

Efficacy and Tolerability of a Once Daily Formulation of *Ginkgo biloba* Extract EGb 761[®] in Alzheimer's Disease and Vascular Dementia: Results from a Randomised Controlled Trial

Authors

R. Ihl¹, M. Tribanek², N. Bachinskaya³, for the GOTADAY Study Group

Affiliations

¹ Geriatric Psychiatry Centre, Maria-Hilf Hospital Krefeld, Krefeld, Germany

² Clinical Research Department, Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany

³ Institute of Gerontology, Academy of Medical Sciences, Kiev, Ukraine

Key words

- dementia
- Alzheimer's disease
- vascular dementia
- *Ginkgo biloba*
- EGb 761
- randomised controlled trial

Abstract



Introduction: A 24-week randomised controlled trial was conducted to assess the efficacy of a 240mg once-daily preparation of *Ginkgo biloba* extract EGb 761[®] in 404 outpatients ≥50 years diagnosed with mild to moderate dementia (SKT 9–23), Alzheimer's disease (AD) or vascular dementia (VaD), with neuropsychiatric features (NPI total score ≥5).

Methods: Separate analyses were performed for diagnostic subgroups (probable or possible AD; VaD).

Results: 333 patients were diagnosed with AD and 71 with VaD. EGb 761[®] treatment was supe-

rior to placebo with respect to the SKT total score (drug-placebo differences: 1.7 for AD, $p < 0.001$, and 1.4 for VaD, $p < 0.05$) and the NPI total score (drug-placebo differences: 3.1 for AD, $p < 0.001$ and 3.2 for VaD, $p < 0.05$). Significant drug-placebo differences were found for most secondary outcome variables with no major differences between AD and VaD subgroups. Rates of adverse events in EGb 761[®] and placebo groups were essentially similar.

Conclusion: EGb 761[®] improved cognitive functioning, neuropsychiatric symptoms and functional abilities in both types of dementia.

received 29.11.2010
revised 09.07.2011
accepted 18.07.2011

Bibliography

DOI <http://dx.doi.org/10.1055/s-0031-1291217>
Published online ahead of print:
November 15, 2011
Pharmacopsychiatry 2012;
45: 41–46
© Georg Thieme Verlag KG
Stuttgart · New York
ISSN 0176-3679

Correspondence

**Prof. Dr. med. Dipl.-Psych.
R. Ihl**
Clinic of Geriatric Psychiatry
Alexian Hospital Maria-Hilf
Krefeld
Diessemer Bruch 81
47805 Krefeld
Germany
Tel.: +49/2151/334 7904
Fax: +49/2151/334 7901
ralf.ihl@alexianer-krefeld.de

Introduction



Efficacy and safety of daily doses of 240mg *Ginkgo biloba* special extract EGb 761[®] in dementia have been demonstrated in a series of clinical trials and endorsed by systematic reviews [1–4]. EGb 761[®] is a scavenger of oxygen free radicals [5] that improves mitochondrial function [6, 7], decreases blood viscosity and enhances microperfusion [8]. In preclinical models it has been found to inhibit the formation of synaptotoxic A β oligomers [9] to antagonise β -amyloid toxicity [10] and to stimulate neurogenesis via CREB phosphorylation [11, 12].

Patient adherence to the prescribed dosage regimen, a prerequisite for clinical efficacy of any drug, increases with decreasing number of doses to be taken per day [13–15]. Therefore, a once-daily formulation of EGb 761[®] was developed and tested for efficacy and tolerability in a phase III clinical trial in patients with mild to moderate dementia [16]. The confirmatory analysis was performed for the total study sample including patients with probable Alzheimer's disease (AD) according to the research diagnostic criteria

specified by the National Institute of Neurological and Communicative Disorders and Stroke together with the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) [17], probable vascular dementia (VaD) according to the diagnostic criteria published by the National Institute of Neurological Disorders and Stroke together with the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS/AIREN) [18] or possible AD with cerebrovascular disease (CVD) according to the relevant subsets of these criteria.

Separate efficacy and safety analyses were performed for the subgroups with AD (including probable AD and possible AD with CVD) and VaD as specified a priori in the study protocol. The results of these subgroup analyses are reported here.

Methods



The study was conducted in accordance with the Declaration of Helsinki (year 2000 revision) and the International Conference on Harmonization

(ICH) tripartite guideline for good clinical practice (GCP). The protocol was approved by the Ethics Committee of the State Pharmacology Centre at the Ukraine Ministry of Health. Patients were recruited by the outpatient clinic of the Department of Psychiatry of the National Medical University in Kiev and 19 further outpatient clinics of neurological or psychiatric hospitals in Ukraine between April and November 2006. From all patients and caregivers oral and written informed consent was obtained before enrolment.

Patients and methods have been reported in detail elsewhere [16]. Briefly, outpatients aged 50 years or above with mild to moderate dementia due to probable AD, possible AD with CVD or VaD were enrolled in this randomised, controlled, double-blind, multi-centre trial. The NINCDS/ADRDA research diagnostic criteria for probable or possible AD [17] and the NINDS/AIREN criteria for probable VaD or CVD [18] were applied to establish clinical diagnoses. A recent (1 year old at most) CT or MRI scan had to be consistent with the clinical diagnosis. The Test for the Early Detection of Dementia with Differentiation from Depression (TE4D) [19], which includes the Clock-Drawing Test (CDT), was used to prove cognitive impairment (cognitive score of 35 or lower, deficits in memory and at least one further cognitive domain). A total score on the SKT cognitive test battery [20] of 9–23 was required, which roughly corresponds to a range from 25 to 14 on the Mini Mental Status Examination (MMSE) or 17–35 on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and covers the mild to moderate range of dementia severity. All patients had neuropsychiatric symptoms of dementia as indicated by a total score on the 12-item Neuropsychiatric Inventory (NPI) [21] of at least 5 and at least one item score (other than delusion or hallucination) of at least 3. The patients were randomly allocated to receive 240 mg EGb 761® or placebo once daily for a period of 24 weeks. Patients with significant psychiatric (e.g., major depression or sub-syndromal depression with scores of 20 or above on the Hamilton Rating Scale for Depression) or severe somatic disorders and patients needing any type of medication that could have influenced the test scores and ratings used for efficacy assessment (e.g., psychoactive drugs) were excluded from the study.

The SKT cognitive test battery and the 12-item NPI were defined as primary outcome measures. The SKT consists of 3 memory tasks scored by the number of items not remembered and 6 concentration tasks scored by the time used for completion [20,22]. Using images rather than word lists for memory testing, the SKT is easy to use in international trials. Its validity across various

cultures and languages, including Russian-speaking countries, has been demonstrated [23]. A culturally adapted, validated version of the NPI in Russian language is available and was used in this study. Secondary outcome measures were the NPI caregiver distress score, the Clinical Global Impression of Change as adapted by the Alzheimer's Disease Cooperative Study (ADCS-CGIC) [24], the Alzheimer's Disease Activities of Daily Living International Scale (ADL-IS) [25], the DEMQOL-proxy quality of life scale [26], and the Verbal Fluency Test (category fluency for animals as adapted by Mahoney [27]). Tests and scales were administered at baseline, after 12 and after 24 weeks of treatment. The scales were chosen to reflect meaningfulness of treatment effects in everyday life (ADL-IS, DEMQOL-Prox, ADCS-CGIC) and caregiver distress (NPI).

For the purpose of the planned subgroup analyses reported here, classification of patients by type of dementia in accordance with NINCDS/ADRDA and NINDS/AIREN criteria was done by the investigators and verified by an independent neurologist experienced in dementia research who was blinded to treatment, but had access to all data relevant for diagnosis and classification of dementia.

The primary analysis of all randomised patients was performed using an analysis of covariance with the covariates treatment, centre and baseline values; it is reported elsewhere [16]. The methods of the pre-planned exploratory analyses of subgroups with different types of dementia were laid down in the statistical analysis plan which was fixed prior to unblinding. These results with means and 95% confidence intervals are reported here together with the respective p-value of the two-sided t-test for continuous variables and chi-squared test or Fisher's exact test, as appropriate, for categorical variables. As no method for formal control of the type-I error rate was ensured for these analyses, p-values have to be considered as explorative.

Results



Of the 410 patients randomised, no efficacy data were available after baseline for 4 patients of the EGb 761® group and 2 patients of the placebo group. Hence, 404 patients (EGb 761®: 202; placebo: 202) were included in the intention-to-treat (ITT) analysis (full analysis set, FAS). Of these, 333 patients were diagnosed as having AD (probable AD or possible AD with CVD) and 71 had VaD. Demographic and baseline data are presented in **Table 1**. Of those diagnosed with AD, 121 had probable AD and 212 had possible AD with CVD). The average adherence to the drug

	AD		VaD	
	EGb 761® [n = 163]	Placebo [n = 170]	EGb 761® [n = 39]	Placebo [n = 32]
gender female	109 (66.9%)	111 (65.3%)	30 (76.9%)	22 (68.8%)
age (years)	64.9 (9.5)	64.2 (8.7)	65.8 (10.0)	66.5 (10.7)
height (cm)	165.9 (8.3)	166.7 (8.2)	165.3 (7.0)	166.1 (8.7)
weight (kg)	73.8 (14.3)	73.8 (13.8)	72.5 (14.7)	75.9 (12.2)
duration of memory problems (years)	4.7 (4.1)	4.6 (3.1)	5.6 (4.6)	5.8 (5.0)
SKT total score	16.4 (3.8)	17.0 (3.8)	17.8 (3.9)	18.3 (3.4)
NPI total score	16.3 (8.2)	16.9 (8.2)	16.6 (8.0)	17.8 (7.8)
NPI caregiver distress	9.3 (5.5)	10.0 (5.3)	11.0 (6.2)	10.5 (5.8)
ADL-IS mean score	2.0 (0.6)	2.0 (0.5)	1.9 (0.6)	2.1 (0.5)
DEMQOL-proxy total score	88.1 (11.8)	88.3 (10.8)	87.1 (11.3)	86.4 (11.5)
Verbal Fluency Test	6.3 (2.2)	6.5 (2.3)	6.5 (1.9)	6.3 (1.8)

Table 1 Demographic data and baseline scores; absolute numbers (per cent) or means (sd).

regimen was above 99%; only 1 patient of the active treatment group and 2 patients of the placebo group were outside the acceptable range of 80–120%.

Changes from baseline in all primary and secondary outcome measures and broken down by type of dementia are shown in **Table 2**. Patients treated with EGb 761[®] improved by 1.4 points on average on the SKT irrespective of the type of dementia, whereas there was little or no change during placebo intake (**Fig. 1**). Regarding neuropsychiatric symptoms as well as caregiver distress related to these symptoms, patients with VaD seemed to respond more readily to EGb 761[®] treatment than those with AD, whereas there also was a slight improvement in the NPI total score in the VaD patients receiving placebo (**Fig. 2**). For all secondary outcome variables, except quality of life, significant improvement over placebo was found for EGb 761[®] in both diagnostic subgroups with no important differences in magnitude. Quality of life improved under EGb 761[®] treatment in both the AD and VaD subgroups, however due to a strong placebo effect in the vascular subgroup this was significant only for the AD group. The results for the AD subgroup, broken down further by the absence (probable AD) or presence (possible AD with CVD) of

CVD are shown in **Table 3**. There were no conspicuous differences in efficacy related to vascular pathology.

Clinically meaningful improvements in cognitive functioning as indicated by a decrease in SKT scores by at least 3 points (which corresponds to approximately 4 points on the ADAS-cog [28]) were achieved under EGb 761[®] treatment in 53 out of 163 (33%) patients of the AD group (placebo: 24/170, 14%; $p < 0.001$, Fisher's exact test) and in 11 out of 39 (28%) patients of the VaD group (placebo: 6/32, 19%; $p = 0.412$, Fisher's exact test). With respect to neuropsychiatric symptoms, clinically relevant improvements by at least 4 points in the NPI total score [29] under EGb 761[®] treatment were observed in 70 out of 163 (43%) patients of the AD group (placebo: 38/170, 22%; $p < 0.001$, Fisher's exact test) and in 21 out of 39 (54%) patients of the VaD group (placebo: 10/32, 31%; $p = 0.092$, Fisher's exact test). According to independent interviewers' global rating with the aid of the ADCS-CGIC, 52% of AD patients and 64% of VaD patients exhibited an overall improvement upon treatment with EGb 761[®] (placebo: 26% and 22%, respectively; $p < 0.001$ for both comparisons, Fisher's exact test). Details for the ADCS-CGIC categories are depicted in **Fig. 3**.

Table 2 Changes from baseline to week 24; means and 95% confidence intervals; two-sided p-values for t-test.

	AD			VaD		
	EGb 761 [®] [n=163]	Placebo [n=170]	p-value	EGb 761 [®] [n=39]	Placebo [n=32]	p-value
SKT total score	-1.4 -1.9; -1.0	+0.3 -0.1; +0.7	<0.001	-1.4 -2.3; -0.5	-0.0 -1.0; +0.9	0.043
NPI total score	-2.9 -3.8; -2.0	+0.2 -0.7; +1.2	0.001	-4.5 -6.6; -2.3	-1.3 -3.4; +0.9	0.036
NPI caregiver distress	-1.0 -1.5; -0.5	+0.4 -0.2; +0.9	<0.001	-2.0 -3.3; -0.7	+0.1 -0.9; +1.1	0.012
ADCS-CGIC	3.4 3.3; 3.6	4.0 3.9; 4.2	<0.001	3.4 3.1; 3.7	4.3 3.8; 4.7	0.003
ADL-IS mean score	-0.16 -0.20; -0.11	-0.00 -0.05; +0.05	<0.001	-0.12 -0.22; -0.02	+0.09 -0.03; 0.21	0.006
DEMQOL-proxy total score	+3.3 +2.0; +4.7	+1.1 +0.1; +2.1	0.008	+3.5 +0.8; +6.3	+2.7 +0.1; +5.4	0.667
Verbal Fluency Test	+0.7 +0.5; +1.0	-0.1 -0.3; +0.2	<0.001	+0.8 +0.4; +1.2	-0.3 -0.9; +0.4	0.004

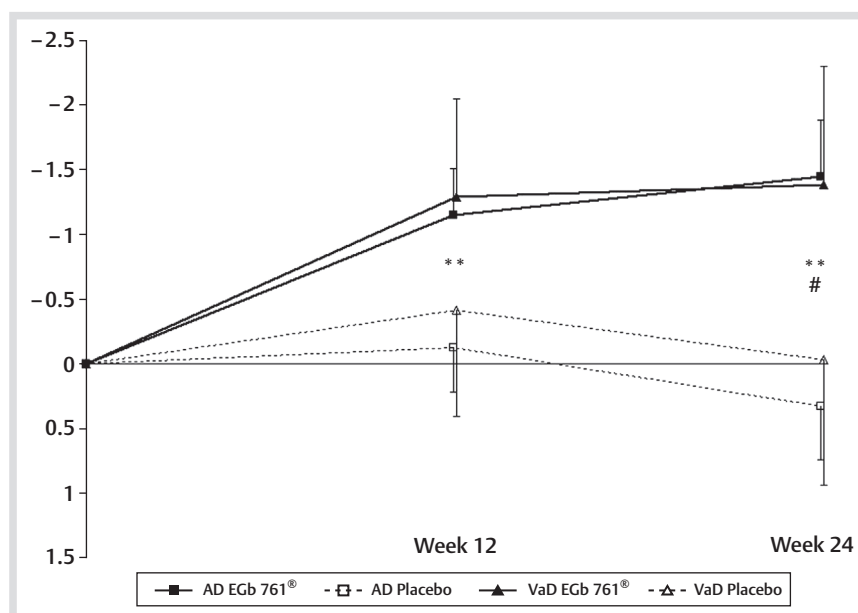


Fig. 1 Change in SKT total score from baseline over week 12 to week 24, means and lower (EGb 761[®]) or upper (placebo) half of the 95% CI; ** $p < 0.001$ for AD, # $p < 0.05$ for VaD (t-test, drug-placebo comparisons).

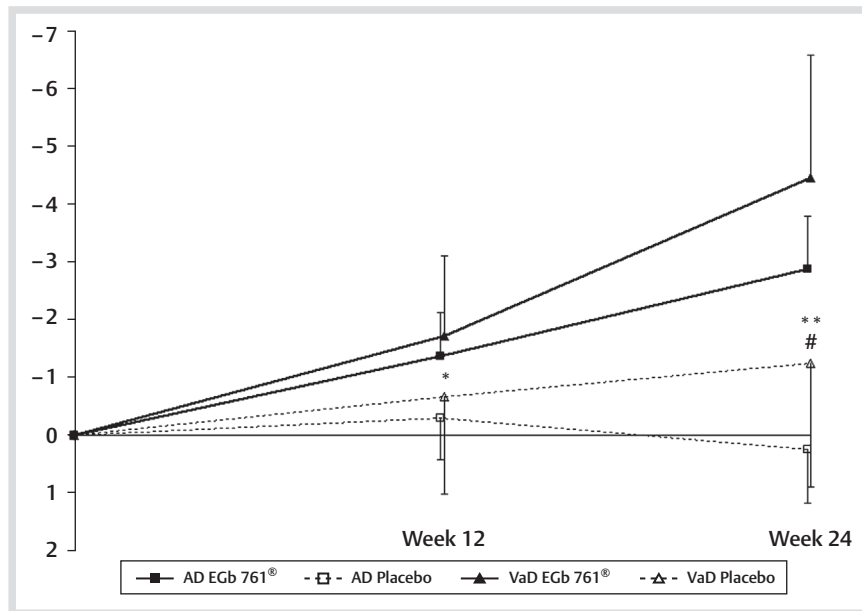


Fig. 2 Change in NPI total score from baseline over week 12 to week 24, means and lower (EGb 761®) or upper (placebo) half of the 95%-CI; * $p < 0.05$ for AD, ** $p < 0.001$ for AD, # $p < 0.05$ for VaD (t-test, drug-placebo comparisons).

Table 3 Changes from baseline to week 24; means and 95% confidence intervals; two-sided p-values for t-test.

	Probable AD			AD with CVD		
	EGb 761® [n=64]	Placebo [n=57]	p-value	EGb 761® [n=99]	Placebo [n=113]	p-value
SKT total score	-1.1 -1.5; -0.5	+0.3 -0.3; +1.0	0.003	-1.7 -2.2; -1.1	+0.3 -0.2; +0.9	<0.001
NPI total score	-3.0 -4.8; -1.2	+0.7 -1.3; +2.7	0.006	-2.8 -3.8; -1.8	0.0 -1.0; +1.0	<0.001
NPI caregiver distress	-1.2 -2.2; -0.2	+0.4 -0.8; +1.5	0.039	-0.9 -1.4; -0.3	+0.3 -0.2; +0.9	0.004
ADCS-CGIC	3.5 3.2; 3.8	4.0 3.7; 4.3	0.014	3.4 3.2; 3.6	4.1 3.8; 4.3	<0.001
ADL-IS mean score	-0.15 -0.22; -0.08	-0.03 -0.12; +0.07	0.038	-0.16 -0.22; -0.11	+0.01 -0.04; +0.07	<0.001
DEM-QOL-proxy total score	+4.8 +2.5; +7.0	+0.1 -1.6; +1.9	0.001	+2.4 +0.8; +4.0	+1.6 +0.4; +2.8	0.424
Verbal Fluency Test	+0.5 +0.2; +0.9	-0.2 -0.6; +0.2	0.009	+0.8 +0.5; +1.2	0.0 -0.4; +0.3	<0.001

Rates of adverse events (AE) were somewhat smaller under EGb 761® as compared to placebo in the AD subgroup with 181 AEs reported for 105 (63%) patients treated with EGb 761® and 216 AEs observed in 120 (70%) patients receiving placebo. With 74 AEs in 34 (85%) patients treated with EGb 761® and 45 AEs in 21 (66%) patients the rate of AEs was slightly higher in the active treatment group of the VaD subsample. The most frequently reported AEs were headache, respiratory tract infection, increased blood pressure and dizziness; frequencies were essentially similar between treatment groups. There were 4 serious AEs in 4 patients, one per subgroup and treatment. No major bleeding occurred in either group.

Discussion

In prospectively specified subgroup analyses we found essentially similar effects of EGb 761® treatment in AD and VaD. This is in line with findings from earlier randomised controlled trials of the same product at the same daily dose [30, 31]. One study did not seem to support efficacy in Alzheimer's disease [32], yet

the sample for that study was recruited from patients in the USA who did not take a cholinesterase inhibitor when those drugs were already widely prescribed there. Moreover, in contrast to the present study, patients with clinically significant neuropsychiatric symptoms were excluded. In a subgroup analysis of those patients who had at least some mild neuropsychiatric symptoms EGb 761® was found significantly superior to placebo in cognitive and global outcome measures [32].

Recruited from a population in which the prescription of cholinesterase inhibitors was uncommon and using relatively liberal eligibility criteria, our sample can be assumed to be fairly representative of the patients with dementia encountered in everyday practice.

The classification by type of dementia was based on widely accepted clinical criteria and CT or MRI. Considering that the clinical criteria are far from perfect [33–35] and that there was no central MRI reading, the possibility of a certain rate of misclassifications must be acknowledged. While the NINDS/AIREN criteria for probable VaD are quite stringent, ensuring high specificity but hampered by low sensitivity, distinguishing between probable AD and possible AD with cerebrovascular disease may sometimes be more

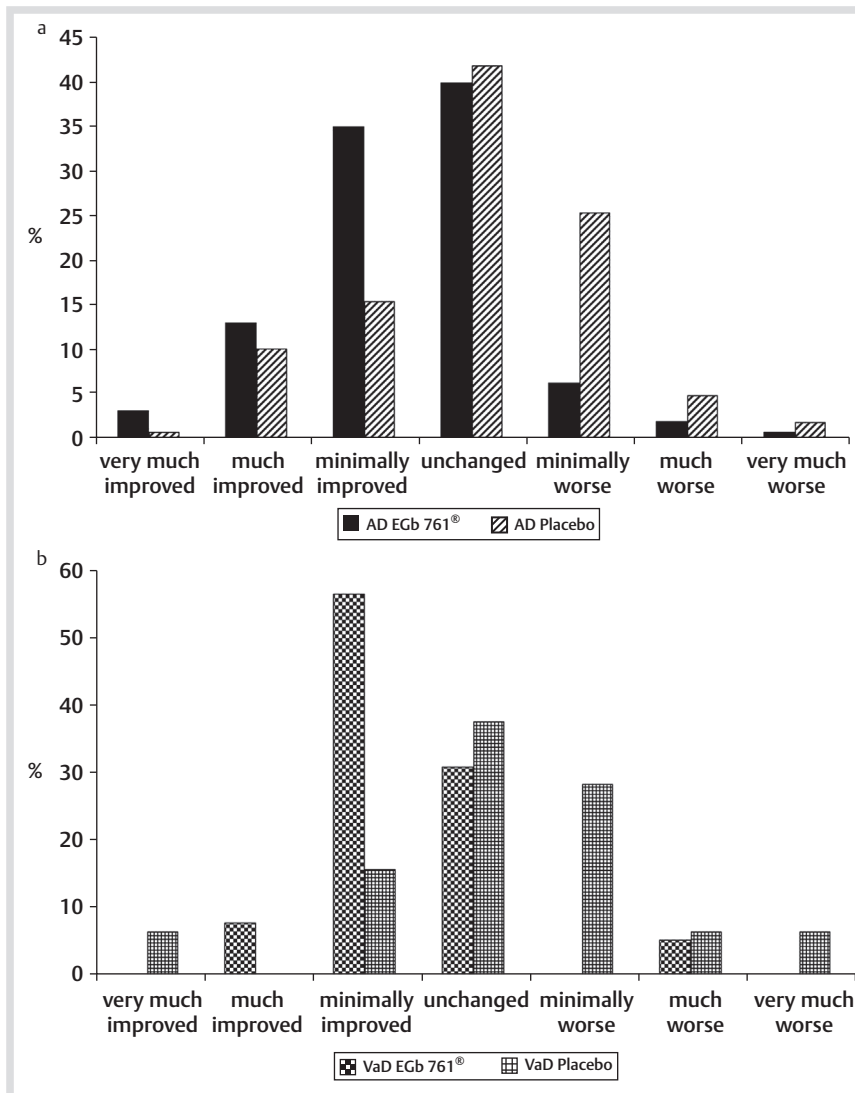


Fig. 3 ADCS-CGIC ratings (categorical) at week 24; **a** AD subgroup; **b** VaD subgroup; $p < 0.001$ for AD and VaD subgroups (chi-squared test, drug-placebo comparison).

difficult, e.g., if white matter lesions are sparse but inspection of the eye fundus indicates atherosclerosis of cerebral vessels. With central review and verification, however, diagnoses should be sufficiently homogeneous and misclassifications limited to an extent not to distort the results of the subgroup analyses as reported here. Similar efficacy in dementias of both Alzheimer's and vascular origin make the *Ginkgo biloba* extract EGb 761[®] particularly feasible for the treatment of dementia in primary care settings. Taking into account the high prevalence of mixed pathologies [34, 36, 37] and the difficulties of correct diagnostic classification even in a specialist care setting [33, 34] on the one hand and the AD-specific mechanisms of other anti-dementia agents on the other, EGb 761[®] will still be an appropriate choice, if in a primary care setting a pure or predominant primary degenerative aetiology cannot be ascertained beyond reasonable doubt. As demonstrated in this and earlier studies [30, 31] the drug is also effective in vascular dementia for the treatment of which cholinesterase inhibitors are not approved. Using the once-daily formulation of EGb 761[®] tested in the present study, high treatment compliance could be achieved. In a real-life setting, this treatment regimen requires only one reminder every day, be it associated with a patient's invariable habits, a visit by the nursing service or a phone call by a caring relative.

Acknowledgements



The clinical trial was sponsored by Dr. Willmar Schwabe GmbH & Co. KG Pharmaceuticals, Karlsruhe, Germany. The sponsor was involved in the conception of the study as well as in the interpretation of the data.

References

- 1 IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ginkgohaltige Präparate bei Alzheimer Demenz. Abschlussbericht. Auftrag A05-19B. Version 1.0. [Ginkgo in Alzheimer's disease. IQWiG Reports. Commission No. A05-19B.] Cologne: IQWiG; 2008
- 2 Kasper S, Schubert H. Ginkgo-Spezialextrakt EGb 761[®] in der Behandlung der Demenz: Evidenz für Wirksamkeit und Verträglichkeit. [Ginkgo biloba extract EGb 761[®] in the treatment of dementia: evidence of efficacy and tolerability]. Fortschr Neurol Psychiatr 2009; 77: 494–506
- 3 Weinmann S, Roll S, Schwarzbach C et al. Effects of *Ginkgo biloba* in dementia: systematic review and meta-analysis. BMC Geriatrics 2010; 14; doi:10.1186/1471-2318-10-14
- 4 Wang BS, Wang H, Song YY et al. Effectiveness of standardized *Ginkgo biloba* extract on cognitive symptoms of dementia with a six-month treatment: A bivariate random effect meta-analysis. Pharmacopsychiatry 2010; 43: 86–91
- 5 Kampkötter A, Pielarski T, Rohrig R et al. The *Ginkgo biloba* extract EGb 761[®] reduces stress sensitivity, ROS accumulation and expression of catalase and glutathione S-transferase 4 in *Caenorhabditis elegans*. Pharmacol Res 2007; 55: 139–147

- 6 Eckert A, Keil U, Kressmann S et al. Effects of EGb 761® *Ginkgo biloba* extract on mitochondrial function and oxidative stress. *Pharmacopsychiatry* 2003; 36 (Suppl 1): S15–S23
- 7 Abdel-Kader R, Hauptmann S, Keil U et al. Stabilization of mitochondrial function by *Ginkgo biloba* extract (EGb 761®). *Pharmacol Res* 2007; 56: 493–502
- 8 Költringer P, Langsteger W, Eber O. Dose-dependent hemorheological effects and microcirculatory modifications following intravenous administration of *Ginkgo biloba* special extract EGb 761. *Clin Hemorheol* 1995; 15: 649–656
- 9 Wu Y, Wu Z, Butko P et al. Amyloid- β -induced pathological behaviors are suppressed by *Ginkgo biloba* extract EGb 761® and ginkgolides in transgenic *caenorhabditis elegans*. *J Neurosci* 2006; 26: 13102–13113
- 10 Bastianetto S, Ramassamy C, Doré S et al. The *Ginkgo biloba* extract (EGb 761®) protects hippocampal neurons against cell death induced by β -amyloid. *Eur J Neurosci* 2000; 12: 1882–1890
- 11 Tchanchou F, Xu Y, Wu Y et al. EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in transgenic mouse model of Alzheimer's disease. *FASEB J* 2007; 21: 2400–2408
- 12 Tchanchou F, Lacor PN, Cao Z et al. Stimulation of neurogenesis and synaptogenesis by bilobalide and quercetin via common final pathway in hippocampal neurons. *J Alzheimers Dis* 2009; 18: 787–798
- 13 Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001; 23: 1296–1310
- 14 Cals JW, Hopstaken RM, Le Doux PH et al. Dose timing and patient compliance with two antibiotic treatment regimens for lower respiratory tract infections in primary care. *Int J Antimicrob Agents* 2008; 31: 531–536
- 15 DeJesus E, Ruane P, McDonald C et al. Impact of switching virologically suppressed, HIV-1-infected patients from twice-daily fixed-dose zidovudine/lamivudine to once-daily fixed-dose tenofovir disoproxil fumarate/emtricitabine. *HIV Clin Trials* 2008; 9: 103–114
- 16 Ihl R, Bachinskaya N, Korczyn A et al. Safety of a once-daily formulation of *Ginkgo biloba* extract EGb 761® in Dementia with Neuropsychiatric Features. A randomized controlled trial. *Int J Geriatr Psychiatry*, in press; doi: 10.1002/gps.2662
- 17 McKhann G, Drachman D, Folstein M et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; 34: 939–944
- 18 Román GC, Tatemichi TK, Erkinjuntti T et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology* 1993; 43: 250–260
- 19 Ihl R, Biesenbach A, Brieber S et al. A head-to-head comparison of the sensitivity of two screening tests for dementia. Mini-mental-state-examination (MMSE) and the test for the early detection of dementia with discrimination from depression (TE4D). *Psychogeriatrics Polska* 2005; 2: 263–271
- 20 Kim YS, Nibbelink DW, Overall JE. Factor structure and scoring of the SKT test battery. *J Clin Psychol* 1993; 49: 61–71
- 21 Cummings JL. The neuropsychiatric inventory: Assessing psychopathology in dementia patients. *Neurology* 1997; 48 (Suppl 6): S10–S16
- 22 Erzigkeit H. SKT Manual. Castrop-Rauxel: Geromed; 1992
- 23 Lehfeld H, Rudinger G, Rietz C et al. Evidence of the cross-cultural stability of the factor structure of the SKT short test for assessing deficits of memory and attention. *Int Psychogeriatr* 1997; 9: 139–153
- 24 Schneider LS, Olin JT, Doody RS et al. Validity and reliability of the alzheimer's disease cooperative study-clinical global impression of change. *Alzheimer Dis Assoc Disord* 1997; 11 (Suppl 2): S22–S32
- 25 Reisberg B, Finkel S, Overall J et al. The Alzheimer's disease activities of daily living international scale (ADL-IS). *Int Psychogeriatr* 2001; 13: 163–181
- 26 Smith SC, Lamping DL, Banerjee S et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess* 2005; 9, No. 10
- 27 Mahoney R, Johnston K, Katona C et al. The TE4D-Cog: a new test for detecting early dementia in English-speaking populations. *Int J Geriatr Psychiatry* 2005; 20: 1172–1179
- 28 Ihl R, Grass-Kapanke B, Jänner M et al. Neuropsychometric tests in cross sectional and longitudinal studies – a regression analysis of ADAS-Cog, SKT and MMSE. *Pharmacopsychiatry* 1999; 32: 248–254
- 29 Mega MS, Masterman DM, O'Connor SM et al. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. *Arch Neurol* 1999; 56: 1388–1393
- 30 Kanowski S, Herrmann WM, Stephan K et al. Proof of efficacy of the *Ginkgo biloba* extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiatry* 1996; 29: 47–56
- 31 Napryeyenko O, Sonnik G, Tartakovsky I. Efficacy and tolerability of *Ginkgo biloba* extract EGb 761® by type of dementia: analyses of a randomised controlled trial. *J Neurol Sci* 2009; 283: 224–229
- 32 Schneider LS, DeKosky ST, Farlow MR et al. A randomized, double-blind, placebo-controlled trial of two doses of *Ginkgo biloba* extract in dementia of the Alzheimer's type. *Curr Alzheimer Res* 2005; 2: 541–551
- 33 Holmes C, Cairns N, Lantos P et al. Validity of current clinical criteria for Alzheimer's disease, vascular dementia and dementia with Lewy bodies. *Br J Psychiatry* 1999; 174: 45–50
- 34 Korczyn AD. Mixed dementia – the most common cause of dementia. *Ann NY Acad Sci* 2002; 977: 129–134
- 35 Hachinski V. Shifts in thinking about dementia. *JAMA* 2008; 300: 2172–2173
- 36 Schneider JA, Arvanitakis Z, Bang W et al. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 2007; 69: 2197–2204
- 37 Matthews FE, Brayne C, Lowe J et al. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council cognitive function and ageing study. *PLoS Med* 2009; 6: e1000180