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Study of oral EGb 761® Ginkgo biloba extract added to standard treatment after acute stroke

Submission date
02/12/2020

Recruitment status
No longer recruiting

Registration date
03/12/2020

Overall study status
Completed

Last Edited
18/04/2023

Condition category
Circulatory System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
Ginkgo biloba extract EGb 761® (the active pharmaceutical ingredient in Ginaton tablets) is known to have a number of beneficial effects on the body systems.
Clinical trials have demonstrated that EGb 761® improves cognitive performance (e.g. memory, attention, problem-solving), neuropsychiatric symptoms and activities of daily living in patients with dementia (Alzheimer's disease, vascular dementia or mixed forms) and aging-associated mild impairment in cognitive function. An injectable preparation of Ginaton has been found beneficial in the treatment of acute ischemic stroke. It is reasonable therefore to assume that treatment with EGb 761® tablet after acute ischemic stroke will foster the recovery from stroke-related cognitive impairment and diminish or prevent cognitive impairment developing after acute ischemic stroke. Considering the beneficial effects of EGb 761® on neuropsychiatric symptoms (NPS), including depression, loss of drive and anxiety, in patients with dementia and aging-associated cognitive impairment, an attenuation or prevention of post-stroke depression and other NPS may be expected.

Study aims
To assess the feasibility of patient selection, treatment regimen and outcome measures and to obtain preliminary data for sample size estimation for a trial to evaluate treatment effects on cognitive and emotional functioning as well as safety and tolerability of Ginkgo biloba extract EGb 761® in patients who had suffered an acute ischemic stroke.

Who can participate?
Adults aged 50 years or older who suffered an acute ischemic stroke at least 7 but no longer than 14 days before baseline.

What does the study involve?
The study is designed as a randomized, open-label, parallel-group study. The eligible patients will be assigned by chance to either the EGb761® group or the reference group. A patient who is assigned to the EGb761® group will received 80 mg EGb761®, i.e. 2 tablets at 40 mg, three times a day for 24 weeks in addition to the standard treatment as judged appropriate by his

doctor. A patient who is assigned to the reference group will receive the standard treatment as judged appropriate by her/his doctor in accordance with Chinese guidelines for the secondary prevention of ischemic stroke.

At 4 trial visits (Screening, Baseline, Week 12 and Week 24) rating scales and tests validated for use in China will be used to evaluate the stroke-related neurological deficits, cognitive performance in the domains memory, attention/concentration, executive functioning, language, visuospatial abilities and communication (Montreal Cognitive Assessment - MoCA, Hopkins Verbal Learning Test - HVLT, Shape Trail Test - STT, Verbal Fluency Test - VFT, Digit Symbol Substitution Test - WAIS-R DSST) and neuropsychiatric symptoms like depression, anxiety, apathy and overall neuropsychiatric symptom burden (Hospital Anxiety and Depression Scale - HADS, Neuropsychiatric Inventory - NPI, Clinical Global Impression of Change - CGI-C). At trial visits week 6 and week 18 the phone call with the subject and informant was performed to inquire about any adverse events and changes in concomitant medication. The subjects were observed and checked for ischemic stroke recurrence at all trial visits as well. The safety was additionally assessed based on adverse events (AEs), physical and neurological examination, vital signs, ECG and laboratory tests.

What are the possible benefits and risks of participating?
The main benefit all patients participating in this study will get is the extended care by stroke experts (phone calls and visits until 6 months after acute stroke), the repeated clinical and laboratory examinations, cognitive testing and psychological evaluation. This will keep the subjects aware of the importance of taking the medications to lower the risk for another stroke. It also increases the chance to detect any critical adverse events that may be caused by such treatment and any untoward development of subject’s condition that might increase the risk for another stroke or other cardio-vascular events. Those subjects assigned to receive EGb 761® treatment may further benefit from its cognition-enhancing and neuropsychiatric symptoms diminishing effects.
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 24 weeks. The risk associated with participation in this study is very low. Blood-drawing may lead to local hematoma, local infection and inflammation or systemic infection. The risk for such complications is low and can be minimized by applying state-of-the-art procedures. No risk is associated with the administration of cognitive tests, psychological rating scales and other trial-related procedures. The risk of suffering an adverse reaction to EGb 761® is very low. Side effects are very rare and usually mild in nature. Mild gastrointestinal disturbances, allergic skin reactions (reddening, swelling, itching), or headache, may occur. Bleeding from single organs has been reported, but studies have not shown any influence of therapeutic doses of EGb 761® on blood clotting, platelet function or the blood-thinning effects of anti-platelet agents and anticoagulants.
The basic treatments for the prevention of stroke recurrence are not study-related treatments; these are the treatments all patients get anyway. Hence, the risks possibly associated with these treatments are not trial-related risks.

Where is the study run from?
Seven medical hospitals in Shanghai and Beijing (China)

When is the study starting and how long is it expected to run for?
May 2013 to June 2018

Who is funding the study?
Dr. Willmar Schwabe GmbH & Co. KG (Germany)

Who is the main contact?
Dr Robert Hoerr
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
523079.01.102

Study information

Scientific Title
Randomized, open-label, parallel-group study to assess the feasibility of patient selection, treatment regimen and outcome measures and to obtain preliminary data for sample size estimation for a trial to evaluate treatment effects on cognitive and emotional functioning of Ginkgo biloba extract EGb 761® in patients who had suffered an acute ischemic stroke

Acronym
not available

Study objectives
The knowledge about the dynamics of cognitive abilities after acute ischemic stroke and about the sensitivity of available cognitive tests to measure the natural course as well as treatment-

related changes in general is limited. Currently, no data are available on the possibility of improving cognitive and psychological outcomes by concomitant treatment with oral EGb 761® when added to the standard therapies and initiated shortly after acute stroke. To this end, a broad spectrum of instruments from cognitive tests to psychiatric rating scales will be assessed and evaluated in an exploratory data analysis to obtain further information on the natural course of neuropsychiatric symptoms and to provide a basis for the planning of subsequent studies.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/12/2013, Ethics Review Board (HIRB), Huashan Hospital Affiliated to Fudan University (Floor 9, Outpatient and Emergency building, Huashan Hospital, No.12, Urumchi Middle Road, Jingan District, Shanghai, China; no telephone number provided; no email provided), ref: 2013M-010

Study design
Multicenter randomized open-label reference-controlled parallel-group trial

Primary study design
Interventional

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Acute ischemic stroke

Interventions
Participants are randomized for a 24-week acute treatment phase. The participants assigned to the EGb 761® treatment group receive 2 x 40 mg EGb 761® three times daily as an add-on to the standard treatment for the prevention of recurrent stroke. The parallel group received the standard treatment for the prevention of recurrent stroke (according to Chinese guidelines for the secondary prevention of ischemic stroke).

Treatments (EGb 761® as add-on to the standard treatment or standard treatment alone) were assigned to patient numbers by a computer program. By allocating patient numbers in ascending order to the patients enrolled, treatments were allocated strictly at random to the patients, while concealment was upheld. The duration of treatment was 24 weeks.

At four trial visits (screening, baseline, week 12 and week 24) rating scales and tests validated for use in China are used to evaluate the stroke-related neurological deficits (National Institute of Stroke Scale - NIHSS), cognitive performance in the domains: memory, attention /concentration, executive functioning, language, visuospatial abilities and communication (Montreal Cognitive Assessment - MoCA, Hopkins Verbal Learning Test - HVLT, Shape Trail Test - STT, Verbal Fluency Test - VFT, Digit Symbol Substitution Test - WAIS-R DSST) and neuropsychiatric symptoms like depression, anxiety, apathy and overall neuropsychiatric symptom burden (Hospital Anxiety and Depression Scale - HADS, Neuropsychiatric Inventory - NPI, Clinical Global Impression of Change - CGI-C). At trial visits week 6 and week 18 there is a phone call with the participant and informant to inquire about any adverse events and changes

in concomitant medication. The participants are observed and checked for ischemic stroke recurrence at all trial visits as well. Safety is additionally assessed based on adverse events (AEs), physical and neurological examination, vital signs, ECG and laboratory tests.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Ginkgo biloba extract EGb 761®

Primary outcome(s)
1. Stroke-related neurological deficits measured using the National Institute of Stroke Scale (NIHSS) at study visits Screening, Week 12, Week 24
2. Cognitive performance measured at Baseline, Week 12, Week 24:
2.1. Memory and attention/concentration by the Montreal Cognitive Assessment (MoCA)
2.2. Executive functioning, language and visuospatial abilities by the Hopkins Verbal Learning Test (HVLT), Shape Trail Test (STT), Verbal Fluency Test (VFT), Digit Symbol Substitution Test (WAIS-R DSST)
3. Depression and anxiety measured by the Hospital Anxiety and Depression Scale (HADS) at Baseline, Week 12, Week 24
4. Apathy and overall neuropsychiatric symptom burden were measured by the Neuropsychiatric Inventory (NPI) at Baseline, Week 12, Week 24
5. Global evaluation of changes in the patient's neuropsychiatric status the rating scale Clinical Global Impression of Change (CGI-C) was used at Week 12 and Week 24

Key secondary outcome(s))
1. Ischemic stroke recurrence checked for by the researcher at all trial visits
2. Safety assessed by:
2.1 Adverse events (AEs) measured by self-report at all study visits
2.2. Physical and neurological examination measured by the researcher (at visits Screening and Week 24)
2.3. Vital signs measured by the researcher (at all visits)
2.4. ECG and laboratory tests measured by the researcher (at Screening and visit Week 24)

Completion date
14/06/2018

Eligibility

Key inclusion criteria
1. Male or female patients aged 50 years or older. The patients will be enrolled while they are inpatients treated for acute ischemic stroke; study-related treatment and procedures will be continued after discharge from the hospital, i.e. they will be treated as outpatients most of the time.
2. Written informed consent according to applicable law; patient must be mentally and physically capable of giving informed consent
3. Written informed consent from an informant to accompany the patient to the study visits and to provide the requested information (partner, close relative, close friend)

4. Clinical stroke at least 7 but no longer than 14 days before baseline
5. Score of 20 or lower on the NIHSS
6. MRI scan indicating acute ischemic cerebral infarction and no signs of haemorrhage /haematoma, tumor, normal pressure hydrocephalus or other serious cerebral disorder or abnormality; of note: lacunes, white matter hyperintensities and/or mild atrophy consistent with a pre-dementia state of Alzheimer's disease or cerebrovascular disease are acceptable
7. Sufficient Chinese language skills to understand and respond to all interview questions, complete questionnaires and undergo neuropsychological testing without the assistance of an interpreter
8. An informant (partner, close relative, close friend) is available and willing to accompany the patient to the clinical visits and to provide information about the patient's cognitive problems, functional activities and neuropsychiatric symptoms; this person should have regular personal contact with the patient (at least four times a week)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
201

Key exclusion criteria
1. Participation in another experimental drug trial at the same time or within the past 4 weeks before enrolment
2. Long-term hospitalization (i.e. expected duration more than 6 weeks after screening or unpredictable duration) of the patient for treatment or nursing home placement for bedside care. (Please note: Assisted living facility residence or stay in a rehabilitation facility is acceptable if the patient is not bedridden and does not need general bedside nursing and if an informant is available who sees the patient on a regular basis and accompanies him/her to the study visits.)
3. Signs of intracranial haematoma, tumor, hydrocephalus or other findings indicating a serious brain disease or abnormality (except lacunes, white matter hyperintensities and/or slight atrophy consistent with pre-dementia states of Alzheimer's disease or cerebrovascular disease)
4. Any type of dementia (e.g. dementia in Alzheimer's disease, vascular dementia) or other major neurological disorder (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 supra-nuclear palsy, Creutzfeldt-Jakob disease, infectious CNS disease, brain tumor, subdural hematoma, multiple sclerosis, seizure disorder, recent brain trauma, etc)
4.1. The disease listed under this criterion (e.g. Alzheimer’s disease, Pick disease) are chronic diseases, i.e. if a patient has ever been diagnosed with one of these diseases, the disease must still be present when the patient is screened for the study. Exceptions are infectious brain disease, brain tumor, subdural hematoma and brain trauma.

4.2. As infectious brain diseases and brain tumor surgery are likely to permanently damage brain structures, patients should be excluded, if they had suffered one of these conditions at any time before.
4.3. Patients who had suffered a brain trauma or subdural hematoma within the last 6 months before screening should also be excluded. Brain trauma or subdural hematoma suffered more than 6 months before screening are acceptable, as long as there are no residual functional deficits of a type and severity that would require exclusion according to criterion No. 5.
5. Aphasia, dysarthria, paresis of the dominant upper extremity, 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 neuropsychological test performance. The critical question is, whether any of these deficits is likely to interfere with neuropsychological test performance. Minor deficits may be acceptable, if they can be assumed not to influence test performance. For the Digit-Symbol Substitution Test (DSST) and the Shape Trail Test (STT) the patient must be able to hold and move a pencil precisely and quickly, because both are timed tasks. For the Hopkins Verbal Learning Test (HVLT) and the Verbal Fluency Test (VFT) the patient is required to actively produce speech and to pronounce the words clearly enough to be understood.
6. Patients with major short-term fluctuations of their condition (as judged by the investigator).
7. History of or current Major Depression, Generalized Anxiety Disorder, or other psychiatric disorder as defined by DSM-IV/DSM-5 criteria (If there was a single episode of such a psychiatric disorder before the stroke, the last episode must have been finished at least one year before enrolment.)
8. Any use of antidementia drugs, nootropics, cognition-enhancing drugs, cholinergic and anticholinergic drugs. If such drugs were taken before the stroke, a sufficient washout period must be observed (12 weeks for all Ginkgo biloba products, 4 weeks for all other drugs) before entering the randomised treatment period. If such drugs were only used for the treatment of the acute ischemic stroke, no washout period must be observed (for details see Section 4.5 of protocol). This (like protocol section 4.5) refers to intake of a Ginkgo biloba product or any other of the named drugs before the stroke, e.g. for mild cognitive impairment or inner ear problems. In this case, a washout is required. No washout period is required if a patient receives Ginaton injections or any other of the named drugs during the course of acute stroke treatment, because this is only a short-term treatment.
9. Any regular use of psychoactive drugs (e.g. tranquilizers, antidepressants, antipsychotics etc.). Occasional use (no more than 3 times a week) of short-acting benzodiazepines or valerian extract preparations for sleep disturbances is acceptable, but not on the two days preceding a testing session
10. Any use of hemorheologic drugs, anti-Parkinson drugs, reserpin-containing drugs, opioids or barbiturate-containing drugs. If such drugs were taken before the stroke, a washout period of at least 8 weeks before entering the randomised treatment period must be observed (for details see Section 4.5. of the protocol). If such a drug was administered only for a short time during the treatment of the acute stroke, no washout period is required. It should be noted that the use of acetylsalicylic acid or other antiplatelet agents is allowed, as such drugs are commonly prescribed in post-stroke patients to prevent recurrent stroke.
11. Alcohol or substance addiction or abuse (i.e. consumption at higher quantities or frequencies than generally socially accepted) within the last 10 years
12. Severe, uncontrolled cardiovascular disease, especially:
12.1. Severe (stage IV acc. to the Canadian Cardiovascular Society) or unstable angina pectoris
12.2. Decompensated congestive heart failure (NYHA stage IV)
12.3. Myocardial infarction within the last 6 months
12.4. Uncontrolled hypertension (systolic pressure ≥180 mmHg, diastolic pressure ≥115 mmHg)
12.5. Known clinically significant cardiac arrhythmias (Lown classes IVb and V, bifascicular bundle branch block)

12.6. Atrial fibrillation
13. Severe renal or hepatic dysfunction (serum creatinine or serum ASAT, ALAT or Gamma-GT above three times the upper limit of the reference range)
14. Insufficiently controlled insulin-dependent diabetes mellitus (HbA1c > 8%)
15. Clinically significant anaemia (Hb <12 g/100 ml (<7.5 mmol/l) in men or Hb <10 g/100 ml (<6.2 mmol/l) in women)
16. Known or suspected clinically significant thyroid dysfunction
17. Vitamin B12 and/or folic acid deficiency
18. Known HIV infection or Lues of any stage
19. Active malignant disease (Exception: prostate cancer T1N0M0 which does not require treatment within the next 7 months except hormone therapy)
20. Known hypersensitivity to Ginkgo biloba, Ginkgo biloba extract or any ingredient of the drug under study
21. 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)
22. Any circumstances that do not allow the patient to be followed up at the scheduled intervals
23. 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

Date of first enrolment
17/01/2014

Date of final enrolment
16/05/2016

Locations

Countries of recruitment
China

Study participating centre
Huashan Hospital Affiliate to Fudan University
No.12, Wulumuqi Middle Road
Jingan District
Shanghai
China
-

Study participating centre
Changhai hospital Affiliate to Second Military Medical University
No. 168, Changhai Road
Yangpu District

Shanghai
China
-

Study participating centre
10th Hospital Affiliate to Tongji University
No. 301, Yanchang Middle Road
Zhabei district
Shanghai
China
-

Study participating centre
Zhongshan Hospital Affiliate to Fudan University
No. 180, Fenglin Road
Xuhui District
Shanghai
China
-

Study participating centre
6th Hospital Affiliate to Shanghai Jiao Tong University
No. 600, Yishan Road
Xuhui District
Shanghai
China
-

Study participating centre
9th Hospital Affiliate to Shanghai Jiao Tong University
No. 639, Zhizaoju Road
Huangpu district
Shanghai
China
-

Study participating centre
Chinese People’s Liberation Army General Hospital
No. 28, Fuxing Road
Haidian district
Beijing

China
-

Sponsor information

Organisation
Dr Willmar Schwabe (Germany)

ROR
https://ror.org/043rrkc78

Funder(s)

Funder type
Industry

Funder Name
Dr Willmar Schwabe (Germany)

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available. Since the trial was conducted in China, making datasets publicly available was uncommon. Thus, no wording related to this topic was incorporated in the patient information and consent form or the application to the ethics committee. Making data publicly available, even in completely anonymized form, was therefore not covered by patients' consent and ethics committee approval.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		29/03/2023	18/04/2023	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes