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Ginkgo biloba extract EGb 761® in dementia with neuropsychiatric features: A randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg

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ABSTRACT

A multi-centre, double-blind, randomised, placebo-controlled, 24-week trial with 410 outpatients was conducted to demonstrate efficacy and safety of a 240 mg once-daily formulation of *Ginkgo biloba* extract EGb 761® in patients with mild to moderate dementia (Alzheimer's disease or vascular dementia) associated with neuropsychiatric symptoms. Patients scored 9 to 23 on the SKT cognitive battery, at least 6 on the Neuropsychiatric Inventory (NPI), with at least one of four key items rated at least 4. Primary outcomes were the changes from baseline to week 24 in the SKT and NPI total scores. The ADCS Clinical Global Impression of Change (ADCS-CGIC), Verbal Fluency Test, Activities of Daily Living International Scale (ADL-IS), DEMQOL-Proxy quality-of-life scale and 11-point box scales for tinnitus and dizziness were secondary outcome measures. Patients treated with EGb 761® ($n = 200$) improved by 2.2 ± 3.5 points (mean ± sd) on the SKT total score, whereas those receiving placebo ($n = 202$) changed only slightly by 0.3 ± 3.7 points. The NPI composite score improved by 4.6 ± 7.1 in the EGb 761®-treated group and by 2.1 ± 6.5 in the placebo group. Both drug-placebo comparisons were significant at $p < 0.001$. Patients treated with EGb 761® also showed a more favourable course in most of the secondary efficacy variables. In conclusion, treatment with EGb 761® at a once-daily dose of 240 mg was safe and resulted in a significant and clinically relevant improvement in cognition, psychopathology, functional measures and quality of life of patients and caregivers.

1. Objectives and background

The ageing of populations and the resulting increase in people's risk for both Alzheimer's disease (AD) and vascular dementia (VaD) has significant implications worldwide. The forecast indicates a considerable increase in the number of demented elderly from 25 million in the year 2000 to 63 million in 2030 (Wimo et al., 2003). In spite of the urgent need for treatments (Lindesay et al., 2010), extensive research and enormous investments in research, it still remains unclear what causes AD (Daviglus et al., 2010). This seriously hampers the development of curative new drugs and has led to the failure of recently tested, putatively causal treatments (Holmes et al., 2008; Green et al., 2009). In the absence of causal treatments for AD, and faced with fragmentary knowledge about AD pathogenesis together with evidence of multiple and common risk factors for AD and VaD (Daviglus et al., 2010; Förstl, 2003; Newman et al., 2005) as well as a large proportion of dementias with mixed pathologies (Schneider et al., 2007), substances that interfere with both AD and vascular pathology and that have previously proven effective in the treatment of dementia syndromes should be considered as therapeutic options.

The *Ginkgo biloba* extract EGb 761® interferes with various pathomechanisms relevant to dementia, such as Aβ aggregation and toxicity (Wu et al., 2006), mitochondrial dysfunction (Abdel-Kader et al., 2007) and compromised hippocampal neurogenesis (Tchantchou et al., 2007). EGb 761® decreases blood viscosity and

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enhances microperfusion (Költringer et al., 1995). In a recent study, EGb 761® specifically increased dopamine levels in rat pre-frontal cortex, a region involved in working memory and monitoring of actions (Yoshitake et al., 2010). Recent reviews and meta-analyses of randomised controlled trials concluded that EGb 761® is effective in the treatment of dementia, including Alzheimer's disease, vascular dementia and mixed forms (Weinmann et al., 2010; Janssen et al., 2010). The drug seems to be particularly useful when dementia is accompanied by neuropsychiatric symptoms (NPS) (Weinmann et al., 2010; Ihl et al., 2010; Schneider et al., 2005). Inconclusive results have been achieved in prevention trials completed so far (DeKosky et al., 2008; Vellas et al., 2010), yet prevention is something clearly distinct from symptomatic treatment.

The objective of the present clinical trial was to confirm the findings of a preceding study of the same dosage regimen of EGb 761® in dementia (Ihl et al., 2011) and to further substantiate clinically relevant treatment effects of the once-daily formulation containing 240 mg of *G. biloba* extract EGb 761® on cognition and psychopathology in patients with AD and VaD, both associated with NPS.

2. Patients and methods

The clinical trial was conducted in accordance with the Declaration of Helsinki, the harmonized tripartite guideline for Good Clinical Practice (GCP) issued by the International Conference on Harmonization (ICH, 1996) and the requirements of the local legislation. The protocol was approved by the National Ethics Committee of the Republic of Moldova, the Ethics Committee of the Republican Clinical Mental Hospital Minsk, Republic of Belarus, and the Ethics Committee under the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation. Oral and written informed consent was obtained from all patients and caregivers before any trial-related procedures were undertaken. Investigators and clinical staff involved in the clinical trial underwent comprehensive briefing on the provisions of applicable laws and international GCP standards by experienced clinical research professionals.

2.1. Clinical trial population

Outpatients were recruited at 17 psychiatry or neurology clinics in three countries with Russian-speaking populations (Republic of Belarus, Republic of Moldova, and Russian Federation). These countries were chosen, because cholinesterase inhibitor use was not common and the quick recruitment of untreated patients with dementia speaking the same language to a placebo-controlled study was possible. Patients were eligible for this clinical trial if they were at least 50 years of age (no upper limit) and were suffering from mild to moderate AD or VaD. The diagnosis was based on the following criteria: a) probable AD in accordance with the NINCDS-ADRDA criteria (McKhann et al., 1984), b) possible AD with cerebro-vascular 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 have been present for at least 6 months. An MRI scan, consistent with the diagnosis of AD, VaD or AD with CVD and without evidence of other brain lesions, recorded not longer than 1 year prior to the screening visit had to be available.

The "Test for Early Detection of Dementia with Discrimination from Depression" (TE4D) (Ihl et al., 2000; Mahoney et al., 2005) was used as a screening instrument and to verify the presence of cognitive impairment in at least two domains. This was preferred to the "Mini-Mental State Examination" (MMSE) because of its higher sensitivity and specificity to discriminate between demented and non-demented subjects (Mahoney et al., 2005; Ihl et al., 2005). A total score of 35 or below, i.e. in the range indicating dementia, was required for inclusion. Patients were shown to have mild to moderate dementia as demonstrated by a total score from 9 to 23 (both inclusive) on the SKT test battery (Syndrom-Kurztest) (Erzigkeit, 1992; Kim et al., 1993), which roughly corresponds to a range from 14 to 25 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) (Sunderland et al., 1989) was used as a second screening instrument, the score of which had to be below 6. Patients were required to have a total score of at least 6 on the 12-item Neuropsychiatric Inventory (NPI) (Cummings, 1997), with at least one of the items "anxiety", "apathy/indifference", "irritability/lability" or "depression/dysphoria" rated 4 or higher. Severe depression was excluded by requiring a score below 20, with item 1 rated no higher than 3 on the 17-item "Hamilton Rating Scale for Depression" (HAMD) (Hamilton, 1960).

The presence of a caregiver/close relative who was willing to ensure that the patient complied with all aspects of the protocol was required: This included ensuring regular drug intake, reporting adverse events, accompanying the patient to the clinical visits and providing information about the patient. This person had to have regular personal contact with the patient on at least 4 days a week and to participate actively in caring for the patient in order to be able to provide information on the patient's behaviour and ability to perform activities of daily living.

Patients were excluded from the clinical trial 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, syphilis infection or gastrointestinal disease with uncertain absorption were not acceptable. Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs, anti-Parkinson drugs or Ginkgo products was prohibited during the clinical trial and for at least 8 weeks preceding randomisation.

2.2. Clinical trial design and intervention

This was a double-blind, parallel-group, multi-centre clinical trial. A screening period (up to 4 weeks) was required for examinations and washout of discontinued medications, followed by a 24-week treatment period. Randomisation (1:1, stratified by centre and in blocks of four), was performed with the aid of a validated computer program that linked random numbers to drug or placebo treatment, respectively. The sealed randomisation code was stored safely at the biometrics unit, and the length of randomisation blocks within which numbers of drug and placebo were balanced was not disclosed to investigators. Upon successful screening, each patient was assigned the treatment package with the lowest drug number still available at a site. Active drug and placebo tablets were indistinguishable in appearance, packaging and labelling. Patients were requested to take one tablet in the morning. Drug dispensation and return was handled by persons not involved otherwise in the conduct of the clinical trial, usually the hospital pharmacists. The investigational product, EGb 761®,[2] is a dry extract from *G. biloba* leaves (35–67:1), extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0–27.0% ginkgo

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

flavonoids calculated as ginkgo flavone glycosides and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, C and 2.6–3.2% bilobalide, and contains less than 5 ppm ginkgolic acids. In this trial, a once-daily formulation containing 240 mg of EGb 761® per tablet was used.

2.3. Outcome measures

Primary efficacy measures were the SKT, a 9-item cognitive test battery, the score of which ranges from 0 to 27, and the 12-item NPI, which assesses frequency and severity of neuropsychiatric symptoms (composite score) and ranges from 0 to 144. On both scales, higher scores indicate more severe impairment. The SKT was used for cognitive testing because it is well validated across many cultures and languages, including Russian (Lehfeld et al., 1997a,b). For memory testing it uses images instead of word lists to circumvent the problem of creating equivalent word lists in different languages, and in the stage of dementia scores are equivalent across countries (Lehfeld et al., 1997a,b), which is not generally the case for the cognitive subscale of the Alzheimer's Disease Assessment Scale (Verhey et al., 2004). An NPI version in Russian language was used that had been culturally and linguistically validated following standard procedures.

The NPI caregiver distress score (range 0–60); the Clinical Global Impression of Change (CGIC) as adapted 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; the DEMQOL-Proxy, which is a health-related quality-of-life scale for people with dementia (Smith et al., 2005); and the Verbal Fluency Test (animal fluency, as adapted by Mahoney et al. (2005)) were chosen as secondary efficacy variables. Patient self-ratings of presence and severity of dizziness and tinnitus were documented using 11-point box scales, 0 representing absence and 10 indicating extreme severity of a symptom. All cognitive tests and all interviews, except the ADCS-CGIC, were administered by the investigators and sub-investigators all of whom were psychiatrists or neurologists. The ADCS-CGIC ratings were done by independent physicians or psychologists who were not otherwise involved in the trial or the treatment of the patients and who had no knowledge of the results of other ratings and cognitive tests. Investigators and investigational staff were trained in the administration of tests and scales by an experienced geriatric psychiatrist and neuropsychologist. This involved demonstration and exercises using original scales and test kits. All efficacy assessments were performed at baseline, at week 12 and 24.

Safety was evaluated by physical examination, electrocardiography and laboratory tests at screening and week 24. Adverse events were recorded at all visits and during phone calls at weeks 6 and 18.

2.4. Sample size, data sets and statistical analysis

The trial was conducted to confirm the clinical efficacy 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. In the confirmatory analysis, this was done for both the primary cognitive efficacy variable "change of the SKT total score" and the primary variable for the assessment of the effects on neuropsychiatric symptoms "change of the NPI total composite score (items 1–12)" between baseline and week 24. The intersection-union principle (Berger, 1982) was used to test the hypothesis concerning the difference between EGb® 761 and placebo with respect to both endpoints. Thus, a difference between EGb 761® and placebo could be established at a two-sided type I error rate of $\alpha = 0.05$ if both single null-hypotheses (no difference in the change of the SKT total score, no difference in the NPI composite score) were rejected at level $\alpha = 0.05$ (two-sided). The two single null-hypotheses were tested applying an analysis of covariance model with the factors treatment and centre and the baseline value of the respective variable as a covariate.

The confirmatory analysis was primarily based on the full analysis set (FAS) including all patients who received randomised clinical trial medication at least once and having at least one measurement of the primary efficacy parameters during the randomised treatment period. Missing Data were handled by the last observation carried forward method (LOCF-method).

A sensitivity analysis (per protocol analysis) was performed including all patients of the full analysis set without major protocol violations (per protocol set, PPS). All patients who received randomised clinical trial medication at least once were analysed with regard to safety measures (safety analysis set, SAF).

The sample size was determined to provide a power of at least 95% for the rejection of the two null-hypotheses for each of the primary variables SKT and NPI at a type I error rate of $\alpha = 0.05$. This assures a power of at least 90% for the simultaneous rejection of both null-hypotheses. The sample size calculation was based on a common standard deviation of 4 points for the change of the SKT total score and 7 points for the change of the NPI total score, each between baseline and week 24. The sample size was assumed to be high enough to detect a clinically relevant difference between the treatment groups of at least 2 points with respect to change of the SKT total score and a difference of at least 2.5 points with respect to the change of the NPI total score. Under these assumptions, $2 \times 205 = 410$ patients were needed for the full analysis set in order to fulfil the power requirements given above if the two sample t-test were to be used for the analysis.

3. Results

3.1. Patient sample

Of 472 patients who were screened for eligibility, 410 were randomised and 62 failed screening and did not take any trial medication. All randomised patients received the allocated treatment at least once and were included in the SAF. The first patient entered the clinical trial in March 2008, and the last patient was completed in October 2009.

Eight patients of the SAF could not be included in the FAS due to missing efficacy assessments after baseline evaluation. Thus the FAS, on which the primary statistical analysis was based, consisted of 402 patients. The PPS comprised 371 patients without relevant protocol deviations. Since both FAS and PP analyses yielded nearly identical results, only those for the FAS analysis are provided. Patient disposition is depicted in Fig. 1, demographic characteristics and baseline data are summarised in Table 1. No clinically relevant differences were detected between the treatment groups.

Most patients had concomitant diseases at baseline, the most common of which were vascular disorders (EGb 761®: 86%, placebo: 85%; mainly hypertension and atherosclerosis), nervous system disorders (EGb 761®: 85%, placebo: 80%; mainly dizziness and CVD), cardiac disorders (EGb 761®: 55%, placebo: 45%; mainly coronary artery disease), and ear and labyrinth disorders (EGb 761®: 52%, placebo: 49%; mainly tinnitus). More than 75% of the patients were taking concomitant medications when starting trial medication, with agents acting on the renin–angiotensin system (EGb 761®: 54%, placebo: 48%), antithrombotic agents (EGb 761®: 29%, placebo: 23%) and beta blocking agents (EGb 761®: 18%, placebo: 18%) being the most frequently taken types of drugs.

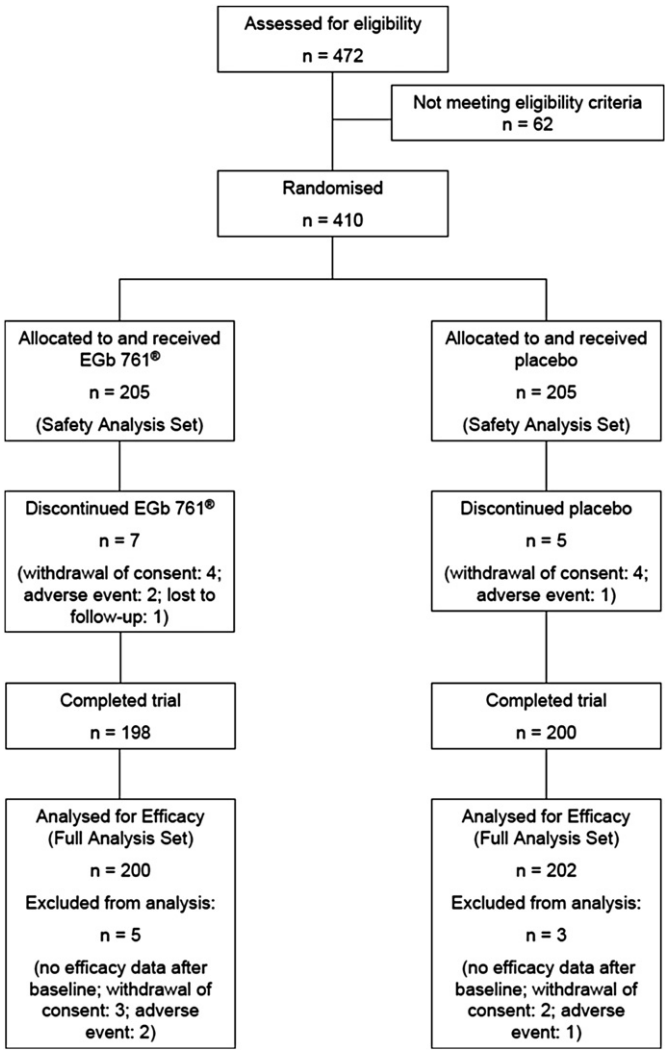

Fig. 1. Patient disposition and flow.

Table 1
Baseline characteristics of the full analysis set; means ± standard deviations and *p*-values of the two-sided *t*-test or numbers (percent) and *p*-values of the two-sided Chi-square test.

		EGb 761® ($N = 200$)	Placebo ($N = 202$)	*p*-value
Sex female		139 (69.5)	140 (69.3)	0.966
Age [y]		65.1 ± 8.8	64.9 ± 9.4	0.870
Weight [kg]		75.7 ± 13.3	72.5 ± 12.8	0.017
Height [cm]		166.9 ± 7.8	166.1 ± 7.4	0.282
Duration of memory problems [y]		3.2 ± 2.2	3.4 ± 2.8	0.815
Type of dementia	Probable AD	107 (54)	101 (50)	0.781
	Possible AD with CVD	73 (36)	79 (39)	
	Probable VaD	20 (10)	22 (11)	
SKT total score		15.1 ± 4.1	15.3 ± 4.2	0.593
NPI total score		16.8 ± 6.9	16.7 ± 6.4	0.961
NPI caregiver distress score		10.2 ± 5.3	10.1 ± 5.1	0.883
Verbal Fluency Test		7.6 ± 1.9	7.6 ± 1.9	0.769
TE4D cognitive score[a]		29.4 ± 4.0	28.9 ± 4.8	0.234
TE4D depression score[a]		3.9 ± 3.3	4.0 ± 3.6	0.814
ADL-IS mean score		1.7 ± 0.6	1.8 ± 0.6	0.573
DEMQOL-Proxy total score		85.7 ± 10.6	86.0 ± 10.3	0.810
11-point box scale tinnitus		1.4 ± 1.8	1.4 ± 1.8	0.996
11-point box scale dizziness		2.0 ± 1.8	1.8 ± 1.8	0.280

[a] TE4D scores at screening, the test was not repeated at baseline.

Overall, the treatment groups were well balanced with regard to medical history and concomitant medication.

Use of psychoactive drugs was rare: Three patients took antipsychotics (EGb 761®: 2, placebo 1) for short periods (up to 14 days), two patients (both on EGb 761®) took anxiolytics for two to four days, and six patients (EGb 761®: 5, placebo: 1) occasionally took sedatives (only valerian/valerate products). Prior short-term treatment with nootropics or cholinesterase inhibitors (ChEI) was reported for 13 patients (ChEI: 1) randomised to EGb 761® and for 24 patients (ChEI: 3) of the placebo group. Caregivers were immediate family (adult child, 44%), spouses (31%) or other relatives or friends (25%).

Compliance with the investigational treatment regimen, estimated from the number of unused tablets returned at week 12 and week 24, turned out to be very good during the whole double-blind treatment period (EGb 761®: 99.6 ± 7.3%; placebo: 99.8 ± 1.8%).

3.2. Primary outcome measures

Patients treated with EGb 761® improved in both cognitive test performance and neuropsychiatric symptoms, whereas there was little 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, Figs. 2 and 3).

In individual patients, a decrease in the SKT total score by at least 3 points, which is fairly equivalent to a 4-point decrease in the ADAS-cog score, is considered as clinically meaningful (Ihl et al., 1999; Rogers et al., 1998), and so is a decrease by 4 points or more in the NPI total score (Mega et al., 1999). So defined clinically significant responses were observed more frequently among patients treated with EGb 761® (SKT: 43%, NPI 57%) than in those taking placebo (SKT: 23%, NPI: 39%). The differences between treatment groups were statistically significant for both comparisons ($p < 0.001$).

Improvements and response rates under EGb 761® treatment were similar for patients with probable AD and those with CVD (i.e. possible AD with CVD or probable VaD), whereas placebo response was slightly higher in patients with CVD. Due to the well-known low sensitivity of the NINDS/AIREN criteria for probable vascular dementia this subgroup was too small to perform meaningful analyses.

A quantitative interaction of treatment by centre was observed (Källén, 1997). In 14 of 15 centres analysed (at least 16 patients each; 3 smaller centres were pooled) the effects of EGb 761® were more pronounced than in the placebo group for at least one of the primary efficacy parameters.

Table 2
Changes from baseline in primary and secondary outcome measures, score at week 24 for ADCS-CGIC; full analysis set; means (95% confidence intervals); *p*-values of the ANCOVA for the primary efficacy variables and of two-sided *t*-test for secondary efficacy variables.

	EGb 761® ($N = 200$)	Placebo ($N = 202$)	*p*-value
SKT total score	−2.2 (−2.7; −1.8)	−0.3 (−0.9; 0.2)	<0.001[a]
NPI total score	−4.6 (−5.6; −3.6)	−2.1 (−3.0; −1.2)	<0.001[a]
NPI caregiver distress score	−2.4 (−3.1; −1.8)	−0.5 (−1.1; 0.0)	<0.001
ADCS-CGIC	3.1 (3.0; 3.3)	3.8 (3.6; 4.0)	<0.001
ADL-IS overall mean score	−0.11 (−0,16; −0.06)	0.04 (0.0; 0.08)	<0.001
DEMQOL-Proxy total score	3.5 (2.2; 4.7)	1.5 (0.3; 2.7)	0.027
Verbal Fluency Test	0.7 (0.3; 1.0)	0.0 (−0.3; 0.3)	<0.01
TE4D cognitive score[b]	2.9 (2.2; 3.6)	0.7 (0.2; 1.3)	<0.001
11-point box scale dizziness	−0.6 (−0.8; −0.5)	−0.2 (−0.4; −0.1)	<0.001
11-point box scale tinnitus	−0.4 (−0.5; −0.2)	−0.3 (−0.4; −0.1)	0.31

[a] *p*-value of the analysis of covariance with treatment and centre as factors and the baseline value as covariate.
[b] TE4D difference to screening, the test was not done at baseline.

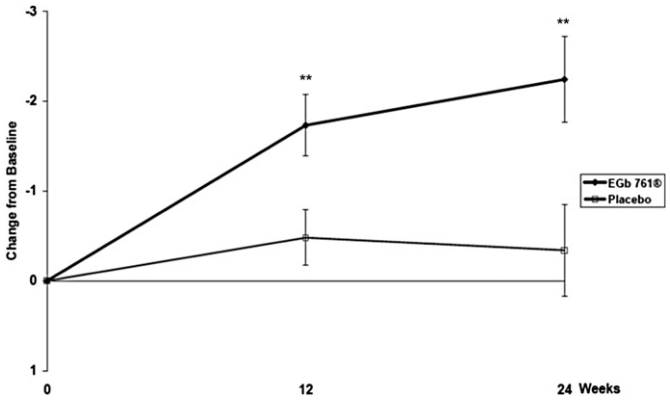

Fig. 2. Change in SKT total score from baseline to week 24; full analysis set ($n = 410$); means and 95% confidence intervals; $^{**}p < 0.001$, ANCOVA with treatment and centre as factors and the baseline value as covariate.

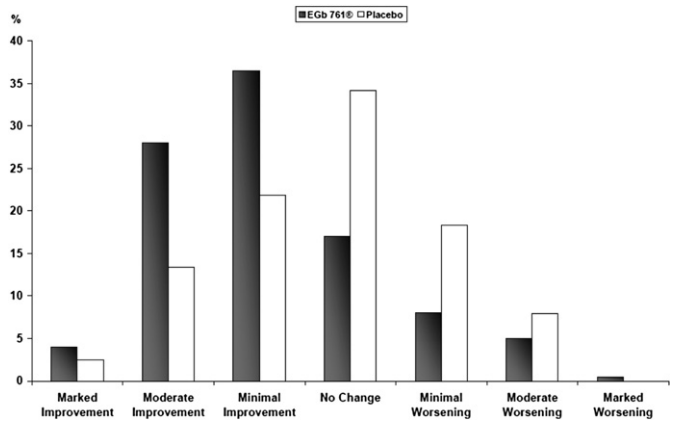

Fig. 4. Clinical global impression of change (ADCS-CGIC) at week 24; full analysis set ($n = 410$); $p < 0.001$, Chi-square test.

3.3. Secondary outcome measures

There was a consistent statistically and clinically relevant superiority of EGb 761® over placebo across most of the secondary outcome measures (Table 2), including improved ability to cope with the demands of everyday living, improved quality of life and clinicians' global judgement (Table 2, Fig. 4).

3.4. Safety and tolerability

Between baseline and two days after the end of the treatment period, 119 adverse events (AEs) were reported by 91 patients (44.4%) treated with EGb 761® and 126 AEs were documented for 82 patients (40.0%) of the placebo group. AEs observed for at least three per cent of patients in either treatment group are summarized in Table 3. No major differences were discernible, except for dizziness, which was more than three times more frequent in the placebo group (7.3%) than in the active treatment group (2.0%). For 59 AEs in 50 patients of the EGb 761® group and for 61 AEs in 46 patients of the placebo group a causal relationship could not be ruled out in double-blind assessment. There was no event of bleeding or impaired blood clotting in the group treated with EGb 761®.

Three serious adverse events (SAEs) were observed during treatment with active drug: a lethal cardiac arrest due to chronic heart failure in a patient suffering from multiple illnesses; a lethal ischaemic infarction in the region of the terminal branches of the middle and posterior cerebral arteries in a patient with a history of diabetes mellitus, hypertension, atherosclerosis, myocardial infarction and a previous stroke; and a transitory ischaemic attack in the region of the left medial cerebral artery in a patient with insufficiently controlled arterial hypertension. One SAE, a death due to pneumonia, probably caused by aspiration due to a bulbar syndrome, was reported in the placebo group. All SAEs were judged by the investigators to be related to concomitant conditions and unrelated to the trial medication.

The incidence and the profile of AEs reflect the typical pattern of events expected in elderly patients with dementia and cerebrovascular disease. The most common adverse event potentially related to treatment was headache, which is an unspecific symptom that is often reported by patients in any study, yet the frequency of headaches was slightly higher in the placebo group (EGb 761®: 5.9%, placebo: 6.3%).

Physical and neurological examination, 12-lead ECG, blood pressure, heart rate, and laboratory tests did not reveal any conspicuous or systematic changes under EGb 761® treatment.

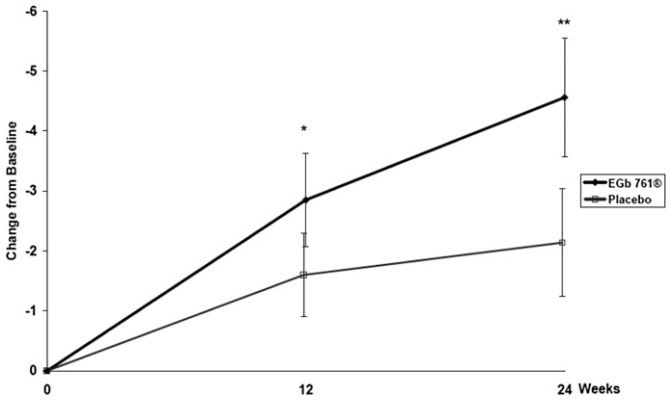

Fig. 3. Change in NPI composite score from baseline to week 24; full analysis set ($n = 410$); means and 95% confidence intervals; $^{*}p < 0.01$, $^{**}p < 0.001$, ANCOVA with treatment and centre as factors and the baseline value as covariate.

4. Discussion

The present clinical trial demonstrates the efficacy of the once-daily administration of EGb 761® at a dose of 240 mg in the treatment of dementia. Active treatment was significantly superior to placebo in improving patients' cognitive performance and neuropsychiatric symptoms which were the primary outcomes of the study. Using the NPI as co-primary outcome measure, rather than a functional or global assessment was a logical consequence of the

Table 3
Adverse events reported by at least 3% of patients of either treatment group with onset during and within two days after randomised treatment (safety analysis set); number and per cent of patients with adverse events.

	EGb 761® ($N = 205$)		Placebo ($N = 205$)		EGb 761® − placebo Diff. of rates with 95% CI[a]
	N	%	*N*	%	
Headache	15	7.3	17	8.3	−1.0 [−6.4; 4.4]
Dizziness	4	2.0	15	7.3	−5.4 [−9.9; −1.3]
Viral respiratory tract infection	8	3.9	6	2.9	1.0 [−2.9; 4.9]
Hypertension	5	2.4	8	3.9	−1.5 [−5.3; 2.2]
Somnolence	8	3.9	4	2.0	2.0 [−1.6; 5.8]
Upper abdominal pain	5	2.4	7	3.4	−1.0 [−4.7; 2.6]

[a] 95% confidence intervals calculated according to Newcombe (1998), Method 10.

choice of the target population, i.e. patients with clinically significant NPS. The clinical significance of the drug effects was demonstrated by the consistency of both primary outcomes and corroborated by the secondary outcomes, including functional abilities, global assessment, quality of life and response rates. As a consequence, the distress experienced by caregivers due to the patients' aberrant behaviours was alleviated.

The results are in line with those from former well-controlled clinical trials of EGb 761® which, according to the most recent reviews and meta-analyses, demonstrate efficacy and clinical benefits of EGb 761® in the treatment of dementia (Weinmann et al., 2010; Janssen et al., 2010). In particular, they are consistent with the findings from a recently published, independent trial using the same once-daily formulation of EGb 761® and an identical design (Ihl et al., 2011), thus confirming efficacy and safety of the 240 mg once-daily regimen.

In contrast to many anti-dementia drug trials performed during the 1990s, we did not exclude patients with clinically significant NPS, but decided to specifically select such patients. Taking into account that up to 80% of patients with dementia have NPS, with depression, apathy and anxiety being the most prevalent symptoms (Di Iulio et al., 2010; Steinberg et al., 2008), our patient sample was probably more representative of dementia patients seen in everyday practice. There have been two concerns about patients with NPS in anti-dementia drug trials: improving cognitive performance with drugs that have anti-depressant rather than cognition-enhancing effects and interference of the effects of psychoactive drugs with efficacy assessments. The latter is negligible, since only a low rate of participants received an additional psychopharmacological medication. The former is unjustified, because Powlishta et al. (2004) demonstrated that in patients with dementia, cognitive performance is determined by the severity of dementia and is not further aggravated by depression. Hence, improvement in cognitive function is not to be expected by antidepressant treatment alone.

The low average age of the patients and the enrolment of outpatients only might limit the generalizability of our findings. The average age reflects the life expectancy in Eastern European countries, which is clearly lower than in the Western world. However, the considerable burden of co-morbidity found in our patient sample seems to compare fairly well with that of older patients with dementia seen in Western countries. Moreover, the age range extends to 87 years and there was no relationship between age and treatment outcomes in this trial, suggesting that the study results were not biased by the patients' age. A considerable proportion of patients with dementia live in nursing homes, but due to the limited requirements and possibilities to perform instrumental activities of daily living in a nursing home, ADL scales used in studies of outpatients would not be feasible for inpatients. Taking into account, however, that caregiver distress related to NPS is a significant predictor of nursing home placement (de Vugt et al., 2005), our outpatient sample was probably not fundamentally different from nursing home patients.

According to Bornhöft et al. (2006), one of the fundamental questions regarding the external validity of a clinical trial is to what extent the inclusion and exclusion criteria define the "everyday or target" population. The patients included in the present study were selected by the widely used diagnostic criteria proposed by the NINCDS/ADRDA (McKhann et al., 1984) and NINDS/AIREN (Román et al., 1993) working groups. Due to the rare use of cholinesterase inhibitors and memantine in Eastern European countries, the study sample could be drawn from the broad spectrum of dementia patients normally referred to investigators' clinics rather than from minority groups of patients who either did not respond to or did not tolerate other treatments. Since the pharmacodynamics of EGb 761® interfere with both Alzheimer's and cerebro-vascular pathology, there was no need to exclude patients with VaD or those with AD and CVD, who represent the largest proportion of patients with dementia (Schneider et al., 2007; Korczyn, 2002). For methodological reasons, it is not possible to admit all patients seeking treatment for dementia to a phase-III study. However, by recruiting our study sample from the vast majority of dementia patients who have NPS (Di Iulio et al., 2010; Steinberg et al., 2008), by admitting the large proportion of patients with cerebro-vascular pathology (Schneider et al., 2007; Korczyn, 2002), and by running the study in a region where the recruitment of unmedicated dementia patients was possible, we achieved a sample that can be considered to be representative of the "everyday or target" population. Hence, there is reason to assume that our findings are relevant to the patients with mild to moderate dementia encountered in daily practice.

The validity of outcome measures most of which were developed in Western countries needs consideration. As mentioned above, the SKT battery, which may not be used as commonly as the ADAS-cog, is particularly feasible for multi-national research programs, because it uses images instead of word lists to test memory functions. The test has been validated in cross-cultural studies including Russian-speaking populations (Lehfeld et al., 1997a,b), and SKT total scores are highly correlated with ADAS-cog scores, suggesting that to a large extent both tests measure the same abilities (Ihl et al., 1999). The NPI is a widely used rating scale for the evaluation of severity and treatment-related changes of NPS that has been adapted linguistically and culturally in accordance with standard procedures for administration in Russian-speaking countries. To further demonstrate the clinical relevance of cognitive improvement in terms of activities of daily living and a global rating, as required by current guidelines (EMEA, 2008), we also administered the ADL-IS and the ADCS-CGIC, which consistently indicated superiority of EGb 761® over placebo. The ADL-IS was developed and validated in an international research project in which, among Japan, Western European and North American countries, Russia was involved (Lehfeld et al., 1997b). The 7-point scale of the ADCS-CGIC as well as the instructions and key words of the working sheets, although easy to understand, were adapted by forward and backward translation and reconciliation by a bilingual psychiatrist. Altogether, the assessment instruments used in the present study can be regarded as feasible and valid for use in Russian-speaking countries.

Overall, the present clinical trial corroborates findings from previous studies that showed *G. biloba* extract EGb 761®, and specifically at a 240 mg daily dose, to be both safe and effective in the treatment of patients with dementia associated with neuropsychiatric features.

Role of funding source

Employees of the sponsor (RH, SS) were involved in the planning and conduct of the trial, in the data analysis and interpretation as well as in the preparation of the manuscript.

Contributors

H. Herrschaft was involved in the development of the trial protocol and in quality assurance measures. A. Nacu was the Coordinating Investigator, S. Likhachev and I. Sholomov were investigators in the trial and were involved in data collection. R. Hoerr designed the study and wrote the trial protocol, S. Schlaefke was in charge of data management and analysis. All authors contributed to and have approved the final manuscript.

Author disclosure

H. Herrschaft has consulted for Dr. Willmar Schwabe GmbH & Co. KG. A. Nacu, S. Likhachev and I. Sholomov participated in the study as investigators and received investigator fees. R. Hoerr and S. Schlaefke are employees of Schwabe receiving fixed salaries.

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