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Effects of Ginkgo biloba extract on blood levels of the drug rivaroxaban and on blood clotting

Submission date	**Recruitment status**	[X] Prospectively registered
09/10/2020	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
03/11/2020	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
02/02/2021	Other	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

When Ginkgo biloba extract is taken together with anticoagulant drugs (e.g., phenprocoumon, warfarin) or thrombocyte aggregation inhibitors (e.g., clopidogrel, acetylsalicylic acid or other nonsteroidal antirheumatic drugs), it may have an influence on the effect of these drugs. Available trial results do not indicate interactions between warfarin and Gingko biloba. This study investigates if the intake of Gingko biloba extract has an influence on the effects of the new oral anticoagulant rivaroxaban on blood coagulation, and if Ginkgo biloba extract influences the body's resorption, distribution, metabolism or excretion of rivaroxaban. An additional aim is to investigate if rivaroxaban - given in single doses - is safe and well-tolerated if it is administered concomitantly with Ginkgo biloba extract used repeatedly.

Who can participate?

Healthy volunteers aged over 18

What does the trial involve:

All participants undergo screening examinations to check their eligibility. Examinations include vital signs, physical and laboratory examinations, ECG, testing for drugs, alcohol, COVID-19, HIV, and a pregnancy test for women with childbearing potential. Participants are hospitalised for 3 days. On day 1 they take one tablet of the anticoagulant rivaroxaban, which is followed by repeated blood drawing (11 times in 48 hours) for measuring levels of rivaroxaban. On day 3 the participants go home without further treatment. They are again hospitalised on day 7. After some safety measurements (physical exam, vital signs, safety lab, ECG, drug, alcohol and COVID-19 tests, pregnancy test for women with childbearing potential) they take one tablet of Ginkgo biloba extract on the morning of day 8, followed by one tablet of rivaroxaban 1 hour later, then the blood drawing is done again until day 10. On days 9 and 10 the participants take one tablet of EGb 761 every morning. On day 10 they leave the hospital, continuing to take one tablet of Ginkgo biloba extract per day at home until day 14. On day 14 the participants are hospitalised the third time. They undergo the same safety examinations as during the hospitalisations before and on day 15 they take the last tablet of EGb 761 in the morning, followed by another tablet of rivaroxaban 1 hour later. Again 11 blood drawings within 48 hours will be done and the trial will be finished on day 17 with safety examinations (vital signs, physical exam, safety lab, ECG and a pregnancy test for women with childbearing potential).

What are the possible benefits and risks of participating?
The benefit for the participants is that they receive comprehensive medical care before enrollment and during their participation in the trial, which must not be paid by health insurance or the participants themselves. Participants with concomitant diseases (increased risk of bleeding, gastrointestinal diseases etc.) are excluded from participation. The planned assessments in this trial (measurement of vital signs, electrocardiogram [ECGs], blood, and urine sampling) are standard procedures and will be performed by qualified personnel. The total volume of blood collected per subject in this trial will not exceed 500 ml. Participation in this trial presents a minimal risk for SARS-CoV-2 infection during participation. As long as the coronavirus disease (COVID-19) pandemic situation is ongoing, there is a risk of a SARS-CoV-2 infection for participants as for the general population. This risk during trial participation is, however, not increased compared to the general population. Both trial drugs are known as well tolerated. Nevertheless, there are some undesirable effects:
Ginkgo biloba extract: headache (very frequently); lightheadedness/dizziness (frequently); diarrhoea, stomach ache, nausea, vomiting (frequently); hypersensitivity reactions (frequency not known); allergic skin reactions (reddening, swelling, itching); frequency not known; bleeding in singular organs (eyes, nose, brain, gastrointestinal tract); frequency not known
Rivaroxaban: based on its mode of action, in general the risk for occult or visible bleeding is increased. The most common side effects observed with rivaroxaban (may affect up to 1 in 10 people) are anaemia (including changes in respective laboratory parameters), dizziness, headache, bleeding in the eye, hypotension, haematoma, epistaxis, haemoptysis, gingival bleeding, gastrointestinal bleeding, gastrointestinal and abdominal pain, dyspepsia, nausea, constipation, diarrhoea, vomiting, increases in liver transaminases, pruritus, rash, ecchymosis, cutaneous and subcutaneous bleeding, pain in the extremities, bleeding in the urogenital tract (including haematuria and menorrhagia), decrease in kidney function (including increases of creatine and urea values in the blood), fever, peripheral oedema, decreased capabilities (including tiredness, asthenia), and bleeding after surgery.

Where is the study run from?
Dr. Willmar Schwabe GmbH & Co. KG (Germany)

When is the study starting and how long is it expected to run for?
January 2019 to February 2021

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

Who is the main contact?
1. Susanne Kraft
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2. Dr Friedeborg Seitz

Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-004672-19

Protocol serial number
523079.01.115

Study information

Scientific Title
A clinical trial to investigate the effects of Ginkgo biloba extract EGb 761® on the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy volunteers

Acronym
NOAK 2020

Study objectives
No hypotheses available

Rationale: Although no clinically relevant interactions of EGb 761® are known to date, it cannot be excluded that intake of EGb 761® might enhance the effects of drugs that inhibit blood coagulation or have an influence on the activity of cytochrome P450 isoenzymes 3A4, 1A2, and 2C19. Herbal drug interactions of Gingko biloba extracts have been discussed in various reviews. No satisfactory trials on potential interactions of EGb 761® with direct anticoagulants are available to date.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 17/09/2020, Ethics Committee of Landesärztekammer Baden-Württemberg (Liebknechtstr. 33, D-70565 Stuttgart; +49 (0)711 76 98 9 - 831; sandra.goepfrich@laek-bw.de); ref: AM-2020-016#A1

Primary study design
Interventional

Study design
Single-centre open-label fixed-sequence interventional trial

Study type(s)
Other

Health condition(s) or problem(s) studied
Pharmacokinetics and pharmacodynamics of rivaroxaban

Interventions
Screening of subject (Days -7 to -1);
Trial Phase 1: participants hospitalized for days 0 - 3: one single dose of rivaroxaban on day 1, pharmacokinetic and pharmacodynamic measures from 30 min pre-dose to 48 hours post-dose, discharge from hospital: day 3; days 4 - 6 outpatient without treatment.
Trial Phase 2: participants hospitalized for days 4 - 7: one dose of EGb 761 and one single dose of rivaroxaban on day 8; EGb 761 intake from day 8 - 15; pharmacokinetic and pharmacodynamic measures from 30 min pre-dose rivaroxaban to 48 hours post-dose rivaroxaban, discharge from hospital on day 10; days 11 - 13 outpatient with EGb 761 intake. Trial phase 3: participants hospitalized for days 14 - 17: last dose of EGb 761 and one single dose of rivaroxaban on day 15; pharmacokinetic and pharmacodynamic measures from 30 min pre-dose rivaroxaban to 48 hours post-dose rivaroxaban, discharge from hospital and end of trial on day 17.

Rivaroxaban concentrations are determined in the concentration range of 2 - 500 ng/ml in K2EDTA human plasma using a 100 µl sample specimen. Rivaroxaban is extracted by protein precipitation and subsequently applied to high-pressure liquid chromatography (HPLC) coupled to tandem mass spectrometry with a fully validated method established in the bioanalytical laboratory.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Ginkgo biloba special extract EGb 761, 240 mg film-coated tablets (Tebonin® konzent 240 mg), rivaroxaban 20 mg film-coated tablets (Xarelto®)

Primary outcome(s)
1. Pharmacokinetic outcome variables:
1.1. AUC0 ∞ and Cmax of rivaroxaban (primary PK endpoints) based on plasma concentrations of rivaroxaban measured using high-pressure liquid chromatography (HPLC) coupled to tandem mass spectrometry at sampling timepoints: predose to rivaroxaban intake (0 h), 0,5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h after intake
1.2. AUC0 t, AUC0 tz, %AUCtz ∞, tmax, MRT, t1/2λz of rivaroxaban based on plasma concentrations of rivaroxaban measured using high-pressure liquid chromatography (HPLC) coupled to tandem mass spectrometry at sampling timepoints: predose to rivaroxaban intake (0 h), 0,5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h after intake
2. Pharmacodynamic outcome variables:
Emax and AUEC of anti-Factor Xa activity, based on plasma concentrations of anti-Factor Xa, measured using the standard method at the laboratory (automated chromogenic test method) at sampling timepoints: predose to rivaroxaban intake (0 h), 0,5 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h after intake
3. Safety outcome variables:
3.1. Adverse events (AEs) measured by interview personally or by phone call every day from day -7 to day 17 including follow-up if an AE is not finished on day 17

3.2. Safety lab panel: clinical chemistry, haematology, urinalysis, pregnancy test, alcohol breath test, urine drug screen, SARS-CoV-2 viral DNA test on days -2, -1, 8, 15 and 17
3.3. Vital signs: body temperature, blood pressure in supine position on days -2, -1, 1 - 3, 8 – 10, 15 – 17
3.4. ECG: standard 12-lead ECG after 5 min in supine position on days -2, -1, 8, 15 and 17
3.5. Physical examination: physical inspection of general status, nutritional condition, head/neck, heart/circulatory system, lungs/respiratory tract, abdomen/gastrointestinal system, kidneys, urogenital tract, musculoskeletal system, nervous system, blood vessels/pulse status, lymph nodes, skin/hair/nails, psychiatric status; on days -2, -1, 7, 14 and 17

Key secondary outcome(s)
There are no secondary outcome measures

Completion date
03/02/2021

Eligibility

Key inclusion criteria
1. Male and female volunteers
2. Age at least (≥) 18 years at screening
3. Caucasian
4. Body mass index (BMI) 18.0 – 29.9 kg/m² (included)
5. Healthy on the basis of specified criteria evaluated at the screening visit (physical examination, ECG, vital signs, safety and coagulation laboratory)
6. Signed informed consent in accordance with the legal requirements

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
42

Key exclusion criteria
1. Participation in a further clinical trial at the same time or within the past 3 months before screening
2. Female subjects: pregnancy or lactation
3. Female subjects of childbearing potential not using adequate contraception

4. Positive pregnancy test at screening or Day -1
5. Gastrointestinal disorders with uncertain absorption of orally administered drugs (e.g., partial or total gastrectomy, enterectomy, inflammatory bowel disease, celiac disease, symptomatic lactose intolerance, other disorders associated with chronic diarrhoea)
6. Hypersensitivity to any of the IMPs or components thereof
7. Hereditary galactose intolerance, lactase deficiency, or glucose-galactose malabsorption
8. Any condition which constitutes a contra-indication for treatment with EGb 761® (e.g., high bleeding risk, regular intake of coagulation-inhibiting drugs, epilepsy or history of seizures)
9. Any condition which constitutes a contra-indication for treatment with rivaroxaban (e.g., acute, relevant bleeding, lesions, clinical situations with increased risk of severe bleeding)
10. Presence of any possibly relevant active co-morbidity (including conditions that might affect absorption, distribution and elimination of the investigational compounds; acute or chronic infections)
11. Use of any concomitant medication within 2 weeks or less than 5× t½ of the respective medication before first administration
12. Presence of any possibly confounding clinical laboratory at screening including but not confined to abnormal values for complete blood count, coagulation, serology and clinical chemistry, if assessed as clinically relevant by the investigator.
Note:
As neither rivaroxaban nor EGb 761® are hepatotoxic, slight elevations are acceptable for hepatic parameters if there is no indication of apparent disease: 10% above upper limit of normal (ULN) for alanine aminotransferase (ALT), 20% above ULN for aspartate aminotransferase (AST) or bilirubin (except in case of Gilbert's disease: elevated bilirubin is not relevant).
Slight elevation (10%) acceptable for renal parameters (except for creatinine) if there is no indication of apparent disease [Breithaupt-Grögler et al., 2017]
13. Depiction of bleeding tendencies defined by the presence of pathological coagulation parameters performed at screening, including but not confined to prothrombin time (Quick,), von Willebrand factor (vWF), platelet function assay PFA-100 and factor XIII
14. Positive test for human immunodeficiency virus (HIV) antibodies, hepatitis B-virus surface antigen (HBsAg), or anti-hepatitis C virus antibodies (anti-HCV) at screening
15. Positive immunological testing on occult blood in faeces at screening
16. Positive test for blood in urine at screening (except due to menses in female subjects)
17. Elevated blood pressure (confirmed by second measurement): Systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg at screening
18. Pulse rate < 50 or > 90 bpm at rest at screening.
19. Relevant abnormality in 12-lead ECG at screening including, but not confined to prolonged HR-controlled QTc (normal ranges: QTcB ≤ 450 ms [male subjects] or ≤ 470 ms [female subjects])
20. Smoking of any kind
21. Demonstrating excess in xanthine consumption (more than 5 cups of coffee or equivalent per day)
22. History of alcohol and/or drug abuse
23. Daily use of ≥ 24 g (men)/ ≥ 12 g (women) of pure alcohol regularly per day
24. Positive drug or alcohol test at screening or on Day -1
25. Trial personnel or first degree relatives of investigators
26. Blood donation or blood loss (> 500 mL) or plasma donation (> 250 mL) within the last 3 months before the trial
27. Known or suspected not to be reliable, or unwilling or unable to adhere to the trial directives and restrictions
28. Any condition in the opinion of the investigator that may jeopardise a safe trial participation
29. History of COVID-19
30. Prior contact with SARS-CoV-2 positive or COVID-19 patient within the last 4 weeks prior to

admission to the ward
31. Positive SARS-CoV-2 viral test

Date of first enrolment
10/11/2020

Date of final enrolment
11/01/2021

Locations

Countries of recruitment
Germany

Study participating centre
CRS Clinical Research Services Mannheim GmbH
Grenadierstraße 1
Mannheim
Germany
D-68167

Sponsor information

Organisation
Dr. W. Schwabe GmbH & Co. KG

Funder(s)

Funder type
Industry

Funder Name
Dr. W. Schwabe GmbH & Co. KG

Results and Publications

Individual participant data (IPD) sharing plan
The current data-sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date