Summary of results

Version 1.0

Clinical Trial to Explore Treatment Effects of Ginkgo biloba Extract EGb 761® in Patients with Different Types of Vertigo and Effect Modification by Type of Vertigo, Chronicity and Concomitant Pathologies

Clinical trial no. 523079.01.114

EudraCT no. 2016-000316-15

Date of report: 25 Sep 2019

First subject enrolled: 28 October 2016

Last subject completed: 22 February 2018

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1 Summary

Sponsor: Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany

Title of clinical trial: Clinical Trial to Explore Treatment Effects of Ginkgo biloba Extract EGb 761® in Patients with Different Types of Vertigo and Effect Modification by Type of Vertigo, Chronicity and Concomitant Pathologies

Relevant Amendments: Not applicable – no substantial amendments

Co-ordinating investigator One co-ordinating investigator in Poland.

Investigators: The study was conducted by twelve investigators in Poland.

Trial sites: The study was conducted in twelve trial sites in Poland.

Trial period:
First subject enrolled: 28 October 2016
Last subject completed: 22 February 2018

Publications: None

Clinical phase: Phase IIb

Objective:

- To explore whether causes, risk factors, chronicity of vertigo and accompanying features influence the treatment effect of EGb 761® in terms of improvement and response rates
- To identify groups of patients that benefit most of EGb 761®

Methodology: This was a phase IIb, multicentre, uncontrolled, open-label, explorative clinical trial in adult patients with different types of vertigo. There were maximum four visits and two phone calls for each patient. The screening visit could take place on the same day as the baseline visit (day 0) or up to preferably 7 but maximum 14 days before the baseline visit. During the 12-week treatment period, face-to-face and telephone contacts were scheduled every 3 weeks with a window of ±1 week: week 3 phone call, week 6 visit, week 9 phone call, week 12 visit. The maximum trial duration for the individual patient was 15 weeks.

<u>Vestibular diagnostic tests</u>
The following vestibular diagnostic tests were performed within the

time window of the screening visit (or within 3 months before baseline visit): ENG or VNG including caloric testing, vHIT, VEMPs, Dix-Hallpike test (was only performed if necessary to exclude BPPV).

Vertigo related examinations

The following vertigo related examinations were performed at baseline visit and week 12 visit: spontaneous nystagmus test with Frenzel glasses (alternatively by VNG), Romberg test and Unterberger stepping test.

Scales, inventories, questionnaires related to vertigo

Severity of vertigo-specific symptoms and general impairment of daily life were assessed at baseline visit, week 6 visit and week 12 visit by means of the following questionnaires: VSS-SF (Yardley et al. 1992, 2004), DHI (Jacobson & Newman 1990), and 11-point box scale for severity of vertigo.

Risk factors and concomitant symptoms

For identification of subgroups that benefit most from EGb 761® treatment and to evaluate the effects of EGb 761® on concomitant symptoms the following questionnaires representing risk factors and concomitant symptoms were assessed at baseline visit, week 6 visit and week 12 visit: HADS (Zigmond & Snaith 1983, Herrmann 1997), PSQ, (Levenstein 1993), SDS (Sheehan 1996), TMT-A /TMT-B (Reitan 1958, Tombaugh 2004).

Safety / tolerability

The safety of the trial medication was assessed by means of AEs throughout the whole trial and by the vital signs blood pressure and pulse, physical examination, ENT examination, and safety laboratory data (hematology, coagulation, clinical chemistry, urinalysis) at baseline visit and week 12 visit.

Abbreviations (in alphabetic order):

AEs:	Adverse events
BPPV:	Benign paroxysmal positional vertigo
DHI:	Dizziness Handicap Inventory
ENG:	Electronystagmography
ENT:	Ears-Nose-Throat
HADS:	Hospital Anxiety and Depression Scale
PSQ:	Perceived Stress Questionnaire
SDS:	Sheehan Disability Scale
TMT-A:	Trail-Making Test Form A
TMT-B:	Trail-Making Test Form B
VEMPs:	Vestibular evoked muscular potentials
vHIT:	Video head impulse test
VNG:	Videonystagmography
VSS-SF:	Vertigo Symptom Scale – Short Form

Number of subjects included in the analysis:

				Subjects taken into account for the analysis of		
				Safety	Efficacy	
	Planned to be treated	Screened	Treatment started	Safety evaluable set (SES)	Full analysis set (FAS)	Per protocol set (PP)
EGb 761®	175	206	179	179	174	153
Total	175	206	179	179	174	153

Diagnosis and main criteria for inclusion:

Patients included were men and women ≥18 years of age with a vertigo syndrome for at least 2 weeks and a score of >25 in the Dizziness Handicap Inventory.

Patients who suffered from a type of vertigo for which other treatments were recommended by current guidelines or expert consensus were excluded (e.g., BPPV, Ménière's disease, vestibular migraine, somatoform phobic vertigo, and acute vestibular neuritis/acute central or peripheral vertigo within the first two weeks of onset).

Test preparation, dose and mode of administration:

Ginkgo biloba special extract EGb 761®

120 mg EGb 761® twice daily (2x1 film-coated tablet per day)
Oral administration

Duration of treatment: 120 mg EGb 761® twice daily for 12 (±1) weeks

Criteria for evaluation:

Efficacy:

<u>Main variables describing treatment effects</u>

- Differences in mean scores from baseline to week 6 visit and week 12 visit for
  - VSS-SF
  - DHI
  - Vertigo severity (11-point box scale)

<u>Further variables describing treatment effects</u>

- Analysis of treatment effects (main variables) by main risk factors
  - Depression (according to HADS at baseline)
  - Anxiety (according to HADS at baseline)
  - Stress (according to PSQ at baseline)
  - Cardiovascular disease (at baseline)
  - Vascular risk factors (at baseline)

- Cognitive slowing (according to TMT-A and TMT-B at baseline)

- Explorative analysis of main variables to describe treatment effects by further potential factors (age, gender, stressful life events, hearing impairment, type of vertigo, chronicity of vertigo, duration of vertigo, and etiology of vertigo)
- Responder analysis for the three vertigo scales (VSS-SF, DHI, and vertigo severity) with moderate response defined as improvement of ≥15% and strong response defined as improvement of ≥30%
- Responder analyses by main risk factors and further potential factors

Safety:

- Frequency and severity of serious adverse events (SAEs) and non-serious AEs
- Change in vital signs comparing baseline to week 12 visit
- Change in safety laboratory results comparing baseline to week 12 visit

Statistical methods:

The safety evaluable set (SES) was based on all patients having taken at least one EGb 761® tablet.
The analysis of treatment effects of EGb 761® was based on the full analysis set (FAS), including all patients who had received the EGb 761® treatment and had at least one follow-up treatment effect value available, and on the per protocol set (PP) including all patients from the FAS who completed the trial without any relevant protocol deviation.

For each of the treatment effect assessments of EGb 761® the patient groups were compared with methods of descriptive data analysis. Descriptive statistics were computed to describe the empirical distributions; 95%-confidence intervals were calculated within the patient groups and between the patient groups. Furthermore, descriptive p-values were calculated with appropriate statistical tests, e.g. analysis of covariance (ANCOVA) with baseline as covariate. Moreover, continuous variables were described by medians and mean values, standard deviation, first and third quartiles, minimum and maximum were used as indices of dispersion. Categorical variables were described in contingency tables as absolute numbers and percentages. All analyses and statistical tests were performed in an exploratory manner.

Results:

Demographic data:

Baseline demographic data for the full analysis set (FAS) show that there was a higher percentage of women than men (77.6% versus 22.4%). Patients were on average 52.2 ± 14.5 years old, had a mean height of 166.0 ± 7.9 cm, a mean weight of 72.2 ± 13.3 kg.

Demographic data (FAS)

Parameter			Total (N= 174)	
Age (years)	Mean	± SD	52.2	± 14.5

FAS (N=174)

Outcome	**Baseline (N_{valid}= 171 / 174 / 174)**		**Difference W6 - baseline (N_{valid}=170 / 174 / 174)**				**Difference W12 - baseline (N_{valid}=170 / 174 / 174)**			
Score points	**Mean Median**	**± SD Q25% Q75%**	**Mean Median**	**± SD Q25% Q75%**	**LSMEAN p-value**	**SEM**	**Mean Median**	**± SD Q25% Q75%**	**LSMEAN p-value**	**SEM**
VSS-SF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DHI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W6 = week 6 visit; W12 = week 12 visit.
VSS-SF = Vertigo Symptom Scale - Short Form (total score ranges from 0-60 with higher scores indicating more severe problems);
DHI = Dizziness Handicap Inventory (total score ranges from 0-100 with higher scores indicating more severe problems);
Vertigo severity assessed on an 11-point box scale anchored by word description at each end (0=no vertigo, 10=extremely severe vertigo);
LSMEAN = Least square means; SEM = Standard error of mean.
LSMEAN, SEM and p-value calculated from ANCOVA with follow up values (value of week 6 visit and value of week 12 visit) as dependent variable and baseline value as covariate.

Secondary variables describing treatment effects

Analysis of treatment effects by main risk factors

DEPRESSION (according to HADS)

The impact of the risk factor DEPRESSION according to HADS (subscore depression) on the three main variables describing treatment effects (VSS-SF, DHI and vertigo severity) was investigated for the subgroups with a HADS-D score [redacted] at baseline.

Compared to baseline, the scores of the three main variables (VSS-SF, DHI and vertigo severity) [redacted] till week 12 visit in [redacted] patients with a HADS-D score [redacted] and patients with a HADS-D score [redacted]. The [redacted] in VSS-SF, DHI and vertigo severity were [redacted] the three main variables within each subgroup [redacted]. Patients with normal depression scores [redacted] than patients with borderline abnormal or abnormal depression scores [redacted] if the changes were adjusted for different baseline values. The subgroup differences [redacted] at the week 12 visit for the change from baseline in VSS-SF, DHI and vertigo

severity score were [redacted] for vertigo severity and [redacted] for VSS-SF and DHI.

In the PP the results were similar, the subgroup differences [redacted] at the week 12 visit for the changes from baseline in VSS-SF, DHI and vertigo severity scores [redacted] for vertigo severity.

Main treatment effect variables by risk factor DEPRESSION according to HADS (FAS)

Out-come	**Base-line**	**Difference W6 - baseline**		**Difference W12 - baseline**		**Base-line**	**Difference W6 - baseline**		**Difference W12 - baseline**		**Comp-arison W12**
Score points	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**p-value**
	[redacted]					[redacted]					
N_{valid}	[redacted]					[redacted]					
VSS-SF	[redacted]					[redacted]					[redacted]
DHI	[redacted]					[redacted]					[redacted]
Vertigo severity	[redacted]					[redacted]					[redacted]

W6 = week 6 visit; W12 = week 12 visit.
VSS-SF = Vertigo Symptom Scale - Short Form (total score ranges from 0-60 with higher scores indicating more severe problems);
DHI = Dizziness Handicap Inventory (total score ranges from 0-100 with higher scores indicating more severe problems);
Vertigo severity assessed on an 11-point box scale anchored by word description at each end (0=no vertigo, 10=extremely severe vertigo);
HADS = Hospital Anxiety and Depression Scale (total score for subscale depression ranges from 0-21);
LSMEAN = Least square means;
LSMEAN and p-value calculated from ANCOVA with follow up values (value of week 6 visit and value of week 12 visit) as dependent variable and baseline value as covariate.
For the last column, p-values were calculated from the same model but including the respective risk factor as additional factor.

ANXIETY (according to HADS)

The impact of the risk factor ANXIETY according to HADS (subscore anxiety) on the three main variables describing treatment effects (VSS-SF, DHI and vertigo severity) was investigated for the subgroups with a HADS-A score [redacted] and [redacted] at baseline.

Compared to baseline, the scores of the three main variables (VSS-SF, DHI and vertigo severity) [redacted] till week 12 visit in [redacted] patients with a HADS-A score [redacted] and patients with

a HADS-A score [redacted]. These [redacted] were [redacted] the three main variables within [redacted] subgroup. The subgroup difference [redacted] at the week 12 visit for the change from baseline in VSS-SF, DHI and vertigo severity score [redacted] for [redacted] main variable. The results in the PP were similar to those in the FAS .

Main treatment effect variables by risk factor ANXIETY according to HADS (FAS)

Out-come	**Base-line**	**Difference W6 - baseline**		**Difference W12 - baseline**		**Base-line**	**Difference W6 - baseline**		**Difference W12 - baseline**		**Comp-arison W12**
Score points	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**p-value**
			[redacted]					[redacted]			
N_{valid}	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]		
VSS-SF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DHI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W6 = week 6 visit; W12 = week 12 visit.
VSS-SF = Vertigo Symptom Scale - Short Form (total score ranges from 0-60 with higher scores indicating more severe problems);
DHI = Dizziness Handicap Inventory (total score ranges from 0-100 with higher scores indicating more severe problems);
Vertigo severity assessed on an 11-point box scale anchored by word description at each end (0=no vertigo, 10=extremely severe vertigo);
HADS = Hospital Anxiety and Depression Scale (total score for subscale anxiety ranges from 0-21);
LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA with follow up values (value of week 6 visit and value of week 12 visit) as dependent variable and baseline value as covariate.
For the last column, p-values were calculated from the same model but including the respective risk factor as additional factor.

STRESS (according to PSQ)

The impact of the risk factor STRESS on the three main variables describing treatment effects (VSS-SF, DHI and vertigo severity) was investigated by the PSQ questionnaire for the subgroups with a stress index [redacted] and [redacted] at baseline.

Compared to baseline, the scores of the three main variables (VSS-SF, DHI and vertigo severity) [redacted] till week 12 visit in [redacted] patients with a PSQ stress index [redacted] and patients

with PSQ stress index [redacted]. These [redacted] were [redacted] for [redacted] the three main variables within [redacted] subgroup. The subgroup difference [redacted] at the week 12 visit for the change from baseline in VSS-SF, DHI and vertigo severity score [redacted] main variable . The results in the PP were similar to those in the FAS.

Main treatment effect variables by risk factor STRESS according to PSQ (FAS)

Out-come	**Base-line**	**Difference W6 - baseline**		**Difference W12 - baseline**		**Base-line**	**Difference W6 - baseline**		**Difference W12 - baseline**		**Comp-arison W12**
Score points	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**p-value**
	[redacted]					[redacted]					
N_{valid}	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]		
VSS-SF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DHI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W6 = week 6 visit; W12 = week 12 visit.
VSS-SF = Vertigo Symptom Scale - Short Form (total score ranges from 0-60 with higher scores indicating more severe problems);
DHI = Dizziness Handicap Inventory (total score ranges from 0-100 with higher scores indicating more severe problems);
Vertigo severity assessed on an 11-point box scale anchored by word description at each end (0=no vertigo, 10=extremely severe vertigo);
PSQ = Perceived Stress Questionnaire; PSQ index ranges from 0 to 1;
LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA with follow up values (value of week 6 visit and value of week 12 visit) as dependent variable and baseline value as covariate.
For the last column, p-values were calculated from the same model but including the respective risk factor as additional factor.

CARDIOVASCULAR DISEASE

The impact of the risk factor CARDIOVASCULAR DISEASE (i.e. any cardiovascular diseases documented in the medical history) on the three main variables describing treatment effects (VSS-SF, DHI and vertigo severity) was analysed with respect to presence or absence of this risk factor.

Compared to baseline, the scores of the three main variables (VSS-SF, DHI and vertigo severity) [redacted] till week 12 visit in [redacted] patients with cardiovascular disease and patients without cardiovascular disease . These [redacted] were [redacted] the three main variables within [redacted] subgroup. The subgroup difference (cardiovascular disease “yes” vs. “no”) at week 12 visit for the change from baseline in VSS-SF, DHI and vertigo severity score [redacted] the three main variables. The results in the PP were similar to those in the FAS .

Main treatment effect variables by risk factor CARDIOVASCULAR DISEASE (FAS)

Out-come	**Base-line**	**Difference W6 - baseline**		**Difference W12 - baseline**		**Base-line**	**Difference W6 - baseline**		**Difference W12 - baseline**		**Comp-arison W12**
Score points	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**p-value**
	No					**Yes**					
N_{valid}	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]		

Main treatment effect variables by VASCULAR risk factors (FAS)

Out-come	Base-line	Difference W6 - baseline		Difference W12 - baseline		Base-line	Difference W6 - baseline		Difference W12 - baseline		Comp-arison W12
Score points	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**p-value**
	No					**Yes**					
N_{valid}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
VSS-SF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DHI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W6 = week 6 visit; W12 = week 12 visit.
VSS-SF = Vertigo Symptom Scale - Short Form (total score ranges from 0-60 with higher scores indicating more severe problems);
DHI = Dizziness Handicap Inventory (total score ranges from 0-100 with higher scores indicating more severe problems);
Vertigo severity assessed on an 11-point box scale anchored by word description at each end (0=no vertigo, 10=extremely severe vertigo);
LSMEAN and p-value calculated from ANCOVA with follow up values (value of week 6 visit and value of week 12 visit) as dependent variable and baseline value as covariate.
For the last column, p-values were calculated from the same model but including the respective risk factor as additional factor.

<u>COGNITIVE SLOWING (according to Trail Making Test A/B)</u>

The impact of the risk factor COGNITIVE SLOWING on the three main variables describing treatment effects (VSS-SF, DHI and vertigo severity) was investigated by the patient's trail-making performance in part A and part B of the Trail Making Test (TMT-A and TMT-B) at baseline for the subgroups who needed ≥median and <median time to complete TMT-A and TMT-B.

- Cognitive slowing (according to TMT-A)

Compared to baseline, the scores of the three main variables (VSS-SF, DHI and vertigo severity) [redacted] till week 12 visit in [redacted] the subgroup ≥median time and the subgroup <median time to complete TMT-A. These [redacted] were [redacted] the three main variables within [redacted] subgroup. The subgroup difference (≥median vs. <median time to complete TMT-A) at week 12 visit for the change from baseline in VSS-SF, DHI and

vertigo severity score was [redacted] the three main variables. The results in the PP were similar to those in the FAS.

Main treatment effect variables by risk factor COGNITIVE SLOWING according to Trail Making Test A (FAS)

Out-come	Base-line	Difference W6 - baseline		Difference W12 - baseline		Base-line	Difference W6 - baseline		Difference W12 - baseline		Comp-arison W12
Score points	Mean ± SD Median	Mean ± SD Median	LS-MEAN ± SEM p-value	Mean ± SD Median	LS-MEAN ± SEM p-value	Mean ± SD Median	Mean ± SD Median	LS-MEAN ± SEM p-value	Mean ± SD Median	LS-MEAN ± SEM p-value	p-value
			[redacted]					[redacted]			
N_{valid}	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]		
VSS-SF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DHI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W6 = week 6 visit; W12 = week 12 visit.
VSS-SF = Vertigo Symptom Scale - Short Form (total score ranges from 0-60 with higher scores indicating more severe problems);
DHI = Dizziness Handicap Inventory (total score ranges from 0-100 with higher scores indicating more severe problems);
Vertigo severity assessed on an 11-point box scale anchored by word description at each end (0=no vertigo, 10=extremely severe vertigo);
In Trail Making Test A, patient was to draw lines to connect circled numbers in a numerical sequence (i.e., 1-2-3, etc.) as rapidly in possible, hence patients who needed <median time to complete TMT-A had a better cognitive function).
LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA with follow up values (value of week 6 visit and value of week 12 visit) as dependent variable and baseline value as covariate.
For the last column, p-values were calculated from the same model but including the respective risk factor as additional factor.

- Cognitive slowing (according to TMT-B)

Compared to baseline, the scores of the three main variables (VSS-SF, DHI and vertigo severity) [redacted] till week 12 visit in [redacted] the subgroup ≥median time [redacted] the subgroup <median time to complete TMT-B. These [redacted] were [redacted] the three main variables within [redacted] subgroup. The subgroup difference (≥median vs. <median time to complete TMT-B) at week 12 visit for the change from baseline in VSS-SF, DHI and vertigo severity score neither was [redacted] the three main variables. The results in the PP were similar to those in the FAS.

Main treatment effect variables by risk factor COGNITIVE SLOWING according to Trial Making Test B (FAS)

Out-come	Base-line	Difference W6 - baseline		Difference W12 - baseline		Base-line	Difference W6 - baseline		Difference W12 - baseline		Comp-arison W12
Score points	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**Mean ± SD Median**	**LS-MEAN ± SEM p-value**	**p-value**
			[redacted]					[redacted]			
N_{valid}	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]		[redacted]		
VSS-SF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DHI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo severity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W6 = week 6 visit; W12 = week 12 visit.
VSS-SF = Vertigo Symptom Scale - Short Form (total score ranges from 0-60 with higher scores indicating more severe problems);
DHI = Dizziness Handicap Inventory (total score ranges from 0-100 with higher scores indicating more severe problems);
Vertigo severity assessed on an 11-point box scale anchored by word description at each end (0=no vertigo, 10=extremely severe vertigo);
In Trail Making Test B, patient was to draw lines to connect circled numbers and letters in an alternating numeric and alphabetic sequence (i.e., 1-A-2-B, etc.) as rapidly in possible, hence patients who needed <median time to complete TMT-B had a better cognitive function).).
LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA with follow up values (value of week 6 visit and value of week 12 visit) as dependent variable and baseline value as covariate.
For the last column, p-values were calculated from the same model but including the respective risk factor as additional factor.

Exploring further potential factors

For the factor CHRONICITY OF VERTIGO, [redacted] difference [redacted] between subgroups (intermittent vs. continuous) was obtained in the ANCOVA at the week 12 visit regarding the main variables VSS-SF, DHI, and vertigo severity. The results indicate that mean score [redacted] main variables (VSS-SF, DHI, vertigo severity) describing treatment effects was [redacted] in the subset of patients with intermittent vertigo compared to the subset of patients with continuous vertigo.

For the factor DURATION OF VERTIGO, a [redacted] difference or [redacted] between the LSMEANS of the two subgroups (>6 months vs. ≤6 months) was obtained in the ANCOVA model regarding the main variable DHI at the week

12 visit. The results indicate that [redacted] of DHI scores was [redacted] in the subset of patients with vertigo [redacted] compared to the subset of patients with vertigo [redacted] months.

Responder analysis

Overall responder analysis

As defined in the SAP before start of the clinical part of the trial, an improvement ≥15% was considered as moderate response and improvement ≥30% as strong response.

The overall response rate (≥15% improvement over the VSS-SF, DHI and vertigo severity baseline score) was [redacted]% at the week 6 visit and [redacted]% at the week 12 visit. Approximately [redacted] patients were [redacted] responders with [redacted]% improvement at the week 6 visit and [redacted] patients were [redacted] responders at the week 12 visit. The results in the PP were similar to those in the FAS. The mean percentage score [redacted] were [redacted] for DHI and vertigo severity compared to VSS-SF [redacted] at the week 6 visit ([redacted]% and [redacted]% vs. [redacted]%, respectively) and the week 12 visit ([redacted]% and [redacted]% vs. [redacted]%, respectively).

Responder analyses by main risk factors and further potential factors

Pre-planned subgroup analyses showed that response to treatment with EGb 761® was [redacted] in patients without vs. with depression [redacted], patients with intermittent vs. continuous vertigo, and patients with vertigo [redacted] months vs. [redacted] months.

Results of safety analysis

Extent of exposure and compliance

In the SES, the mean exposure to EGb 761® was 83.4 ± 14.7 days with a median of 85.0 days. The mean drug compliance was 97.8 ± 8.9% with a median of 99.4%.

Adverse events of any causality

Before begin of treatment 2 AEs in 2 patients occurred.

The subsequent analysis reflects the AEs reported in the SES during both the 12-week treatment period and the post treatment exposure phase.

In total, 34 patients experienced a total of 62 AEs. The number of events per observation day (incidence rate) was 0.0041.

Number and incidence of AEs of any causality (SES)

Treatment	Trial period	Patients in trial	Patients (%) with adverse events	Observation days	Number of adverse events	Events per observation days
240 mg EGb 761®	During screening period	179	2 (1.1%)	1046	2	0.0019

associated with [redacted] from treatment with EGb 761® for [redacted] describing treatment effects. Patients with vascular risk factors or diseases and patients with cognitive slowing did [redacted] those without these features.

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