No Significant Effect of Ginkgo Biloba Special Extract EGb 761 in the Treatment of Primary Raynaud Phenomenon: A Randomized Controlled Trial

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Background: Medicinal treatment of vasospastic Raynaud phenomenon is limited to primarily vasodilator medicines.

Objective: To explore the possible beneficial effects and tolerability of 120 mg two times a day of Ginkgo Biloba special extract EGb 761 in patients suffering from Raynaud disease (RD) (primary Raynaud phenomenon).

Methods: In a placebo-controlled, double-blind, pilot study, 41 patients with RD were randomized to either the active treatment group (EGb 761, n = 21) or placebo group for 10 weeks, after an initial 2-week run-in phase. The primary efficacy variables were self-reported changes of the frequency, duration, and severity of vasospastic attacks between the placebo-controlled run-in phase and the end of the study.

Results: Most of the patients were female, and both groups were perfectly matched with respect to demographic characteristics. The frequency of daily attacks reduced from 3.6 ± 2.3 to 2.4 ± 2.6 (−33%) in the EGb 761 group and from 2.9 ± 2.0 to 2.0 ± 1.8 (−31%) in the placebo group with no significant difference according to the ordinary least squares test ($P = 0.3564$). Furthermore, no significant differences were found with respect to the duration and severity of vasospastic attacks between the EGb 761 and placebo groups ($P = 0.4392$ and $P = 0.7187$, respectively). In all, 17 adverse events (AEs) were reported, 6 AEs from 5 patients in the EGb 761 group and 11 AEs from 8 patients in the placebo group. Serious AEs did not occur.

Conclusion: EGb 761 treatment showed an excellent safety profile in patients with RD but could not demonstrate a statistically significant reduction in clinically relevant symptoms compared with placebo.

Key Words: Ginkgo biloba, EGb 761, Raynaud phenomenon, placebo-controlled

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INTRODUCTION

Raynaud phenomenon in the absence of other disorders is called primary or idiopathic Raynaud phenomenon or Raynaud disease (RD). It is characterized by excessive vasoconstriction, usually in the digits of the hands and/or feet, typically brought on by exposure to a temperature drop or emotional stress. The vasospastic attacks are frequently associated with pain and/or paresthesia due to sensory nerve ischemia.[1,2] RD should be clearly distinguished from secondary Raynaud phenomenon, in which the symptoms are associated with an underlying condition, often a connective tissue disease, autoimmune, inflammatory, or hematopoietic disease. The estimated prevalence of RD varies considerably, affecting 3%–11% of the general population of which most are women.[3,4] Although involvement of the autonomic nervous system, endothelial dysfunction, and changes in blood components have been linked to the clinical presentation of RD, the exact pathophysiological mechanisms of this disorder remain unknown.[1,5]

Treatment of RD strongly depends on the etiology of the disorder and on the presence and severity of the individual symptoms. Lifestyle modification, such as avoidance of cold exposure and caffeine, discontinuation of smoking, and sufficient body insulation, is the first option for the prevention of vasospastic attacks in RD.[6,7] So far, medicinal treatment of RD is limited to primarily vasodilator medicines. In particular, calcium channel antagonists such as nifedipine have been proven useful.[8] Nevertheless, the use of calcium channel blockers is frequently associated with an unacceptably high level of side effects such as edema, flushes, erythema, dizziness, nausea, palpitations, and drowsiness.[9,10] Furthermore, in about 50% of patients, there is no beneficial effect.[11] Considering the high prevalence of RD in the general population and the side effect profile of the present drug therapies, there still is a need for the development of new treatment concepts.

Ginkgo biloba special extract EGb 761 has been widely used to improve peripheral blood circulation.[12] Studies have

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No beneficial effects for EGb 761 in comparison with placebo could be demonstrated in patients with primary Raynaud phenomenon.

EGb761 has an excellent safety profile in patients with primary Raynaud phenomenon.

Trial registration: EudraCT No. 2005-003623-39.

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reported that EGb 761 may improve the rheological properties of the blood through decreased aggregation and enhanced deformability of erythrocytes.[13] Furthermore, EGb 761 is known to exhibit vasoregulatory activity via regulation of the balance between prostacyclin and thromboxane.[14] A more recent study has shown that EGb 761 protects against endothelial dysfunction through modulation of nitric oxide generation.[15] These different modes of action of EGb 761 could be beneficial for treatment of patients with Raynaud phenomenon. A beneficial effect of Ginkgo biloba in patients with RD was demonstrated in a study by Muir et al.[16] A significant 56% reduction in the number of vasospastic attacks was observed in the Ginkgo biloba–treated group (n = 9) versus placebo (n = 10).

The aim of the present study was to further examine the beneficial effects of Ginkgo biloba special extract EGb 761 in patients with primary Raynaud phenomenon. Therefore, a placebo-controlled, randomized, double-blind, pilot study was designed to study the effects of EGb 761 (240 mg/d) on the frequency, severity, and duration of the attacks in RD and on other clinical signs such as color anomalies, paresthesia, dysesthesia, stiffness, and social and work activities.

MATERIALS AND METHODS

Study Design

A randomized, placebo-controlled, double-blind, monocenter, pilot study with 2 parallel groups was conducted in the Netherlands. The clinical study was approved by the Medical Ethics Committee and registered in the EudraCT database under No. 2005-003623-39. The study was conducted in accordance with the regulation in the Netherlands, the Declaration of Helsinki, and in adherence to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline for Good Clinical Practice. No changes to the approved protocol were applied during the study period. The reporting of this randomized clinical trial is according to the updated guidelines of the Consolidated Standards of Reporting Trials.[17]

Subject Population

All eligible patients were recruited at a single center, the Radboud University Nijmegen Medical Centre (Nijmegen, the Netherlands). The first patient was included on December 5, 2005, and the last patient completed the study on April 28, 2006. Eligible patients were all adults aged ≥18 years, suffering from RD (primary or idiopathic Raynaud phenomenon characterized by excessive vasoconstriction, usually in the digits of the hands and/or feet, typically brought on by exposure to a temperature drop or emotional stress), for at least 2 years with regularly occurring attacks, depending on the outside temperature, before enrollment and a history of episodic digital or toe pallor. Furthermore, each eligible patient had to provide written informed consent. Exclusion criteria were (1) secondary Raynaud phenomenon excluded by expert opinion and laboratory results; (2) connective tissue disease (systemic scleroderma, rheumatoid arthritis, juvenile chronic arthritis, systemic lupus erythematosus, polymyositis–dermatomyositis, overlap connective tissue disease, and Sjögren syndrome), cryoglobulinemia, cold agglutinins disease, thrombocytosis; (3) large vessel disease (atherosclerosis, polyarteritis nodosa); (4) pharmacological treatment of RD or intake of preparations containing Ginkgo biloba extracts within the last 2 weeks before enrollment into the study; and (5) concomitant pharmacological treatment with calcium channel blockers, L-arginine/NO supplementation, prostanoids, angiotensin-converting enzyme inhibitors, α-adrenergic blockers, endothelin 1 receptor antagonists, serotonin reuptake inhibitors, drugs with effects on the vasculature (eg, antioxidants), pentoxifyllin, or other preparations containing Ginkgo biloba extracts. In case of concomitant medication use, participants were asked to interrupt at least 2 weeks before enrollment; (6) participation in a further clinical trial at the same time or within the previous 4 weeks before enrollment into this study; (7) pregnancy or lactation; (8) female patients with childbearing potential without adequate contraception; and (9) severe internal or systemic disease (eg, cardiac, hepatic, and/or renal diseases).

Only patients who have sought medical attention for their complaints and of whom well-documented clinical presentation was available were recruited in this study.

Intervention

During a 2-week run-in period, patients received 1 film-coated placebo tablet 2 times a day. In the run-in period, only patients were blinded with respect to the drug assignment (single blinded). Subsequently, patients were randomized to a 10-week treatment period of 1 film-coated tablet of 120-mg EGb 761 or matching placebo tablet 2 times a day (a total daily dose of 240-mg EGb 761 or placebo). During the treatment period, both the patients and the participating investigators were blinded to drug assignment (double blinded). Both in the run-in period and in the treatment period, the tablets were taken per os in the morning and evening, respectively, not chewed, with some fluid. The individual duration per patient was added to 12 weeks for this clinical trial. During this period of 12 weeks, 4 visits took place. Visit 1 at the start of the run-in period (week 2), visit 2 before the start of double-blind treatment (week 0), visit 3 after 4 weeks of treatment (week 4), and visit 4 after 10 weeks (week 10) of treatment. Study medication was provided and packaged by Dr. Willmar Schwabe GmbH & Co. KG (Karlsruhe, Germany). Compliance to treatment was calculated as the percentage of the number of actually used tablets and the planned number of tablets according to the protocol.

Objectives

Primary endpoints were frequency, duration, and severity of vasospastic attacks. The frequency and duration of attacks were recorded by the patient in an especially designed "patient diary" on a daily basis whenever an attack occurred. Severity of attacks was rated by the patients once a day during the whole period of the trial.

Secondary efficacy variables were change in par- and dysesthesia of fingers or toes, tingling, itching, formication, pain, burning, and numbness as reported by the patient at each visit on a 10-step Likert scale; coordination problems,

problems in button up of shirts/blouses as reported by the patient at each visit on a 10-step Likert scale; interaction with daily activities and work, reported by the patient as each visit on a 10-step Likert scale; subjective assessment of color anomalies of fingers, cyanosis, lividness, and erythema as reported by the patient at each visit on a 10-step Likert scale; impact of trigger factors, according to the patient's opinion and reported by the patient at each visit on a 10-step Likert scale; efficacy assessment of both the patient and the investigator after 4 and 10 weeks of treatment, using a 7-step symmetrical scale (very much improved to very much worse); and the number of patients who expressed to continue treatment after 10 weeks of treatment.

With respect to safety, the following secondary outcome variables were monitored: adverse event (AE) surveillance: adverse and serious AEs will be monitored and related to the system organ classes, severity, and the relationship to the study medication; laboratory parameters: blood samples were drawn at visit 1 and visit 4 to assess blood parameters during the course of the study. The blood parameters consisted of hematology: hemoglobin, hematocrit, red blood cell, white blood cell and platelet count, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration; differential blood count: neutrophils, eosinophils, lymphocytes, and monocytes; serum chemistry: creatinine, total bilirubin, aspartate transaminase, alanine aminotransferase, Gamma GT, sodium, potassium, calcium, urea, cholesterol, triglyceride, glucose, activated partial thromboplastin time, and epinephrine platelet function assay.

All data were recorded into case report forms on a continuous basis by the principal investigator at the Radboud University, Nijmegen Medical Centre, and where applicable by the patients in the patient diary. The completed original case report forms and diaries were forwarded to the Biometrics Department of Dr. Willmar Schwabe for entry into the study database.

Sample Size

The study was powered based on the observed changes in the frequency of attacks by Ginkgo biloba as published by Muir et al.[16] With a 1-sided level of significance of 0.025 and a power of 80%, the number of patients in each group was calculated as 20. Hence, a total sample size of 40 patients was thought to provide enough power to prove efficacy for at least 1 of the 3 primary outcome variables. To recruit this number of patients, a 2-month inclusion period was anticipated.

Randomization

Randomization was carried out by the Biometrics Department of Dr. Willmar Schwabe GmbH & Co. KG. The medication numbers from 5001 to 5060 were allocated to the 2 treatment groups in a balanced way, and a corresponding sealed randomization list was produced by means of the validated equidistribution property random number generator RCODE. The length of the balanced blocks (block size of 10) was fixed in a separated document that was withheld from the study site. The randomization list was kept sealed in a secure location at Dr. Willmar Schwabe. It was not opened before all data were completely entered into the database, the database was locked, and all patients had been definitely allocated to the analysis set. In addition, the participating study center received a sealed code break envelope for each medication number. The center was clearly instructed that the envelopes could only be opened if knowledge of the treatment group allocation was absolutely necessary for medical reasons. After completion of the study, all code break envelopes were returned to Dr. Willmar Schwabe and checked for completeness and intactness. At visit 2, patients were randomized to treatment by the principal investigator and enrolled into the study.

Statistical Methods

Primary outcome variables were the frequency, duration, and severity of vasospastic attacks. The change from baseline (week 0) was analyzed for each of these variables in a confirmatory analysis, calculating the mean value per day for the 7 days preceding randomization (= baseline value) and the 14 days preceding end of treatment (weeks 8–10 = postbaseline value). The differences between postbaseline and baseline values were considered for the confirmatory analysis. Assuming that EGb 761 was at least as effective as placebo with respect to the primary variables, the closed test procedure based on the ordinary least squares (OLS) test[18] was used to test this hypothesis. The OLS tests were performed at a 1-sided local level with $\alpha = 0.025$.

The confirmatory analysis was primarily based on the full analysis set (FAS), including all patients who received randomized study treatment at least once. Missing values for the primary variables were replaced by the mean values of the nonmissing values, but only when at least half of the foreseen measurements were available (ie, at least 4 measurements before randomization or at least 7 postbaseline, respectively). To eliminate the impact of dropouts on efficacy results, in addition, a subset of observed cases (OC) was evaluated. This subset included data only from patients randomized who did not discontinue prematurely and were available for evaluation at the designated assessment times. In addition to the evaluation of the FAS, a per-protocol analysis was performed including all randomized patients without major protocol violations. Regular descriptive statistics were performed with regard to the secondary efficacy variables. Student t tests and χ^2 tests were used to compare means and calculate the 2-sided P values between the 2 treatment groups. The safety analysis set was based on the set of all patients who took at least 1 dose of the randomized study medication.

RESULTS

Patient Flow and Demographics

The flow diagram of patients through each phase of the study is shown in Figure 1. A total of 44 patients were included in the run-in phase of the study. Three of the included patients were not randomized due to dropout before baseline: 1 did not meet a selection criterion, 1 was withdrawn due to worsening of the primary diagnosis, and

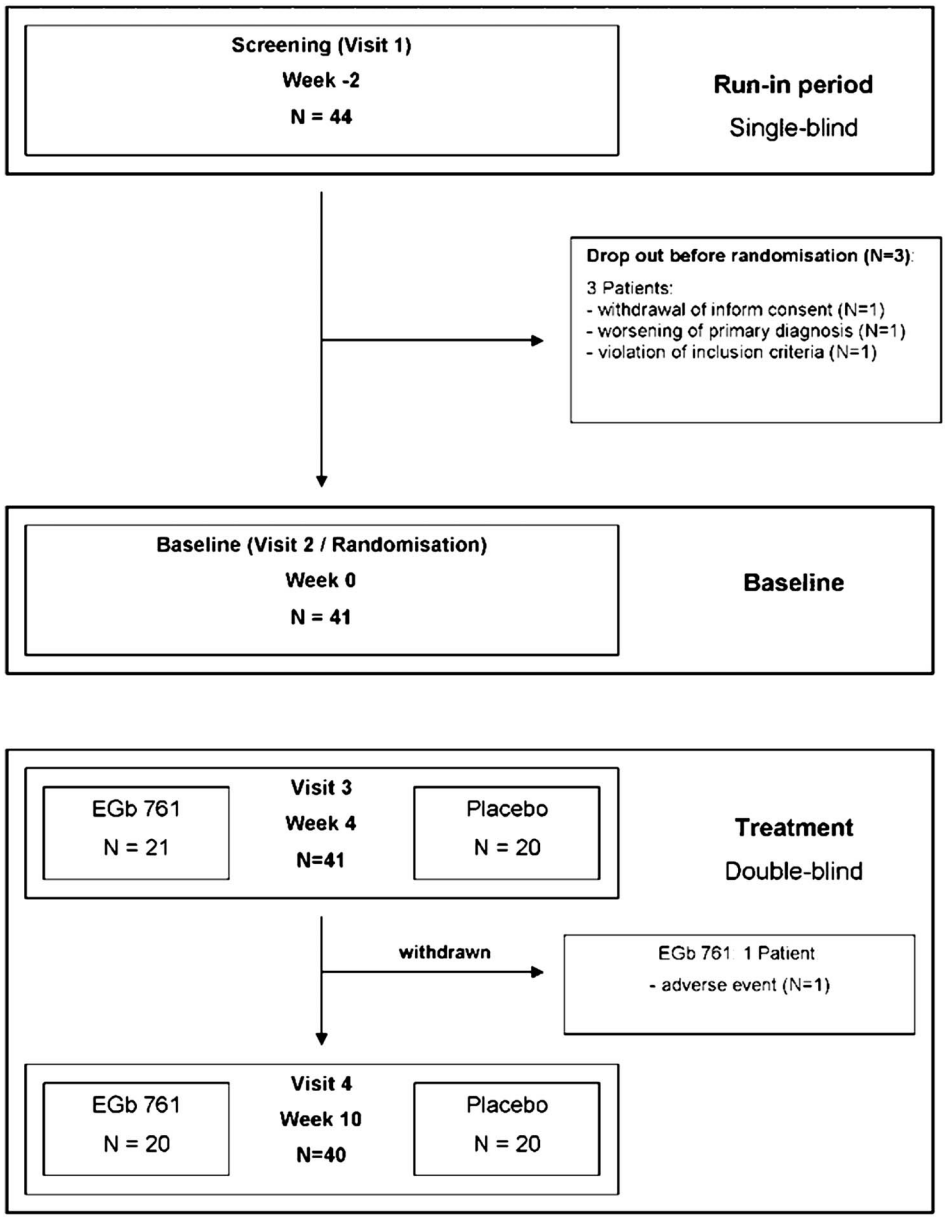

FIGURE 1. Flow chart of patients through each phase of the study.

1 patient revoked his informed consent before randomization. Forty-one patients (EGb 761: 21, placebo: 20) were included into the randomized treatment phase of the study. During the active treatment phase, 1 patient in the EGb 761 group terminated the study prematurely due to an AE (dyspnea). A total of 40 patients (EGb 761: 20, placebo: 20) completed the 10-week treatment phase. The FAS (FAS with last observation carried forward) included all patients who had at least 1 filled out postbaseline diary page (EGb 761: 21, placebo: 20). For 2 of 21 patients in the EGb 761 group, relevant protocol violations were observed (with respect to the use of concomitant medication, n = 2). In the placebo group, relevant protocol violations were observed for 5 of 20 patients: missing multiple diary pages (n = 3), use of concomitant medication (n = 1), and violation of visit schedule (n = 1). Therefore, the per-protocol set consisted of 19 patients in the EGb 761 group and 15 patients in the placebo group. The OC analyses set included 17 patients in the EGb 761 group and 15 patients in the placebo group. The clinical trial ended due to regular study termination.

As shown in Table 1, the majority of patients included in the study were female. Both treatment groups were comparable at baseline with respect to demographic data because no significant differences were observed between the EGb 761- and placebo-treated group with respect to sex, age, height, and weight (Table 1). In addition, no significant differences were observed with respect to mean duration of the disease (EGb 761: 23 ± 14, placebo: 23 ± 17), concomitant disease, and prior medication (data not shown). Furthermore, there were no relevant treatment group differences regarding

TABLE 1. Demographics and Disease Status

Characteristics	EGb 761 n = 21	Placebo n = 20	P*
Male, %	19	10	0.4126
Female, %	81	90	—
Mean age, y	47 ± 13	49 ± 13	0.7060
Height, cm	172 ± 8	169 ± 5	0.1416
Weight, kg	67 ± 11	68 ± 10	0.8660

FAS values are either expressed as percentage of total or as mean ± SD.
*Two-sided *P* value of the χ^2 test and *t* test indicated no significant differences between the EGb 761 and placebo groups.

smoking habits, alcohol consumption, childbearing potential, and vital signs (data not shown). Most of the patients (≥80%) documented fingers and toes as affected body parts and pallor, cyanosis, hyperemia, and pain as present symptoms of the primary diagnosis. Treatment compliance turned out to be very good, with 100% ± 7% for the EGb 761 group and 97% ± 4% for the placebo group.

Efficacy Parameters

The primary efficacy parameters were the changes in frequency, duration, and severity of vasospastic attacks between the 7 days preceding randomization (= baseline values) and the 14 days preceding the end of treatment (= postbaseline values). As shown in Table 2, the reduction of the primary parameters frequency and duration of vasospastic attacks during the double-blind treatment period was slightly more pronounced in the EGb 761 group than in the placebo group (Table 2). No differences were observed for the variable severity of vasospastic attacks. The resulting 1-sided *P* value of the OLS test for the global null hypothesis (the mean change in frequency and duration of vasospastic attacks in the EGb 761 group is not higher than in the placebo group) was 0.3433 for the FAS. The null hypothesis could therefore not be rejected, and a statistically significant difference in primary efficacy parameters between the treatment groups could not be shown in this study. This result was confirmed by a sensitivity analysis for the per-protocol set ($P = 0.2484$) and OC ($P = 0.3077$).

Concerning the secondary efficacy parameters such as color anomalies, paresthesia, dysesthesia, stiffness, social and work activities, and impact of trigger factors, no significant or clinically relevant differences were observed between the EGb 761- and placebo-treated group (data not shown). Other secondary parameters were the efficacy assessment of the patient and investigator after 4 and 10 weeks of treatment. As shown in Table 3, no significant differences were observed between the EGb 761 and placebo groups with respect to the rating of the efficacy by the patients and the investigator, after 4 and 10 weeks of treatment, respectively. Under the FAS, 38.1% patients of the EGb 761 group declared that they would continue treatment after the end of the study versus 50% of patients in the placebo group.

Tolerability and Safety

During the double-blind treatment period, a total of 17 AEs were observed in 13 of 41 patients (31.7%). The number of AEs in the EGb 761 group (6 AEs reported by 5 patients) was somewhat lower compared with the placebo group (11 AEs reported by 8 patients). None of the AEs were classified as serious. A causal relationship to the study medication could not be excluded in 3 of 21 patients (14.2%) in the EGb 761 group and 4 of 20 patients (20.0%) in the placebo group (Table 4). One of the patients in the EGb 761 group terminated the study prematurely due to a mild dyspnea, which was assessed as "unlikely related" to the intake of the study medication.

Specific attention in this clinical trial was paid to the measurements of coagulation parameters and platelet activity as safety laboratory parameters. No (significant) differences were observed between the 2 treatment groups, with respect to activated partial thromboplastin time (seconds) before (week -2; EGb 761, 29 ± 2; placebo, 30 ± 5) and after treatment (week 10; EGb 761, 29 ± 2; placebo, 30 ± 5) and epinephrine platelet function assay (seconds), before (week -2; EGb 761, 118 ± 32; placebo, 144 ± 66) and after treatment (week 10; EGb 761, 135 ± 65; placebo, 156 ± 71). Furthermore, no mentionable changes regarding other laboratory parameters, physical examination, blood pressure, heart rate, or temperature of both hands were observed in the treatment groups throughout the course of the study (data not shown).

DISCUSSION

This randomized, placebo-controlled, double-blind, single-center, pilot study was conducted to further explore

TABLE 2. Primary Efficacy Parameters: Frequency, Duration, and Severity of Attacks

	EGb 761 n = 21			Placebo n = 20			
Parameters	Baseline	Postbaseline	Change	Baseline	Postbaseline	Change	P*
Frequency (daily)	3.6 ± 2.3	2.4 ± 2.6	1.2 ± 1.5	2.9 ± 2.0	2.0 ± 1.8	0.9 ± 1.4	0.3564
Duration, min	80.2 ± 68.8	47.4 ± 63.0	32.8 ± 50.0	80.7 ± 61.5	50.9 ± 84.7	29.7 ± 81.8	0.4392
Severity†	5.1 ± 2.2	3.8 ± 2.5	1.3 ± 2.3	4.4 ± 1.9	3.1 ± 1.8	1.3 ± 2.4	0.7187

FAS values are expressed as mean ± SD.
*One-sided *P* value of the OLS test for the single null hypothesis indicating acceptance of the hypothesis that the mean change in the EGb 761 group is not higher than in the placebo group.
†Documented on a scale from 0 (none) to 10 (very severe).

TABLE 3. Secondary Efficacy Parameters: Assessment of Patient and Investigator

Efficacy Assessment	EGb 761 n = 21		Placebo n = 20	
	4 wks	10 wks	4 wks	10 wks
Investigator*	4.1 ± 0.5	4.8 ± 0.9	4.4 ± 1.2	5.1 ± 1.2
Patient*	4.1 ± 0.7	4.7 ± 0.9	4.3 ± 1.4	5.0 ± 1.1

FAS values are expressed as mean ± SD.

*Assessment of the subjective clinical efficacy using a 7-item symmetrical scale from 1 (very much worse) to 7 (very much improved). The *t* tests indicated no significant differences between the EGb 761 and placebo groups.

the possible beneficial effects of EGb 761 in patients with primary Raynaud phenomenon. After 10 weeks of treatment with 240-mg EGb 761 per day, during a period of the year with lowest outside temperature, the frequency of vasospastic attacks decreased by 33%. However, a comparable reduction in the number of attacks (31% compared with baseline) was observed after 10 weeks of placebo treatment ($P = 0.3564$). The relatively high placebo response in the treatment of patients with RD can be explained by the fact that the symptoms and course of this disease are highly influenced by context factors such as seasonal variations and personal lifestyle.[19] Similar high placebo responses in RD have been reported in other studies as well.[9,20] Placebo response is also influenced by expectations of improvement when entering a trial. A recent study by Choi et al,[21] directly comparing nifedipine sustained release with a Ginkgo biloba extract in the treatment for primary Raynaud phenomenon, found a comparable reduction in vasospastic attacks on Ginkgo biloba treatment (31%) as in the present study, but no comparison to a placebo was made. The other primary outcome variables in the present pilot study, duration and severity of vasospastic attacks, decreased over the 10-week treatment period as well but with no significant differences between the EGb 761 and placebo group either ($P = 0.4392$ and $P = 0.7187$, respectively). In addition to the primary outcome criteria, several clinical signs of RD were monitored through self-assessment questionnaires during the course of the trial to investigate possible changes with respect to improvement of quality of life (eg, coordination problems, interaction with daily activities and work, impact of trigger factors). However, no significant or clinically relevant differences were observed between the 2 treatment groups with respect to any of these secondary efficacy variables.

TABLE 4. Number and Incidence of Adverse Drug Reactions

MedDRA Preferred Term	EGb 761 n = 21		Placebo n = 20	
	Patients	Events	Patients	Events
Headache	2	2	2	2
Dyspnea	1	1	0	0
Epistaxis	0	0	1	1
Nausea	0	0	1	1
Rash	0	0	1	1

Safety analyses set (randomized patients only) of the frequency of patients with and numbers of AEs, for which a causal relationship to the study medication could not be excluded.

The present pilot study demonstrated no significant effects with EGb 761 compared with placebo in patients with primary Raynaud phenomenon. These findings are in contrast with an earlier placebo-controlled study by Muir et al,[16] which showed a highly statistically significant reduction in the number of vasospastic attacks per day on treatment with a Ginkgo biloba extract (56% reduction with Ginkgo vs. 27% with placebo) and a positive trend toward changes in other clinical and laboratory parameters. However, the duration of attacks and their severity remained comparable in both groups. One potential explanation for these observed differences in effect size is that other Ginkgo biloba extracts and dosages are studied. In the study by Muir et al,[16] a relatively high dose of a Ginkgo biloba extract (Seredrin) was studied, 360 mg (3 tablets) a day, compared with 240 mg (2 tablets) a day of Ginkgo biloba special extract EGb 761 in the present trial. It is possible that a higher dosage of EGb 761 would have yielded a larger effect, similar to that of the Ginkgo biloba extract in the Muir study. However, because a Seredrin tablet of 120 mg (www.healthperception.co.uk) contains less Ginkgo flavonoids (8% vs. 24%) and terpene lactones (2% vs. 6%) than a 120-mg tablet of special extract EGb 761, it is unlikely that the difference in effect size between the 2 studies is just a matter of dose–response effects. Another noticeable difference between the Muir study and the present trial is the severity of RD. Although inclusion criteria in the Muir study were not described, on enrollment, patients suffered on average of about 8 (placebo group) to 13 (Ginkgo group) vasospastic attacks per week. The patients in the present study suffered from RD on average for a period of 23 years and reported 20 (placebo group) to 25 (EGb 761 group) attacks per week at baseline. It is therefore plausible that patients with more severe RD, as in the present study, are less responsive to Ginkgo biloba treatment than patients with mild symptoms of RD, as in the Muir study.[16] Another aspect that may have affected differences in outcome is that in the present study, a single-blind run-in phase of 2 weeks on placebo tablets was chosen. However, possible placebo effects after the run-in phase were not accounted for as placebo responders were not excluded from inclusion into the active treatment phase.

In previous studies, it has been shown that EGb 761 can inhibit the vasospastic response of mouse cutaneous arterioles to platelet activation[14] and protects against endothelial dysfunction through modulation of nitric oxide generation.[15] From these pharmacological effects of EGb 761, it has been expected that EGb 761 would decrease the frequency and duration of vasospastic attacks in patients with RD. Beneficial effects with EGb 761 have been reported for other vascular disorders, such as vascular and mixed dementia[22] and peripheral vascular disease.[23] However, in the present study, EGb 761 failed to show a significant improvement of symptoms in patients with Raynaud phenomenon compared with placebo. In this regard, it is noteworthy to consider about several limitations associated with the present study. The objective of the present study to detect significant differences for multiple

endpoints (frequency, duration, and severity of attacks) upon treatment with EGb 761 was most likely not realistic, considering the relatively small sample size (n = 41). In this context, it is important to mention that the relatively small study of Muir et al[16] was the only basis for the sample size calculation in this trial. This is particularly important as the populations of both trials differ. Another limitation is that only 1 single medical center was involved and EGb 761 treatment was evaluated after a 10-week period with no long-term follow-up. Because patients included were severely affected by RD (on average for a period of 23 years), a larger possibly significant effect may have been observed with a longer treatment period on EGb 761. Furthermore, a longer run-in phase under placebo may have achieved more stable baseline values.

Strengths of the study are the rigorous randomized, double-blind, placebo-controlled design of the study. Recently, the need to perform such well-designed trials on herbal preparations has been addressed in a meta-analysis of the efficacy of complementary and alternative medicine in the treatment of RD.[24] Furthermore, the present study had clear inclusion criteria, highly matched groups, used a well-characterized and standardized Ginkgo biloba extract, and showed good compliance with respect to drug intake. Furthermore, specific attention in this clinical trial was paid to the measurements of coagulation parameters and platelet activity as safety laboratory parameters because several case reports have been published on the possible causal relationship between hemorrhagic complications and Ginkgo biloba intake.[25–30] However, no mentionable changes were observed regarding these laboratory parameters and on physical examination, blood pressure, heart rate, and temperature of both hands. In addition, the incidence of AEs was comparable between the 2 treatment groups. Thus, overall, the study demonstrated that EGb 761 is a safe and well-tolerated herbal medicinal product in these patients.

Currently, pharmacological treatment of Raynaud phenomenon remains unsatisfactory. The development and testing of new potential therapeutic approaches are therefore of great clinical importance. Although previous studies have suggested that Ginkgo biloba may be such a promising agent, the results of the present pilot study could not demonstrate additional beneficial effects for EGb 761 in comparison to placebo for the treatment of RD. Further research on EGb 761 in the treatment of RD, including a larger clinical trial with long-term intervention and follow-up, is therefore warranted.

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