

Efficacy and safety of a once-daily formulation of Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: a randomized controlled trial

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Objective: To test the efficacy and safety of a once-daily formulation of EGb 761 in the treatment of patients with dementia with neuropsychiatric features.

Methods: Multi-centre trial of 410 outpatients with mild to moderate dementia (Alzheimer's disease, vascular dementia or mixed form) scoring between 9 and 23 on the SKT cognitive test battery, at least five on the Neuropsychiatric Inventory (NPI) and three or higher in at least one item of the NPI. Patients were randomly allocated to double-blind treatment with 240 mg of EGb 761 or placebo once daily for 24 weeks. Primary outcomes were the changes from baseline in the SKT total score and the NPI total score. The Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC), Activities of Daily Living International Scale (ADL-IS), NPI distress score, DEMQOL-Proxy quality-of-life scale and Verbal Fluency Test were secondary outcomes.

Results: At endpoint, patients treated with EGb 761 ($n = 202$) improved by -1.4 (95% confidence interval $-1.8; -1.0$) points on the SKT and by -3.2 ($-4.0; -2.3$) on the NPI total score, whereas those receiving placebo ($n = 202$) deteriorated by $+0.3$ ($-0.1; 0.7$) on the SKT and did not change on the NPI total score ($-0.9; 0.9$). Both drug-placebo comparisons were significant at $p < 0.001$. EGb 761 was significantly superior to placebo with respect to all secondary outcome measures. Adverse event rates were similar for both treatment groups.

Conclusions: EGb 761, 240 mg once-daily, was found significantly superior to placebo in the treatment of patients with dementia with neuropsychiatric symptoms. Copyright © 2010 John Wiley & Sons, Ltd.

Key words: dementia; Alzheimer's disease; vascular dementia; Ginkgo biloba; EGb 761; randomized controlled trial

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Introduction

Dementing disorders in old age are increasing at a fast rate (Korczyn and Vakhapova, 2007). In spite of much

research and enormous investment in research, the pathogenesis of Alzheimer's disease (AD) is not clarified yet. This limits the development of rational therapies. The combination of AD and vascular

dementia (VaD) is extremely common, making itself the most common type of dementia (Korczyn 2002; Matthews *et al.*, 2009). Presently, therapy of people with dementia is of limited value, and available drugs provide only a mild symptomatic effect.

Recent research has provided evidence of the efficacy of the Ginkgo biloba extract EGb 761 in the treatment of elderly individuals with or without cognitive impairment (Mix and Crews, 2002; Hoerr *et al.*, 2008). However, studies into the prevention of cognitive decline and conversion to dementia in elderly individuals have yielded somewhat inconsistent results (DeKosky *et al.*, 2008; Dodge *et al.*, 2008; Snitz *et al.*, 2009). The mechanism of action of the drug is still not fully elucidated, but there is evidence of neuroprotective properties (Ramassamy *et al.*, 2007). EGb 761 is a polyvalent radical scavenger (Kampkötter *et al.*, 2007) that improves mitochondrial function (Eckert *et al.*, 2003; Abdel-Kader *et al.*, 2007), decreases blood viscosity and enhances microperfusion (Költringer *et al.*, 1995), inhibits the formation of synaptotoxic A β oligomers (Wu *et al.*, 2006) and antagonizes β -amyloid toxicity (Bastianetto *et al.*, 2000). Its clinical efficacy in dementia has been demonstrated by a number of clinical trials involving patients with AD and vascular dementia (VaD) (Ernst and Pittler, 2005; Napryeyenko and Borzenko, 2007). In a recent review the daily dose of 240 mg was found to be more beneficial than 120 mg (IQWiG, 2008). The drug seems to be particularly useful when dementia is accompanied by neuropsychiatric symptoms (Hoerr 2003; Schneider *et al.*, 2005; Napryeyenko and Borzenko, 2007). Another important feature of the Ginkgo biloba extract is its safety record, derived from large placebo-controlled studies (Kanowski *et al.*, 1996; Napryeyenko and Borzenko, 2007; DeKosky *et al.*, 2008).

Compliance to prescription drug regimens can be compromised in elderly patients by age-related circumstances. Polypharmacy may cause reluctance to take the amount of pills prescribed, and a failing memory may lead to inadvertent skipping of single doses or even longer drug omissions. The problem may aggravate, when a person becomes demented and develops severe memory deficits. Whereas patients with moderately severe to severe dementia require permanent care which includes drug administration, people with early stage dementia may still live mostly independently and receive only a minimum of care. Optimizing drug regimens is a prerequisite for efficacy in such cases. A host of studies have shown that once-daily regimens may increase adherence considerably (Claxton *et al.*, 2001). Not only is the number of tablets

to be swallowed every day kept to a minimum, drug intake may also require a single reminder. If a patient with early dementia is visited by a home care service only once a day, better drug adherence can be attained by once-daily dosing. Therefore, a once-daily formulation of Ginkgo biloba extract EGb 761, an anti-dementia drug, was developed.

The *Ginkgo One Tablet A Day* (GOTADAY) study was designed to assess the clinical efficacy and tolerability of a once-daily formulation containing 240 mg of Ginkgo biloba extract EGb 761 in demented individuals.

Patients and methods

The study was conducted in adherence to the Declaration of Helsinki (year 2000 revision) and the harmonized tripartite guideline for good clinical practice (GCP) issued by the International Conference on Harmonization (ICH, 1996). The protocol was approved by the Ethics Committee of the State Pharmacology Centre at the Ukraine Ministry of Health. Oral and written informed consent has been obtained from all patients and caregivers before any study-related procedures were undertaken. Investigators and clinical staff involved in the trial were trained by experts in legal requirements and GCP standards. At a start-up meeting, they were trained by an experienced psychiatrist and neuropsychologist in the administration of tests and rating scales used for efficacy assessment.

Study population

Patients were recruited at 20 outpatient clinics of psychiatric or neurological hospitals in Ukraine. They were eligible for this study if they were at least 50 years of age (no upper limit) and had one of the following diagnoses: (a) probable AD in accordance with the NINCDS-ADRDA criteria (McKhann *et al.*, 1984), (b) possible AD with cerebrovascular disease (CVD) as defined by the NINDS-AIREN criteria (Román *et al.*, 1993) or (c) probable VaD according to NINDS-AIREN. Symptoms of dementia had to be present for at least 6 months. A CT or MRI scan no more than 1 year old had to be available, consistent with the inclusion diagnosis and showing no evidence of other brain lesions that could account for the cognitive deficit. The Test for Early Detection of Dementia with Discrimination from Depression (TE4D) (Ihl *et al.*, 2000; Brinkmeyer *et al.*, 2004; Mahoney *et al.*, 2005)

was used as a screening instrument and to verify the presence of cognitive impairment in at least two domains. It was preferred to the Mini-Mental State Examination (MMSE) because of its higher sensitivity and specificity to discriminate between demented and non-demented subjects (Ihl *et al.*, 2005; Mahoney *et al.*, 2005). A total error score of 35 or worse was required for inclusion. Patients had to have mild to moderate dementia as evidenced by a total score from 9 to 23 (both inclusive) on the SKT test battery (Kim *et al.* 1993), which roughly corresponds to a range from 25 to 14 on the MMSE or 17 to 35 on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) (Ihl *et al.*, 1999). The clock-drawing test (CDT) after Sunderland (Sunderland *et al.*, 1989) was employed as a second screening instrument, the score of which had to be below 6. Patients had to score at least 5 on the 12-item Neuropsychiatric Inventory (NPI) (Cummings, 1997), with at least one item score (other than delusion or hallucination) being 3 or higher. Severe depression was excluded by requiring a score below 20 on the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960). The presence of a caregiver was required who was able and willing to provide information on the patient's behaviour and ability to perform activities of daily living.

Patients were excluded from the study if they had any other type of dementia or neurological disorder, major short-term fluctuations in symptom severity, current or recent major depression or other psychiatric disorder, severe or insufficiently controlled cardiovascular, renal, or hepatic disorder, diabetes, anaemia, or thyroid dysfunction. Patients suffering from active malignant disease, HIV or syphilis infection, or gastrointestinal diseases with uncertain absorption, were not acceptable. Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorrhologically active drugs, anti-Parkinson drugs or Ginkgo supplements was prohibited during the study and for at least 8 weeks preceding randomization.

Study design and intervention

This was a double-blind, multi-centre trial with two parallel treatment groups. A screening period (up to 4 weeks) was required for examinations and washout of discontinued medications, followed by a 24-week treatment period. Randomization (1:1, stratified by centres and in blocks of four) was performed with the aid of a validated computer program that linked

random numbers to drug or placebo, respectively. The sealed randomization code was stored safely at the biometrics unit, and the length of randomization blocks within which numbers of drug and placebo were balanced was not disclosed to investigators. Upon successful screening, each patient was assigned the lowest medication number still available at the site and handed over the corresponding drug package. Drug and placebo tablets were indistinguishable by appearance, packaging and labelling. Patients had to take one tablet in the morning. Drug dispensation and return was handled by persons not involved otherwise in the conduct of the trial, usually the hospital pharmacists. The investigational product, EGb 761¹ is a dry extract from Ginkgo biloba leaves (drug-extract ratio 35-67:1), adjusted to 22.0–27.0% ginkgo flavonoids and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalide, with a content of ginkgolic acids below 5 ppm. In this trial, a once-daily formulation containing 240 mg of EGb 761 was used.

Outcome measures

Primary efficacy measures were the SKT, a cross-culturally validated 9-item cognitive test battery the score of which ranges from 0 to 27, with higher scores indicating more severe impairment, and the 12-item NPI, which assesses frequency and severity of neuropsychiatric symptoms (total score, range 0–144). Secondary efficacy measures were the NPI caregiver distress score (range 0–60); the Clinical Global Impression of Change (CGIC) developed by the Alzheimer's Disease Cooperative Study (ADCS) (Schneider *et al.*, 1997); the Alzheimer's Disease Activities-of-Daily-Living International Scale (ADL-IS) (Reisberg *et al.*, 2001); rates of clinically meaningful response in primary outcomes (improvement by at least three points on the SKT (Rogers *et al.*, 1998; Ihl *et al.*, 1999) or by at least four points on the NPI total score (Mega *et al.* 1999)); the DEMQOL-Proxy, a health-related quality of life scale for people with dementia (Smith *et al.*, 2005); and the Verbal Fluency Test (animal fluency, as modified by Mahoney *et al.*, 2005). Patient self-ratings of presence and severity of dizziness and tinnitus, symptoms often associated with old age, were documented using 11-point box scales, 0 representing absence and 10 indicating extreme

¹Manufacturer: Dr. Willmar Schwabe GmbH & Co. KG Pharmaceuticals, Karlsruhe, Germany; EGb 761[®] is a registered trademark of Dr. Willmar Schwabe GmbH & Co. KG Pharmaceuticals.

severity of a symptom. Investigators and investigational staff were trained in the administration of tests and scales by an experienced geriatric psychiatrist and neuropsychologist, using original test material, demonstration and test ratings. Safety was assessed by documentation of adverse events, physical examination, electrocardiography and laboratory tests. All efficacy assessments were performed at baseline, week 12 and week 24.

Safety was assessed by physical examination, electrocardiography and laboratory tests at screening and week 24. Adverse events were recorded at baseline, week 6 and week 18 phone calls and study termination.

Statistical analysis and sample size

The aims of the study were the evaluation of efficacy, tolerability and safety of a once-daily formulation of 240 mg EGb 761 in patients suffering from AD, VaD or AD with vascular components, all with neuropsychiatric symptoms. The primary cognitive efficacy variable was the change of the SKT total score between baseline and week 24, the primary variable for the assessment of the neuropsychiatric efficacy was the change of the NPI total score (items 1–12) during the trial period. The hypothesis concerning the difference between EGb 761 and placebo with respect to *both* endpoints was tested according to the intersection-union principle (Berger, 1982) at a two-sided type I error rate of $\alpha = 0.05$. Thus, a difference between EGb 761 and placebo could be established when both single null-hypotheses (no difference in the change of the SKT total score, no difference in the NPI total score) were rejected at $\alpha = 0.05$. This procedure controls the experimentwise type I error rate of $\alpha = 0.05$. The analysis of the two single null-hypotheses was performed by applying an analysis of covariance procedure with the factors treatment and centre and the baseline-value of the respective variable as a covariate.

The analysis was primarily based on the full analysis data set according to the intention to treat (ITT) principle including all patients who received randomized study treatment at least once and having at least one measurement of the primary efficacy parameters during the randomized treatment period.

For sensitivity analysis, a per-protocol (PP) analysis was performed including all patients of the full analysis set without major protocol violations.

The sample size of 2×205 patients was calculated to detect a difference in changes from baseline to week 24 between EGb 761 and placebo groups of 2

points on the SKT and 2.5 points on the NPI at a type I error rate of 0.05 and a power for the simultaneous rejection of both null hypotheses of at least 90%.

Results

Patient sample

Study profile and patient disposition are depicted in Figure 1. The first patient was enrolled in April 2006; the last patient completed the treatment period in May 2007. Of the 410 patients who were randomized and received drug (safety analysis set), 404 patients who had data for the primary outcome variable after baseline make up the full analysis set (FAS) for ITT analysis. Demographic characteristics and baseline data are summarized in Table 1. The sub-sample for PP analysis consisted of 374 patients after exclusion of 12 patients who had major protocol violations and 18 patients who discontinued prematurely for reasons other than potentially drug-related adverse events or lack of efficacy. Since both analyses yielded nearly identical results, only those for the ITT analysis are provided.

Most patients had concomitant medical conditions with nervous system disorders (EGb 761: 89%, placebo: 93%), vascular disorders (EGb 761: 92%, placebo 90%) and cardiac disorders (EGb 761: 74%, placebo: 74%) being most prevalent. HAMD scores were higher than 15 (but lower than 20) in 23 patients (EGb 761: 10, placebo: 13). About 67% of the patients were taking concomitant prescription medications. Drugs to treat hypertension and cardiac diseases were prescribed most frequently: drugs acting on the renin-angiotensin system (EGb 761: 39%, placebo: 36%), beta-blocking agents (EGb 761: 10%, placebo: 11%), calcium antagonists (EGb 761: 6%, placebo: 4%), and antithrombotic agents (6% in each group). No other type of drug was taken by more than 5% of patients. Only two patients of the actively treated group and seven patients of the placebo group took hypnotic/sedative drugs occasionally, one patient of each treatment group took an anxiolytic drug, and two patients of the placebo group took an antipsychotic or antidepressant drug, respectively. None of the study participants had taken a cholinesterase inhibitor or any Ginkgo product before enrolment and only six patients of each treatment group had taken a nootropic drug which had been discontinued at least eight weeks before baseline. Caregivers were children (56%), spouses (23%) or other relatives or friends (21%).

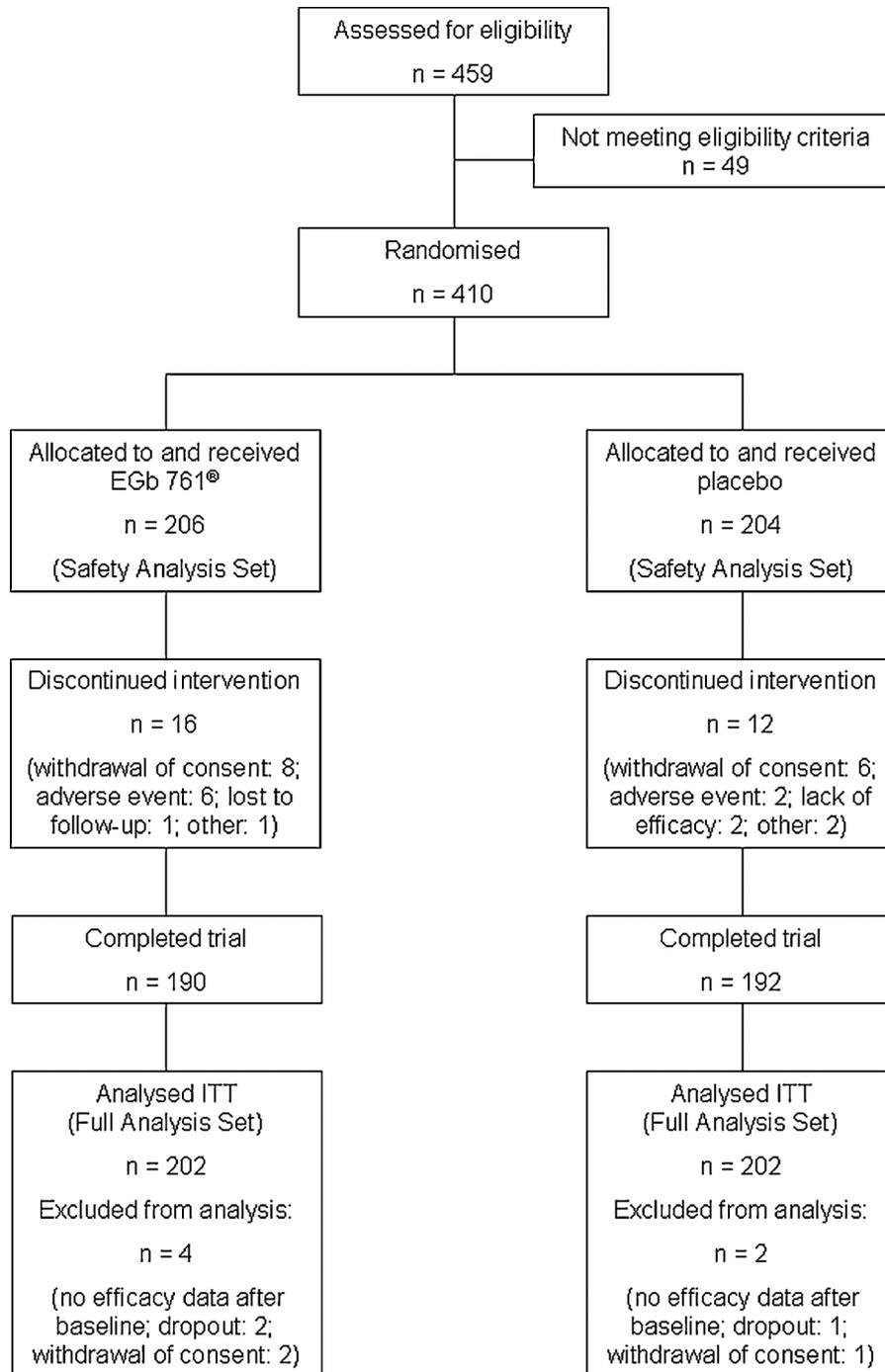


Figure 1 Patient disposition.

Primary outcome measures

Patients treated with EGb 761 improved in both cognitive test performance and neuropsychiatric symptoms, whereas there was minimal or no change in the placebo group. This resulted in statistically significant superiority of EGb 761 over placebo in both

primary outcome measures ($p < 0.001$, Table 2, Figures 2 and 3).

A clinically significant improvement in cognition (Rogers *et al.*, 1998), i.e. a decrease by at least three points of the SKT total score, which roughly corresponds to a 4-point change on the ADAS-cog (Ihl *et al.* 1999), was found in 32% of EGb 761-treated

Table 1 Baseline characteristics of the full analysis set; means \pm standard deviations and two-sided p -values of t -test or numbers (percent) and two-sided p -values of χ^2 -test

	EGB 761 ($n = 202$)	Placebo ($n = 202$)	p -value
Gender			
Female	139 (69%)	133 (66%)	0.524
Male	63 (31%)	69 (34%)	
Diagnosis			
Probable AD	64 (32%)	57 (28%)	0.364
Possible AD with CVD	99 (49%)	113 (56%)	
Probable VaD	39 (19%)	32 (16%)	
Age (years)	65 \pm 10	65 \pm 9	0.550
Height (cm)	166 \pm 8	167 \pm 8	0.298
Weight (kg)	74 \pm 14	74 \pm 14	0.666
BMI (kg/m ²)	27 \pm 4	27 \pm 4	0.976
Duration of memory problems (years)	4.9 \pm 4.2	4.8 \pm 3.5	0.797
Duration of dementia (years)	2.1 \pm 2.3	2.4 \pm 2.5	0.209
TE4D cognitive score	26.2 \pm 5.3	26.0 \pm 5.0	0.389
SKT total score	16.7 \pm 3.9	17.2 \pm 3.7	0.163
NPI total score	16.4 \pm 8.1	17.0 \pm 8.2	0.393
NPI distress score	9.6 \pm 5.6	10.0 \pm 5.4	0.477
Verbal Fluency Test	6.4 \pm 2.1	6.5 \pm 2.2	0.630
ADL-IS overall mean score	1.9 \pm 0.6	2.0 \pm 0.5	0.259
DEMQOL-Proxy total score	87.9 \pm 11.7	88.0 \pm 10.9	0.975
11-point box scale tinnitus	1.3 \pm 1.8	1.5 \pm 1.8	0.178
11-point box scale dizziness	2.0 \pm 1.9	2.1 \pm 1.8	0.872

patients and in 15% of those receiving placebo ($p < 0.001$). Improvements by at least four points in the NPI total score (Mega *et al.*, 1999) were documented for 45% of patients treated with EGB 761 and for 24% of those taking placebo ($p < 0.001$).

Secondary outcome measures

There was consistent and statistically significant superiority of EGB 761 over placebo across all secondary outcome measures (Table 2), including activities of daily living, quality of life and clinicians' global judgment (Figure 4).

Safety and tolerability

For 139 patients (67.5%) treated with EGB 761 255 adverse events were reported during the course of the treatment period. For 141 patients (69.1%) of the placebo group 261 adverse events were documented. Adverse events that occurred in at least 5% of patients in either treatment group are summarized in Table 3. Of the placebo group, seven times as many patients reported events of tinnitus than of the EGB 761 group, whereas no major difference was discernible for all other types of events. In each treatment group, two serious adverse events were observed: an ischaemic stroke (in a patient with long-standing hypertension

Table 2 Changes from baseline in primary and secondary outcome measures, change score for ADCS-CGIC; full analysis set; means (95% confidence intervals) and p -values of t -test

	EGB 761 ($n = 202$)	Placebo ($n = 202$)	p -value
Primary outcome measures			
SKT total score	-1.4 (-1.8, -1.0)	+0.3 (-0.1, +0.7)	<0.001
NPI total score	-3.2 (-4.0, -2.3)	0.0 (-0.9, +0.9)	<0.001
Secondary outcome measures			
ADCS-CGIC change score	3.4 (3.3, 3.5)	4.1 (3.9, 4.2)	<0.001
NPI distress score	-1.2 (-1.7, -0.7)	+0.3 (-0.2, +0.8)	<0.001
Verbal Fluency Test	+0.7 (+0.5, +1.0)	-0.1 (-0.3, +0.1)	<0.001
ADL-IS overall mean score	-0.2 (-0.2, -0.1)	0.0 (0.0, +0.1)	<0.001
DEMQOL-Proxy total score	+3.4 (+2.2, +4.6)	+1.4 (+0.4, +2.3)	0.008
11-point box scale tinnitus	-0.5 (-0.6, -0.3)	-0.1 (-0.2, 0.0)	<0.001
11-point box scale dizziness	-0.8 (-1.0, -0.6)	-0.3 (-0.5, -0.2)	<0.001

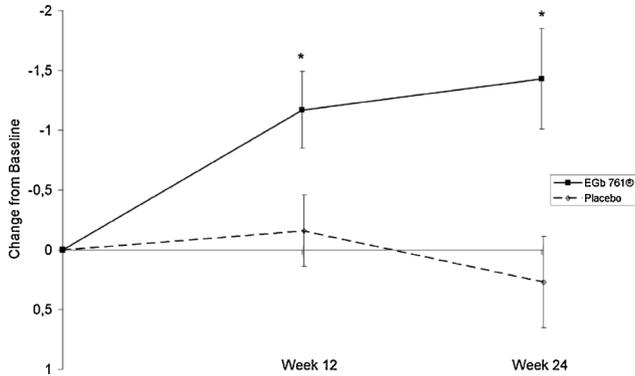


Figure 2 Change in SKT total score from baseline to week 24; full analysis set ($n = 410$); means and 95% confidence intervals. * $p < 0.001$, two-sided t -test.

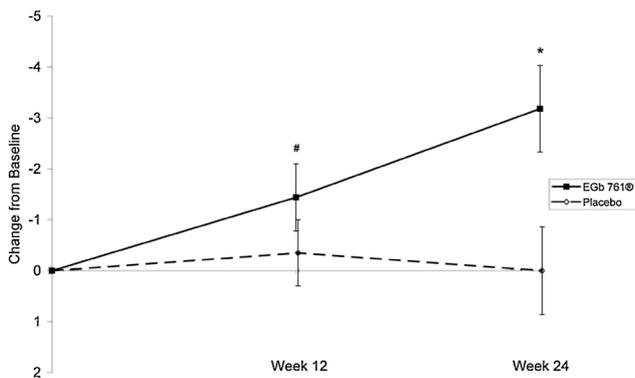


Figure 3 Change in NPI total score from baseline to week 24; full analysis set ($n = 410$); means and 95% confidence intervals. # $p < 0.05$, * $p < 0.001$, two-sided t -test.

and a history of recurring ischaemic attacks) and a stage IV lung cancer in the EGb 761 group; an ischaemic stroke and a rapid deterioration of intellectual and motor function in the placebo group. All serious adverse events were considered by the investigators as unrelated to the study medication.

Discussion

The study has shown the feasibility of once-daily administration of EGb 761 at doses of 240 mg. Active treatment was significantly superior to placebo in improving patients' cognitive performance, neuropsychiatric symptoms, functional abilities and overall condition. As a consequence, the distress perceived by caregivers due to the patients' aberrant behaviours was alleviated. This was the first study that assessed the effect of EGb 761 on patients' quality of life which, in fact, was improved significantly beyond the placebo effect.

A direct comparison of drug effects found in different studies must be interpreted with caution, because of differences in patient characteristics, such as age, degree of cognitive impairment and severity of neuropsychiatric symptoms. The drug-placebo differences on the SKT found in the present trial are intermediate between those reported from a 26-week trial (Kanowski and Hoerr, 2003) and a 22-week trial (Napryeyenko and Borzenko, 2007) of EGb 761 both using a 120 mg b.i.d. regimen. This seems consistent with both intermediate baseline severity of cognitive impairment and intermediate burden of neuropsychiatric symptoms at baseline in the patients of the

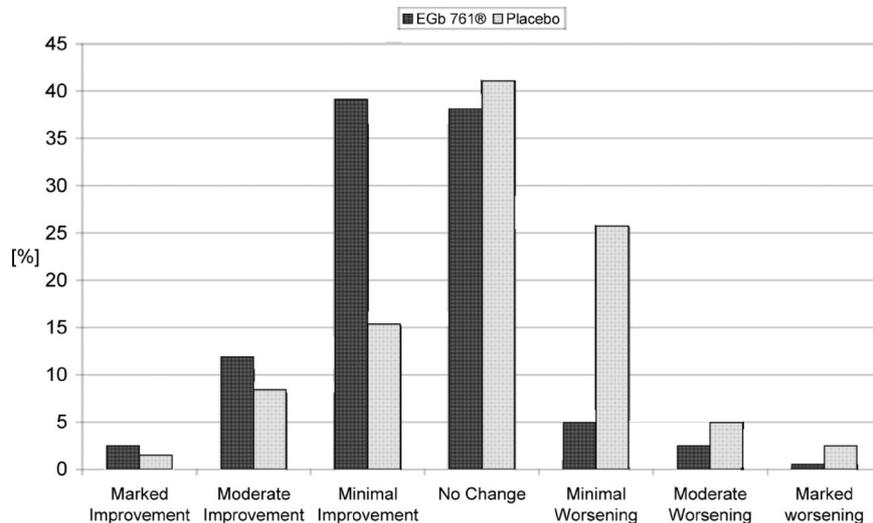


Figure 4 Clinical Global Impression of Change (ADCS-CGIC) categorical ratings at week 24; full analysis set ($n = 410$); $p < 0.001$, χ^2 -test.

Table 3 Adverse events reported for at least 5% of patients of either treatment group; safety analysis set; absolute numbers (%) of patients.

Adverse event	EGB 761 (n = 206)	Placebo (n = 204)
Headache	43 (20.9)	38 (18.6)
Respiratory tract infection (incl. rhinitis, bronchitis, bronchopneumonia)	27 (13.1)	20 (9.8)
Blood pressure increased, hypertension	22 (10.7)	21 (10.3)
Dizziness	19 (9.2)	23 (11.3)
Diarrhoea	9 (4.4)	13 (6.4)
Angina pectoris	6 (2.9)	12 (5.9)
Tinnitus	2 (1.0)	15 (7.4)

present study. Drug-placebo differences with regard to the percentages of patients rated as improved in the global assessment, 11% upon 120 mg b.i.d. (Kanowski and Hoerr, 2003) and 28% in the present study, further support the notion that the 240 mg once-daily regimen is not inferior to the 120 mg b.i.d. regimen. As for all anti-dementia treatments, the effects are moderate in size, but the drug-placebo difference of 1.7 on the SKT, which corresponds to a difference of about 2.2 on the ADAS-cog (Ihl *et al.*, 1999), as well as the 17% drug-placebo difference between response rates in the cognitive domain are in the same range as corresponding drug-placebo differences reported for cholinesterase inhibitors, e.g. 1.6–2.9 points on the ADAS-cog (Corey-Bloom *et al.*, 1998; Rösler *et al.*, 1999) and 8–27% in response rates (Rogers *et al.*, 1998; Rösler *et al.*, 1999; Wilcock *et al.*, 2000).

Adverse event rates at placebo level support the notion that there are no issues with safety and tolerability of 240 mg of EGB 761 taken once daily. There have been reports of intracranial bleeding temporally associated with the intake of Ginkgo products, most of them of unknown quality, part of them multi-ingredient products, in some instances during aspirin or warfarin medication (Ernst *et al.*, 2005). However, in specific studies of EGB 761, neither an effect on blood coagulation, platelet function or bleeding time could be detected (Bal dit Sollier *et al.*, 2003; Köhler *et al.*; 2004, Halil *et al.*, 2005) nor an interaction with aspirin or warfarin (Jiang *et al.*, 2005; Wolf, 2006; Gardner *et al.*, 1984).

A major strength of this study is the relatively liberal selection criteria that permitted recruitment of patients from the mainstream of daily practice. Taking into account that the majority of patients with dementia have both Alzheimer-type and vascular brain pathology (Snowdon *et al.*, 1997; Neuropathology Group of the MRC-CFAS, 2001; Korczyn, 2002; Schneider *et al.*, 2007; Matthews *et al.*, 2009), patients with either

pathology as well as those with mixed pathology were enrolled. Moreover, rather than excluding patients suffering from clinically significant behavioural and psychological symptoms, such patients, who make up the majority of dementia patients, were selected specifically. EGB 761 was therefore tested in a patient sample that most likely resembles the population that requires anti-dementia therapy in clinical practice.

Cholinesterase inhibitors are inaccessible to the majority of dementia patients in Ukraine, and therefore none of the study participants had taken a cholinesterase inhibitor before study entry, and psychoactive drug use was sparse during the study. Hence, there was little potential of bias due to previous and concomitant drug intake. However, the effects of combined therapy with EGB 761 and other anti-dementia drugs may be worth studying in the future.

Overall, the study has shown that the once-daily dosing regimen of EGB 761 is both safe and effective in the treatment of dementia with neuropsychiatric features.

Conflict of interest

RI is a scientific advisor to Schwabe Pharmaceuticals and has presented clinical data on EGB 761[®] at scientific meetings, NB is a scientific advisor to Schwabe Pharmaceuticals and participated in the study as clinical investigator, AK provided scientific advice to Schwabe Pharmaceuticals and was involved in the verification of clinical data, VV was involved in the verification of clinical data, ON was involved in the study as principal investigator, RH and MT are employees of Schwabe Pharmaceuticals.

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Key Points

- Several studies have demonstrated clinical efficacy of Ginkgo biloba extract EGB 761 at daily doses of 240 mg in dementia.
- In this trial, a 240 mg once-daily dosage form of EGB 761 significantly improved cognition, neuropsychiatric symptoms, overall assessment and quality of life in patients with dementia as well as behaviour-related distress of caregivers.
- EGB 761 was safe and well tolerated, there was no excess rate of adverse events compared to placebo.

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