Summary of results

Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Trial to Confirm the Efficacy, Safety and Tolerability of Ginkgo biloba Special Extract EGb 761® in Patients Suffering from Mild Mental Impairment (MMI)

Study No. 523001.01.071

EudraCT-No. 2005-003747-31

Date of report: 18 August 2016

First subject included: 27 December 2005

Last subject last visit: 14 February 2007

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Summary

Sponsor: Dr. Willmar Schwabe GmbH & Co. KG
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Study drug: EGb 761®, 240 mg film-coated tablets

Active ingredient: EGb 761® (special extract of Ginkgo biloba leaves)

Test medication: One tablet contains: 240 mg dry extract from Ginkgo biloba leaves (35-67:1), extraction solvent: acetone 60% (w/w).
The extract is adjusted to 22.0 – 27.0 % ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0 – 7.0 % terpene lactones consisting of 2.8 – 3.4 % ginkgolides A, B, C and 2.6 – 3.2 % bilobalide and contains less than 5 ppm ginkgolic acids.

Reference medication: Placebo

Study title: Randomised, double-blind, placebo-controlled, parallel-group trial to confirm the efficacy, safety and tolerability of Ginkgo biloba special extract EGb 761® in patients suffering from mild mental impairment (MMI)

Study centres: The study was conducted in 5 study centres in Latvia

Study period: First subject included: 27 December 2005
Last subject last visit: 14 February 2007

Publications: Grass-Kapanke B, Busmane A, Lasmanis A, Hoerr R, Kaschel R (2011): Effects of Ginkgo Biloba Special Extract EGb 761® in Very Mild Cognitive Impairment (vMCI). Neuroscience & Medicine 2: 48-56

Objectives: To assess treatment effects and tolerability of EGb 761® in subjects below the age of retirement with very mild cognitive impairment (vMCI), also named mild mental impairment, MMI).

Methodology: The study was conducted as a randomised, double-blind, placebo-controlled clinical trial with two parallel groups. After a 1-week screening period the patients were randomised to a 12-week treatment period with either EGb 761® or placebo (double-blind).

Number of subjects included in the study:

	Planned to be randomised (total sample)	Included	Rando-mised	Safety analysis set	Efficacy: Full analysis set	Efficacy: Per protocol set
EGb 761®	150		150	150	149	142
Placebo	150		150	150	147	132
All	300	320	300	300	296	274

Source data: appendix table 16.2.II.2.2

Diagnosis and main criteria for inclusion: Patients included were men or women (aged 45 to 65 years) who had a perceived cognitive impairment present for at least 3 months. In order to be eligible for study inclusion, all patients were required to have a widely preserved general cognitive functioning, as evidenced by a total score above 23 in the MMSE without an indication of dementia.

Test and control preparation, dose and mode of administration:

Double-blind treatment period:

One film-coated tablet of 240 mg EGb 761® or matching placebo once per day.

Duration of treatment: Twelve weeks of double-blind treatment, according to the protocol.

Criteria for evaluation: Wechsler Memory Scale III (WMS III) – Faces I, Wechsler Memory Scale III (WMS III) – Faces II, Wiener Test System Determination Test (DT), Wiener Test System Arbeitsleistungsserie (ALS), Appointments Test (TT), SF-36 Health Survey, Mental Balance Scale (Befindlichkeitsskala, BfS').

Safety:
Adverse events surveillance, physical examination, vital signs, and laboratory tests.

Statistical methods: This was the first clinical trial with EGb 761® in patients with very mild cognitive impairment. Therefore, a formal sample size calculation based on former experience was not possible. Two cognitive variables (WMS III - Faces II, WTS-DT) and a variable concerning mental balance (BfS') were therefore chosen as efficacy variables of major interest and to calculate a reasonable sample size. Evaluation of these outcome variables was done one-sided under control of the type-I error rate $\alpha=0.025$. The analysis (ANCOVA) included treatment, the baseline-value of the corresponding variable and centre effects. For further investigation, p-values based on one-sided t-tests were calculated for all efficacy variables which are presented in this report. The concept underlying this statistical analysis was based on the assumption that EGb 761® would show superior effects compared to placebo. Therefore, one-sided tests were conducted. No adjustment of the type-I error-rate was performed. Thus, the p-values should be interpreted as explorative.

It must be considered that there is very limited room for improvement in very mild impairment and, therefore, separate

analyses were performed for a subgroup with more distinct memory impairment, as specified prospectively in the statistical analysis plan. This subgroup was defined by a baseline score below the median in a visual delayed recognition task (i.e. < 33 in the WMS III subtest Faces II). Visual episodic memory impairment is one of the earliest indicators of imminent Alzheimer's disease and, hence, low functioning even in the easiest of the memory tests administered seems to be a more reliable indicator of veritable impairment than low functioning in the very demanding tests. The so defined subgroup appears therefore to deserve particular interest.

Results

Demographic data:

(absolute (relative) frequency and two-sided p-value of the χ^2-test or mean ± standard deviation, median and two-sided p-value of the t-test respectively)

Full analysis set				
		EGb 761® (N=149)	**Placebo** (N=147)	**p-value**
Sex	Male	28 (18.8)	24 (16.3)	0.58
	Female	121 (81.2)	123 (83.7)	
Age [y]		55±6 55	54±6 54	0.26
Height [cm]		167±8 166	167±8 166	0.84
Weight [kg]		78±16 78	77±14 76	0.55
BMI		28±5 27	28±5 27	0.48
Level of education	Less than 9 school years completed	2 (1.3)	9 (6.1)	0.03
	Completed 9-10 years of school	11 (7.4)	4 (2.7)	
	Completed job training	57 (38.3)	55 (37.4)	
	High-school graduation	16 (10.7)	26 (17.7)	
	University / college degree	63 (42.3)	53 (36.1)	

Source data: appendix table 16.2.II.4.1

The mean baseline scores of all neuropsychological tests were between the age-adjusted norms and one standard deviation below, indicating that – on average – the cognitive impairment was very mild.

Results of efficacy analysis:

(mean ± standard deviation, median and two-sided p-value of the t-test for baseline values or one-sided p-value of the t-test for comparison of changes in the treatment groups, respectively)

Full analysis set				
		EGb 761® (N=149)	**Placebo** (N=147)	**p-value**
WMS III - Faces I >	Baseline (Day 0)	35.3±4.9 35.0	35.4±5.3 35.0	0.81
	Week 12 - Day 0	4.1±5.3 4.0	3.1±4.8 3.0	0.04
WMS III - Faces II >	Baseline (Day 0)	33.9±5.7 33.0	33.2±5.7 33.0	0.30
	Week 12 - Day 0	4.8±5.9 4.0	4.4±4.9 3.0	0.27
DT overall (correct) >	Baseline (Day 0)	308.5±44.8 320.0	314.5±36.6 323.0	0.21
	Week 12 - Day 0	8.9±42.6 5.0	5.1±37.0 6.0	0.21
ALS answered >	Baseline (Day 0)	746.1±153.3 737.0	777.1±159.2 779.0	0.09
	Week 12 - Day 0	44.2±119.6 40.0	17.8±85.3 18.0	0.01
TT Score (immediate recall) >	Baseline (Day 0)	12.0±4.3 12.0	12.6±4.5 13.0	0.21
	Week 12 - Day 0	5.6±5.2 5.0	4.6±5.5 4.0	0.06
TT Score (delayed recall) >	Baseline (Day 0)	9.3±3.9 9.0	9.4±3.9 9.0	0.82
	Week 12 - Day 0	5.5±5.7 5.0	4.3±5.3 4.0	0.03
SF-36 Factor score Physical health>	Baseline (Day 0)	65.3±17.9 68.0	68.9±17.6 72.3	0.08
	Week 12 - Day 0	9.0±15.9 10.0	5.7±16.4 6.3	0.04
SF-36 Factor score Mental health >	Baseline (Day 0)	63.0±16.7 66.2	65.2±18.0 70.3	0.29
	Week 12 - Day 0	11.1±17.7 9.8	9.0±16.7 7.1	0.15
BfS' <	Baseline (Day 0)	20.3±9.7 18.0	20.6±10.0 19.0	0.79
	Week 12 - Day 0	-2.3±10.8 -2.0	-4.1±10.8 -4.0	0.92

> a higher score indicates better performance
< a lower score indicates better performance
Source data: appendix table 16.2.II.6.2.1

Baseline scores (means, 95%-CI) and changes from baseline (means, 95%-CI) for more markedly impaired subsample (Faces II at baseline < 33), one-sided p-values for between-group comparisons of changes (t-test)

Test/Scale	Baseline Scores		Changes Baseline to Week 12		p-Values
	EGb 761® (n = 63)	**Placebo** (n = 70)	**EGb 761®** (n = 63)	**Placebo** (n = 70)	**(Week 12)**
WMS III – Faces I	32.38 31.16-33.61	32.49 31.25-33.72	6.11 4.64-7.58	4.16 2.88-5.43	0.02
WMS III – Faces II	28.60 27.86-29.35	28.37 27.57-29.18	8.73 7.33-10.13	6.47 5.18-7.77	0.01
WTS-ALS – Answered Stimuli	756.44 716.87-796.02	791.01 754.74-827.29	40.27 9.58-70.96	0.77 -22.86-24.40	0.02
WTS-DT – Correct Reactions	312.56 301.50-323.61	321.24 313.19-329.30	12.51 2.81-22.21	3.43 -3.52-10.38	0.07
TT (Appointments Test) – Immediate Recall	12.60 11.40-13.81	13.04 12.16-13.93	5.84 4.38-7.31	3.96 2.76-5.15	0.02
TT (Appointments Test) – Delayed Recall	9.60 8.49-10.71	9.63 8.87-10.39	5.41 3.95-6.87	2.87 1.77-3.97	0.003
BfS' (Mental Balance Scale)	19.27 16.81-21.73	18.84 16.59-21.09	-2.51 -5.38-0.37	-4.51 -6.89-(-2.14)	0.86
SF36 – Factor Score Physical Health	67.31 63.28-71.35	70.84 66.85-74.83	11.96 8.75-15.18	8.18 4.01-12.35	0.08
SF36 – Factor Score Mental Health	65.18 61.29-69.08	68.27 64.18-72.35	10.82 6.34-15.30	10.75 6.95-14.56	0.49

Results of safety analysis:

EGb 761® – begin of AE between begin and 2 days after end of active treatment

(absolute (relative) frequency)

There were 32 adverse events in the EGb 761® group.

Placebo – begin of AE between begin and 2 days after end of active treatment

(absolute (relative) frequency)

There were 32 adverse events in the placebo group.

Frequency of patients with serious adverse events

No serious adverse events occurred during the study.

Conclusion

This randomised, placebo-controlled, double-blind clinical trial with two parallel groups was conducted to assess the clinical efficacy, safety and tolerability of the Ginkgo biloba special extract EGb 761® in mild mental impairment (MMI). After a 1-week screening period the patients were randomised to a 12-week treatment period with either EGb 761® or placebo (double-blind).

It was planned to include 300 men or women, 45 to 65 years old who had a perceived cognitive impairment present for at least 3 months. In order to be eligible for study inclusion, all patients were required to have a widely preserved general cognitive functioning, as evidenced by a total score above 23 in the MMSE without an indication of dementia.

The statistical procedure applied in the analysis was specified in detail in the study protocol and the statistical analysis plan (SAP), which was prepared on 2 May 2007 before breaking the blind.

Efficacy variables were the WMS III – Faces I, WMS III – Faces II, the Wiener Test System Arbeitsleistungsserie (ALS, Work Performance Series), the Wiener Test System Determination Test (DT), the Appointments Test (TT), the Befindlichkeitsskala (BfS', Mental Balance Scale) and the SF-36 HealthSurvey.

The efficacy analysis was based on the FAS including all patients who received study medication and had at least one post treatment outcome assessment of the efficacy parameters. The assessment of the safety of EGb 761® as compared to placebo was based on those patients who received study medication at least once (safety analysis set). The incidence and intensity of adverse events, the laboratory parameters and vital signs were compared between the treatment groups.

All 300 randomised patients were included in the safety analysis set. Four patients of the safety analysis set could not be included in the FAS due to missing post treatment outcome assessments (FAS: EGb 761®: 149 patients; placebo: 147 patients). The treatment groups were similar with respect to age, weight, and height. The patients in the EGb 761® group had a slightly better level of education than the patients in the placebo group. All study participants were Caucasians. There were no relevant treatment group differences regarding

BMI, smoking habits, alcohol consumption, childbearing potential and vital signs at screening.

During the 12 weeks of randomised treatment, the EGb 761® group showed consistently larger improvements in all cognitive tests, although statistical significance was achieved for only three of six cognitive outcomes (WMS III – Faces I, WTS-ALS, TT Delayed Recall) in the FAS. Regarding the psychological rating scales, there were slight improvements in all scales in both treatment groups, with significant superiority of EGb 761® only in the SF-36 Factor Physical Health (FAS).

In the prospective subgroup of patients with more distinct cognitive impairment at baseline, improvements in cognitive tests were larger and drug-placebo differences were more pronounced, with statistical significance for five of six tests and borderline significance ($p = 0.07$) for one test (WTS-DT).

From the baseline scores of cognitive tests and the pattern of treatment effects it can be concluded that there were ceiling effects in some less-demanding tests and considerable practice effects, both to the disadvantage of the EGb 761® group in the FAS. In the prospective subgroup of patients with more distinct cognitive impairment, ceiling effects were no longer present and practice effects were smaller, both leading to larger drug-placebo differences.

Overall, during the active treatment period, a total of 64 adverse events were reported in 46 patients. In each treatment group, 32 adverse events occurred in 23 patients. In both treatment groups, the majority of adverse events were reported during the first four weeks of treatment. In both treatment groups, no events were rated as being severe in intensity.

No serious adverse events occurred during the study. The incidence of adverse events was similar in the two treatment groups.

No mentionable changes regarding laboratory parameters, physical examination, blood pressure or heart rate were observed in the treatment groups throughout the course of the study.