Table 2).

Safety

AEs were reported in 71%, 69%, 82%, and 87%, respectively, of the placebo, 3mg, 5mg, and 10mg groups (Table 4). The majority were mild or moderate. The most common AE was elevated creatinine kinase (5.9%, 14.3%, 9.1%, and 13.5%, respectively). Cholinergic AEs such as diarrhea, nausea, anorexia, and abdominal discomfort were reported in some patients; however, no difference in incidence was noted between the placebo and any donepezil groups. Adverse parkinsonian events were reported in 2.9%, 8.6%, 12.1%, and 2.7%. The mean UPDRS part III score somewhat improved in all active groups at the final evaluation, whereas the score worsened in placebo, although the differences among groups did not reach the significance level (see Table 2). Adverse behavioral events were 11.8%, 22.9%, 15.2%, and 8.1% in the placebo, 3mg, 5mg, and 10mg groups, respectively; nevertheless, these differences were not statistically significant. The proportions of AEs leading to withdrawal were similar between groups: 11.8%, 8.6%, 3.0%, and 8.1%, respectively. Serious AEs occurred in 5.9%, 5.7%, 6.1%, and 10.8% of the respective groups. Of these, only 2 events, agitation in the placebo group and subarachnoid hemorrhage in the 3mg group, were judged to be related to the study drug. One serious AE in the 10mg group (worsening of hallucinations) occurred while the patient was still taking 3mg/day during the titration period. There were no clinically relevant differences in vital signs or electrocardiogram between the groups.

Discussion

In the present study, we found that donepezil improved both cognition and behavior in patients with DLB compared to placebo. Patients given 5 or 10mg donepezil showed greater improvement in the majority of the cognitive and behavioral measures, including the MMSE and NPI. Donepezil treatment also led to improved global function and reduced caregiver burden in this population. Because consistent improvements in many different measures across broad domains were observed, despite the exploratory nature of this study due to several limitations as discussed below, we believe that our findings demonstrated encouraging effects of donepezil for patients with DLB.

The majority of cognitive measures showed significant between-group differences. In particular, there was an apparent improvement in overall cognitive function, especially with the higher 2 doses; the mean changes in MMSE score favored donepezil by 2.0 to 3.8 points. This difference was larger than that reported in other studies of ChEIs in DLB, AD, and Parkinson disease

TABLE 4: Adverse Events

AEs	Placebo, n = 34	3mg, n = 35	5mg, n = 33	10mg, n = 37
Total	24 (70.6%)	24 (68.6%), $p = 1.000$	27 (81.8%), $p = 0.391$	32 (86.5%), $p = 0.146$
Severe AEs	2 (5.9%)	1 (2.9%)	0 (0.0%)	1 (2.7%)
Serious AEs	2 (5.9%)	2 (5.7%)	2 (6.1%)	4 (10.8%)
AEs leading to withdrawal	4 (11.8%)	3 (8.6%)	1 (3.0%)	3 (8.1%)
Gastrointestinal disorders	8 (23.5%)	1 (2.9%), $p = 0.013$	10 (30.3%), $p = 0.589$	13 (35.1%), $p = 0.310$
Anorexia	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.4%)
Diarrhea	4 (11.8%)	0 (0.0%)	4 (12.1%)	3 (8.1%)
Abdominal discomfort	1 (2.9%)	0 (0.0%)	2 (6.1%)	0 (0.0%)
Nausea	1 (2.9%)	0 (0.0%)	0 (0.0%)	2 (5.4%)
Vomiting	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Parkinson symptoms	1 (2.9%)	3 (8.6%), $p = 0.613$	4 (12.1%), $p = 0.197$	1 (2.7%), $p = 1.000$
Psychiatric symptoms	4 (11.8%)	8 (22.9%), $p = 0.341$	5 (15.2%), $p = 0.733$	3 (8.1%), $p = 0.702$

Probability values are for the comparison between placebo and each active group.

with dementia (PDD).[15,32,33] Improvement was also noted in the attentive–executive domains. We presume that a ceiling effect caused the nonsignificant outcome in the visuoperceptual domain.

Also noteworthy was the improvement of neuropsychiatric features and reduction of caregiver burden in the donepezil groups. The beneficial effect of donepezil was evident on each symptom domain characteristic of DLB (delusion, hallucination, and cognitive fluctuation), as generally consistent with the previous rivastigmine study[15] except for apathy. For NPI-2, a linear dose–response relationship was demonstrated. Caregiver burden also was reduced significantly at the highest dose, 10mg/day.

Patients who received donepezil also demonstrated improved global function, as measured by CIBIC-plus. A higher percentage of patients showed improvement, and fewer patients worsened in each donepezil group than in placebo. The beneficial effect seemed greater than those of ChEIs reported for patients with AD and PDD.[33–35] In a trial of rivastigmine for PDD, improvement of activities of daily living, which would reflect treatment-induced changes in cognitive, behavioral, and motor symptoms, was reported.[33] Such an outcome may also be useful to compare the clinically meaningful impacts of the treatment among trials.

AEs were not rare; however, only approximately 8% of the study population withdrew due to AEs, and the prevalence of withdrawal or AEs, including typical cholinergic side effects, did not differ among treatment groups. Although symptoms of parkinsonism were reported as AEs somewhat more frequently in the 3 and 5mg groups than in the placebo group, the difference was not reflected in the mean UPDRS part III score. Indeed, the score demonstrated numerical, although nonsignificant, improvement in the highest dose group. Cholinergic treatment theoretically exacerbates parkinsonism. However, the possible beneficial effects of donepezil observed in this study suggest that the use of ChEIs should not necessarily be avoided in the treatment of DLB due to concern of possible parkinsonism. These unexpected effects, despite not being confirmed, might be explained by a complicated neuronal network for motor control.

As the discontinuation rate was relatively low, and there was no significant difference among groups, it is unlikely that exclusion bias caused by early termination affected the efficacy results. Both the LOCF analysis and

the mixed-effect model analysis consistently showed favorable results.

As an aim of this study was to explore targetable clinical presentations of DLB, we did not set a specific primary endpoint despite assigning multiple efficacy outcome measures, which could be a major limitation. In addition, cognitive fluctuation was measured by an unestablished tool, which is well equipped but not yet validated. Another limitation is that nearly half of the centers enrolled only 1 or 2 patients, which may have caused an inter-rater discordance of the clinical ratings, although a training and certification course was mandatory for the investigators. Also, the small sample, short duration of treatment, and lack of formal dose–response comparison are evident limitations. Nevertheless, the results of this study strongly suggest that donepezil is safe in patients with DLB, and provide a preliminary indication of its clinical effectiveness in terms of cognitive function, behavioral symptoms, and global function of DLB, and consequently in effecting a reduction of caregiver burden. The findings of the present study with donepezil should be verified in a confirmatory clinical trial. In addition, long-term effects should be examined. Although both 5mg/day and 10mg/day seemed to be beneficial, 10mg/day was somewhat more beneficial in terms of behavioral symptoms. The optimum dose should be determined in a follow-up trial, in which dose titration with patients unable to tolerate 10mg/day being allowed to take 5mg/day would be a sensible design.

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Potential Conflicts of Interest

E.M.: consultancy, Lundbeck; grants/grants pending, Eisai, FUJIFILM RI, Nihonmediphysics; speaking fees, Eisai, FUJIFILM RI, Janssen, Johnson & Johnson, Lundbeck, Nihonmediphysics, Novartis. M.I.: grants/grants pending, Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, Nihonmediphysics, Novartis, Pfizer, Takeda, Tsumura; speaking fees, Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, MSD, Nihonmediphysics, Novartis, Ono Pharmaceutical, Pfizer, Takeda, Tsumura. K.K.: board membership, Tsumura; speaking fees, Eisai, Tsumura, Janssen, FUJIFILM RI, Novartis, Pfizer, Nihonmediphysics, Daiichi Sankyo; paid manuscript preparation, Tsumura.

Appendix

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Influences of Donepezil on Cardiovascular System—Possible Therapeutic Benefits for Heart Failure—DOnepezil Cardiac TEst Registry (DOCTER) Study

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Abstract: To study prospectively influences of donepezil, an acetylcholinesterase inhibitor against Alzheimer disease, on cardiovascular system, we evaluated cardiovascular changes occurring during new initialized treatment with donepezil in 49 dementia patients over 6 months. No patient suffered from cardiovascular events. In clinical changes between baseline and the first evaluation after donepezil treatment, heart rate and plasma brain natriuretic peptide (BNP) levels as a marker for heart failure did not change (BNP: 59.62 ± 62.71 pg/mL at baseline to 53.18 ± 42.34 pg/mL at first evaluation; $P = 0.262$). We further examined plasma BNP levels in 2 groups into which the patients were divided at baseline according to the cut-off plasma BNP level of 60 pg/mL. In patients with high level of BNP, the BNP levels decreased after administration of donepezil (116.39 ± 76.58 pg/mL at baseline to 82.24 ± 46.64 pg/mL at first evaluation; $P = 0.011$) with the tendency to be reduced in the follow-up period. BNP did not change in patients with low level of BNP. Donepezil seemed to be safe in patients with dementia without symptomatic heart disease and significantly decreased plasma BNP levels in patients with subclinical chronic heart failure.

Key Words: donepezil, cardiovascular system, plasma brain natriuretic peptide, chronic heart failure

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INTRODUCTION

The prognosis of chronic heart failure (CHF) patients remains poor despite increasing use of renin-angiotensin-aldosterone system inhibitors, beta-adrenoreceptor blockers and cardiac resynchronization therapy among other treatment modalities.[1–6] Sympathetic nervous system activation and impaired vagal heart rate control, both, herald a poor prognosis in CHF patients. Yet, current treatments focus on pharmacological and nonpharmacological strategies to attenuate sympathetic influences on the cardiovascular system. Treatments augmenting cardiac vagal activity are an interesting alternative approach.[7–10] Electrical vagal nerve stimulation markedly improved long-term survival in rats with CHF after large myocardial infarctions.[7] The observation suggests that pharmacological interventions augmenting acetylcholine, the neurotransmitter mediating vagal influences on the heart, may elicit cardioprotective actions. Indeed, we reported a beneficial effect of donepezil, an acetylcholinesterase inhibitor, on cardiac function and survival in a murine CHF model.[11] Whether or not donepezil treatment is also beneficial in CHF patients is unknown. In our recent retrospective analysis, donepezil-treated patients with Alzheimer disease had a lower risk of cardiovascular death than untreated patients.[12] Although these findings should not be overinterpreted, they contrast with current clinical practice as donepezil is rarely prescribed in dementia patients with cardiovascular disorders. Therefore, we carried out the prospective noninterventional DOCTER (DOnepezil Cardiac TEst Registry) study to evaluate clinical events and cardiovascular responses occurring before and after donepezil treatment in dementia patients.

METHODS

Subjects

We prospectively registered 49 consecutive dementia patients (43 patients with Alzheimer disease and 6 patients with diffuse Lewy body disease) in whom the treating physician had decided to initiate donepezil treatment. The criteria for enrollment in this study were clinically stable condition except dementia. Patients were registered between April 2008 and August 2010 in 4 hospitals (Doujin Hospital, Inan hospital, Noichi-chuou Hospital, and Kochi Medical School Hospital) participating in the DOCTER study. The end point was to evaluate cardiovascular events and to assess the changes in clinical responses including plasma brain natriuretic peptide (BNP) levels from the baseline to 6

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months. The treating physicians in each patient made clinical decision such as administering or discontinuing donepezil, changing the doses of donepezil, or adding or deleting other medications. Informed consent was obtained from all patients and their families in accordance with the guidelines of the Ethics Committee on Medical Research of Kochi Medical School.

Clinical Evaluation

Evaluation of the patients included medical history, clinical examination, 12-lead electrocardiography (ECG), and laboratory data. Peripheral blood samples were collected at the time of clinical evaluation. Plasma BNP concentrations, which is a useful CHF biomarker, were measured by enzyme immunoassay (Doujin Hospital, Noichi-chuou Hospital, and Kochi Medical School Hospital) (TOSOH, Tokyo, Japan) or chemiluminescent enzyme immunoassay (Inan hospital) (Shionogi, Osaka, Japan). Each patient was evaluated before donepezil administration as baseline and after 1 month, 3 months, and 6 months of donepezil treatment. Donepezil doses were 3 or 5 or 10 mg per day. For analysis of changes in plasma BNP levels, we excluded 5 patients in whom cardiovascular medications were changed during follow-up as follows: 1 patient with an added diuretic, 1 with an added angiotensin II receptor blocker, 1 with an added calcium antagonist, 1 with a discontinued angiotensin-converting enzyme inhibitor, and 1 with a discontinued angiotensin II receptor blocker.

For prospective survival and cardiovascular morbid events, 4 modes of death were defined as follows: (1) sudden and unexpected death, in which collapse occurred in the absence of or <1 hour from the onset of symptoms in patients who previously experienced a relatively stable or uneventful clinical course, (2) heart failure–related death, which was in the context of progressive cardiac decompensation, (3) stroke-related death, which occurred as a result of probable or proven embolic stroke, and (4) noncardiovascular death. Cardiovascular morbid events included the following (1) hospitalization for heart failure, (2) stroke admission, and (3) hospitalization for arrhythmias. Data on survival and clinical status of patients were obtained during serial clinic visits or by direct communication with their physicians for patients who were followed up at other institutions.

Statistical Analyses

All data are expressed as means ± SD (range) or frequency (percentage). Differences in continuous variables were assessed by paired t tests. The Wilcoxon signed-rank test was used for analysis of BNP levels. Statistical significance was defined by $P \leq 0.05$. All statistical analyses were performed with JMP version 8.0.1 (SAS Institute Inc, Cary, NC).

RESULTS

Clinical Characteristics at Registration

Clinical characteristics of the 49 patients at registration are shown in Table 1. Patients were aged from 65 to 95 years (mean age: 80 ± 7 years) and 25 (51%) were men. In cognitive function, the means score on the Mini-Mental State Examination was 19.5 ± 5.0 points or 11.3 ± 4.9 points on the revised Hasegawa dementia scale. All patients were asymptomatic or mildly symptomatic (New York Heart Association functional class I or II) in terms of heart failure symptoms. Two patients (4%) had documentation of atrial fibrillation, 1 with paroxysmal atrial fibrillation defined as atrial fibrillation expected to convert to sinus rhythm within 7 days of onset and the other with chronic atrial fibrillation defined as persistent atrial fibrillation for more than 7 days after its onset. Three patients (6%) received a permanent pacemaker implantation (2 for complete atrioventricular block and one for sick sinus syndrome). Two patients had a history of heart failure admission, 1 with ischemic cardiomyopathy and the other with valvular heart disease. In ECG, mean heart rate was 67.4 ± 14.0 beats per minute, PQ interval was 175 ± 28 msec (3 patients having first-degree atrioventricular block), and corrected QT interval was 415.3 ± 26.5 msec. Five patients showed complete right bundle branch block (RBBB), and 1 patient had incomplete RBBB. In the laboratory test, BNP ranged from 5.2 to 513.9 pg/mL (mean: 69.4 ± 89.4 pg/mL).

TABLE 1. Baseline Characteristics of the Study Population

	Patients (n = 49)
Age at registration, yrs	80.4 ± 7.0 (65–95)
M/F gender, n (%)	25/24 (51)/(49)
Cognitive function, MMSE or HDS-R	MMSE 19.5 ± 5.0 (7–29), HDS-R 11.3 ± 4.9 (2–18)
Body weight, kg	50.70 ± 9.40 (35.8–73.2)
Systolic blood pressure, mmHg	138.1 ± 20.9 (102–182)
Diastolic blood pressure, mmHg	74.3 ± 12.1 (45–102)
Pulse, beats/min	72.3 ± 9.8 (51–93)
Rhythm	
Sinus rhythm, n	44 (90)
Atrial fibrillation, n	2 (4)
Pacemaker, n	3 (6)
History of heart failure admission, n	2 (4)
ECG	
Heart rate, beats/min.	67.4 ± 14.0 (49–139)
PQ interval, msec	175.3 ± 27.9 (124–300)
QTc time, msec	415.3 ± 26.5 (367–501)
QRS time, msec	00.5 ± 22.8 (76–161)
Laboratoy data	
BNP, pg/mL	69.37 ± 89.41 (5.2–513.9)
Medications	
ACEI or ARB, n	10 (20)
Calcium antagonist, n	18 (37)
α blocker, n	3 (6)
Diuretics, n	4 (8)
Digitalis, n	1 (2)
Statin, n	11 (22)
Antiplatelet agent, n	15 (31)
Warfarin, n	2 (4)

Data are expressed as means ± SD (range) or frequency (percentage). M, male; F, female; MMSE, Mini-Mental State Examination; HDS-R, revised Hasegawa's dementia scale; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker.

Baseline medical treatment for cardiovascular conditions of the patients is also shown in Table 1.

Clinical Course and Cardiovascular Changes

Most patients were treated wtih 5 mg per day of donepezil at 1 month, 3 months, and 6 months (3 mg per day of donepezil at 1 month in 10 patients, 3 mg per day at 3 months in 4 patients, 3 mg per day at 6 months in 3 patients, 10 mg per day at 3 months in 2 patients, and 10 mg per day at 6 months in 3 patients). During the 6-month follow-up period, no patient died or suffered from cardiovascular events. Forty-one patients completed follow-up with donepezil treatment and treatment was discontinued in 8 patients during the 6-month period as follows: 6 patients were hospitalized due to progression of dementia or appetite loss and 2 patients moved to other institutes.

Table 2 shows clinical changes in parameters between baseline and the first evaluation after donepezil treatment. Body weight decreased but the change was not clinically important. The corrected QT interval was prolonged significantly initially after donepezil intake, though no patient had episodes of torsades de pointes. During the 6-month follow-up period, no patient had remarkable bradycardia. There were some patients who had changes in ECG findings: new appearance of complete RBBB in 1 patient, disappearance of complete RBBB in 1 patient, change from incomplete RBBB to complete RBBB in 1 patient, and paroxysmal atrial fibrillation with maintenance of sinus rhythm in 1 patient.

Plasma BNP levels as a clinical biomarker for CHF did not increase (Table 2). But BNP levels showed a wide individual range. Therefore, we examined plasma BNP levels in 2 groups into which the patients were divided at baseline according to the cut-off plasma BNP level of 60 pg/mL because a BNP value of about 60 pg/mL has been reported to indicate abnormal diastolic dysfunction.[13] Figure 1 shows changes in plasma BNP levels in each group between baseline and the first evaluation after administering donepezil. In the group with high BNP values at baseline, the BNP levels significantly decreased after administration of donepezil (Fig. 1A, n = 16). BNP levels had the tendency to be lower during follow-up after initial administering donepezil (Fig. 2A). On the other hand, plasma BNP values did not change in the group with plasma BNP levels <60 pg/mL at baseline (Figs. 1B, 2B, n = 29). Donepezil never introduced bradycardia and hypotension (Table 3).

TABLE 2. Clinical Changes in Parameters Between Baseline and the First Evaluation After Donepezil treatment

	Baseline	First Evaluation	*P*
Body Weight, kg, n = 43	50.98 ± 9.34	50.40 ± 9.60	0.025
Systolic blood pressure, mmHg, n = 47	138.1 ± 20.9	134.0 ± 24.	0.310
Diastolic blood pressure, mmHg, n = 47	74.3 ± 12.1	72.9 ± 15.6	0.567
Pulse, beats/min, n = 44	72.3 ± 9.8	74.8 ± 11.6	0.200
ECG			
Heart rate, beats/min, n = 43	65.5 ± 8.8	66.4 ± 10.6	0.579
PQ interval, msec, n = 42	174.6 ± 27.9	173.6 ± 31.5	0.738
QTc time, msec, n = 43	415.9 ± 25.9	421.2 ± 25.7	0.018
QRS time, msec, n = 43	101.1 ± 23.2	100.0 ± 23.1	0.545
Laboratoy data			
BNP, pg/mL, n = 45	59.62 ± 62.71	53.18 ± 42.34	0.262

Data are expressed as means ± SD.

DISCUSSION

In this prospective registry study, we did not observe adverse cardiovascular events in patients treated with the acetylcholinesterase inhibitor donepezil. Remarkably, patients with subclinical CHF exhibited a decrease in plasma BNP,

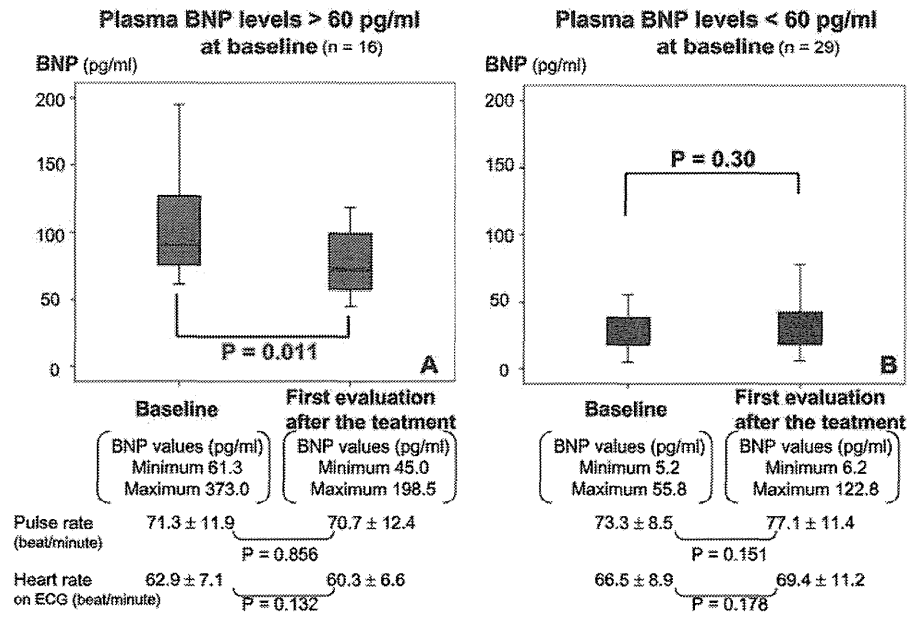

FIGURE 1. Changes in plasma BNP levels between baseline and the first evaluation after administering donepezil.

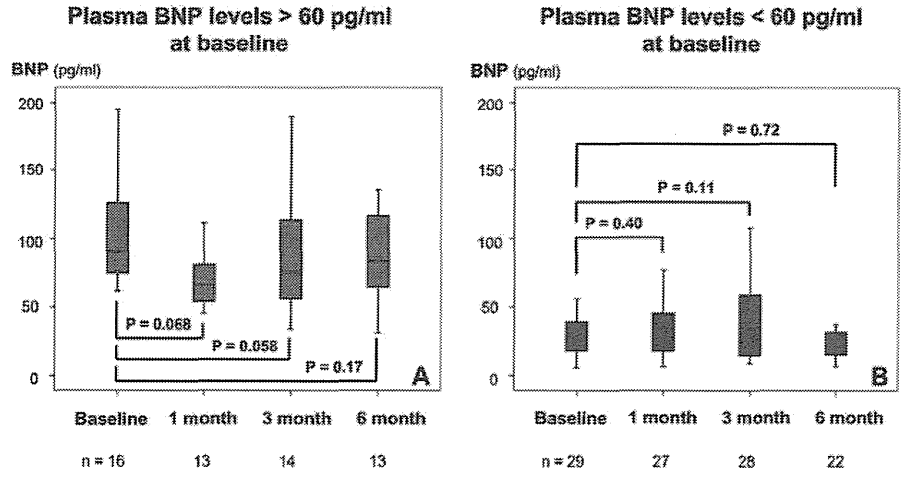

FIGURE 2. Serial changes in plasma BNP levels during the 6-month follow-up period.

which is an established risk marker for CHF deterioration, on donepezil treatment.

Donepezil is a centrally acting acetylcholinesterase inhibitor improving cognitive function in Alzheimer disease patients.[14] However, donepezil also increases acetylcholine availability in peripheral tissues. Donepezil treated patients often experience gastrointestinal adverse effects including loss of appetite, nausea, and vomiting. In addition, donepezil can cause bradycardia, sick sinus syndrome, or other arrhythmias including torsades de pointes resulting from QT prolongation through excessive cholinergic stimulation.[15–19] In our study, no patient experienced serious or life-threatening cardiovascular events including hospitalization for arrhythmias. Furthermore, the CHF biomarker plasma BNP did not increase on donepezil. Donepezil treatment was associated with reductions in plasma BNP levels in patients with baseline values >60 pg/mL, who were considered to have subclinical CHF.[13] Generally, plasma BNP values increase with aging in older adults. In our previous cohort study with community-dwelling elderly subjects, plasma BNP levels significantly increased over a 1-year period in both groups into which participants were divided according to plasma BNP levels of less than or greater than 60 pg/mL (Kahoku Longitudinal Aging Study, data available upon request). Therefore, the decrease in plasma BNP levels in our study is clinically significant from the viewpoint of therapeutic benefits for CHF. Indeed, Sato et al[12] reported results of a retrospective cohort investigation showing that overall survival and cardiovascular survival were significantly better in donepezil-treated patients in

TABLE 3. Serial Changes in Clinical Parameters During the 6-Month Follow-Up Period

	Baseline	1 Month	3 Months	6 Months
In the Group With Plasma BNP Levels >60 pg/mL at Baseline				
Body weight, kg	50.50 ± 8.00 (n = 17)	50.56 ± 7.64 (n = 14)	47.54 ± 7.97 (n = 12)	48.42 ± 8.76 (n = 10)
Systolic blood pressure, mmHg	145.6 ± 21.6 (n = 17)	143.6 ± 24.9 (n = 15)	140.6 ± 25.0 (n = 14)	135.5 ± 22.3 (n = 14)
Diastolic blood pressure, mmHg	74.3 ± 11.9 (n = 17)	76.2 ± 9.2 (n = 15)	72.1 ± 17.7 (n = 14)	71.6 ± 13.4 (n = 14)
Pulse, beats/min	71.3 ± 11.8 (n = 16)	70.9 ± 11.7 (n = 16)	68.2 ± 11.4 (n = 14)	69.7 ± 9.1 (n = 14)
ECG				
Heart rate, beats/min	68.4 ± 20.7 (n = 16)	61.2 ± 7.3 (n = 14)	61.6 ± 9.5 (n = 12)	61.4 ± 9.6 (n = 13)
PQ interval, msec	184.4 ± 18.4 (n = 14)	190.0 ± 25.8 (n = 14)	187.5 ± 24.8 (n = 12)	188.1 ± 24.6 (n = 13)
QTc time, msec	420.3 ± 24.6 (n = 16)	424.9 ± 25.9 (n = 14)	425.0 ± 41.5 (n = 12)	432.4 ± 46.3 (n = 12)
QRS time, msec	103.7 ± 25.5 (n = 16)	105.2 ± 26.8 (n = 14)	100.0 ± 24.0 (n = 12)	108.2 ± 34.0 (n = 13)
In the group with plasma BNP levels <60 pg/mL at baseline				
Body weight, kg	50.90 ± 10.30 (n = 28)	51.44 ± 10.30 (n = 24)	50.24 ± 11.45 (n = 24)	52.47 ± 12.06 (n = 18)
Systolic blood pressure, mmHg	133.8 ± 19.6 (n = 30)	130.5 ± 22.3 (n = 30)	134.0 ± 17.9 (n = 30)	132.6 ± 15.4 (n = 22)
Diastolic blood pressure, mmHg	74.3 ± 12.4 (n = 30)	72.5 ± 17.8 (n = 30)	72.6 ± 9.7 (n = 30)	72.5 ± 12.2 (n = 22)
Pulse, beats/min.	72.8 ± 8.7 (n = 28)	77.3 ± 11.6 (n = 26)	73.2 ± 9.5 (n = 29)	73.0 ± 8.4 (n = 21)
ECG				
Heart rate, beats/min	66.8 ± 8.7 (n = 29)	69.1 ± 11.7 (n = 26)	65.9 ± 9.6 (n = 27)	65.3 ± 10.8 (n = 22)
PQ interval, msec	170.9 ± 30.8 (n = 29)	167.0 ± 34.0 (n = 26)	168.3 ± 30.6 (n = 27)	175.9 ± 29.8 (n = 22)
QTc time, msec	412.5 ± 27.6 (n = 29)	418.2 ± 26.9 (n = 26)*	419.7 ± 24.1 (n = 27)*	424.0 ± 31.5 (n = 22)
QRS time, msec	98.8 ± 21.4 (n = 29)	97.5 ± 22.0 (n = 26)	99.4 ± 23.1 (n = 27)	102.5 ± 24.9 (n = 22)

Data are expressed as means ± SD (number of the patients).
All follow-up data except *QTc time are not statistically changed compared with baseline data.
*$P < 0.05$ versus QTc time at baseline.

the first 3–4 years of follow-up than in untreated patients matched for age, sex, and race to serve as a control group.[12] This agent may be beneficial for pathopysiology of CHF.

Although the mechanisms of donepezil's beneficial effects on CHF have not been clarified, the effect of vagal enhancement through administration of donepezil is possible. There have been several experimental studies showing that vagal nerve stimulation has cardioprotective effects in part through activation of hypoxia-inducible factor-1 alpha, preservation of phosphorylated connexin 43 protein, and reducing levels of thrombomodulin and beta-thromboglobulin.[8,9,20] It is well known that a large dosage of donepezil has a bradycardiac effect on the vagally innervated heart and that bradycardia itself is beneficial for CHF patients. However, in the present study, pulse rate and heart rate on ECG did not change significantly between baseline and the first evaluation in the 2 groups with plasma BNP values less than and greater than 60 pg/mL (Fig. 1). We reported cardioprotective effects of vagal nerve stimulation through activation of phosphatidylinositol-3 kinase and Akt and preservation of the mitochondrial transmembrane potential, independent of a heart rate-slowing mechanism.[9] In the present study, we do not get the impression that cardioprotective effect of donepezil is dose dependent among 3 mg to 10 mg per day although the number of patients in each group (different doses of donnepezil) was so small. Donepezil would also have a cardioprotective effect through a different mechanism from its heart rate-slowing effect.

The present study has several limitations that we need to pay attention to. First, the study cohort was small in size. Second, the number of patients with apparent cardiac disorders was small. Third, we were not able to evaluate CHF status by echocardiography. Given the limitations of our study, possible beneficial effects on CHF should not be overinterpreted. However, our results and data from the previous studies suggest that donepezil has therapeutic benefits for CHF. In this study, we have obtained the clinical relevance to go to the next stage performing a prospective study with using noninvasive assessment including echocardiography, Holter ECG, and biomakers to verify the beneficial effects of donepezil in CHF patients.

CONCLUSIONS

Usual doses of donepezil seemed to be safe in patients with dementia without symptomatic heart disease and significantly decreased plasma BNP levels in patients with subclinical CHF (BNP $>$ 60 pg/mL).

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Original Research Article

Long-Term Safety and Efficacy of Donepezil in Patients with Dementia with Lewy Bodies: Results from a 52-Week, Open-Label, Multicenter Extension Study

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Key Words
Cholinesterase inhibitors · Cognitive fluctuations · Dementia with Lewy bodies · Donepezil

Abstract
Background/Aims: To investigate the safety and efficacy of long-term administration (52 weeks) of donepezil in patients with dementia with Lewy bodies (DLB). ***Methods:*** This was a 52-week, multicenter, open-label extension study. Up to 8 weeks after the completion of the preceding randomized, placebo-controlled trial (RCT), patients started treatment with 3 mg of donepezil daily for 2 weeks, followed by 5 mg daily for the remaining 50 weeks. Cognitive function, behavioral and psychiatric symptoms, cognitive fluctuations, and caregiver burden were assessed using the Mini-Mental State Examination, Neuropsychiatric Inventory, Cognitive Fluctuation Inventory, and the Zarit Caregiver Burden Interview, respectively. Safety parameters were monitored throughout. ***Results:*** In total, 108 patients were enrolled in the study. Cognitive function and dementia-related behavioral symptoms, including cognitive fluctuations, were improved after the start of donepezil treatment, and improvement was maintained for 52 weeks. Reduction in caregiver burden observed in the preceding RCT returned to the baseline level at 52 weeks. There was no significant imbalance in the incidence of adverse events (AEs) by onset time, and delayed AE onset induced by the long-term administration of donepezil was unlikely to appear. ***Conclusion:*** The long-term administration of donepezil at 5 mg/day was well tolerated in patients with DLB and is expected to exhibit lasting effects, improving impaired cognitive function and psychiatric symptoms up to 52 weeks.

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Introduction

Dementia with Lewy bodies (DLB) is a common form of dementia in the elderly, accounting for 10–15% of patients with dementia and constituting the second largest group after Alzheimer's disease (AD) [1]. The core clinical features of DLB include neuropsychiatric symptoms and parkinsonism, as well as cognitive impairment characterized by deficits in attention, executive function, and visual perception [2].

Compared with patients with AD, cholinergic neurotransmission is more defective in patients with DLB [3]. In addition, although cholinergic losses in DLB affect both brainstem and basal forebrain presynaptic nuclei, postsynaptic cortical muscarinic and nicotinic receptors are functionally more intact [4]. For these reasons, it is suggested that cholinesterase inhibitors (ChEIs) may be effective for treating DLB. In fact, usefulness of ChEIs such as galantamine, rivastigmine, and donepezil in the treatment of DLB symptoms has been reported in several open-label studies [5–9] and two randomized controlled trials [10, 11]. Their usefulness has also been reported in several clinical trials of Parkinson's disease dementia, which is considered to fall into same category as DLB [12, 13]. Recently, we reported in a 12-week, randomized, placebo-controlled trial (RCT) that donepezil at 5 and 10 mg/day produces significant cognitive, behavioral, and global improvements in DLB patients, with a relatively low discontinuation rate due to adverse events (AEs) [11].

Due to the progressive nature of DLB, it is clear that long-term treatment is essential; however, evidence of the long-term safety and efficacy of ChEIs has not been well established, as there is only one report assessing the long-term use of rivastigmine [8]. Also, worsening of parkinsonism and cardiac dysrhythmia are major concerns in the use of ChEIs. Patients with DLB may be more susceptible to bradyarrhythmic side effects due to the autonomic insufficiency associated with the disease [14]. Therefore, the benefits of long-term treatment with ChEIs in those patients remain an important clinical question.

Based on our findings from the preceding RCT, which suggested short-term benefits of treating DLB patients with donepezil, we designed an open-label extension study to investigate the safety and efficacy of long-term administration (52 weeks) of donepezil at 5 mg/day in patients with DLB who had completed the preceding RCT.

This study was registered as No. NCT00598650.

Patients and Methods

Patients

Patients who satisfied the consensus diagnostic criteria for probable DLB [2] and who had completed the preceding phase 2, 12-week, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of donepezil [11] were subsequently recruited for this 52-week extension study. The study was conducted in 48 psychiatric and neurological specialty centers throughout Japan between February 2008 and March 2011.

Key inclusion and exclusion criteria for this extension study were the same as for the preceding RCT, and were described in detail in that study [11]. Briefly, patients diagnosed with probable DLB with mild to moderate-severe dementia and behavioral symptoms [10≤ Mini-Mental State Examination (MMSE) ≤26, Neuropsychiatric Inventory (NPI) ≥8 at baseline of the preceding RCT], aged ≥50 years, were asked to participate in the study. Patients with conditions which might affect their cognitive functions, including focal vascular lesions and other neurological or psychiatric diseases, were excluded from this study. Patients who had severe extrapyramidal disorders (Hoehn & Yahr staging ≥IV), systolic blood pressure of <90 mm Hg, pulse rate of <50 b.p.m., or QT interval prolongation (QTc ≥450 ms) were also excluded. In order to collect reliable information about the patient's condition from his or her caregiver, patients were also required to have a reliable caregiver who spent at least 4 h per day with them for at least 3 days per week.

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Study Design

This was a 52-week, multicenter, open-label extension study to assess the long-term safety and efficacy of daily administration of 5 mg of donepezil for the management of DLB. This study was a preplanned study, planned simultaneously with the preceding RCT. In the preceding RCT, patients were randomly assigned in a 1:1:1:1 ratio to receive a placebo or 3, 5, or 10 mg of donepezil. Up to 8 weeks after the completion of the RCT, eligible patients who agreed to participate started the treatment period of this extension study with 3-mg doses of donepezil for 2 weeks, which was then increased to 5 mg per day for the remaining 50 weeks. Dose adjustment to 3 mg was permitted only when continuation of treatment with 5-mg doses was judged to be difficult due to AEs, in which case the dose was maintained throughout the remaining treatment period. During the transition period between the two studies, administration of donepezil was not allowed. In order to maintain blinding of the preceding RCT, the treatment with donepezil in this extension study was started after the data of each patient from the RCT had been fixed. It was not until 3 months after the last patient was enrolled in this study that the key code of the RCT was broken.

Written informed consent was again obtained from all caregivers and patients (if capable) before the start of this extension study. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional review board of each participating center.

Outcome Measures

Cognitive function was assessed using the MMSE [15]. Behavioral and psychiatric symptoms of dementia and fluctuations in cognition were assessed using the NPI [16] and Cognitive Fluctuation Inventory (CFI), respectively. The CFI is a newly developed questionnaire to assess cognitive fluctuations in patients with dementia [6, 11]. It employs the same format as the NPI, so as to enable practical comparison with the other symptoms assessed by the NPI. Its content validity has been assured based on reviews by experts, and reliability (both inter- and intrarater reliability) was demonstrated to be sufficient as a measure of cognitive fluctuation [unpubl. data]. These measures were assessed at 0, 4, 8, 16, 24, 32, 40, and 52 weeks. We also assessed caregiver burden using the Zarit Caregiver Burden Interview (ZBI) [17] at 0, 24, and 52 weeks.

Safety

All AEs, including abnormalities in vital signs, electrocardiograms, and laboratory tests, were recorded during the entire study period. The causal relationship to donepezil, severity, and outcome of each AE was assessed by attending physicians. For the assessment of parkinsonism, the patients' motor functions were assayed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III [18].

Statistical Analyses

Safety analyses were performed on patients who received at least one dose of donepezil and who also provided safety assessment data after baseline. Of these patients, those with at least one available efficacy evaluation were included in efficacy analysis. Baseline demographic and clinical characteristics were summarized with descriptive statistics. For continuous variables, means and standard deviations were calculated. For categorical variables, the frequency of each category was calculated.

In this analysis, no formal primary endpoint was predefined due to the exploratory nature of this study. For safety, incidence rates of AEs were calculated by treatment period. The summary statistics of vital signs and UPDRS scores at each evaluation were also determined. For efficacy measures, mean change from baseline to each evaluation point was calculated. Mean change was also calculated by defining week 0 of the preceding RCT as baseline. These changes were calculated by treatment group in the preceding RCT. Values at the final evaluation were imputed using a last observation carried forward (LOCF) method. Statistical comparisons between baseline and each evaluation point were performed using paired t tests. All statistical tests were two tailed, and $p < 0.05$ was considered to indicate statistical significance.

Results

Baseline Characteristics

Out of 123 patients who had completed the RCT, 113 provided written informed consent to be screened. Of these, 108 patients who met the inclusion criteria were enrolled into the study performed at 40 sites. Two patients whose diagnosis was suspected not to meet clinical

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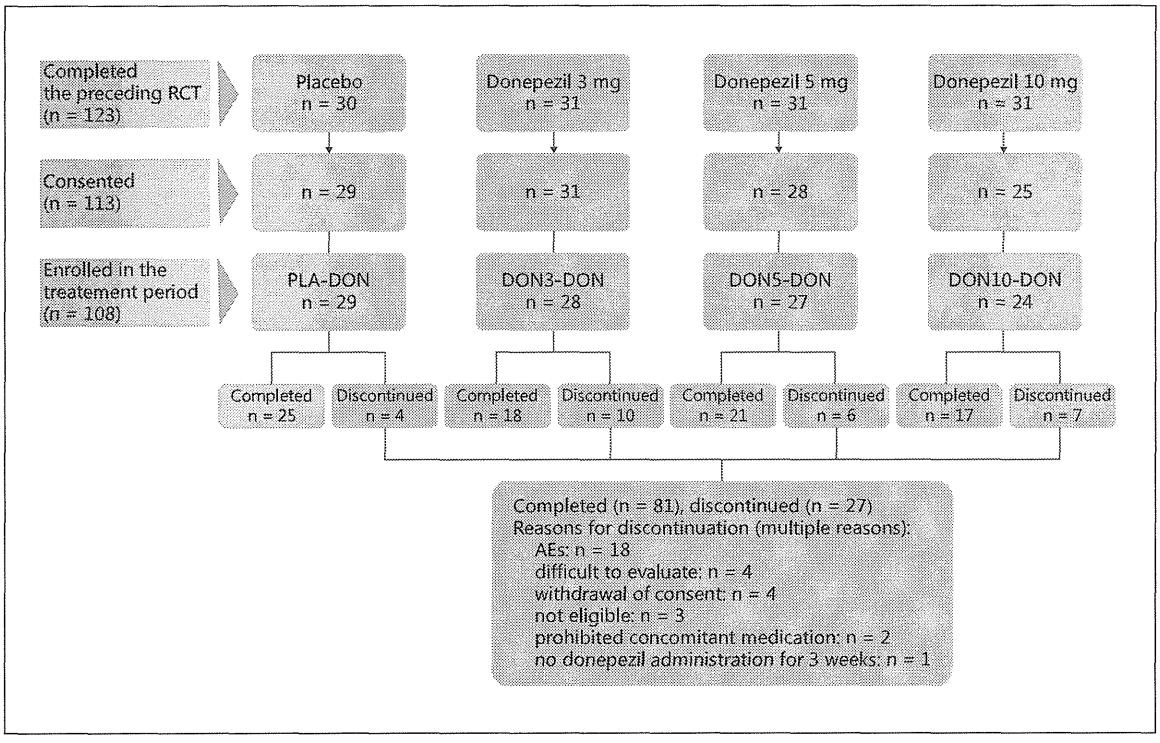

Fig. 1. Disposition of patients in the extension study.

criteria of probable DLB and another 2 patients with lack of efficacy data were excluded from the efficacy analysis population. The efficacy population (n = 104) consisted of 28 patients from the placebo group in the preceding RCT (referred as 'PLA-DON'), 27 patients from the donepezil 3-mg group (referred as 'DON3-DON'), 26 patients from the donepezil 5-mg group (referred as 'DON5-DON'), and 23 patients from the donepezil 10-mg group (referred as 'DON10-DON'; fig. 1). Baseline patient characteristics of the efficacy population are summarized in table 1. Mean scores of the MMSE, NPI-10, and the CFI at baseline were 20.9, 13.1, and 2.3, respectively.

The mean transition period from the final administration in the preceding study to the initiation of this extension study was 12.6 days (SD: 5.8, range: 6–28). Mean changes in MMSE, NPI, and CFI scores in the transition period by group are shown in table 2. Attenuation in the treatment effect was observed in most of the DON-DON groups. Nevertheless, the MMSE scores in the DON5-DON and DON10-DON groups were still more than 3 points higher compared with the PLA-DON group, even after washout prior to the start of the extension study (table 1). Compared to the PLA-DON group, a better NPI score was still observed in the DON5-DON group (approximately 5 points better) and the DON10-DON group (approx. 7 points better) after the washout period (table 1). Compared with patients with a shorter washout period, those with a longer washout period (2 weeks or longer) were more likely to show deterioration in these measures.

Of the 108 patients enrolled in the study, 90 patients (83.3%) completed 24 weeks (18 patients discontinued: 6 patients from 0 to 8 weeks, 6 patients from 8 to 16 weeks, and 6 patients from 16 to 24 weeks), and 81 patients (75%) completed 52 weeks. The overall discontinuation rate of this study was 25% (n = 27), and 18 patients discontinued treatment

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Table 1. Patient demographics and baseline characteristics of the efficacy population (n = 104)

	Overall (n = 104)	Treatment group in the preceding placebo-controlled study			
		PLA-DON (n = 28)	DON3-DON (n = 27)	DON5-DON (n = 26)	DON10-DON (n = 23)
Age, years	79.1±5.7	79.0±4.6	80.3±4.8	78.7±6.6	78.2±6.6
Sex, n (%)					
Male	37 (35.6)	9 (32.1)	14 (51.9)	13 (50.0)	1 (4.3)
Female	67 (64.4)	19 (67.9)	13 (48.1)	13 (50.0)	22 (95.7)
Weight, kg	48.7±9.2	48.0±8.3	50.4±10.2	50.6±8.8	45.5±9.1
Parkinsonism, n (%)					
Yes	90 (86.5)	25 (89.3)	23 (85.2)	23 (88.5)	19 (82.6)
No	14 (13.5)	3 (10.7)	4 (14.8)	3 (11.5)	4 (17.4)
Hoehn & Yahr, n (%)					
I	19 (21.1)	4 (16.0)	6 (26.1)	3 (13.0)	6 (31.6)
II	34 (37.8)	7 (28.0)	10 (43.5)	10 (43.5)	7 (36.8)
III	37 (41.1)	14 (56.0)	7 (30.4)	10 (43.5)	6 (31.6)
IV and V	0	0	0	0	0
MMSE	20.9±5.1	18.6±4.3	20.1±6.2	23.1±3.5	21.9±5.0
NPI	13.1±16.8	15.5±13.4	17.7±24.4	10.3±15.4	8.0±7.4
CFI	2.3±3.0	3.3±2.7	2.1±3.0	2.2±3.4	1.4±2.4
ZBI	24.7±15.7	26.9±14.6	26.6±18.1	23.6±16.4	21.1±13.3

Values are mean ± SD, unless otherwise specified.

Table 2. Mean change in MMSE, NPI, and CFI from the end of the preceding RCT to the start of this extension study by treatment group in the preceding RCT

Scores by treatment group	Overall		Washout period			
			<2 weeks		≥2 weeks	
	n	mean ± SD	n	mean ± SD	n	mean ± SD
MMSE						
PLA-DON	27	0.2±2.2	14	−0.1±2.0	13	0.5±2.5
DON3-DON	27	−0.9±3.0	12	−0.5±2.2	15	−1.2±3.5
DON5-DON	26	−0.8±2.7	12	0.4±2.4	14	−1.9±2.5
DON10-DON	22	0.1±2.7	14	0.7±2.7	8	−1.0±2.4
NPI						
PLA-DON	28	−0.3±5.1	14	−1.3±4.3	14	0.7±5.7
DON3-DON	27	1.9±8.4	12	−0.3±5.0	15	3.6±10.1
DON5-DON	26	3.7±12.5	12	8.3±15.7	14	−0.1±7.5
DON10-DON	21	0.3±4.8	14	−0.5±4.3	7	2.0±5.7
CFI						
PLA-DON	28	0.1±2.0	14	0.0±1.4	14	0.2±2.6
DON3-DON	27	−0.2±1.8	12	−1.1±1.5	15	0.5±1.8
DON5-DON	26	0.7±2.2	12	1.3±2.9	14	0.1±1.1
DON10-DON	21	−0.2±1.9	14	−0.4±2.2	7	0.0±1.3

The negative MMSE scores, the positive NPI scores, and the positive CFI scores indicate deterioration.

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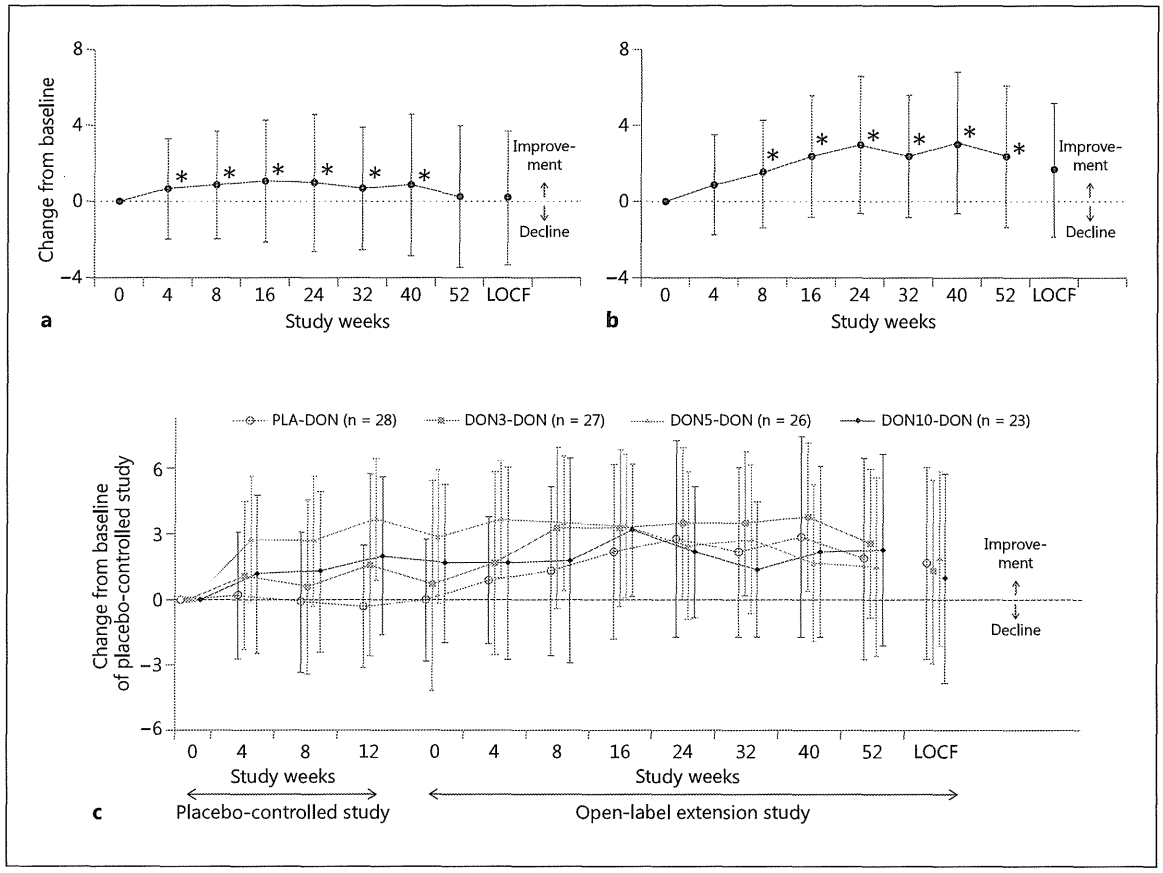

Fig. 2. Mean changes in MMSE scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period (n = 103). **b** Mean change in the placebo group of the preceding RCT (n = 27). **c** Mean cumulative changes by treatment group in the preceding RCT throughout both the preceding RCT and this extension study (no statistical test was performed).

due to AEs (fig. 1). Three patients underwent a dose reduction from 5 to 3 mg/day due to the occurrence of AEs. Of these, 2 patients completed the study with a dose of 3 mg/day without premature termination of the study, despite having an AE occur even after the dose reduction.

Efficacy

Mean scores in MMSE significantly improved at 4–40 weeks compared with baseline (fig. 2a). The mean (SD) changes at 52 weeks and at the final evaluation (LOCF) from baseline were 0.3 ± 3.7 and 0.2 ± 3.5, respectively, indicating that baseline values were maintained over 52 weeks. In the PLA-DON group (fig. 2b), the mean (SD) changes at 52 weeks and at the final evaluation (LOCF) from baseline were 2.0 ± 4.4 and 1.7 ± 4.4, respectively, and the largest change was observed at 40 weeks (3.0 ± 4.3). Significant improvement was demonstrated at all the evaluation points after 8 weeks. If the results are analyzed by defining week 0 of the previous RCT as baseline, although there was up to an 8-week washout period, MMSE scores in DON-DON groups improved throughout the RCT and the subsequent 52-week extension study (longer than 64 weeks in total; fig. 2c). On the other hand, in the PLA-DON group, improvement in MMSE scores was found only during the extension period.

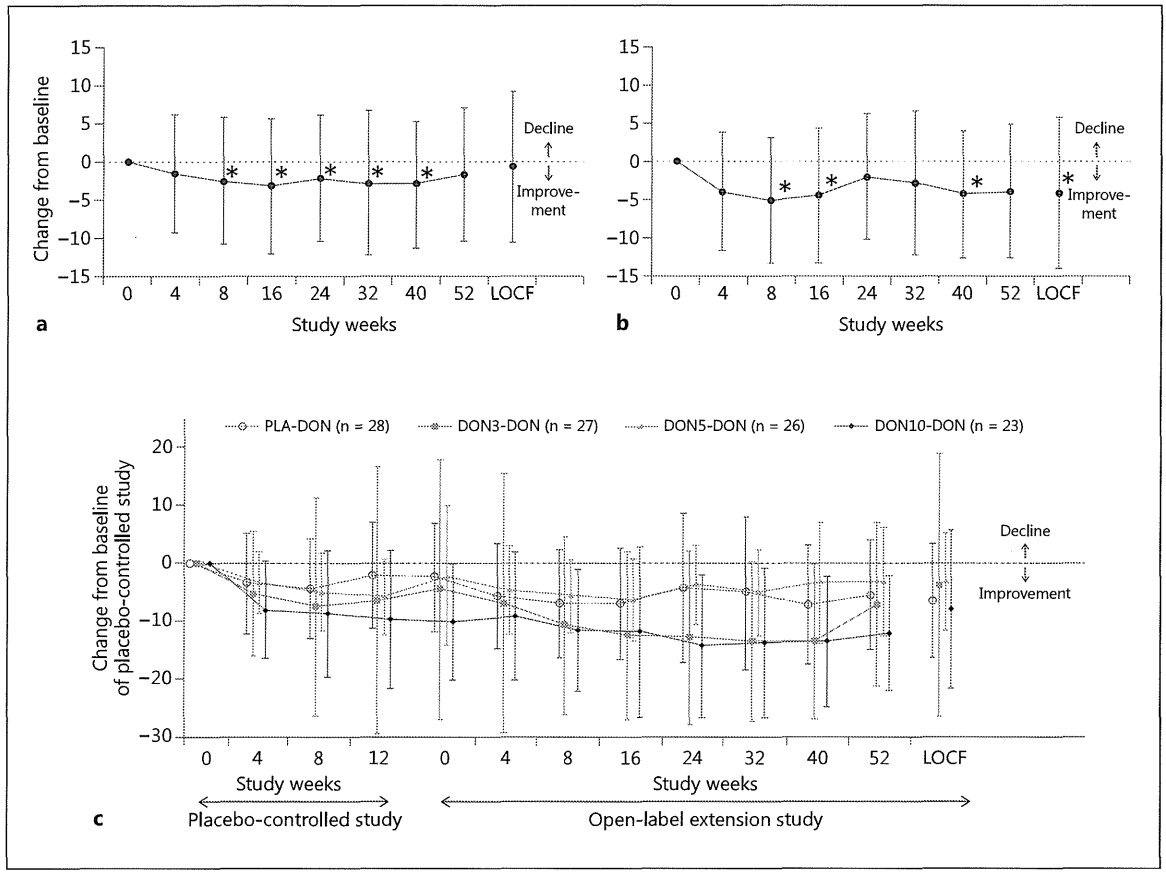

Fig. 3. Mean changes in NPI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period (n = 104). **b** Mean change in the placebo group in the preceding RCT (n = 28). **c** Mean cumulative changes by treatment group in the preceding RCT throughout both the preceding RCT and this extension study (no statistical test was performed).

Changes in NPI scores during the treatment period are shown in figure 3a. The mean (SD) changes at 52 weeks and at the final evaluation (LOCF) from baseline were −1.9 ± 9.8 and −0.7 ± 11.1, respectively. A significant improvement in the scores compared to baseline was observed at 8–40 weeks, and the largest change was observed at 16 weeks (−3.6 ± 9.9). In the PLA-DON group, significant improvement was demonstrated at 8, 16, and 40 weeks, and at the final evaluation point (LOCF; fig. 3b). The mean changes at 52 weeks and at the final evaluation point (LOCF) were −4.1 ± 10.1 and −4.3 ± 9.7, respectively. During the entire treatment period, combining both the preceding study and this extension study, improvement was maintained in all the DON-DON groups, even though there was up to an 8-week washout period (fig. 3c).

The changes in CFI scores during the treatment period are shown in figure 4a. Significant improvement compared to baseline was observed at 24 and 32 weeks, and this improvement was maintained throughout the treatment period. In the PLA-DON group, significant improvement was demonstrated at 8 and 16 weeks (fig. 4b). The mean (SD) changes at 52 weeks and at the final evaluation point (LOCF) were −1.0 ± 2.7 and −1.0 ± 2.6, respectively, and the largest change was observed at 8 weeks (−1.4 ± 1.8). If the results are analyzed by defining week 0 of the preceding RCT as baseline, CFI scores in all the DON-DON

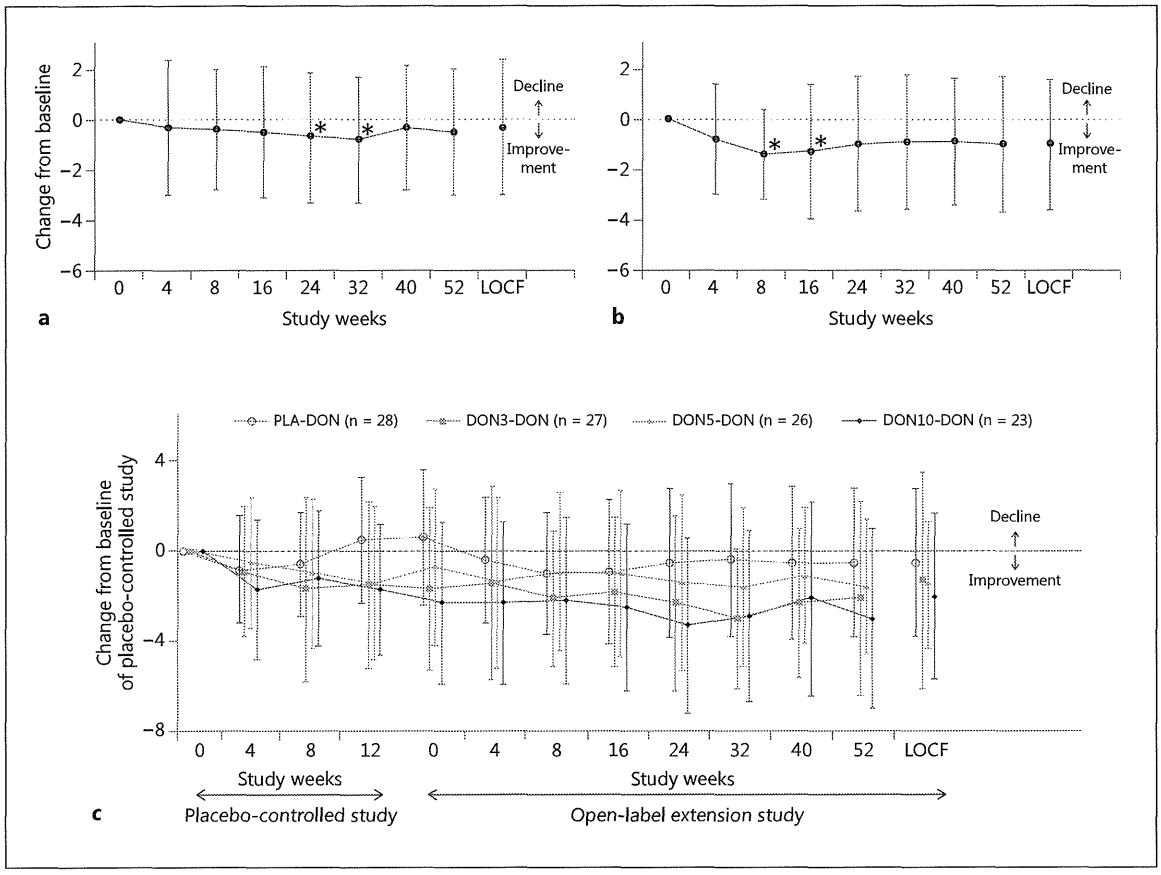

Fig. 4. Mean changes in CFI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period (n = 104). **b** Mean change in the placebo group in the preceding RCT (n = 28). **c** Mean cumulative changes by treatment group in the preceding RCT throughout both the preceding RCT and this extension study (no statistical test was performed).

groups improved throughout the RCT and the subsequent 52-week extension study (fig. 4c).

With regard to caregiver burden, a significant deterioration was demonstrated at 52 weeks and at the final evaluation point (LOCF) compared to baseline (fig. 5a). In the PLA-DON group, however, improvements in scores were observed during the treatment period, although they were not statistically significant (fig. 5b). In the DON-DON groups, ZBI scores were likely to be improved during the preceding RCT; however, this degree of improvement disappeared during the extension period (fig. 5c).

Safety

The incidence of AEs in the safety analysis set was 94.4% (102/108). Incidence rates of AEs did not differ among the four groups stratified according to the preceding RCT (89.7% in PLA-DON, 96.4% in DON3-DON, 92.6% in DON5-DON, and 100.0% in DON10-DON). Twenty-seven serious AEs were reported in 25 patients. Serious AEs observed in more than 1 patient included compression fractures (n = 3), pneumonia (n = 3), and dehydration (n = 2). Four events (myocardial infarction, subarachnoid hemorrhage, asphyxia, and acute pancreatitis) resulted in the deaths of 3 patients. Myocardial infarction and acute pancreatitis were deter-

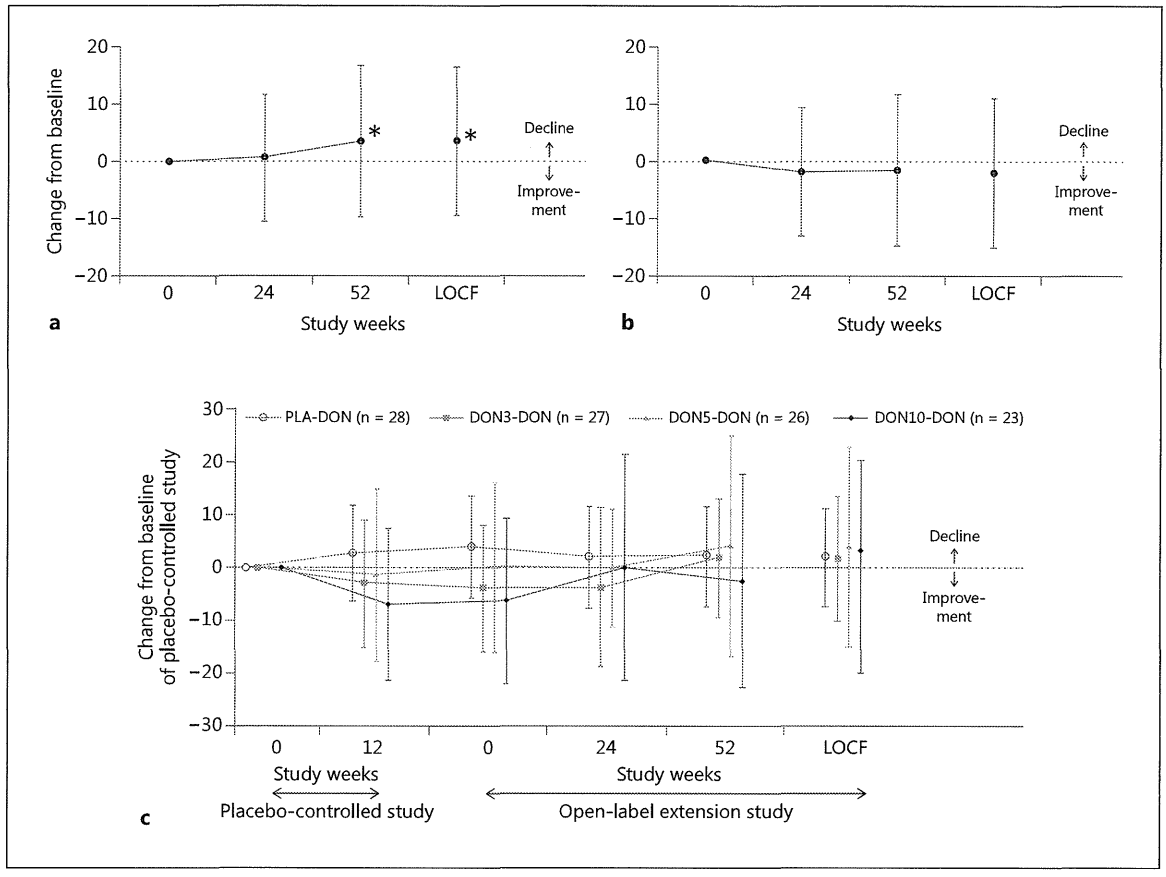

Fig. 5. Mean changes in ZBI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period (n = 103). **b** Mean change in the placebo group in the preceding RCT (n = 28). **c** Mean cumulative changes by treatment group in the preceding RCT throughout both the preceding RCT and this extension study (no statistical test was performed).

mined to be the results of adverse drug reactions. Major frequently observed AEs are shown in table 3. They included increased blood creatine phosphokinase and contusion (12 patients each, 11.1%), followed by nasopharyngitis, blood pressure increase, fall (11 patients each, 10.2%), and diarrhea (10 patients, 9.3%).

AEs associated with parkinsonism were reported in 12.0% (n = 13) of the patients throughout the study period. Most of them (12/13) were mild to moderate in severity. No notable increase in these AEs was observed according to the treatment period. A modest and insignificant rise in the mean UPDRS score (range: 0.5–1.1) was noted at 24 and 52 weeks, and at the final evaluation point (LOCF).

The incidence of abnormal changes in pulse rate and abnormal electrocardiograms was 1.9 (2 patients) and 7.5% (8 patients), respectively. The mean pulse rate decreased modestly at every evaluation point compared to baseline (range: −0.3 to −1.8). AEs related to them included prolonged QT (2 patients), supraventricular extrasystoles (2 patients), first-degree atrioventricular block (1 patient), bradycardia (1 patient), sinus bradycardia (1 patient), and ventricular extrasystoles (1 patient) on electrocardiogram. None of these events was serious or clinically significant (e.g., leading to discontinuation or dose reduction).