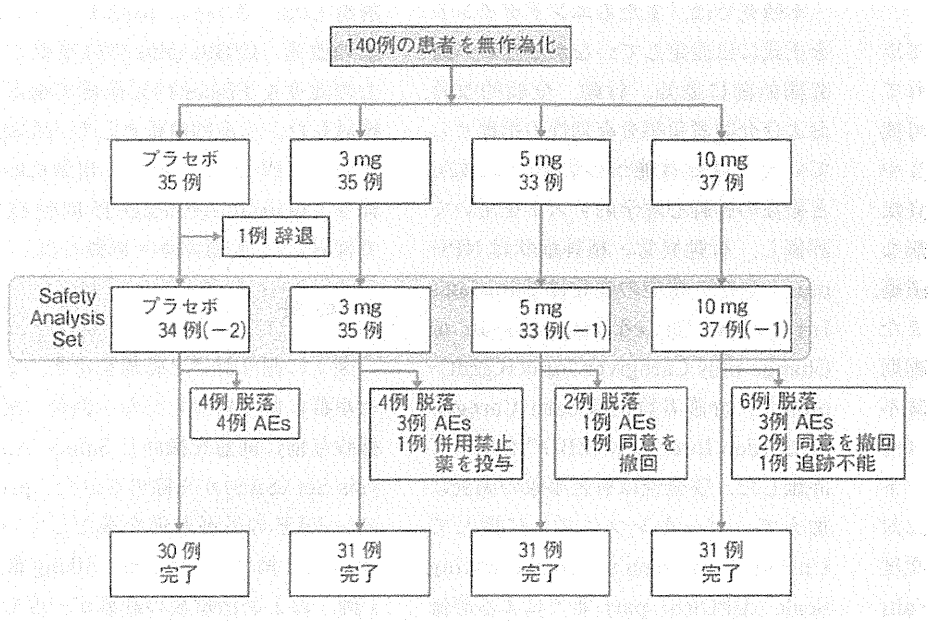

図1　患者の割り付けと転帰
AEs：有害事象

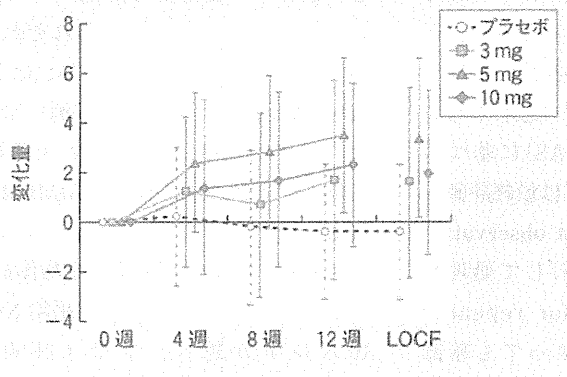

図2　MMSEの変化

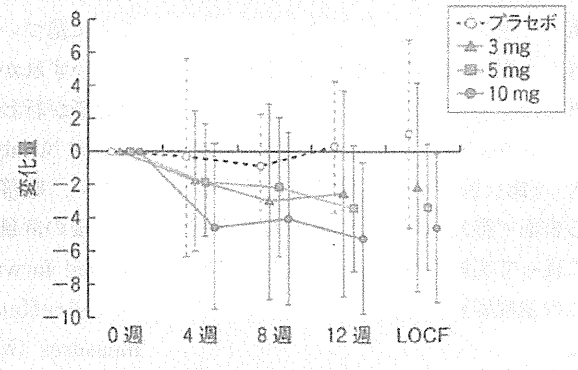

図3　NPI-10の変化

(それぞれ$p<0.001$)で良好であった(図2〜6)．3 mg/日群はCIBIC-plusで有意に良好($p<0.001$)だったが，MMSEでは有意ではなかった($p=0.017$)．5 mg/日群および10 mg/日群でNPI ($p<0.001$)，および10 mg/日群でZBI ($p=0.004$)に有意な改善が認められた．いずれの実薬群でもWechsler Memory Scale-Revised (WMS-R)の注意／集中とWechsler Adult Intelligence Scale-Ⅲ(WAIS-Ⅲ) symbol digitで有意な改善が示された．傾向性分析では，MMSEおよびCIBIC-plusに関して用量依存性は示されなかったが，NPI-2 (幻覚および認知機能の動揺)では有意な用量依存性が認められた．安全性はこれまでに知られているドネペジルの副作用と

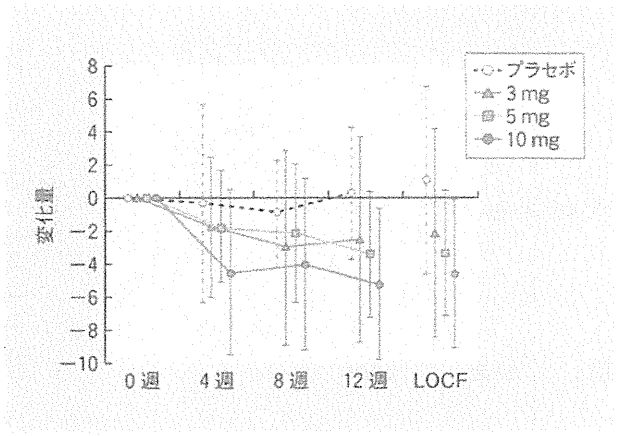

図 4　NPI-2(C)の変化

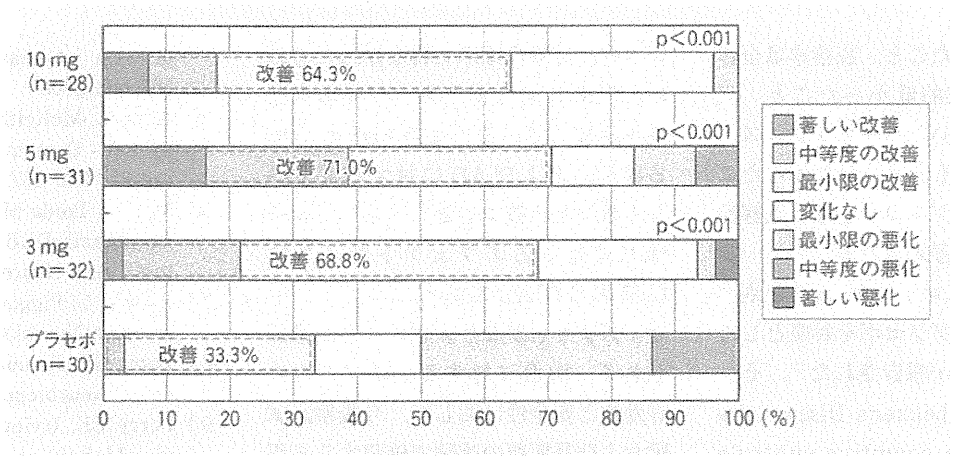

図 5　CIBIC-plus の分布

同程度であり，有害事象の頻度および重篤な有害事象の頻度は各群間で差がなかった．有害事象のために試験中止に至った例はプラセボ，3 mg，5 mg，10 mg 群で 11.8 %，8.6 %，3.0 %，8.1 %であった．パーキンソニズム関連の有害事象は，それぞれの群で 2.9 %，8.6 %，12.1 %および 2.7 %にみられたが，その差は有意ではなかった．その差異は有意水準に達しなかったが，むしろ平均 UPDRS part Ⅲのスコアはプラセボ群で悪化したのに対し，実薬群では幾分改善を示していた(図 7)．

DLB 治療薬としてのドネペジル

ドネペジル 5 および 10 mg/日は，少なくとも 12 週の間，DLB 患者の認知面，行動面，および全般的に改善をもたらし，10 mg/日では介護者の負担を軽減することが示された．本臨床試験は，エンドポイントを正式には設定していない探索的なものであったものの，幅広いドメインの複数の評価尺度に一貫した改善を示したことから，これらの結果は DLB 患者に対するドネペジルの有効性を強く示唆している．また，有害事象はプラセボ群と各実薬

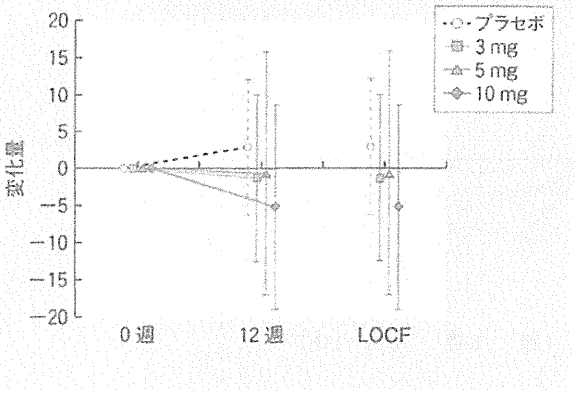

図6　ZBIの変化

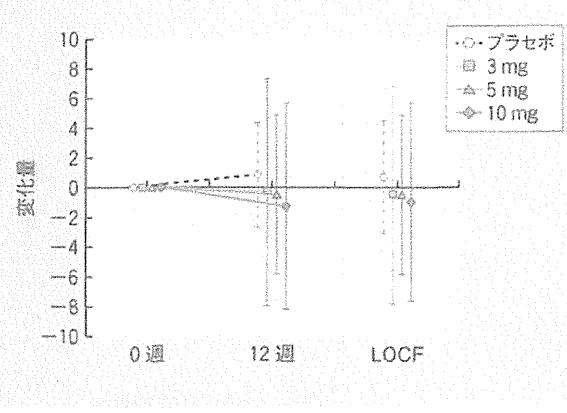

図7　UPDRS part Ⅲの変化

群に差がなかったこと，脱落率は全体で約8％と比較的低かったこと，理論上危惧されていたパーキンソニズムに対する悪影響も認められなかったことから，ドネペジルの安全性と忍容性は良好であると考えられる．

最近，PDDに対する24週のドネペジルの大規模なプラセボを対照とした臨床試験の結果が報告された[21]．それによれば，Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)に関して，ITT分析ではドネペジルの優位性が示されなかったが，治療群－国の交互作用の影響を除去すれば優位性が示され，CIBIC-plusはプラセボ群に比し10 mgは有意に良好であり，副次エンドポイントのMMSEやその他の認知機能検査でも，ドネペジル5 mgおよび10 mg群はプラセボ群に比し有意に良好であり，有害事象はドネペジル群で有意に多かったが，ほとんどは軽微なものだったという．この試験は主要エンドポイントで，有効性は示し得なかったものの，PDDに対してドネペジルの有用性を示唆している．このPDDに対する試験，およびADに対するドネペジル試験と比較すると，ドネペジルのDLBに対するエフェクトサイズは，PDDおよびADに対するエフェクトサイズよりもかなり大きいことが推測される．DLBに対するドネペジルの有効性と安全性に関して，今後検証試験および長期間の試験で確認する必要があるが，現時点でドネペジルは，DLBの認知障害と精神症状の両方に対する治療の第一選択薬と考えられる．

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saori iuchi

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送信日時: 2014年1月10日金曜日 11:00
宛先: 'saori iuchi'
ＣＣ: 'Hiroaki Kazui'
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To: 'Hiroaki Kazui'
Subject: RE: 治験の残金

数井先生

今年の３月末までです。

居内

From: Hiroaki Kazui [mailto:kazui@psy.med.osaka-u.ac.jp]
Sent: Friday, January 10, 2014 10:49 AM
To: 'saori iuchi'
Subject: RE: 治験の残金

居内さんへ

締め切りはいつでしたでしょうか。

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From: saori iuchi [mailto:iuchi@psy.med.osaka-u.ac.jp]
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Subject: 治験の残金

数井先生

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居内 沙織

Dementia
and Geriatric
Cognitive Disorders

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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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Mamoru Hashimoto[a] Noriyuki Matsukawa[f] Kazutaka Matsuo[e]
Masaki Nakagawa[e] on behalf of the Donepezil-DLB Study Investigators

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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.

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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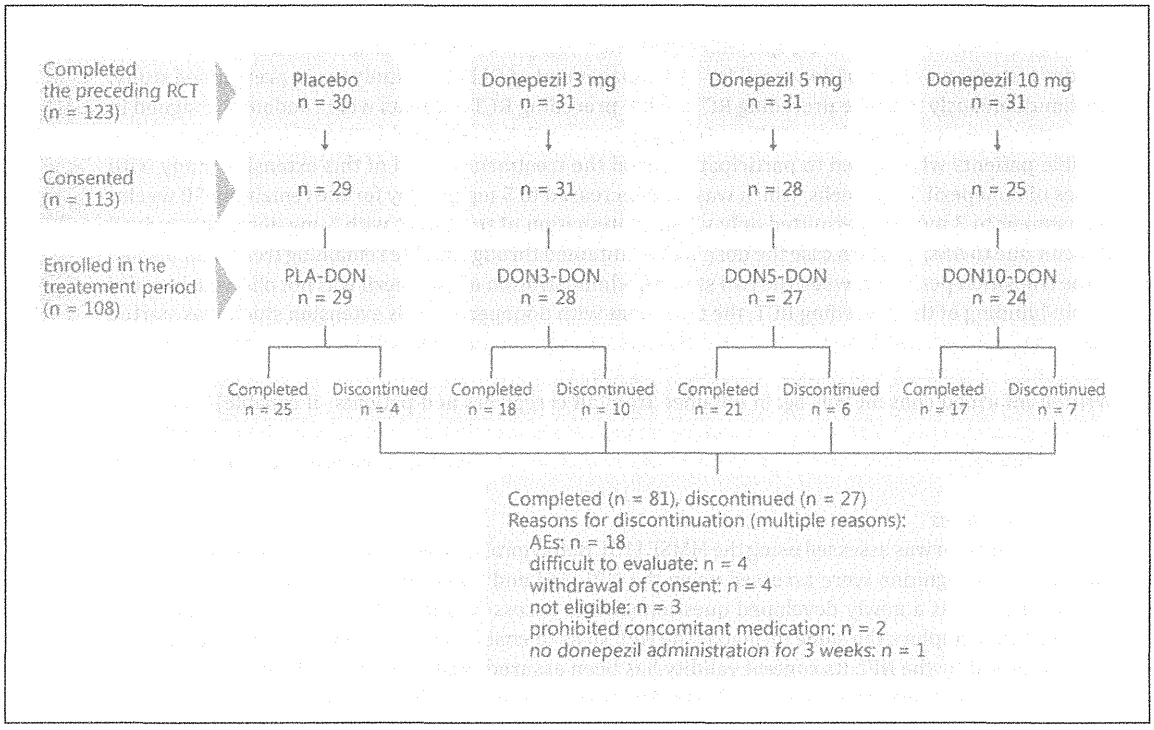

Fig. 1. Disposition of patients in the extension study.

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

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.

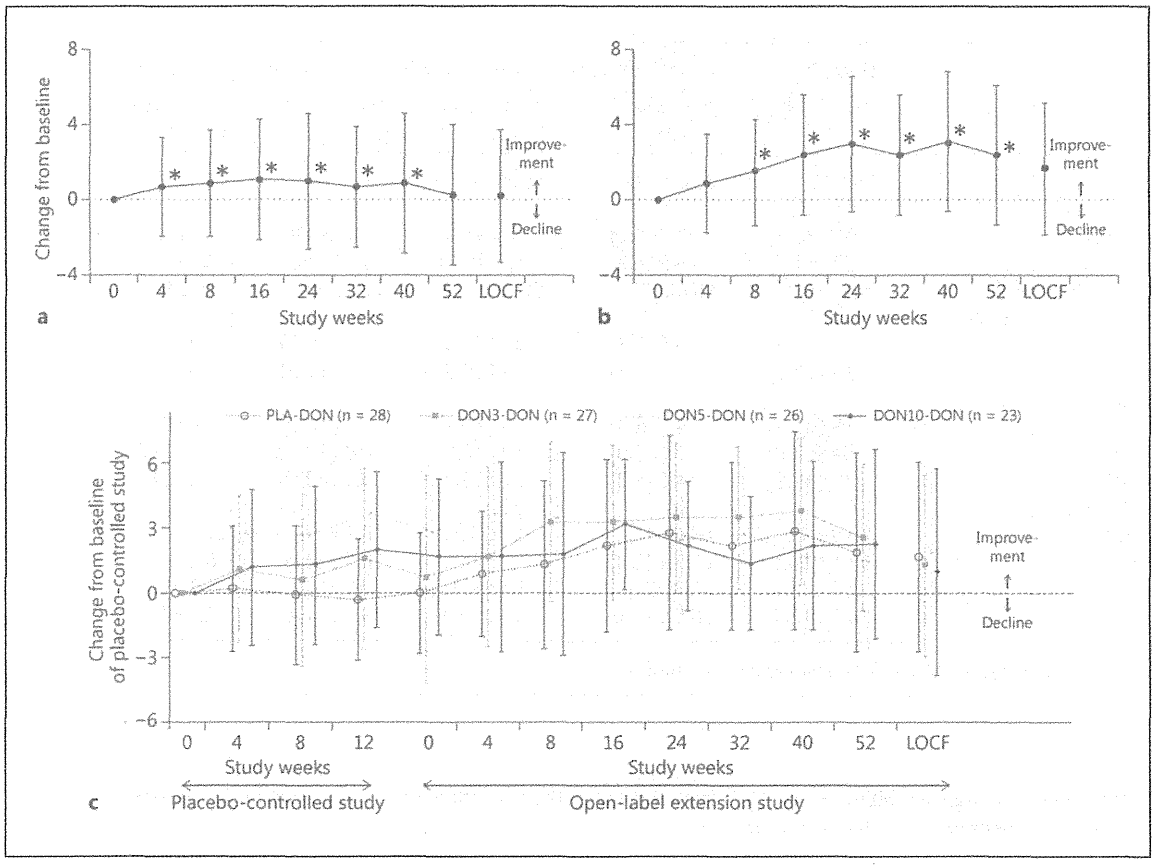

Fig. 2. Mean changes in MMSE scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period (n = 103). **b** Mean change in the placebo group of the preceding RCT (n = 27). **c** Mean cumulative changes by treatment 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.

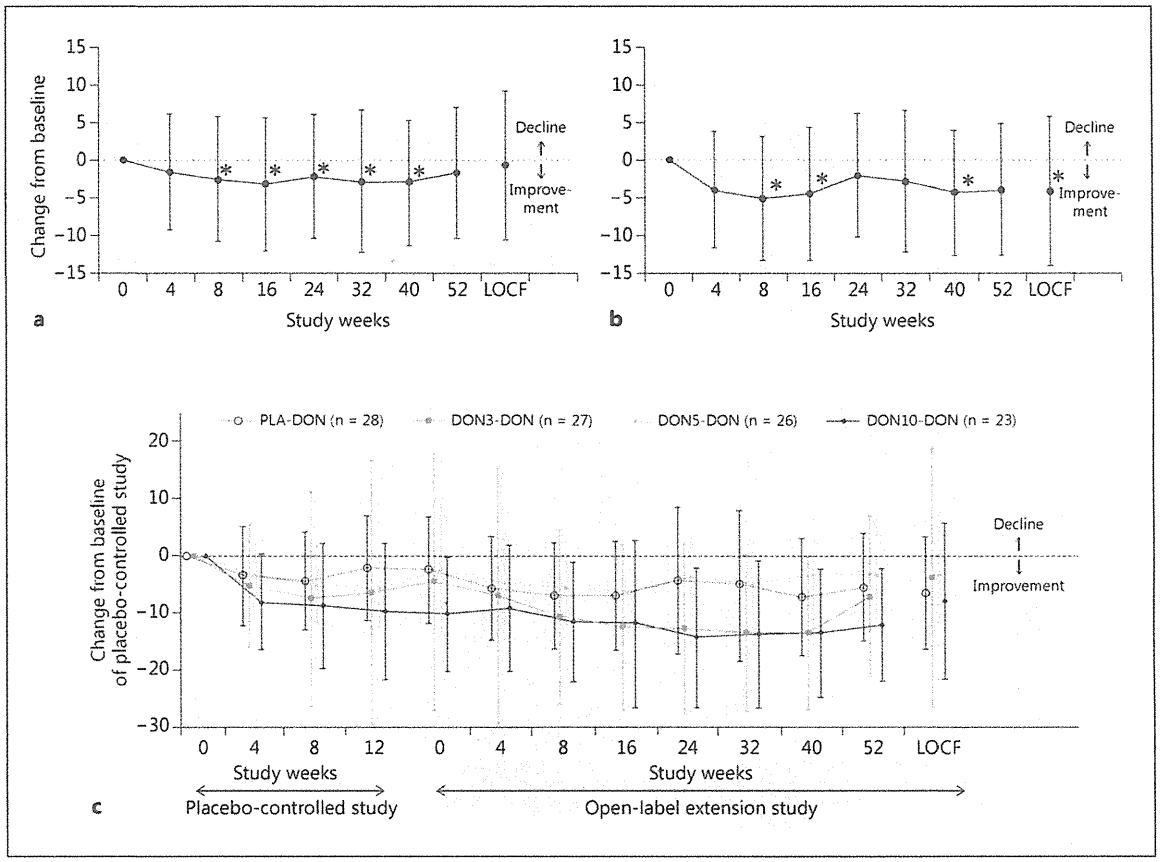

Fig. 3. Mean changes in NPI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period (n = 104). **b** Mean change in the placebo group in the preceding RCT (n = 28). **c** Mean cumulative changes by treatment 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

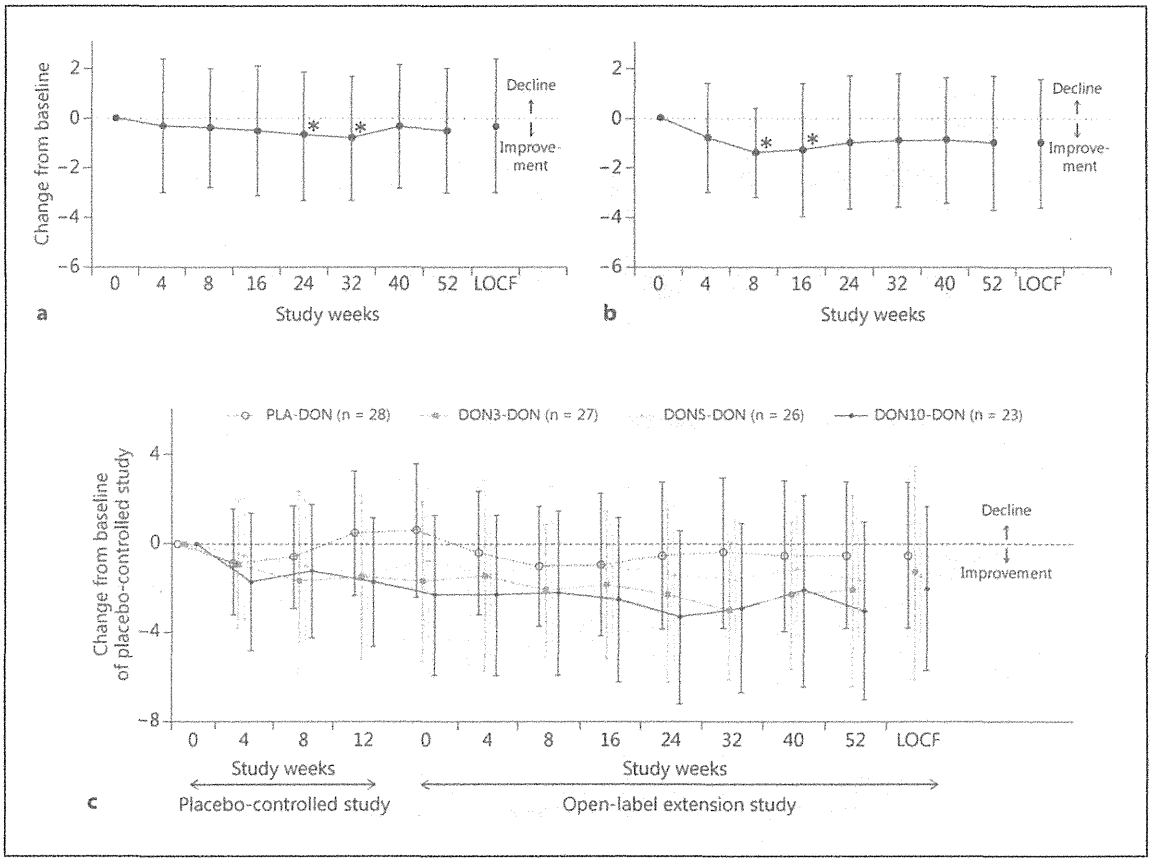

Fig. 4. Mean changes in CFI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period (n = 104). **b** Mean change in the placebo group in the preceding RCT (n = 28). **c** Mean cumulative changes by treatment 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-

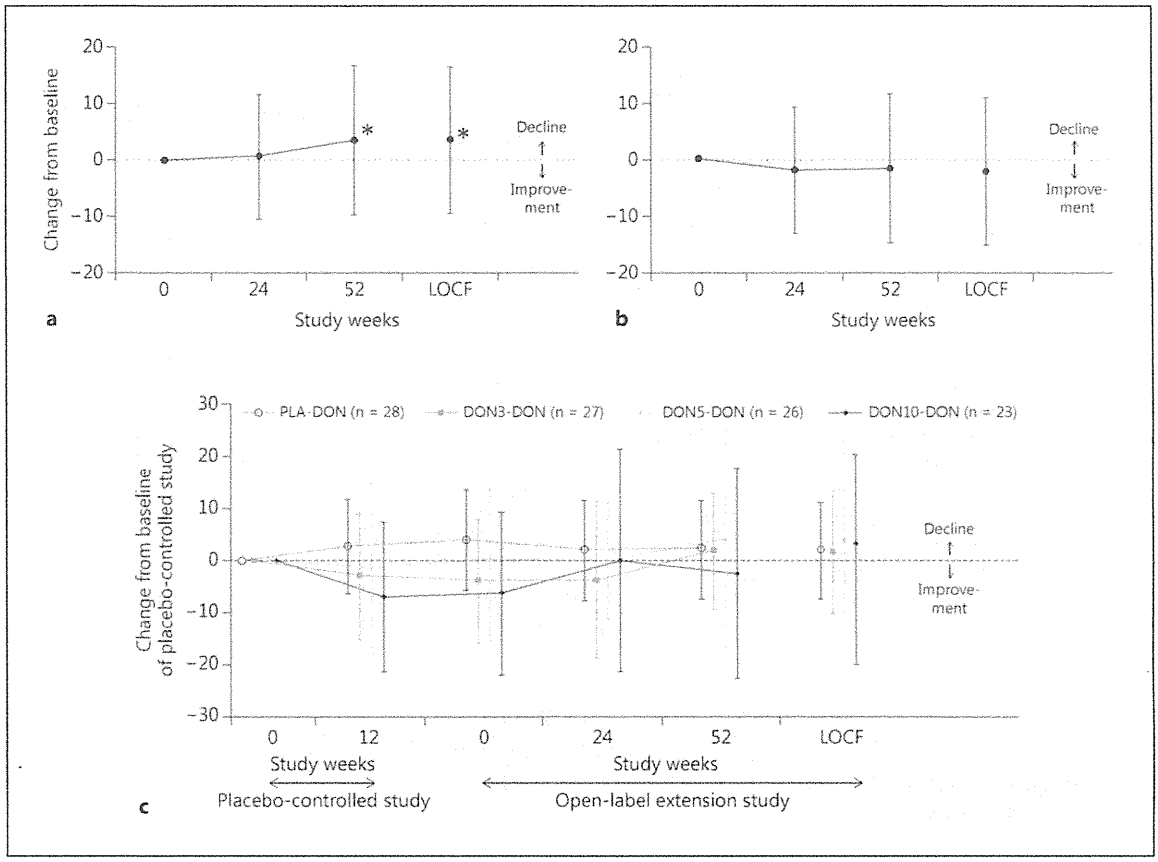

Fig. 5. Mean changes in ZBI scores. * $p < 0.05$ vs. baseline (paired t test). Vertical bars indicate standard deviations. **a** Overall mean change during the treatment period (n = 103). **b** Mean change in the placebo group in the preceding RCT (n = 28). **c** Mean cumulative changes by treatment 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).

Table 3. AEs [n (%)] reported by ≥5% of patients during the entire period (all causality)

	Overall (n = 108)	Time of onset		
		0–12 weeks (n = 108)	12–24 weeks (n = 98)	24–52 weeks (n = 90)
Blood CPK increase	12 (11.1)	8 (7.4)	3 (3.1)	3 (3.3)
Contusion	12 (11.1)	4 (3.7)	5 (5.1)	4 (4.4)
Nasopharyngitis	11 (10.2)	4 (3.7)	4 (4.1)	3 (3.3)
Blood pressure increase	11 (10.2)	8 (7.4)	3 (3.1)	1 (1.1)
Fall	11 (10.2)	5 (4.6)	1 (1.0)	7 (7.8)
Diarrhea	10 (9.3)	3 (2.8)	5 (5.1)	3 (3.3)
Constipation	8 (7.4)	2 (1.9)	4 (4.1)	2 (2.2)
Parkinsonism	8 (7.4)	1 (0.9)	2 (2.0)	6 (6.7)
Blood urine present	7 (6.5)	2 (1.9)	3 (3.1)	3 (3.3)
Protein urine present	7 (6.5)	2 (1.9)	2 (2.0)	4 (4.4)
Decreased appetite	6 (5.6)	1 (0.9)	1 (1.0)	4 (4.4)
Insomnia	6 (5.6)	2 (1.9)	1 (1.0)	3 (3.3)
Compression fracture	6 (5.6)	2 (1.9)	0	4 (4.4)

CPK = Creatine phosphokinase.

AEs associated with gastrointestinal symptoms were reported in 34 patients (31.5%). Diarrhea (10 patients, 9.3%), constipation (8 patients, 7.4%), and decreased appetite (6 patients, 5.6%) were observed relatively frequently.

AEs associated with psychiatric symptoms were noted in 25 patients (23.1%). Six patients (5.6%) experienced insomnia. Visual hallucinations and psychiatric symptoms were recorded as AEs in 5 patients (4.6%), respectively. Incidence rates by onset time did not reveal any notable imbalance.

Discussion

This is the first study to examine long-term safety and efficacy of donepezil in patients with DLB. Overall, 108 patients with DLB who had completed the 12-week, double-blind, comparative RCT subsequently participated in this extension study. The results presented here demonstrate that cognitive function and dementia-related behavioral symptoms, including cognitive fluctuations, were improved after the start of donepezil treatment, and maintained for 52 weeks, or up to 64 weeks if the preceding treatment period is included. Our findings suggest that treatment efficacy of donepezil for these symptoms may be maintained even after the treatment in patients who were followed in this extension study, since no linear decrease in evaluation scores was observed. In accordance with our results, the study of long-term use of rivastigmine in DLB patients revealed that the reduction in MMSE scores was gradual and without statistical significance compared to baseline for 96 weeks [8]. Additionally, no significant worsening of NPI scores was demonstrated, although the decline in the scores seemed sharper after 72 weeks [8]. In contrast, when donepezil was administered to patients with AD for 52 weeks, it was reported that cognitive function, as assessed by the MMSE or Severe Impairment Battery [19], started to decline after 24 weeks [20, 21]. Progression of cognitive impairment in DLB and AD patients has been compared in several studies, but results differ from study to study. Olichney et al. [22] reported that there was a significant difference between DLB and AD groups in mean MMSE decline per year (–5.8 ± 4.5

for the DLB group and −4.1 ± 3.0 for the AD group). Ballard et al. [23] reported that more deterioration in the mean MMSE score per year was observed in an AD group (−4.9 ± 3.6) than a DLB group (−4.3 ± 4.2), although no statistical difference was shown. Furthermore, a similar cognitive decline between a DLB and an AD group was reported by Walker et al. [24]. The mean decline in the MMSE score per year was −3.1 ± 4.3 for the DLB group and −2.6 ± 4.0 for the AD group, with no statistically significant difference. These results indicate that cognitive decline in DLB may be faster than or at least similar to that in AD patients, and, in this respect, patients with DLB might be more likely to benefit from donepezil treatment compared to AD patients. With regard to burden on caregivers, no obvious improvement was shown in ZBI scores, while the treatment effect on cognitive functions, as well as neuropsychiatric symptoms, were improved or at least maintained. Accumulation of caregiving burden over time may prevent caregivers from realizing that a decrease in burden has occurred. However, it is noteworthy that burden on caregivers did not increase throughout the cumulative observational period in our two studies.

Unsurprisingly, a relationship between the washout period and attenuation in the treatment effect was suggested. Among patients who were assigned to the donepezil treatment groups in the preceding RCT, cognitive function and behavioral/psychiatric symptoms deteriorated more in patients with a longer washout period. This could indicate that the treatment effect might eventually diminish if donepezil administration was stopped for a long period of time.

Since there was no significant imbalance in the AE incidence analyzed by onset time, it is therefore suggested that delayed onset of AE induced by long-term donepezil administration is unlikely to appear in these patients. Patients with DLB may be at increased risk of bradyarrhythmia resulting from treatment with ChEIs though [14]. In this long-term study, however, only 2 patients experienced abnormal changes in pulse rate (1 bradycardia and 1 sinus bradycardia), and neither of these were serious. Also, long-term administration of donepezil is unlikely to worsen parkinsonian symptoms since UPDRS scores did not worsen over 52 weeks. Furthermore, only 3 patients received dose reductions to 3 mg/day due to AEs. Two of them completed this study with the reduced dose, thereby enabling the patients to continue treatment with donepezil by reducing the dosage to 3 mg/day. In comparison to a study of donepezil in patients with AD, AEs reported in this study were similar to those reported in the study of AD patients, except for parkinsonism [20].

The major limitation of this study is its open-label, single-arm design. Clearly, a blinded, comparative study is necessary to confirm our findings; however, due to the progressive nature of this disease, leading to acceleration of mortality, allocating patients to a placebo is not appropriate for long periods of time. Because improvement in MMSE scores and NPI scores after donepezil administration in the PLA-DON group showed a similar trend with the results presented in the preceding double-blind RCT, despite the open-label design used in this study, we believe that our results reliably indicate the efficacy of donepezil. It should also be noted that this study cannot determine which donepezil dose might contribute to a better outcome on a long-term basis. Since the preceding RCT suggested the benefit of the administration of a 10-mg dose in a particular group of patients, compared to 3 or 5 mg, further research would be helpful to assess the long-term benefits of administration of 10-mg doses.

In conclusion, the long-term administration of donepezil at 5 mg/day was safe in patients with DLB, and is expected to exhibit lasting effects on improving impaired cognitive function and psychiatric symptoms.

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K.K.: board membership, Dainippon Sumitomo, Eisai, Novartis, Tsumura; speaking fees, Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, Novartis, Nihonmediphysics, Ono, Pfizer, Tsumura; paid manuscript preparation, Tsumura.

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M.H.: speaking fees, Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen, Nihonmediphysics, Novartis, Pfizer.

N.M.: grants/grants pending, Daiichi Sankyo.

K.M., M.N.: employees of Eisai.

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意味性認知症と語義失語

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意味記憶の選択的障害

心理学において従来単一のシステムと見なされてきた記憶を，複数の異なるシステムに区分する考えを提唱したTulving[1]は，意識によって取り出すことが可能な記憶(宣言的記憶)を，個人の出来事や体験を記銘したり再現したりするエピソード記憶と，個人とは独立した知識，すなわち世界の記憶にあたる意味記憶に分類した(図1)．エピソード記憶は，時間的，空間的，情動的な脈絡をもつ個人的体験の記憶であり，その人の同一性や一貫性を保証する自己意識とよばれる高度の精神活動に関与する．一方の意味記憶は，個人の体験を超え時間的標識をもたない知識一般であり，特に言語使用に必要な言語記号の意味と指示対象，およびそれらの関係性について所有している知識である．こころの辞書ともいわれ，知的活動の基盤として働くと考えられる．

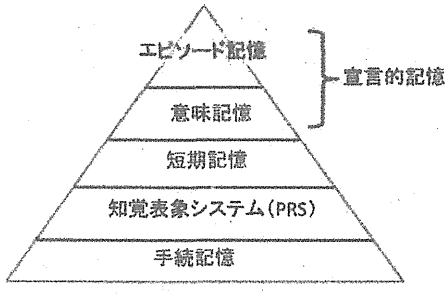

図1　ヒトの記憶の分類(Tulving[2]より一部改変)

記憶は複数の独立したシステムからなり，習熟した動作の習得にあたる手続記憶，体験した知覚がその後，同一，類似対象の同定を促進させるプライミングに代表される知覚表象システム(perceptual representation system：PRS)，入力された情報が数秒間保持される情報の記憶である短期(即時)記憶，個人の体験を超えた知識の獲得や保持の機能をもつ意味記憶，時間的空間的文脈をもつ個人的体験の意識的想起を可能にするエピソード記憶に分類される．下位の記憶は発達段階と対応し，上位のシステムはより下位のシステムに支えられる．エピソード記憶と意味記憶は多くの特性を共有し，宣言的記憶とよばれる．

ある認知システムの独立性を支持し，その神経基盤をさぐる上で重要な方法は，それぞれのシステムが独立して障害される疾患(選択的障害例)の存在である．すなわち，エピソード記憶の選択的障害例である純粋健忘例では個人の体験の記銘と想起は障害されるが，知識に関してはよく保たれ，意味記憶の選択的障害例では個人的体験は記銘も想起も可能であるが，知識として自明の存在であるはずの対象(モノや人)を正しく認知(再認)できないという二重乖離によってそれぞれの存在が明らかとなる．

Warrington(1975)[3]は，連合型視覚失認とよばれる，ありふれた視覚的対象物のもつ意味や重要性を視覚情報から認識する能力が著しく低下した3例について精査を行なった．これらの症例では，対象物の絵や単語を呼称したり照合したり再認する能力が著しく低下していたが，その能力低下を，知能，感覚情報の分析，あるいは言語表出の障害などから説明できないことより，意味記憶の選択的障害例であると結論づけた．

意味性認知症

1．側頭葉限局萎縮病にみられる選択的な進行性意味記憶障害

この後，前頭-側頭葉に局所的萎縮を呈する非アルツハイマー型認知症の概念化を進めていたLund(スウェーデン)とManchester(英国)の研究グループのうち，Manchesterのメンバーであるら(1989)[4]は，前頭-側頭葉に著明な萎縮を呈する変性疾患，とりわけ側頭葉前方部に左右差のある著明な萎縮を呈する3例に，意味記憶情報の欠落による言語や視覚認知における判断の障害が進行性かつ選択的に出現することを公表し，これを意味性認

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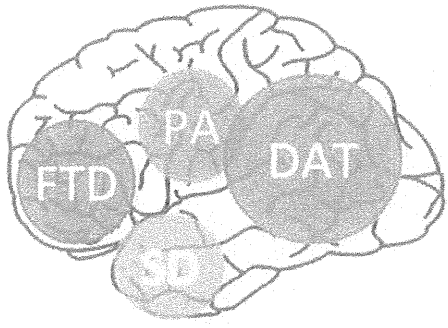

1）アルツハイマー型認知症(dementia of the Alzheimer type：DAT)
2）前頭側頭葉変性症(frontotemporal lobar degeneration：FTLD)
- 前頭側頭型認知症
  (frontotemporal dementia：FTD)
- 進行性非流暢性失語
  (progressive non-fluent aphasia：PA)
- 意味性認知症
  (semantic dementia：SD)

図 2　変性疾患による認知症の分類

変性疾患を代表する認知症のうち，前頭葉・側頭葉前方部に原発性の萎縮を呈する非アルツハイマー型認知症の包括概念である前頭側頭葉変性症(FTLD)は，主に前頭葉と側頭葉前方部に病変の首座をもち，特有の行動障害を呈する前頭側頭型認知症(FTD)，左半球の Sylvius 裂後枝周囲に病変を有する非流暢性の失語像を呈する進行性非流暢性失語(PA)，しばしば左右差を伴い側頭葉前方部に著明な萎縮を呈する意味性認知症(SD)に分類される[5]．

知症(semantic dementia：SD)と命名した．SD の登場により，Warrington の提唱した意味記憶の選択的障害例に，より明確な神経学的基盤と症候学的特徴が与えられた．

SD では，自伝的な記憶に加え，日々の出来事や約束に関する記憶が保たれているのに，語と相貌あるいは物品に関する判断が進行性に障害されてゆく．SD の発話は，自発話・復唱ともに流暢で，発声発語や統語的表出に何ら問題がないにもかかわらず，語の意味理解がきわめて重篤に障害されていた．初期のアルツハイマー型認知症(dementia of the Alzheimer type：DAT)では，側頭葉内側部の萎縮に伴う新しい出来事の記銘および想起の障害，すなわちエピソード記憶障害，さらには後方連合野の働きと考えられる視覚情報処理能力の低下が認められる．一見同様の成績低下があるようにみられる SD 例では，側頭葉前方部の著明な萎縮に伴う意味情報の崩壊により，語の意味理解障害を特徴とする超皮質性感覚失語と，見慣れたはずの目の前の対象物が何か判断できなくなる連合型視覚失認を呈することが明らかとなった．

また，これらの症例では，前頭葉を中心に脳の前方部が限局的に萎縮する前頭側頭型認知症(frontotemporal dementia：FTD)に通ずる，社会的場面における異常行動が早期から出現し，この点においても典型的な DAT と鑑別できる．したがって SD の臨床においては，原発性かつ進行性に障害される特定の認知機能(意味記憶)に注目する必要があるだけでなく，前頭側頭葉に限局性萎縮を呈する前頭側頭葉変性症(frontotemporal lobar degeneration：FTLD)[5](図 2)に共通して認められる行動障害にも注意を払う必要がある．

2．進行性流暢性失語像を呈する認知機能プロフィール

Hodges ら[6]は SD の臨床概念を確立させる目的で，進行性の意味記憶障害を特徴とする 5 例に対して詳細な神経心理学的評価を試み，その共通する認知機能プロフィールを示した．

これらの症例は，いずれも重篤な喚語困難(失名辞)と単語理解の障害，特定の意味カテゴリーから具体語を産生する能力の低下，一般的知識の貧困化を呈し，次第に言語の意味的構成要素の崩壊へと進んでいった．一方で，統語や音韻機能など言語の他の構成要素は，発話面でも理解面でも保たれるという流暢性の失語像を初発症状とした．さらにこの失語症状は，音読における表層性失読とよばれる読み誤りによっても特徴づけられた．表層性失読とは，英語圏では綴り字に例外的な発音を充てる単語(pint)に，規則的な読み(mint, print など int を[int]と発音)を採用し，読み誤る現象(pint[paint]→[pint])である．規則的な読みの単語では綴り字に対する読みの知識で対応できるため誤りなく音読できるが，例外的な発音を充てる単語の読みには，その語に対する知識すなわち意味の助けが不可欠であり，それゆえに意味の喪失によって規則化錯読(pint を[pint]と読む)が出現すると考えられる．こうした読み誤りの一方で，これらの流暢性失語群では非言語的な問題解決能力や視空間認知能力が良好で，自伝的なエピソードについても比較的保たれていたことから，意味記憶の選択的障害としての特徴が際だっていた．症例の中には強迫的な行動障害を示す例も認められた．