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Efficacy and tolerability of *Ginkgo biloba* extract EGb 761® by type of dementia: Analyses of a randomised controlled trial

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ABSTRACT

Secondary analyses of a randomised controlled trial were performed to find out whether treatment effects of *Ginkgo biloba* extract EGb 761® differed by type of dementia. Three hundred ninety-five patients aged 50 years or above, with dementia with neuropsychiatric features were treated with EGb 761® (240 mg/day) or placebo for 22 weeks. Patients scored between 9 and 23 on the Short Syndrome Test (SKT), a cross-culturally validated cognitive test battery. Their total score on the Neuropsychiatric Inventory (NPI) was at least 5. Efficacy was assessed by the SKT test battery (primary outcome measure), the Verbal Fluency Test, the Clock-Drawing Test, the NPI, the Hamilton Rating Scale for Depression (HAMD), and the Gottfries–Bråne–Steen Scale (GBS). Applying standard research diagnostic criteria 214 patients were diagnosed with Alzheimer's disease (probable AD or possible AD with cerebrovascular disease) and 181 with probable vascular dementia (VaD). Under EGb 761® treatment the SKT total score improved by -3.0 ± 2.3 and -3.4 ± 2.3 points in patients with AD and VaD, respectively, whereas the patients on placebo deteriorated by $+1.2 \pm 2.5$ and $+1.5 \pm 2.2$ points, respectively ($p<0.01$ for both drug–placebo differences). Significant drug–placebo differences were found for all secondary outcome variables with no major differences between AD and VaD subgroups. The rate of adverse events tended to be higher for the placebo group.

1. Introduction

The *Ginkgo biloba* extract EGb 761® has been tested for efficacy in dementia in a series of clinical trials which have demonstrated its beneficial effects on cognitive performance, activities of daily living and behavioural symptoms of dementia [1–3]. Comprising effects on blood viscosity and perfusion [4], oxidative stress and mitochondrial function [5,6], insulin resistance [7], formation and toxicity of Aβ oligomers [8,9] as well as on neurotransmitter systems [10,11] the pharmacodynamic profile of EGb 761® does not appear to be specific for one certain type of dementia. Moreover, former clinical trials suggest that the drug has beneficial effects in Alzheimer's disease (AD) and vascular dementia (VaD) [12,13]. Taking this into account, both patients with AD and patients with VaD were enrolled in a recently conducted randomised controlled trial [3]. Considering further that AD and VaD have a number of risk factors in common [14–17], that clinico-pathological studies have shown a high coincidence of AD-specific and vascular pathology [18,19], that cerebrovascular lesions contribute to cognitive and functional deterioration in AD [18,20], and that therefore mixed pathology may underlie a considerable proportion of dementia cases [21,22], this type of trial appears to be justified.

To assess the efficacy of EGb 761® by type of dementia, separate analyses were performed for the AD and VaD subgroups as specified prospectively in the protocol of the clinical trial published recently by Napryeyenko et al. [3].

2. Methods

The trial was carried out in accordance with the Declaration of Helsinki (year 2000 revision), the harmonised tripartite guideline for good clinical practice (GCP) issued by the International Conference on Harmonisation (ICH) [23] and applicable local laws. The protocol was approved by the ethics committee of the State Pharmacology Center at the Ukraine Ministry of Health. At a start-up meeting investigators and clinical staff involved in the trial were trained in legal requirements and GCP standards by experts in GCP and clinical trials methodology, all with long-standing experience in their fields. Informed consent was elicited from all patients before enrolment.

2.1. Participants

Four hundred outpatients were recruited at outpatient clinics of 16 psychiatric or neurological hospitals. They were eligible for this study if they were at least 50 years of age and diagnosed with AD (probable AD or possible AD with cerebrovascular disease) or VaD. Clinical

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diagnoses were established employing the criteria specified by the National Institute for Neurological and Communicative Disorders and Stroke (NINCDS) together with the Alzheimer's Disease and Related Disorders Association (ADRDA) [24] and by the National Institute of Neurological Disorders and Stroke (NINDS) together with the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) [25] as appropriate. A CT or MRI scan, no more than one year old, had to be consistent with the inclusion diagnosis. The Test for Early Detection of Dementia with Discrimination from Depression (TE4D) [26] 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 [26,27]. A total cognitive score of no more than 35 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 [28], 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) [29]. The Clock-Drawing Test (CDT) after Sunderland et al. [30] 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) [31], with at least one item score (other than delusions or hallucinations) being 3 or higher. Severe depression was excluded by requiring a score below 20 on the 17-item Hamilton Rating Scale for Depression (HAMD) [32]. The presence of a caregiver was required who was able and willing to provide information on the patient's behaviour and competence to perform activities of daily living.

Patients were excluded from the study, if they had any other type of dementia or neurological disorder, current or recent major depression or other psychiatric disorder, severe or insufficiently controlled cardiovascular, renal, or hepatic disorder, diabetes, anaemia, or thyroid dysfunction. Active malignant disease, HIV or lues infection and gastrointestinal diseases with uncertain absorption were not accepted. Treatment with other anti-dementia drugs, cognitive enhancers, cholinergic, anti-cholinergic or haemorheologically active drugs, anti-Parkinson drugs or *Ginkgo* supplements was prohibited during the study and at least 8 weeks preceding randomisation.

2.2. Trial design and intervention

The multi-centre trial with two parallel treatment arms was carried out in a double-blind manner. After a medication-free screening period of up to 4 weeks, patients were randomly assigned to receive the *Ginkgo biloba* extract EGb 761® at a daily dose of 240 mg (2×120 mg) or placebo. Centre-stratified randomisation (drug–placebo ratio 1:1) in blocks of four was performed by the sponsor's biometrics unit using a validated computer program that linked ascending drug numbers to active drug or placebo, respectively. The randomisation list was sealed and stored safely at the sponsor's biometrics unit, and block length was not disclosed to investigators. Drug and placebo tablets were indistinguishable by appearance, packaging and labelling. After the baseline assessment, each patient was allocated the drug package with the lowest drug number still available at the clinical site. The investigational product, EGb 761® is a dry extract from *Ginkgo biloba* leaves (35–67:1), extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0–27.0% *Ginkgo* 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, with a content of ginkgolic acids below 5 ppm. Drug and placebo were manufactured and provided by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany.

2.3. Outcome measures

The SKT, a 9-item cognitive test battery with scores ranging from 0–27 (higher scores indicating more severe impairment) was defined as primary efficacy measure. Secondary efficacy measures were the 12-item NPI, which assesses frequency and severity of neuropsychiatric symptoms (composite score range 0–144) and caregiver distress caused by such symptoms (score range 0–60); the activities-of-daily-living (ADL) subscale of the Gottfries–Bråne–Steen (GBS) overall geriatric assessment scale [33]; the total score of the GBS (comprised by the intellectual "I", the emotional "E", and ADL subscores, but not the behavioural "S" subscore which was not documented to avoid redundancy); the Verbal Fluency Test (animal fluency) [34]; the CDT and the HAMD. 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 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 and video presentation. Safety was assessed by documentation of adverse events, physical examination, electrocardiography, and laboratory tests. All assessments were performed at baseline, week 12 and week 22 (except adverse events, which were also asked for at week 6 and week 17 phone calls, and the other safety variables, that were only assessed at baseline and week 22).

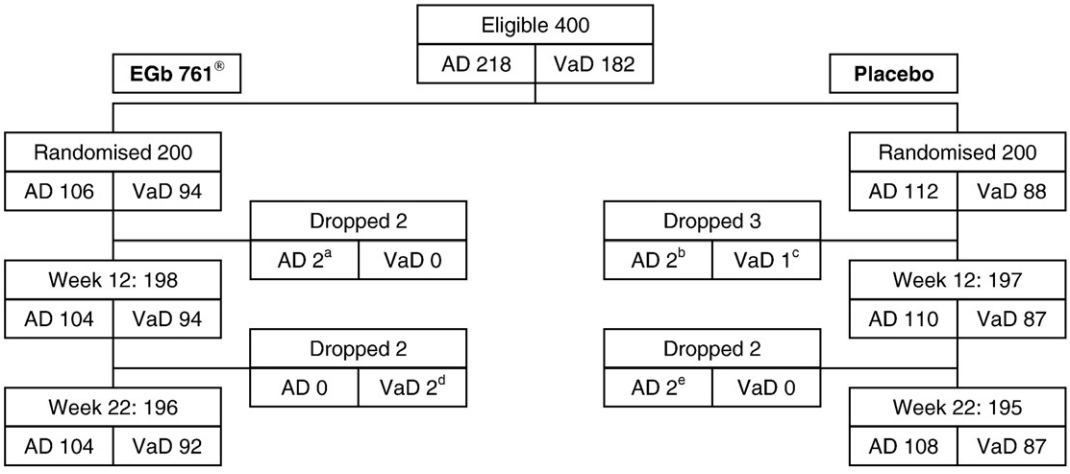

Fig. 1. Disposition of patients; a) adverse event (1), withdrawal of consent (1); b) withdrawal of consent (2); c) withdrawal of consent (1); d) lost to follow-up (1), withdrawal of consent (1); e) withdrawn due to medical reasons (1), withdrawal of consent (1).