S T U D Y P R O T O C O L

(Phase III / IV)

Randomised, Double-blind, Placebo-controlled, Parallel-Group, Multicentre Trial to Confirm the Efficacy, Safety and Tolerability of Ginkgo biloba Special Extract EGb 761® in Patients Suffering from Alzheimer's Disease, Vascular Dementia or Mixed Type Dementia with Neuropsychiatric Symptoms

Study No. 523001.01.061

The information contained in this document is provided to you in confidence as an investigator, potential investigator or consultant, or for a review committee. It is understood that this information will not be disclosed to others without written authorisation from SCHWABE, Karlsruhe, Germany, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

PROTOCOL SYNOPSIS

Objective:	To confirm the clinical efficacy, safety and tolerability of EGb 761® in patients suffering from Alzheimer's disease (AD), vascular dementia (VaD) or mixed type dementia (MixD) with neuropsychiatric symptoms.
Study Design:	Randomised, double-blind, placebo-controlled, multicentre trial with 2 parallel treatment groups, preceded by a maximum 4-week run-in period without trial medication
Drug under Study:	Ginkgo biloba special extract EGb 761®
Reference Drug:	Placebo
Dosage:	➢ Run-in Period: No trial medication ➢ Treatment Period: Active treatment group: 2 x 120mg EGb 761® Placebo group: 2 x 1 tablet placebo
Duration of Treatment:	22 weeks
Number of Patients:	400 randomised outpatients (200 per treatment group; approximately 20 to 30 patients per site)
Primary Outcome Variables:	SKT Test battery (Syndrome Kurz-Test)
Secondary Outcome Variables:	NPI (Neuropsychiatric Inventory, 12 Items); Clock Drawing Test (CDT), Verbal Fluency Test, Hamilton Rating Scale for Depression (HAM-D), Gottfries-Bråne-Steen Scale (GBS); Concomitant Symptoms Scale, adverse events, laboratory tests.
Visits:	4 Visits + 2 Phone Calls: Screening – Baseline – Week 6 (phone call) – Week 12 – Week 17 (phone call) – Week 22
Schedule:	Beginning: October 2003 Planned Completion: September 2004

RESPONSIBILITIES

Responsibilities in this clinical trial are in accordance with the ICH Guideline for Good Clinical Practice if not stated otherwise in this protocol.

Persons Responsible:

Investigators: 12 neurologists, psychiatrists, geriatricians and other qualified physicians in Bulgaria (see Appendix 1)

Co-Investigators: To be determined (see Appendix 1)

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To be determined (see Appendix)

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STUDY FLOW CHART

	Visit / Measure	Screening Visit Week -4		Baseline Visit Day 0	Treatment Period			
					Week 6 (Call)	Week 12	Week 17 (Call)	Week 22
Investigator	Informed Consent	X						
	Medical (incl. Drug) History and Risk Factors	X						
	Physical Examination/Vital Signs	X		X[1]		X[1]		X
	Neurological Examination	X						X
	TE4D, Items 1-9 (incl. CDT and Verbal Fluency)	X						
	NINCDS/ADRDA	X						
	NINDS/AIREN	X						
	Ischemia Score (Rosen Score)	X	M					
	NPI (12 Items)	X	E	X		X		X
	HAM-D	X	D	X		X		X
	Inclusion/Exclusion Criteria	X	I					
	GBS		C	X		X		X
	Concomitant Symptoms Scale	X	A	X		X		X
	Adverse Events		L	X	X	X	X	X
	Termination Record							X
Tasks may be delegated	ECG	X	M					X
	Laboratory	X	O					X
	Drug Dispensation		N	X		X		
	Drug Return		I			X		X
	SKT	X	T	X		X		X
	Verbal Fluency		O	X		X		X
	CDT	X[2]	R	X		X		X
Radiologist	CT	X						

[1] Vital Signs only
[2] included in TE4D

See 9. Study schedule, page 23 + 24

1 INTRODUCTION: MOTIVATION AND ETHICAL ASPECTS

1.1 Disease under Study

The primary risk factor for both Alzheimer's disease and vascular dementia is age. Hence, the prevalence of dementia is increasing as longevity is becoming the rule.

Alzheimer's disease is considered the most frequent cause of dementia in the elderly. It leads to a progressive deterioration of higher cerebral functions. Typical histologic features are neuritic plaques and neurofibrillary tangles located predominantly in temporoparietal regions of the cerebral cortex. Aberrant cleavage of the transmembraneous amyloid precursor protein (APP) with accumulation of the amyloidogenic ß-A4 fragment and hyperphosphorylation of intracellular tau-protein underlie the formation of these characteristic features. The causal pathogenesis of the disease is still to be elucidated. In a small percentage of cases, clearcut genetic defects within DNA regions coding for APP or one of the presenilins can be proved. An impairment of neuronal glucose metabolism, increased activity of oxygen free radicals, cortisol-mediated stress mechanisms, active mediators of inflammation, and deactivation of certain transmitter-receptor systems are consistently found. Most prominent is the acetylcholine deficiency in the hippocampus, but also noradrenaline, dopamine and serotonin concentrations are reduced below normal in several cortical regions.

There is no cure for Alzheimer's disease, but some symptomatic treatments (e. g. acetyl-cholinesterase inhibitors, memantine) may improve memory and other cognitive abilities as well as activities of daily living.

Cerebrovascular Disease (CVD) is another frequent cause of dementia in the elderly. Vascular dementia may be caused by ischaemic brain lesions including global hypoxia, haemodynamic or thromboembolic infarction or may be of vascular origin such as microangiopathy (small vessel disease) or atherosclerosis. Typical histological features of CVD are arterial territorial infarction, watershed infarctions, lacunes, laminar necrosis, granular atrophy, subcortical leukencephalopathy, gliosis or incomplete ischaemic necrosis including hippocampal sclerosis (Román et al. 1993). Frequent forms which cause ischaemic vascular dementia (IVD) are subcortical sclerosis (M. Binswanger), IVD with acute onset, multi-infarct-dementia, and mixed types (Wetterling, 1998). Each of these subgroups represents a more or less different onset and clinical course due to its aetiology. The underlying pathogenetic process of vascular dementia has not yet been clarified, as the neuropathological changes seen with CVD are not necessarily associated with dementia. Important factors in the development of dementia appear to be the volume, localisation and multiplicity of the vascular lesions exacerbated by factors such as white matter disease, vascular risk factors, comorbidity, genetic and demographic factors (Desmond, 1996).

As the pathogenesis of the different subtypes of vascular dementia has not yet been clarified, there is no definite cure for IVD except by reducing vascular risk factors which contribute to the underlying vascular disease. However, symptomatic treatment (e.g. enhancing of cerebral blood flow and protection of nerve cells to prevent them from further ischaemic damage) may improve memory and other cognitive abilities as well as activities of daily living.

In addition to pure forms of Alzheimer's disease and vascular dementia, there is a considerable number of mixed forms (Snowdon et al. 1997). The fact that vascular risk factors were found to be associated with an increased risk for Alzheimer's disease led to the hypothesis that vascular pathology and impaired perfusion may have a causal role in Alzheimer's disease (Hofman et al. 1997). Moreover, strokes may precipitate dementia in Alzheimer's disease (Snowdon et al. 1997) or even trigger Amyloid deposition and thus initiate the pathogenesis of Alzheimer's disease. On the other hand, it is conceivable that Alzheimer's disease and CVD develop independently, both contributing to a progressing syndrome of dementia (Snowdon et al. 1997). Fact is that in clinico-pathological studies usually a considerable number of patients with both cerebrovascular lesions

and features of Alzheimer's disease (plaques and tangles) are found (Snowdon et al. 1997, Neuropathology Group of the MRC CFAS, 2001) and that both types of lesions appear to contribute to dementia (Jagust 2001).

Whereas older antidementia drugs, such as EGb 761®, have always been considered as acting in an unspecific way, thus influencing both Alzheimer's and cerebrovascular pathology, cholinesterase inhibitors were hypothesised to act specifically on the cholinergic deficit in Alzheimer's disease. Meanwhile, findings of clinical trials suggest that drugs belonging to the latter class may also ameliorate the symptoms of vascular dementia or Alzheimer's disease with cerebrovascular pathology (Erkinjuntti et al. 2002, Moretti et al. 2002). Finally, we have closed the circle and arrived at a situation that is essentially similar to that we faced before the advent of cholinesterase inhibitors. We obviously have a continuum between Alzheimer's disease and vascular dementia rather than two clearly distinct diseases, and we have drugs that act on both Alzheimer's disease and vascular dementia. Under such circumstances, requiring a strict selection of either Alzheimer's patients or vascular dementia patients to be enrolled in studies of currently available antidementia drugs would appear arbitrary rather than mandatory on the ground of a scientific rationale. Therefore, the inclusion of patients with Alzheimer's disease, vascular dementia or mixed forms appears to be justified and reasonable.

One core syndrome of dementia is cognitive impairment which serves as key diagnostic feature. Memory impairment and impairment in at least one further domain of cognition are required by currently used criteria (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, DSM-IV, APA 1994) to establish a diagnosis of dementia. In addition, neuropsychiatric symptoms are common in dementia, as well. In a cross-sectional study, 75% of dementia patients exhibited at least one such symptom in the previous month, two or more symptoms were observed in 55% of cases (Lyketsos et al. 2002). Since the beginning of the cognitive impairment, 80% of demented patients had presented at least one neuropsychiatric symptom. The most frequent symptoms in dementia patients were apathy (36%), depression (32%) and agitation/aggression (30%). There were no differences in prevalence of neuropsychiatric symptoms between participants with Alzheimer-type dementia and those with other dementias, including vascular dementia, with the exception of aberrant motor behaviour, which was more frequent in Alzheimer-type dementia. Of note, neuropsychiatric symptoms do not merely present as complications of advanced disease, but are typically associated with dementia from its early beginning (Lyketsos et al. 2002). They should therefore be considered as primary manifestations of dementia, as are cognitive disturbances (Cummings 1997, Lyketsos et al. 2002).

1.2 The Investigational Drug

Ginkgo biloba special extract EGb 761® is produced from dried leaves of the Ginkgo tree. It is obtained in a multiple-stage extraction process, purified to remove unwanted accompanying substances, and standardised to 24 % Ginkgo flavone glycosides and 6 % terpene lactones (ginkgolides, bilobalide), the pharmacologically active constituents.

In animal studies, EGb 761® has been shown to have a beneficial effect on rheological properties of the blood, to increase cerebral perfusion, exert protective effects against ischaemia and hypoxia, influence the energy metabolism of nerve cells, and to have antioedematous and myelin-protective action as well as antioxidant properties. EGb 761® influences various transmitter-receptor systems by modulating receptor density and neurotransmitter uptake. EGb 761® produces marked improvements of learning and memory processes in animal experiments. It has been shown to act as a free radical scavenger in vitro as well as in vivo. After intravenous administration, EGb 761® decreases blood viscosity and enhances cerebral blood flow in humans, without steal effect.

The acute toxicity of EGb 761® is extremely low, with an acute intravenous LD_{50} of 1100 mg/kg in

mice and rats, and an oral LD_{50} of 7725 mg/kg in mice and more than 10 g/kg in rats. Long-term administration of EGb 761® to rats and dogs at oral doses of up to 500 and 400 mg/kg respectively did not lead to any histological, biological, or haematological signs of toxic action. Studies of teratogenicity, reproduction toxicity, and mutagenicity did not show any harmful effects.

The clinical efficacy of EGb 761® has been demonstrated in 13 randomised and placebo-controlled double-blind studies in patients with impairment of cerebral function mostly of vascular origin. Clinical efficacy of EGb 761® has also been demonstrated in 3 randomised, placebo-controlled, double-blind studies concerning Alzheimer-type dementia, and in 3 further studies in mixed populations, comprising patients with vascular dementia and Alzheimer-type dementia. The results of the various studies and subgroup analyses of the studies with mixed populations do not give definitive evidence of qualitative or quantitative differences in efficacy as a function of the target diagnosis. One study was conducted in patients with vascular dementia and beneficial effects of the drug were found with respect to cognitive performance and overall psychopathology. Exploratory analyses of available data suggested that EGb 761® improves both neuropsychiatric symptoms in dementia or impairment of cerebral function and cognitive performance in dementia patients suffering from neuropsychiatric symptoms (Hoerr, in press). The tolerability of EGb 761® has proved to be very good both in the clinical studies and in the many years of use in hospitals and general practice. Suspected cases of adverse drug reactions have been very infrequent. In extremely rare cases following oral administration of Ginkgo biloba extract EGb 761® (e.g. Tebonin® forte), mild gastro-intestinal disorders, headaches or allergic skin reactions have been observed.

Details of the pharmacological, toxicological and clinical trials as well as post-marketing experience are given in the Investigator's Brochure (Version 13, dated 21 February 2003).

1.3 Justification of Dosage, Dosage Regimen and Duration of Treatment

Various oral daily doses have been administered in prospective clinical trials for different treatment periods: 480 mg for 4 weeks, 240 mg for 24 weeks (Kanowski et al. 1996) and 160 mg for 52 weeks (Taillandier et al. 1986). All these doses proved to be safe and were well-tolerated. Dementia trials yielded positive results on application of both the 120 mg (Le Bars et al. 1997, Weitbrecht & Jansen 1986) and the 240 mg (Maurer et al. 1997, Kanowski et al. 1996, Hofferberth et al. 1994) daily dose regimen. Response rates observed upon treatment with 240 mg EGb 761 per day appeared to be higher than those upon 120 mg. As regards the treatment regimen, positive results were obtained in clinical trials both with twice daily (Kanowski et al. 1996, Taillandier et al. 1986) and thrice daily (Le Bars et al. 1997, Maurer et al. 1997, Hofferberth et al. 1994) application. Compliance is generally expected to be better in a twice daily regimen.

Treatment periods of at least 3 to 6 months have been recommended for clinical trials of antidementia agents for symptomatic therapy by several guidelines (Leber 1990; CPMP 1997). The data of EGb 761® dementia trials demonstrate that treatment effects still increase after 12 weeks and are more pronounced after 24 or 26 weeks of treatment.

Hence, it appears to be ethically and scientifically justified to use, daily doses of 240 mg (split into 2 x 120 mg) for a treatment period of 22 weeks in this clinical trial.

1.4 Risk-Benefit Assessment

According to abundant evidence from clinical trials, post-marketing surveillance and many years of therapeutic application, there is no major risk linked to the intake of EGb 761® in daily doses of 240 mg for 22 weeks.

The adverse events potentially associated with EGb 761®, such as gastrointestinal symptoms,

headache and allergic skin reactions, are usually mild and do not constitute a threat to patients. Bleeding has been observed in individual cases after long-term treatment with Ginkgo preparations, some of unknown origin and quality and in some instances under concomitant treatment with anti-platelet or anti-coagulant drugs; however, specific clinical trials with Ginkgo special extract EGb 761® at a dose level of 240 mg per day have shown no effect on coagulation parameters (including PTT, Quick test, bleeding time) and no interaction with acetyl-salicylic acid.

There is nearly no risk associated with the tests and examinations required by this trial protocol, except for a small risk of infection during blood sample drawing. This can be minimised by state of the art execution.

On the other hand, based on pharmacological and earlier clinical findings it can be expected, that patients eligible for this study will benefit to some degree from the treatment with EGb 761®. Even placebo patients usually show slight improvement of cognitive abilities and mental alertness. This is usually interpreted as an unspecific activation due to increased care and demand.

To date, there is no definite cure for Alzheimer's disease or vascular dementia. Some drugs have been approved for the symptomatic treatment of Alzheimer's disease, but the benefits are moderate with an uncertain and probably limited duration. Only a fraction of the patients respond to treatment. Because of the above mentioned limitations, none of the drugs available so far can be regarded as a standard reference drug, so an active comparison is not warranted. In addition, a placebo-controlled trial requires a lower number of patients than a reference-controlled trial for clinical efficacy to be confirmed. Considering the low side effect potential of EGb 761®, the possible benefit for the patients taking part in the trial and the usefulness of more comprehensive documentation of the efficacy of an effective low-risk drug in this type of patients with dementia, this clinical trial appears to be ethically justified on the grounds of a favourable risk-benefit ratio.

2 OBJECTIVES

The objective of this clinical trial is to confirm the clinical efficacy, safety and tolerability of the Ginkgo biloba special extract EGb 761® in Alzheimer´s disease, vascular dementia and mixed type dementia associated with neuropsychiatric symptoms.

Clinical efficacy is expected to manifest itself as a decrease or smaller increase, compared with the placebo group, in the score of the SKT Test battery (Syndrome Kurz-Test) in the patient group treated with EGb 761®.

3 STUDY DESIGN

3.1 Study Type

multicentre
randomised
double-blind
placebo-controlled
parallel-group

3.2 Number of Patients

400 outpatients (approximately –20 - 30 patients per trial site).

3.3 Duration of Observation

Individual duration: 26 weeks
(up to 4-week run-in period, 22-week randomised treatment period)

Total duration of the trial: 12 months
(6 months enrolment period, 6 months screening and treatment)

The duration of the enrolment period may be prolonged in case of delay in patient recruitment.

4 PATIENT SELECTION

Obligatory criteria for patient´s selection are evidence of probable Alzheimer's disease, possible Alzheimer's disease with cerebrovascular disease (CVD), or vascular dementia, and exclusion of any other disease probably involved in the development of dementia.

4.1 Inclusion Criteria

Patients are eligible for inclusion in this study, if they fulfil all of the following criteria:

1. Male or female outpatients aged 50 years or over
2. Suffering from mild to moderate Alzheimer's disease, vascular dementia or mixed type dementia; the diagnosis is based on the diagnostic criteria of NINCDS/ADRDA (McKhann et al. 1985) for probable Alzheimer's disease, on the criteria of NINDS-AIREN (Román et al. 1993) for probable vascular dementia and on the relevant parts of both sets of criteria for possible Alzheimer's disease with cerebrovascular disease
3. Presence of symptoms typical for dementia for at least 6 months
4. Written informed consent according to applicable law; patient must be able to give informed consent
5. Written informed consent from the caregiver/relative
6. TE4D total score ≤ 35
7. Clock Drawing Test (CDT) total score < 6 (Sunderland scoring, Item 7 of TE4D)
8. SKT test battery total score of 9 – 23 (both inclusive) at screening
9. HAM-D (17 Items) total score < 20 and item $1 \leq 3$ at screening
10. NPI: at least one item (other than delusions or hallucinations) ≥ 3 and total score ≥ 5
11. CT or MRI scan no more than 1 year prior to inclusion consistent with the diagnosis of Alzheimer disease, vascular dementia or mixed type dementia and without evidence of other brain lesions.
12. Sufficient Bulgarian language skills to understand and respond to all interview questions and

undergo neuropsychological testing without the assistance of an interpreter

13. A caregiver/close relative is available and willing to ensure that the patient complies with all aspects of the protocol including regular drug intake, reporting adverse events, accompanying the patient to the clinical visits, and rating the activities of daily living; this person should have regular personal contact with the patient on at least 4 days a week and participate actively in caring for the patient

4.2 Exclusion Criteria

Patients with any of the following characteristics must not be included in the study:

1. Participation in another experimental drug trial at the same time or within the past 4 weeks before enrolment

2. Prior participation in clinical trials with Ginkgo biloba

3. Hospitalization of the patient for treatment; assisted living facility residence is acceptable if the patient is not bedridden and does not need general bedside nursing and if a responsible caregiver is available who sees the patient on a regular basis on *at least 4 days a week* and accompanies him/her to the study visits

4. Ischaemic stroke with sequelae within the last three months

5. Dementia of other origin or other neurological disorders, e.g. alcohol associated brain damage, HIV associated cognitive disorder, Parkinson's disease, Huntington's disease, Pick's disease, Wilson's disease, normal pressure hydrocephalus, progressive supranuclear palsy, Creutzfeldt-Jakob disease, infectious CNS disease, brain tumour, subdural hematoma, multiple sclerosis, seizure disorder, brain trauma, etc (including clinical suspicion of the above).

6. Current major depression or history of recurrent major depression or other current axis I psychiatric disorder as defined by DSM-IV criteria before onset of dementia; if such a disorder was present before, the last episode must have been finished at least one year before enrolment.

7. History of head trauma that might be causally related to the dementia because of:
   - its clinical severity or
   - trauma-related lesions in CT or
   - temporal relationship to the onset of dementia or
   - repeated minor head trauma

8. Any use of antidementia drugs, nootropics, cognition enhancing drugs, cholinergic and anticholinergic drugs unless there is a sufficient washout before entering the randomised treatment period (for details see Section 6)

9. Any use of haemorrheologic drugs and anti-Parkinson drugs unless there is a washout of at least 8 weeks before entering the randomised treatment period (for details see Section 6). It should be noted that the use of anticoagulants, acetylsalicylic acid or other antiplatelet agents is allowed, as it is commonly prescribed in patients suffering from CVD

10. Substance addiction or abuse within the last 5 years

11. Severe, uncontrolled cardiovascular disease, especially:
    - severe (stage IV acc. to the Canadian Cardiovascular Society) or unstable angina pectoris
    - decompensated congestive heart failure (NYHA stage IV)

- myocardial infarction within the last 6 months
- uncontrolled hypertension (systolic pressure ≥ 180mmHg/diastolic pressure ≥ 115mmHg)
- known clinically significant cardiac arrhythmias (Lown classes IVb and V, bifascicular bundle branch block)

12. Severe renal or hepatic dysfunction (serum creatinine or serum ASAT, ALAT or Gamma-GT above 3 times the upper limit of the reference range)

13. Insufficiently controlled insulin-dependent diabetes mellitus

14. Clinically significant anaemia

15. Clinically significant thyroid dysfunction as expressed by significant abnormality in TSH

16. HIV infection or Lues of any stage

17. Active malignant disease (Exception: prostate cancer T1N0M0 which does not require treatment within the next 7 months except hormone therapy)

18. Known hypersensitivity to Ginkgo biloba extract

19. Severe and insufficiently corrected loss of vision or hearing, severe language difficulties or any other disability that may prevent the patient from co-operating adequately in the trial or that may interfere with neuropsychologic test performance

20. Active peptic ulcer disease or any gastrointestinal disease with potential impairment of the absorption of orally applied drugs (e.g. Billroth I + II, Crohn´s disease, ulcerative colitis, any kind of enterectomy)

21. Any circumstances that do not allow the patient to be followed up at the scheduled intervals

22. Female patients of childbearing potential

It should be noted that criteria required to prove lack of childbearing potential are treatment with oral contraceptives for at least 6 months, postmenopausal state for at least 2 years, hysterectomy, bilateral tubal ligation or bilateral oophorectomy.

Under no circumstances may patients be randomised to the treatment period more than once.

5 INVESTIGATIONAL PRODUCT

5.1 Active Substance and Pharmaceutical Description

Active treatment group: film-coated tablets containing 120 mg of Ginkgo biloba special extract EGb 761®, adjusted to 28.8 mg flavonol glycosides and 7.2 mg terpene lactones;
SMC-No: 5560

Placebo group: film-coated tablets containing no active drug;
SMC-No: 5560P

EGb 761® is an extract from dried Ginkgo biloba leaves (35-67 : 1 ratio of raw plant material to extract), adjusted to 24% ginkgo-specific flavonol glycosides and 6% terpene lactones (ginkgolides, bilobalide). It contains less than 5 ppm ginkgolic acids.

Active drug and placebo are of identical appearance.

5.2 Application

Dosage:

Active substance group:	240 mg/day EGb 761® (i. e. 2 x 1 tablet containing 120 mg)
Placebo group:	2 placebo tablets/day (i. e. 2 x 1 placebo tablet)

Administration: The film coated tablets are to be swallowed whole with some liquid, one tablet in the morning, one tablet in the evening. The tablets may be taken with or without meals.

Duration of Treatment: 22 weeks

5.3 Packaging

The investigational product will be provided by Dr. Willmar Schwabe GmbH & Co. Every patient is to receive a sufficient number of tablets for each therapeutic phase, whereby unused drug and containers are to be returned to the investigating physician.

Every patient is to receive 2 boxes:
- Box 1 for treatment weeks 1 to 12 contains 13 blister cards with 14 tablets each
- Box 2 for treatment weeks 13 to 22 contains 11 blister cards with 14 tablets each

(i. e. 1 blister card per week plus 1 supplementary blister card per box)

The boxes to be used for one patient will be packed together in a bigger cardboard box labelled with the patient's number.

Labelling of the drug packages has to comply with the ICH GCP Guideline as well as current national law in Bulgaria.

5.4 Handling at Study Site and Storage Conditions

The investigator is to establish a system that ensures proper storage as well as dispensation and return of the investigational product according to the study protocol. Sponsor deliveries must be received and handled by the investigator or another appropriate individual (e.g. a pharmacist) designated by the investigator according to the local regulations. Such receipt as well as the return of unused drug must be documented including the signature of the persons involved.

The investigational product should be stored at a temperature below 25°C and not exposed to sunlight. The investigator will ensure that the investigational product is used only in accordance with the approved protocol. He will also ensure that the patients are instructed to take the tablets as described in section 5.2.

The dispensation of tablets to a patient will be documented by sticking the removable part of the package label to the pertaining field in the case report form. The number of tablets returned by a patient will also be entered into the case report form.

6 CONCOMITANT TREATMENTS

In principle, all previous medication for concomitant diseases is to be continued at unchanged dosage if it cannot be discontinued.
During the course of the study the following therapeutics possibly interfering with efficacy assessment are prohibited, namely:

- Antidepressants and neuroleptics with strong anticholinergic components, such as:
  all trycyclic antidepressants (e.g. Imipramin, Trimipramin, Clomipramin, Opipramol, Amitriptylin, Nortriptylin, Doxepin)

- Possible cognition enhancing drugs of any type including cholinergic agents (e. g. tacrine, donepezil, rivastigmin, metrifonate, galanthamin or any other cholinesterase inhibitor or cholinergic agonist), NMDA-antagonists (e.g. memantine), nimodipine, vasodilators and haemorheological agents with cerebral activity (e. g. bencyclane, buflomedil, hydergine), other cognition enhancers (e. g. piracetam) or any product containing Ginkgo biloba.

- Anticholinergic drugs and anti-Parkinson drugs.

  - e.g. oxybutynin, tolterodine, trospium chloride, propiverin
  - l-dopa, selegilin, amantadin, anticholinergic drugs (e.g. biperiden, benzatropin, metixen etc.)

If any of the above mentioned drugs have been used by the patient, a wash-out period of at least 8 weeks is required before start of the randomised treatment period. For Ginkgo biloba a wash-out period of at least 12 weeks before start of the randomised treatment period is required. Treatment discontinuation must not be followed by any adverse signs or symptoms (e.g. recurrence of former symptoms).

The drug treatments described below might have an effect on ischaemic vascular dementia progression. They may be continued under steady state conditions but should not be initiated during the patient's participation in the trial (unless urgently needed):

- Platelet aggregation inhibitors: acetysalicylic acid, ticlopidine
- Anticoagulants: heparin, coumarin derivatives
- Low-molecular dextran

7 PRIMARY AND SECONDARY OUTCOME VARIABLES

The following data will be recorded directly on the Case Report Forms and **considered to be source data** (i. e. no prior written or electronic record of the data exists):

- SKT test battery,
- NPI (12 items),
- TE4D,
- CDT,
- Verbal fluency,
- Rosen Score,
- GBS
- HAM-D ratings,
- Concomitant symptoms ratings.

It is recommended that copies or summaries of these data be added to the patients' charts or clinical files to have a full record of findings matching the CRF.

Laboratory printouts will be added to the Case Report Forms as source data.

7.1 Primary Variables

- SKT (Syndrome Kurz-Test) as an objective measure of cognitive impairment which is the core syndrome of dementia.

7.2 Secondary Variables

Efficacy:
- Clock Drawing Test (CDT) for evaluation of constructional praxis and visuo-spatial abilities
- NPI (Neuropsychiatric Inventory, 12 items) as an organised global assessment
- Hamilton Rating Scale for Depression (HAM-D) for the assessment of mood symptoms,
- Gottfries-Bråne-Steen Scale (GBS)
- Verbal fluency test
- Concomitant symptoms scale for the documentation of other aging associated symptoms such as tinnitus and dizziness (11-point box scales).

Safety:
- Physical Examination
- Neurological Examination
- Vital Signs
- ECG
- Adverse Events
- Laboratory Tests

8 EXAMINATION METHODS

8.1 Medical History/Risk Factors, Physical and Neurological Examination

The medical history documentation, the general physical and neurological examinations should be performed according to routine procedures and be as comprehensive as necessary to detect relevant somatic or neurological diseases. Risk factors that might exacerbate cerebrovascular disease will be documented to assess the individual risk for each one as antecedents of vascular dementia.

8.2 Vital Signs and Electro-Cardiography (ECG)

A 12-lead electro-cardiogram will be recorded according to standard procedures. A typical 10-second sequence of the ECG printout will be added to the CRF. Blood pressure and heart rate will be measured after the patient has been seated for at least 3 minutes.

8.3 Classifications of Cardiac Diseases

Patients with severe cardiac diseases corresponding to the stages/classes described below must be excluded from participation in this trial.

Coronary Heart Disease:

Canadian Cardiovascular Society stage IV: Any physical activity is associated with pain. Symptoms may be present even at rest.

Congestive Heart Failure:

NYHA stage IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Cardiac Arrhythmias:

Lown 4b: Bursts of premature ventricular beats or episodes of ventricular tachycardia.

Lown 5: Early premature ventricular beats, R-on-T phenomenon.

8.4 Laboratory Tests

All serum, blood and urine laboratory tests will be performed by one central laboratory, located in Germany. The investigator or a person designated by the investigator takes responsibility for the preparation and dispatch of the blood and urine samples according to the procedures specified by the central laboratory.
The routine laboratory tests to be performed at screening (week -4) and study termination (week 22 or early termination visit) include:

Haematology: Haemoglobin, haematocrit, RBC, WBC and platelet count, MCV, MCH, MCHC
Differential blood count: Neutrophils, eosinophils, basophils, lympho-cytes, monocytes

Blood Coagulation: International Normalised Ratio (INR), Partial Thromboplastin Time (PTT)

Serum Chemistry: Creatinine, total bilirubin, ASAT, ALAT, Gamma-GT, sodium, potassium, calcium, urea, cholesterol, triglyceride, glucose

Urine Analysis: Protein, blood and glucose by sticks, additional central laboratory analysis in the case of pathological findings

At screening only: TSH

8.5 Recording Adverse Events

Adverse events will be asked for in a semi-structured manner. A neutral question such as: "Have you been uncomfortable since the last visit?" is useful to learn about subjective symptoms the patient has experienced. Any untoward experience, intercurrent illness and laboratory values changed to abnormal are to be documented as adverse events. Then the patient will be asked if he suffered any expected adverse events as described in the Investigator's Brochure: gastrointestinal complaints, headache, allergic skin reaction or bleeding. Additionally, the patient will be asked: "Have you taken any new medicines, others than those given to you at your last visit?" Since memory disturbances are common in demented patients, the investigator should also ask the relative/caregiver about adverse events which might have occurred since the last visit and about intercurrent illnesses and concomitant medications.

8.6 CT Scan

A CT scan according to standard procedures is to be done in case there is no CT scan available which is no more than 1 year old.

8.7 Test for the Early Detection of Dementia with Differentiation from Depression (TE4D)

The TE4D (Ihl et al. 2000) is a concise test for the detection of dementia and differentiation between dementia and depression-related cognitive impairment. There are nine sub-tests covering a variety of cognitive abilities and two items to quantify symptoms of depression. In a validation study, sensitivity and specificity were 100 percent for the distinction of healthy elderly controls from patients with Alzheimer's disease, patients with depressive disorder from patients with Alzheimer's disease and healthy elderly controls from patients with depressive disorder). High inter-rater ($rs = 0.996$) and test-retest reliabilities ($rs = 0.868$) were found for the dementia-related items. In this study, only the dementia-related part of the TE4D (items 1 to 9) will be administered. A score ≤ 35 is strongly suggestive of the presence of a dementia syndrome.

8.8 Ischaemic Score According to Rosen

The Ischaemic Score according to Rosen is a modification of the Hachinski Ischaemic Score (Rosen et al. 1980). It claims to give a distinction between vascular and primary degenerative dementia. Among several revisions of the original Hachinski scale, the shortened version by Rosen et al. will be used. There is no favour concerning sensitivity and specificity between the original Hachinski scale and the shortened version by Rosen. The scale consists of eight items, representing signs and symptoms associated with cerebrovascular disease: sudden onset of symptoms (2 points), stepwise deterioration (1 point), somatic complaints (1 point), emotional incontinence (1 point), history or presence of hypertension (1 point), history of strokes (2 points), focal neurological symptoms (2 points), focal neurological signs (2 points).

The Ischaemic Score according to Rosen is produced by summing the points assigned to each sign or symptom present. An Ischaemic Score of 4 or more points to dementia of vascular origin, a score of 2 or less points to primary degenerative dementia and a score of 3 does not allow a decision without further assessment.

In this study, the Ischaemic Score according to Rosen will be determined by the neurologist/psychiatrist at the screening visit. The patient must have a score of 4 or more points to be eligible for this study.

8.9 Diagnostic Criteria I (NINCDS/ADRDA)

The diagnostic criteria for probable or possible Alzheimer's disease established by the Work Group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA, McKhann et al. 1984) are widely accepted.

The criteria for **probable** Alzheimer's disease are: Dementia established by clinical examination and confirmed by neuropsychological testing; deficits in two or more areas of cognition; progressive worsening of memory and other cognitive functions; no disturbance of consciousness; onset between ages 40 and 90, most often after age 65; and absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

The diagnosis of **probable** Alzheimer's disease is supported by progressive deterioration of specific cognitive functions; impaired activities of daily living and altered patterns of behavior; family history of similar disorders, and laboratory results of normal lumbar puncture, normal

pattern or nonspecific changes in EEG and evidence of cerebral atrophy on CT with progression documented by serial observation.
Other clinical features consistent with the diagnosis of **probable** Alzheimer's disease include plateaus in the course of progression; associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss; other neurological abnormalities; seizures in advanced disease; and CT normal for age.
Features that make the diagnosis of probable Alzheimer's disease **uncertain** or **unlikely** include: sudden, apoplectic onset; focal neurologic findings such as hemiparesis, sensory loss, visual field deficits and incoordination early in the course of the illness; and seizures or gait disturbances at the onset or very early in the course of the illness.
Clinical diagnosis of **possible** Alzheimer's disease: may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course; may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and should used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

8.10 Diagnostic Criteria II (NINDS-AIREN)

Among several sets of diagnostic criteria for vascular dementia (VaD), those established by the National Institute for Neurological Disorders and Stroke together with the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN, Román et al. 1993) are widely used. The basic requirements for the case definition of VaD are the following: (1) the patient must be demented; (2) there must be evidence of cerebrovascular disease (CVD) demonstrated by either history, clinical examination, or brain imaging; and (3) the two disorders must be reasonably related.

The criteria for probable vascular dementia include all of the following: (1) *Dementia* defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuo-spatial functions, executive functions, motor control, and praxis), established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone. *Exclusionary* are disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing, systemic disorders or other brain diseases (such as Alzheimer's Disease) that in and of themselves could account for the progressive deficits in memory and cognition. (2) *Cerebrovascular disease*, defined by the presence of focal signs on neurological examination such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant cerebrovascular disease by brain imaging including multiple large-vessel infarcts or a single strategically placed infarct, as well as multiple basal ganglia and white matter lacunes or extensive periventricular white matter lesions, or combinations thereof. (3) *A relationship between the above two disorders*, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognised stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.
Clinical features consistent with the diagnosis of **probable** vascular dementia include the following: (a) Early presence of a gait disturbance; (b) history of unsteadiness and frequent, unprovoked falls; (c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease; (d) pseudobulbar palsy; and (e) personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

Features that make the diagnosis of vascular dementia **uncertain** or **unlikely** include (a) early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language, motor skills, and perception, in the absence of corresponding focal lesions on brain imaging, (b) the absence of focal neurological signs, other than cognitive disturbance; and (c) the absence of cerebrovascular lesions on brain CT or MRI.

8.11 Gottfries-Bråne-Steen Scale (GBS)

The Gottfries-Bråne-Steen (GBS, Gottfries et al. 1982, Bråne et al. 2002) scale is a rating scale, developed in Sweden, for evaluating dementia syndromes. It can be used by different types of professionals after a short introduction/training. It is a comprehensive semi-structured observer rating scale. An evaluation is made from an interview with the patient and observation of the patient during the interview. Information from a caregiver or key person may also be needed. The scale includes 27 items and has three subscales, the intellectual (12 items), the emotional (3 items) and the activities of daily living (ADL; 6 items) scales. It also has a selection for rating of some behavioural and psychological symptoms that are common in dementia (6 items). Every item has seven scale steps, of which 0, 2, 4 and 6 are defined. 0 means absence of impairment or symptoms and 6 means maximal impairment or maximal severity of the symptom.
For each item, 0 includes normality, 1-2 indicates mild impairment, 3-4 moderate impairment and 5-6 severe impairment or, in case of the symptoms, 0 indicates absence of the symptom, 1-2 indicates that the symptom is mild, 3-4 that it is moderate and 5-6 that it is severe.
The GBS scale has been translated into about 20 languages, including Russian. In this study, the subscale for behavioural and psychological symptoms will be omitted, because these symptoms will be evaluated using the NPI. Since the calculation of a total score across all subscales is not intended, this should not impact the validity of the parts of the scale to be employed.

8.12 Clock Drawing Test (CDT)

The Clock Drawing Test is a quick test to screen for dementia that has also been found to be sensitive to change (Shulman 2000, Rouleau 1996). It is primarily an assessment of visuo-spatial abilities and constructional praxis, but it also requires semantic memory and ideational skills. Although there are a number of different scoring methods, sensitivity and specificity are within an acceptable range and inter-rater as well as test-retest reliability are high. The version proposed by Sunderland (1989) as modified by Ihl et al. (2000) will be used in this study, because the scoring method is easy to apply. Since it is part of a brief screening battery for dementia, the TE4D (Ihl et al. 2000), part of the investigators will be familiar with it. For this version of the CDT, the subject is provided with a sheet of paper and a pencil. There is no pre-drawn circle, so the subject has to draw the clockface, put in the figures and set the hands to show ten minutes after eleven. At a cut-point between 6 and 7, Ihl et al. (2000) found no overlap between dementia patients and non-demented elderly subjects and only a small overlap between dementia and depression. To further reduce the latter, a cut-point between 5 and 6 is applied in this study. The CDT should be administered by a specifically trained person who may be a physician, a psychologist or a qualified technical assistant.

8.13 Syndrome Kurz-Test (SKT)

The SKT is a cognitive test battery which consists of 9 subtests to assess attention and memory. It has been extensively validated in different countries and languages, and there are age- and intelligence-related norms (Erzigkeit 1992, Kim et al. 1993). A high reliability has been demonstrated for the five parallel forms that may be useful for short-term repetition in patients with preserved learning abilities. Two parallel forms will be employed in this study. This is deemed to be sufficient to avoid significant learning effects in demented patients when tests are performed in 6-week intervals. The SKT total score showed a high correlation with the scores of the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Mini-Mental Status

Examination (Ihl et al. 1999). The test should be administered by a specifically trained person who may be a physician, a psychologist or a qualified technical assistant.

The higher the SKT total score (range 0 – 27), the more severe is the patient's cognitive impairment. To evaluate changes during the treatment, the SKT is applied at screening, at the baseline check and after 12 and 22 weeks of treatment. The SKT total score serves as a primary outcome variable.

8.14 Verbal Fluency

To test the verbal fluency, the subject is asked to name as many examples of the category "animal" as possible within one minute (Rosen 1980). The scoring will be done in accordance with the rules provided for the TE4D (Ihl et al. 2000) with the exception that – taking into account the different purpose – there is no limit for the maximum score at baseline and follow-up visits. At screening, the Verbal Fluency test will be administered as part of the TE4D with the maximum item score of 10.

8.15 Neuropsychiatric Inventory (NPI), 12 Items:

The Neuropsychiatric Inventory (NPI) was developed to assess psychopathology in dementia patients (Cummings et al. 1994, Cummings 1997). It evaluates 12 neuropsychiatric disturbances common in dementia. The severity and frequency of each neuropsychiatric symptom are rated on the basis of scripted questions administered to the patient's caregiver. The NPI also assesses the amount of caregiver distress engendered by each of the neuropsychiatric disorders. The time span considered usually is the past month. A total NPI score and a total caregiver distress score are calculated, in addition to the scores for the individual symptom domains. Content validity, concurrent validity, inter-rater reliability, and test-retest reliability of the NPI are established. The NPI has been demonstrated to be sensitive to treatment effects in Alzheimer's disease. It should be administered by a psychiatrist or a physician experienced in psychiatry.

The higher the NPI total score, the more severe are the patient's neuropsychiatric symptoms. The NPI is applied at screening and baseline visits and repeated after 12 and 22 weeks of treatment. The NPI total score, the single item scores and the caregiver distress score are secondary variables.

8.16 Hamilton Rating Scale for Depression (HAM-D), 17-Item Version

The Hamilton Rating Scale for Depression (HAM-D) is the most widely used observer rating scale for the evaluation of the severity of depressive syndromes (Hamilton 1960). The original 17-item version will be used, since the items 18 to 21 refer to psychosis-related symptoms that are frequently found in, but not necessarily related to, depression in patients suffering from vascular dementia. The single items contain different numbers of categories that are well described verbally. Validity, internal consistency and inter-rater reliability of the HAM-D meet acceptable standards.

Prior to the rating, the patients should be interviewed comprehensively. Information from caregivers or relatives may be used in addition. In the case of repeated ratings, the interviewer should neither ask the patient about changes in his condition nor should he refer to earlier ratings. The ratings should be based on the patient’s condition during the week preceding the interview.

Only patients with HAM-D (17-item) total scores below 20 or with item 1 $\leq$ 3 at screening and baseline visit are eligible for this study. The repeated rating of depressive symptoms is required to assess the drug's influence on such symptoms as well as the potential influence of a change in depression severity on the outcome variables.

8.17 Concomitant Symptoms Scale

This scale, consisting of two similar parts, is for documentation of presence and severity of tinnitus and dizziness, symptoms which are frequent in elderly patients.

In the first part, the presence or absence of tinnitus will be documented. If tinnitus is present, the intensity is to be rated by means of an 11-point box scale with the extreme values 0 (= no tinnitus at all) and 10 (= extremely severe tinnitus). In the second part, the presence or absence of dizziness will be documented. If dizziness is present, the intensity is to be rated by means of an 11-point box scale with the extreme values 0 (= no dizziness at all) and 10 (=extremely severe dizziness).

9 STUDY SCHEDULE

9.1 Screening Visit and Run-in Period / Week –4 to Day 0

Patients who are potentially eligible for the trial are to be informed according to current law before any examination or treatment takes place. After that, their consent in trial participation is to be elicited. The caregiver's/close relative's consent in having a role as informant and supervisor within the study must also be elicited.

Each patient is to undergo screening for eligibility consisting of the following examinations:

- Medical history (including drug history)/Risk Factors
- Physical examination
- Neurological examination
- TE4D, 9 Items (incl. CDT and Verbal Fluency Test)
- Vital signs
- ECG
- Laboratory tests
- Ischemic Score (Rosen Score)
- SKT
- NPI
- HAM-D
- Concomitant Symptoms Scale
- CT scan
- NINCDS/ADRDA criteria
- NINDS-AIREN criteria
- Inclusion/Exclusion criteria

If the patient is to be enrolled in the run-in period, the lowest yet unassigned patient number, consisting of the site number and a successive number determined by the order of enrolment, will be assigned to him/her.

During the run-in period the screening examinations as outlined above have to be completed. If a new CT scan must be done, it has to be done after all other Inclusion-/Exclusion criteria have been checked. In addition, the investigator should be assured that the patient's medical condition is stable and that no significant fluctuation of symptoms takes place during the run-in period.

After all screening results are available the investigator has to complete the *screening checklist* for the patient and fax it to the medical advisor, who will give the final approval for randomisation by fax usually within 24 hours. This has to be taken into account when planning the date of baseline visit.

The duration of the run-in period may not exceed 4 weeks but after completion of screening

examinations the patient may be randomised directly after the approval for randomisation.

9.2 Baseline Visit / Day 0

After the run-in period (up to 4 weeks) and before administering the first dose of the study drug, baseline measurements are to be done on Day 0. Therefore the following examinations will take place:

- Vital signs
- GBS
- NPI
- HAM-D
- SKT
- Verbal Fluency
- CDT
- Concomitant symptoms scale
- Documentation of adverse events

9.3 Treatment Period

When a patient qualifies for the treatment period, he is assigned the package of the investigational product with the lowest yet unassigned drug number. This number is identical with the patient's randomisation number. During the whole treatment period, the patient should only get drugs from this package and with this number.

Drugs are issued to the patients for a 12-week period at day 0 and for a 10-week period at week 12. At the end of each of these periods (week 12 and week 22) the tablets not used by the patients as well as the blisters and boxes are taken back and the patients are questioned about adverse events that may have occurred during that treatment period.

At week 6, week 12, week 17 and week 22 the following examinations and inquiries will be repeated:

- Vital signs (at week 12, week 22 or early termination)
- Physical examination (at week 22 or early termination)
- Neurological examination (at week 22 or early termination)
- ECG (at week 22 or early termination)
- Laboratory tests (at week 22 or early termination)
- NPI (at week 12, week 22 or early termination)
- SKT (at week 12, week 22 or early termination)
- HAM-D (at week 12, week 22 or early termination)
- Verbal Fluency (at week 12, week 22 or early termination)
- CDT (at week 12, week 22 or early termination)
- Concomitant symptoms scale (at week 12, week 22 or early termination)
- Change of concomitant medication (at week 6, week 12, week 17, week 22 or early termination)
- Adverse Events (at week 6, week 12, week 17, week 22 or early termination)
- Compliance check (by inquiry and tablet-counting) (at week 12, week 22 or early termination)
- Completion of "Final Evaluation" record (only at week 22 or at early termination)

The study visits at week 6 and week 17 are performed by phone call with the patient and the caregiver. The investigator only asks for adverse events and for changes in concomitant medication.

Interim phone calls by the study nurse or the local study co-ordinator are advisable to ensure that patients and caregiver have no problems in complying with the study regimen.

Deviations from the scheduled visit dates should be avoided. If inevitable, they should not exceed ± 5 days. If SKT and NPI tests can not be performed on the scheduled visit dates, the deviation should not exceed ± 5 days. At visit week 22 or early termination the tests should be administered not more than 5 days before and 2 days after the last intake of study drug.

10 DISCONTINUATION

10.1 Individual Discontinuation of Treatment

The treatment of every single patient will be finished when the scheduled time of the week 22 visit is reached.

Treatment of a patient will be discontinued in the case of:
- Withdrawal of consent for treatment with the investigational product
- Incidence of a serious adverse event or serious concurrent illness which requires treatment discontinuation
- Non-adherence to instructions given by the physician, only if a risk for the patient may result thereof (protocol violations will be mentioned in the comment field(s) of the CRF)

After treatment discontinuation, the patient will undergo all the efficacy and safety examinations as scheduled.

Trial participation of a patient will be discontinued in the case of
- Withdrawal of consent both for treatment with the investigational drug and for trial-related examinations.
- Stroke within treatment phase; in this case only those data which were inquired from the patient prior to the event of stroke are included to the trial analysis.

In any case, these patients should be strongly encouraged to undergo a final examination.

Patients who drop out after randomisation are not to be replaced.

The "Final Evaluation" record is to be completed for every patient. The reasons, circumstances and findings that led to discontinuation of treatment or withdrawal from the trial are to be entered in detail in this form. Abnormal laboratory findings are to be followed up after discontinuation of the trial medication until normalisation or until a stable condition is reached.

10.2 Discontinuation at a Trial Site

The clinical trial may be discontinued at a study site, if:
- the number of patients planned to be enrolled at this site is completed,
- the progress in patient enrolment remains far behind schedule,
- eligible patients are no longer available at that study site,
- the performance of the trial according to GCP rules can no longer be guaranteed at a study site due to a change in personal, technical or other essential conditions.

10.3 Discontinuation of the Trial

The clinical trial will be terminated when the planned number of patients is completed.
The study may be discontinued prematurely by the sponsor in case of:
- Severe side-effects caused by the trial medication that make discontinuation advisable,
- new knowledge concerning characteristics of the trial medication or
- any medical-ethical reasons demanding such action.

11 ADVERSE EVENTS

11.1 Definitions

Adverse Event (AE): any undesirable experience occurring in a subject, during a clinical trial, whether or not considered related to the investigational product(s). This includes any negative effect on well-being, symptoms or signs of an illness, clinically relevant aggravation of biochemical parameters, concurrent illnesses and accidents.

Events occurring during run-in or follow-up periods without medication, during placebo treatment, or in reference groups with or without any therapy are also considered adverse events. The same holds for aggravation of pre-existing illnesses as well as for consequences of withdrawal, misuse or overdosing of the investigational drug.

Therapy resistance is not considered as an adverse event. Diseases, clinical signs or symptoms as well as pathological laboratory parameters are not judged adverse events when they are already present during the first examination, except when an aggravation or an increase in frequency is noticed.

Serious adverse event means any occurrences that threaten life or damage health seriously or permanently. Considered as serious are especially AEs, which
- result in death,
- are life-threatening,
- require patient hospitalisation or prolongation of existing hospitalisation,
- result in persistent or significant disability/incapacity, or
- are a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Other adverse events are, by definition, not serious. Life-threatening means that the patient was in immediate danger of dying due to the event. In-patient hospitalisation renders an adverse event serious only when it has become really necessary on account of the event (i. e. for treatment), not in case of overprotection or when hospitalisation is due to another illness.

An **unexpected adverse event** is an experience not previously reported (in nature, severity or incidence) in the current investigator's brochure, in the patient information sheet or in the package insert of an approved drug.

Expected adverse events associated with EGb 761 are all those events which are described as expected in the Investigator's Brochure. Adverse events which might occur during EGb 761® treatment are:
- mild gastrointestinal disorders,
- headaches,
- allergic skin reactions and
- eventually bleeding.

11.2 Classifying the Intensity of AEs

The intensity of an AE is to be graded using the terms mild, moderate, and severe.
These are defined as follows:

mild: the event is realised but well tolerated
moderate: the event interferes with usual daily activities
severe: the event makes usual daily activities impossible

Note: A strict difference is to be made between intensity grading and whether an adverse event is serious or not. A rather severe AE does not necessarily need to be serious.

11.3 Assessing the Causes of AEs

The causal relationship to the study medication has to be assessed by the investigator and by the sponsor for every adverse event using one of the following terms:

1 = probable
- reasonable coincidence with administration of study medication
- the AE has already been described as a side effect of the drug, or can be expected
- decrease or disappearance of symptoms after discontinuation of treatment, or dose reduction
- renewed appearance of the AE after repeated exposure to the drug under study
- no reasonable explanation of the AE via the patient's clinical condition

2 = possible
- coincidence with administration of the study medication
- the AE has already been described as a side effect of the drug, or can be expected
- the AE may be caused by several other reasons

3 = unlikely
- reasonable coincidence with administration of the study medication
- the AE has not yet been reported as a side effect of the drug and cannot be expected
- the AE remains persistent after discontinuation of treatment or dose reduction
- repeated exposure to the drug under study is not followed by the same AE
- the AE may be caused by several other reasons

4 = no relationship
- no clear coincidence with administration of the study medication
- the AE has obviously been caused by other reasons, e. g. by the disease itself

5 = assessment impossible
- the available data are insufficient for any reasonable assessment with respect to a causal connection

In all cases where 1, 2 or 3 applies, the suspicion of an adverse drug reaction must be established (case of suspicion).

11.4 Documentation of AEs

Adverse events spontaneously reported by the patient or noticed by the investigator in the course of the clinical trial are to be documented in the appropriate case report form during the control visits (AE form). Adverse events which have been documented in the AE form of a preceding visit should not be documented again in another AE form if persisting. It should, however, not be forgotten to enter the time of cessation of such an AE into the original AE form afterwards. If an AE still persists at the end of the treatment period, this must be indicated on the same original AE form.
Laboratory reports are to be checked for pathological findings. In the case of clinical relevance, such findings must be considered as AEs and documented in the appropriate AE form.

11.5 Reporting of Serious and/or Unexpected AEs

Every serious adverse event - including deaths for any reason - emerging in the course of the study or within two weeks after discontinuation has to be reported immediately, within 24 hours at the latest, by fax to the sponsor:

Dr. Willmar Schwabe GmbH & Co.
-Arzneimittelsicherheit-
Willmar-Schwabe-Str. 4
76227 Karlsruhe
Tel. +49 721 4005-0
Fax +49 721 4005-707

The monitor and/or the project manager responsible will be informed by the recipient.
Information on the following issues - as far as available - should be provided by the investigator in this first fax:

- trial number, drug under study
- patient number (randomisation number)
- demographic data (of the patient)
- adverse event:
  * description
  * time point of showing up
  * intensity
  * duration
  * therapy (patient hospitalisation?)
  * measures taken with respect to study medication
  * relevant clinical information (concomitant medication, concurrent illnesses)
  * findings from examinations and tests (e. g. laboratory, X-ray, etc.)
  * assessment of relationship with the drug under study
  * outcome

- in case of death:
  * date
  * physiological cause
  * autopsy findings (if available)

The documentation of a serious AE is to be entered into <u>both</u>: the AE-form (page 1) and additionally into the SAE-form (page 2). Both pages are to be forwarded by facsimile to the sponsor within 24 hours. As soon as further information which could contribute to the assessment of the event is available, a follow-up report, together with the epicrisis, is to be sent.
The sponsor will meet the liability of reporting cases to the Bulgarian authorities as well as of reporting suspected serious adverse drug reactions to the German Federal Drug Authority (Bundesinstitut für Arzneimittel und Medizinprodukte) within 15 days according to Article 29 of the German Drug Law (Arzneimittelgesetz). No separate reporting by the investigator is required.
Serious or unexpected AEs, which could endanger the safety of patients or the course of the study will be reported to the ethics committee according to local legal prerequisites by the sponsor. If necessary, the investigator will immediately receive a copy of the report to the ethics committee.
Decisions on discontinuation of treatment with the drug under investigation and on therapeutic measures are the responsibility of the investigator. If treatment is discontinued, this has to be documented on the appropriate sheet of the case report form.

11.6 Follow-up of Patients with AEs

Every AE, be it mild or severe, serious or not, has to be followed up by the investigator until it has completely subsided or it can be assumed that it is a chronic condition. If additional tests or examinations are thought to be necessary, these findings should be entered into the case report form as well as the final outcome.

12 DATA ANALYSIS AND STATISTICAL PROCEDURES

12.1 Randomisation

On enrolment in the study, each patient receives a patient number of the form 1xxyy, where xx is the number of the centre and yy is the number of the patient, which is allocated in the order of inclusion in the study. Following the run-in period, the patients who are eligible for inclusion in the randomised treatment period are allocated a drug number. Randomisation is carried out by the biometrical department of Dr. Willmar Schwabe GmbH & Co. The test drug numbers from 5001 to 5500 are allocated proportionally to the treatment groups guaranteeing that a patient is assigned to one of the two treatment groups with equal probability (1:1 randomisation) and a corresponding sealed randomisation list is produced by means of a validated EDP-random number generator RCODE. Randomisation will be performed stratified by centres. The next (in ascending order) drug number of those numbers given to a centre will be assigned to a patient if he or she fulfils the selection criteria. Each of the participating centres should include 20 to 30 patients. The block sizes used are documented in an appendix to the protocol, which is to be stored at the sponsor's site and is not available to the centres.

The test drugs will be provided, packed and labeled with the drugs numbers by the sponsor. Each patient will receive that study medication which is labeled with the drug number allocated to him/her.

In addition to the study medication the centres will receive a sealed code-breaking envelope for each drug number. An identical set of code-breaking envelopes is kept by the sponsor. The code-breaking envelopes contain information about which test drug the patient with the corresponding drug number receives. They may only be opened if knowledge of the treatment group allocation is absolutely necessary for medical reasons. Should it be necessary to open a code-breaking envelope, the date and signature of the person opening the envelope and the precise reasons for opening the envelope are to be documented on the code-breaking envelope. After completion of the study, all code-breaking envelopes will be returned by the monitor responsible to the sponsor, where they will be checked for completeness and intactness.

Patients, who discontinue the study early or are withdrawn from the study after randomisation are not to be replaced.

12.2 Design and Hypotheses

The primary aim of the study is to confirm the efficacy of EGb 761® in patients suffering from Alzheimer's disease, vascular dementia, or mixed type dementia with neuropsychiatric symptoms. In confirmatory analysis, this will be done for the primary efficacy variable "change of SKT between baseline and week 22".

To formalize the statistical approach, the following notation will be used:

$\mu_{S,P}, \mu_{S,V}$: expected value of the change of SKT between baseline and week 22 (week 22 – baseline) for the placebo group and the EGb 761® group, respectively.

The following test problem is defined:

$$H_S^0 : \mu_{S,P} = \mu_{S,V} \text{ vs. } H_S^1 : \mu_{S,P} > \mu_{S,V}.$$

12.3 Evaluation

12.3.1 Confirmatory Analysis

The primary efficacy analysis to test the null-hypothesis H_S^0 uses a *t*-test comparing the mean of EGb 761® with the placebo mean. In view of the large number of centres that will participate in the study (about 35-40) and the relatively small number of patients to be enrolled per centre it is not planned to use an analysis of variance (ANOVA) model and to include a term for centre in the ANOVA. This procedure is along the lines of the proposal in the ICH E9 Guideline (ICH, 1998) on this topic. If the actual number of centres or the number of patients per centre should make inclusion of a term for centre in the ANOVA model sensible this would be defined in the statistical analysis plan which will be finalised before breaking the blind but when being aware of the actual distribution of the patients over the centres. The test for treatment effect will be performed two-sided at a type I error rate of $\alpha = 0.05$.

Confirmatory analysis will primarily be based on the full-analysis data set according to the intention-to-treat (ITT) principle including all patients who were randomised to study treatment. For this analysis, missing values for any of the primary efficacy variable will be replaced in the following manner. If available, the endpoint assessment is used; if missing, the retrieved drop out assessment is used; if this is unavailable, then the last observation available on the patient is used.

In order to assess the impact of drop outs on efficacy results, the following sensitivity analyses with other imputation techniques for missing data will be done which were proposed in an FDA discussion paper on strategies for the evaluation of dementia studies (Leber, 1985). The notations of these imputation methods were adopted from this paper.

Traditional DNDP LOCF (Division of Neuropharmacological Drug Products Last Observation Carried Forward): In this imputation scheme, the goal is to create a score for every patient randomised who received at least one dose of the protocol designated treatment and had at least one post treatment outcome assessment made, either scheduled or unscheduled. The score assigned is determined in the following manner: if available, the endpoint assessment is used. If missing, the last observation available, scheduled or unscheduled, is utilized, provided that the assessment was made while the patient was still considered a participant in the study. This scheme often leads to an analysis of a subset of the patients randomised.

Traditional Observed Cases: No imputation occurs. This subset includes data only from patients randomised who did not discontinue prematurely and were available for evaluation at the designated assessment time (either scheduled interim or endpoint).

Retrieved drop out data: Data obtained from patients randomised who failed to complete the study as planned, but were retrieved and assessed at or as close to the time of their scheduled endpoint had they remained in the study.

Observed Cases + Retrieved drop outs: This imputation scheme generates still another subset from among those randomised in the study. It is formed from the combination of Observed Cases and Retrieved drop outs.

In addition to the analysis of all randomised patients, a per-protocol (PP) analysis will be performed including those patients of the full-analysis data set without major protocol violations.

The assignment of patients to the analysis sets will be done before breaking the blind and be documented in the statistical analysis plan.

12.3.2 Secondary Efficacy Parameters and Subgroup Analyses

An important secondary outcome variable is the overall benefit of the patients measured by the following response criterion: "improvement in SKT of ≥ 3 points between baseline and the end of the treatment period (week 22 or last value available in case of premature study termination) and no worsening in the NPI and the ADL subscale of the GBS between baseline and the end of the treatment period."

For each of the secondary efficacy variables the EGb 761® group will be compared to the placebo group with methods of descriptive data analysis. Descriptive statistics will be computed to describe the empirical distributions, 95%-confidence intervals will be calculated within the treatment groups and between the placebo and the EGb 761® group, and descriptive p-values will be calculated with appropriate statistical tests.

The placebo and EGb 761® group will be compared with respect to the primary and secondary efficacy variables within the subgroups according to the etiology of dementia (as defined in chapters 8.9 and 8.10) and within subgroups of relevant concomitant treatment.

12.3.3 Safety Analysis

Safety variables will be assessed for the safety population which includes all patients randomised to study treatment and who took study medication at least once. Adverse events will be summarized by means of appropriate frequency tables based on coded items and taking into account severity and relationship to study drug. Overall incidence rates will be compared between treatment groups. Vital signs will be summarized by means of descriptive statistics for measured values and for differences from baseline.

Laboratory data will be presented by means of shift tables displaying the numbers of patients switching from baseline to under-treatment-visits between the categories "above normal range", "within normal range", and "below normal range". If adequate (unique normal range applicable to each variable within each gender), descriptive statistics will also be presented for measured values and for changes from baseline.

12.3.4 Homogeneity of the Treatment Groups

Homogeneity of the treatment groups will be assessed by comparing demographics and baseline measurements.

12.4 Sample Size

The sample size calculation is based on a common standard deviation of 6 points for the change of the SKT between baseline and week 22. This value considers estimates of the standard deviation from previous dementia studies and takes into account that the large number of involved centres may further increase the variability of the outcome. Furthermore, a clinically relevant difference of at least 2 points between the active treatment group and placebo is assumed. Under these assumptions, 2 x 200 = 400 patients are required for the full-analysis set to reject the null-hypothesis H_S^0 at $\alpha = 0.05$ (two-sided) with a power of 90% when applying the two-sample *t*-test.

13 INFORMED CONSENT - PATIENTS INSURANCE

It has to be noticed that patients eligible for inclusion into this study must be able to give consent according to legal regulations by themselves.

Prior to commencement of the study, the patients must be informed by a physician of the purpose, objective, procedures and risks of the study. This information must cover the points in the patient information and consent form (Appendix) and, if necessary, also include special information intended for the individual patient. The patient must be allowed sufficient time to make a decision. Consent must be given in writing. Consent has to be documented on the corresponding form which has to remain with the investigating physician. The patient must be assured that all personal data will be treated with the utmost confidentiality. He/she must also be informed that clinical records relevant to the study may be disclosed to the sponsor, the ethics committee, and to authorities responsible in order to verify adherence to applicable laws and Good Clinical Practice.

If information concerning the drug and/or the trial that may be relevant to the patient becomes available during the study, he/she must be informed accordingly.

During participation in the study, each patient is covered by an insurance policy in accordance with local legal provisions. Should an insurance claim become necessary, the investigating physician will notify the monitor and the sponsor immediately so that claims may be raised with the insurance company.

It has to be pointed out to the patient that he/she must not undergo any other medical treatment without agreement of the investigator, and that he/she should report to the investigator any disorder which might be a consequence of taking part in the study. The investigator will bring it to the sponsor's attention who will inform the insurer.

14 ETHICS COMMITTEES

This study protocol will be submitted to the responsible local Ethics Committees in Bulgaria before commencement of the trial.

During the course of the study, the Ethics Committees will be informed by the sponsor about facts, especially AEs, that could endanger the implementation of the study or the patients' safety.

On request, the Ethics Committees will receive a yearly status report about the study. The Ethics Committees will further be informed about an eventual early termination of the study.

15 PATIENT CARE

In addition to the measures described elsewhere, two further measures serve the care of outpatients:

1. If the patient agrees, the family doctor will be informed about the objective and schedule of the study and asked for his support (letter to the family doctor).

2. The patient will receive a card with the most important information on the trial including contact address for other physicians consulted during the trial (e.g. in an emergency).

16 COMPLIANCE MONITORING

When the test medication is dispensed, the patient is to be informed as follows concerning administration:

"Take one tablet in the morning and one tablet in the evening. Swallow it with some fluid and do not chew it". (The tablets may be taken with or without meals).

During the study, the investigating physician will record compliance by questioning the patient. At each examination visit the patients are to return remaining quantities of the study drug together with the containers to the investigator. The investigator is to document the number of unused tablets returned by the patients and to return study drug and containers to the Schwabe Company.

17 QUALITY ASSURANCE

All aspects of the study protocol are to be complied with during the trial period. If changes should become necessary, they are to be discussed without delay by the investigator, the monitor and the sponsor. The study protocol amendment must be issued in written form (see appendix), and should contain a detailed justification of the modification. Amendments must be submitted to the Ethics Committee.

Every deviation from the study protocol has to be documented and justified by the investigator (or a person designated by the investigator) at an appropriate place in the CRF.
All other persons involved in the trial will be instructed by the investigator or monitor concerning their tasks. The investigator will bear responsibility for this.

The investigator agrees to allow the monitor, or an employee of the quality assurance unit of the sponsor, or an external auditor appointed by the sponsor, as the representative of the study director or the sponsor, to personally ascertain the correct implementation and documentation of the study during scheduled visits (approximately every 4 – 8 weeks).

To do this, it is necessary to compare the data entered in the CRF with data from the medical records, etc. Data not relevant for the study's objective should be removed or made unrecognisable.

The investigator agrees to allow an auditor appointed by the sponsor as well as representatives of relevant authorities and the Ethics Committees to verify by a study site audit that implementation and documentation are in accordance with the study protocol, Good Clinical Practice and applicable law. The auditor/representative will have to scrutinise all of the essential documents and to check the correspondence of a random sample of data entered into the case report forms with the source data of clinical records. Therefore the investigator provides direct access to source data/documents and to the locations where trial-related activities take place.

Monitoring as well as auditing may require the presence of the investigator for several hours.

18 DOCUMENTATION

On enrolment of a patient in the run-in period, the monitor is to be informed immediately by fax.

18.1 Case Report Forms

Recorded data are to be entered by the investigator on a continual basis into the case report form. In order to confirm that examinations and documentation have been done according to the protocol, the last page of each part of the case report form refering to a single visit is to be signed by the investigator. If special examinations are to be carried out by another person mentioned in the

protocol or an amendment to the protocol, the forms for documentation of these examinations have to be signed separately by this person. If a staff physician has been instructed by the investigator to assist him in carrying out the study and to enter data into the case report forms, this has to be confirmed in writing on a special form. The monitor has to be informed of this.

If laboratory data deviate from reference values, the investigator must comment on and evaluate this circumstance in the case report form.

Corrections must be carried out so that they are clear and the corrected text remains legible. The correcting person is to indicate the date and sign. If the reason for a correction is not evident, it is to be justified on the CRF.

The original sheets will be collected by the monitor during study site visits and given to the sponsor's biometric department/authorised data management unit. For reasons of security and verification at any time, copies are to remain with the investigator.

Should corrections or additions be necessary after the originals have been sent or given to Schwabe Company, the data management unit processing the data will set up a query list. After having checked and, if necessary, completed this list, the investigator has to sign it and send the original form back to sponsor's biometric department /authorised data management unit within 7 days. A copy remains with the investigator.

All patients to whom the inclusion diagnosis applies and who are screened by the investigator are to be recorded in a separate list (screening log). In case patients are not enrolled in the study, the reason for their non-participation is to be stated in this list. The required forms will be provided by the sponsor. This provides important information regarding the selection criteria and quality of the study.

Participation in the study will be noted in the medical record with study number, investigational drug, randomisation number and treatment period. The investigator will also keep a summary list that facilitates identification of the patients by means of the patient number. This list is intended for his or her own use only and must not be seen by third persons, except for the purpose of monitoring, auditing or authority inspection.

18.2 Integrated Report

The integrated statistical and medical report describes and summarises the performance and results of the clinical trial. The investigator contributes to the medical discussion of the results by medical evaluation of the findings and signs it, if requested.

18.3 Document Storage

An investigator's file provided by the sponsor prior to the commencement of the study will facilitate the co-operation especially with authorities. All the relevant documents which should remain with the investigator after study termination, are to be part of this investigator's file. Together with the investigator's copies of the case report forms, the investigator's file has to be retained by the investigator until the sponsor notifies him in writing of the end of the retaining period. The essential documents have to be retained at least until 2 years after the last approval of a marketing application in an ICH region (i.e. EU, USA, Japan); for the file containing patient identification it is at least 15 years. The investigator's copies of the case report forms can be kept by the sponsor if the investigator lacks facilities. Patients' medical records and other original data are to be kept as long as the hospital, institution or private practice of the investigator allow.

19 LEGAL PREREQUISITES, NOTIFICATION TO AUTHORITIES

The planning, conduct, and evaluation of the clinical trial are to be carried out in accordance with the ICH Guideline for Good Clinical Practice, the Declaration of Helsinki and applicable local laws, each in the currently valid version. The sponsor will submit the application to the appropriate authority.

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I hereby confirm that I took note of the study protocol for the study no. 523001.01.061 and agree to the regulations, further that all questions relevant to the study protocol have been clarified and that I shall conduct the clinical trial in accordance with this Study Protocol and the principles of Good Clinical Practice (see ICH Harmonised Tripartite Guideline of 09 September 1997).

Investigator:

_____ _____

Place, Date Signature >*Investigator*<

Sponsor's Medical Expert and
Leiter der Klinischen Prüfung
According to German
Drug Law

Karlsruhe, 07.04.2003
Place, Date

[redacted]

Statistician:

Karlsruhe, 4.4.03
Place, Date

[redacted]

On behalf of the sponsor:

Karlsruhe, 5.4.03
Place, Date

[redacted]

APPENDICES

1. List of investigators and persons at study sites
2. List of monitors
3. Specimen copy of patient information and consent form
4. Specimen of labelling
5. Form for protocol amendments

Additional Relevant Documents in the Investigator's File:

Declaration of Helsinki
ICH Guideline for Good Clinical Practice
Instruction sheet for patient information
Specimen copy of letter to the family doctor
General conditions and policy of patients' insurance
List of authorised persons
Screening log
List for patient identification
Specimen copy of CRFs