CLINICAL STUDY REPORT

MULTICENTER PROSPECTIVE CONTROLLED RANDOMISED, SINGLE-BLIND STUDY ON THE EFFICACY OF VIBROTACTILE NEUROFEEDBACK IN ADDITION TO GINKGO BILOBA SPECIAL EXTRACT EGB 761® FOR THE TREATMENT OF PRESBYVERTIGO.

Name of study medications:
EGb761®: Dry extract from Ginkgo biloba leaves; 160 mg/day for 12 weeks
VertiGuard® RT: Medical device for individual adaptation of balance training; 10 training days

Indication studied:
Presbyvertigo

Design:
Confirmatory, multicenter, prospective, controlled, randomised, single-blind, two-arm, parallel group study

Sponsor:
Dr. Willmar Schwabe GmbH & Co. KG, Willmar-Schwabe Str. 4, 76227 Karlsruhe, Germany

Protocol No.:
MW029

Protocol Version:
Final Version 4.0, dated 27.06.2017

Phase:
Clinical Phase IV Trial

Eudra-CT No.:
2014-000303-28

Eudamed Nummer:
CIV 14-08-12482

First Patient Screened:
07 January 2015

Last Patient completed:
19 June 2018

Coordinating Investigator:
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Dr. med. Martin Burkart, Dr. Willmar Schwabe GmbH & Co. KG

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Other relevant parties:
See chapter 5

The clinical trial was performed in compliance with ICH-GCP, DIN EN ISO 14155 and all applicable national laws and regulations.

Confidential
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2 SYNOPSIS (D.4)\textsuperscript{1}

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<td>2 HNO Praxis am Neckar, Dr. med. Andreas Horn, Uferstraße 8a, 69120 Heidelberg</td>
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<td>3 Medizinisches Studienzentrum Würzburg, Dr. med. Klaus-Ulrich Oehler, Augustinerstraße 15, 97070 Würzburg</td>
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<tr>
<td>4 Synexus Clinical Research GmbH, Dr. med. Katrin Arelin, Johannisplatz 1, 04103 Leipzig</td>
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| Studied period: | 42 months |
| Date of first screening | 07 JAN 2015 |

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\textsuperscript{1} Notes in brackets reference DIN ISO 14155 Annex D4
Date of first enrolment: 21 JAN 2015  
Date of last patient completed: 19 JUN 2018  
Halt of Recruitment: 11 MAR until 19 MAY 2016

Background:
Balance training with vibrotactile neurofeedback using VertiGuard® RT improves balance in everyday situations and subjective impairment, also in patients with presbyvertigo. Ginkgo biloba dry extract EGB 761® improves learning, subjective impairment in patients with chronic vertigo and efficacy of balance training. The combination of both treatment modalities is expected to work synergistically in this difficult to treat population.

Objectives:
Proof of the efficacy of vibrotactile neurofeedback using VertiGuard® RT in addition to EGB 761® for presbyvertigo.

Description of the safety and tolerability of EGB 761® in patients with presbyvertigo, with and without vibrotactile neurofeedback using VertiGuard® RT.

Methodology:
This clinical trial was designed as a confirmatory, multicenter, prospective, controlled, randomised, single-blind, two-arm, parallel group clinical trial with internal pilot clinical trial.

The clinical trial is divided into a 0–14 day screening period and 80–88 days treatment period with five regular clinical trial visits.

The sample size was recalculated after the data for the primary endpoint of 50 patients were available.

Number of patients (planned and enrolled):
It was planned to enrol 120 patients.
190 patients were screened.
120 patients were randomised.
11 patients did not receive both treatments.
109 patients were included in the “full analysis set” (FAS).
108 patients were allocated to the “per protocol set” (PPS).
85 patients were analysed in the “Additional analysis set” (AAS).
58 patients were analysed in the “Analysis under normal conditions” (NCAS).
120 patients were analysed in the “safety population set” (SAF).
107 patients completed clinical trial.
13 patients discontinued the clinical trial prematurely.

Diagnosis and criteria for inclusion:

Inclusion Criteria:
1. Men and women aged 60 years or older
2. Subjective chronic dizziness for > 3 months
3. Dizziness Handicap Inventory (DHI) score > 25
4. Geriatric Standard Balance Deficit Test (fall risk) > 40%
5. Written informed consent
6. Willingness and ability to participate in all clinical trial-specific measures

**Exclusion Criteria**

1. Haemorrhagic diathesis, coagulation disorder, gastric ulcer or duodenal ulcer
2. Diseases that may affect absorption
3. Severe or acute general illness within the last 4 weeks
4. Acute or chronic otologic, neurological or psychiatric disease during the last 12 months other than age-related presbyvertigo, such as: Depression, stroke, TIA, Parkinson's disease, Alzheimer's disease, seizure disorders, traumatic brain injury, cerebral haemorrhage, multiple sclerosis, sudden idiopathic hearing loss, Meniere's disease, benign paroxysmal positional vertigo
5. Severe or unstable medical disorders such as e.g.
   a. Malignancy with the exception of carcinoma in situ, adequately treated basal cell carcinoma or curative malignore more than 3 years ago
   b. Uncontrolled arterial hypertension
   c. Uncontrolled diabetes mellitus
   d. Known cardiac arrhythmia (Lown Classes IV b and V)
   e. Heart failure NYHA III or IV
   f. Active bacterial infection
   g. Severe coronary heart disease (Stage IV, Canadian Cardiovascular Society), instable angina pectoris, myocardial infarction within the past 6 months
6. Clinically significant ECG or laboratory abnormalities requiring treatment
7. Hypersensitivity to any of the ingredients of the study medication drug
8. Current substance abuse or dependency current or in the medical history
9. Participation in another clinical trial during the last 12 weeks
10. Concomitant medication of one of the following substance classes
    a. Anticoagulants (heparin, vitamin-K-antagonist, dabigatran, apixaban or rivaroxaban)
    b. Anti-dementia drugs or nootropics
    c. benzodiazepines
11. Intake of a Ginkgo biloba preparation within the last 12 weeks
12. Planned surgery or hospitalization during the clinical trial period
13. Other factors that jeopardize the participation in the clinical trial (e.g. insufficient understanding of the nature and scope of the clinical trial, insufficient knowledge of German language)

14. Individuals who are placed on a court or administrative order in an institution

15. Individuals dependent on the sponsor or investigator

### Test products, dose and mode of administration:

**EGb 761®:** EGb 761® is a dry extract of Ginkgo biloba leaves (35-67:1), extracting agent is acetone 60 % (m/m). The registered product is Tebonin® spezial 80 mg which was used in this clinical trial, batch number 0201401. Patients were asked to take 1 tablet orally twice daily (bid) for 12 weeks.

**VertiGuard® RT:** Balance training was performed according to the VertiGuard® RT user manual (Zeisberg GmbH, 72805 Lichtenstein, Germany). Based on the standardized geriatric standard balance deficit test (gSBDT) carried out at visit 2, the software automatically creates a training program of those 6 exercises patient showed the highest deviations compared to the standard value.

The recorded exercises are displayed in the training protocol and printed during training. The training was carried out daily at the study center for 10 days (not at weekend). During the training sessions, the patient performs the selected exercises 5x consecutively with feedback on. The duration of such a training session was about 30 min.

### Treatment arm A:
EGb 761®, 80 mg orally twice daily for 12 weeks including 2 weeks (10 training days) individually adapted balance training with sensitive vibrotactile neurofeedback

### Treatment arm B:
EGb 761®, 80 mg orally twice daily for 12 weeks including 2 weeks (10 training days) individually adapted balance training with non-sensitive “sham” vibrotactile neurofeedback

### Duration of treatment:
For each patient participation in the clinical trial started with given written informed consent at visit 1. Treatment with EGb 761® for 12 weeks started in the morning after visit 2, balance training with VertiGuard RT® was performed for 10 days after 4 weeks of treatment with EGb 761® (visit 3). Regular clinical trial end was Visit 5. Thus, for each patient the total duration of the clinical trial was 80 to 102 days depending on the duration of the screening period, especially and including receipt of screening visit results (1 - 14 days) and the duration of the treatment period (80 – 88 days).

### Criteria for evaluation:

The primary outcome variable for efficacy is change in fall risk in equilibrium situations as measured by VertiGuard® RT during 14 test situations of the geriatric Standard Balance Deficit Test (gSBDT Composite Score) between visit 2 and visit 4 (= 6 weeks of treatment; 4 weeks only EGb 761®, 2 weeks EGb 761® and balance training).

The secondary measurements of efficacy were
- Fall risk in equilibrium situations, changes from visit 2 to visits 3 and 5
- Subjective impairment due to balance disorder
- Hearing ability
- Cognitive performance
- Safety and tolerability

The subjective impairment of dizziness is measured using the Dizziness Handicap Inventory (DHI). The sum score of the given answers reflects the degree of everyday impairment of the patient due to balance disorders. In addition to the sum score subscores for functional, physical and emotional stress were determined.

The hearing ability of the patients was determined on the basis of the hearing threshold at the frequencies 0.5, 1, 2, 4, and 8 kHz in pure tone audiometry.

The cognitive performance of patients was determined using the Trail Making Test. The rate at which a patient performed this test is the result. This test consists of two parts (A and B), both of which are to be completed. The difference between the two test results was also used as an evaluation parameter.

Secondary endpoints for safety and tolerability

- Adverse Events
- Clinically relevant changes of the safety laboratory parameters, ECG or physical examination were recorded as adverse events.

Statistical methods: Due to uncertainties in the data underlying the sample size calculation, the trial was planned as sequential design with internal pilot clinical trial: After data on the primary endpoint were available for 50 patients, the sample size was recalculated based on the observed residual variance of the primary endpoint and drop-out rate, without unblinding the trial. The initial sample size of 62 patients was then adjusted to the a priori defined maximum total number of 120 patients. Details are given in section 4 of the Statistical Analysis Plan (SAP, MW029_SAP v2.0_Final).

At the Blind Data Review Meeting (BDRM), it was noted that there were differences between centers in adjusting the sensitivity of neurofeedback during balance training with VertiGuard® RT, which may affected the primary outcome. It was determined that at center 3 and possibly at center 2 the adjustment of the sensitivity was performed differently than intended. At center 2, there was conflicting information about sensitivity during training. At center 3, exercises were performed with systematically decreasing instead of individually adapted increasing sensitivity. This did not cause a protocol violation but was considered a usage error. Apparently, the instruction for users was not written clear enough ensure identical application of the device at all centers. Therefore, the Analysis Set Under Normal Conditions (NCAS) was defined to consist of the FAS excluding patients from centers 2 and 3. It was decided to do the primary analysis on both, the FAS and the NCAS, and not to perform the PPS-analysis, described in the protocol.

After unblinding and analysing the trial, it became evident that, unexpectedly, the largest difference between treatment groups in the primary endpoint was seen at center 3, the center that performed VertiGuard® RT exercises with systematically decreasing instead
of individually adapted increasing sensitivity. This result might indicate, that adaption of sensitivity threshold might be less important for the efficacy of vibrotactile neurofeedback than expected, provided training and gSBDT-measurements were performed reliably. Therefore, from a medical point of view the efficacy results based on data from centers 1, 3 and 4 were of interest and the Additional Analysis Set (AAS) was defined to consist of the FAS excluding patients from center 2.

The null hypothesis for the primary endpoint was tested with an Analysis of Covariance taking into account the covariates 'treatment group', 'baseline value of the primary response variable' and 'center'. Missing values were addressed by applying the Mixed Model for Repeated Measures (MMRM) procedure. Sensitivity analyses were performed by applying a Complete Case Analysis (CCA), Last Observation Carried Forward (LOCF), and Multiple Imputation (MI). The confirmatory analysis was performed for the FAS and for the NCAS. An ANCOVA was performed for the FAS to identify a possible interaction between treatment group and center.

The secondary variables were analysed as change from baseline at visits 2, 4, and 5 using descriptive methods. Empirical distribution measures for the comparison groups were calculated and compared in a comparative way. Furthermore, descriptive p-values of appropriate statistical tests for group comparisons and associated 95% confidence intervals were calculated and graphical methods were used to support the interpretation of the results. The secondary endpoints were evaluated in the FAS, the NCAS, and the AAS.

Adverse events and safety parameters were evaluated descriptively in the SAF. Multiple occurrences of the same event (MedDRA Preferred Term) are counted only once per patient.

The homogeneity of the comparison groups were examined by descriptive comparisons of demographic data and baseline values.

**Efficacy Results:**

In both treatment groups in total 73 female and 36 male patients aged on average 74 years, were treated over 84 days (Median). Mean duration of dizziness was $4.8 \pm 4.9$ years with a slightly longer history ($5.5 \pm 5.9$ vs $4.1 \pm 3.7$ years) in treatment group B. Otherwise, there were no relevant differences at baseline between the treatment groups.
Primary endpoint A line chart for the change from baseline of the gSBDT composite score for patients in the FAS is presented in Figure 1.

![Line Chart](image)

**Figure 1 gSBDT Composite Score: Change from Baseline by Visit and Treatment Group in the FAS.**

By time there was an increasing effect in either treatment group. In the FAS, NCAS and AAS, the 95% CIs of changes from baseline did not include zero at visits 4 in both treatment groups and in the total sample.

In the **primary analysis in the FAS**, the estimated difference to baseline of the primary endpoint at visit 4 was -6.5 (95% CI -8.6, -4.3) in the treatment group A (sensitive training group) and -4.0 (95% CI -6.1; -1.9) in the treatment group B (sham training group). The estimated difference between the treatment groups was -2.4 (95% CI -5.4; 0.6).

With a p-value of 0.1092, the null hypothesis could not be rejected. Hence, a statistically significant difference between the two treatment arms could not be detected in the FAS. The sensitivity analyses yielded comparable results.

A post-hoc power calculation resulted in an achieved power of 35%.

An analysis of covariance was performed in order to identify potential interaction between treatment group and center. However, there was no evidence of a treatment group-center interaction for the primary endpoint (p-value 0.4714).

In the **primary analysis in the NCAS**, the estimated difference to baseline of the primary endpoint at visit 4 was -7.1 (95% CI -9.5; -4.7) in the treatment group A (sensitive training group) and -5.6 (95% CI -7.9; -3.2) in the treatment group B (sham training group). The estimated difference between the treatment groups was -1.6 (95% CI -4.9; 1.8).

With a p-value of 0.3593, the null hypothesis could not be rejected. Hence, a statistically significant difference between the two treatment arms could not be detected in the NCAS. The sensitivity analyses yielded comparable results.
In the **post-hoc analysis in the AAS** the estimated difference to baseline in the primary endpoint was -7.3 (95% CI -9.5, -5.1) in the treatment group A (sensitive training group) and -4.4 (95% CI -6.6; -2.2) in the treatment group B (sham training group). The estimated difference between the treatment groups was -2.9 (95% CI -6.0; 0.2), p-value 0.0691. The sensitivity analyses yielded comparable results.

The **secondary endpoints** of the efficacy analysis were:

- Fall risk in equilibrium situations, changes from visit 2 to visits 3 and 5

By time there was an increasing effect in either treatment group. In the FAS, NCAS and AAS, the 95% CIs of changes from baseline did not include zero at visits 4 and 5 in both treatment groups and in the total sample. The effect was more pronounced in treatment group A as displayed in Figure 1. This tendency was observed in various secondary analyses of the gSBDT in the FAS, NCAS, and AAS: Composite score, visual, vestibular and proprioceptive components of the gSBDT, average trunk sway in pitch and roll direction, rates of patients with pathological body sway, and rates of patients with gSBDT composite scores >50%. Group differences were more pronounced in the AAS: For example, the proportion of patients with gSBDT composite scores >50% was comparable between groups at visits 1 (69.0%, 72.1%) and visit 2 (73.8%, 72.1%), but consistently lower in the treatment group A (sensitive training group) thereafter (visit 3: 57.1% vs. 74.4%, p=0.0930; visit 4: 38.1% vs. 58.1%, p=0.0645; visit 5: 37.5% vs. 60.5%, p=0.0365).

- Self-perceived handicap due to dizziness

The subjective impairment of dizziness was measured by the Dizziness Handicap Inventory (DHI). The sum score of the given answers reflects the degree of impairment of the patient due to balance disorders. Again, by time there was an increasing overall effect in either treatment group with a more pronounced effect in treatment group A (Figure 2). There was no significant difference between the treatment groups. In the FAS, NCAS and AAS, the 95% CIs of changes from baseline did not include zero at all visits after visit 2 in both treatment groups and in the total sample.
Subscores for functional, physical and emotional stress were also determined. There was no significant difference between the treatment groups. However, the physical impact subscore showed a significant difference in favour of treatment group A at visit 3 (FAS and NCAS) and visit 4 (FAS). This difference diminished over time as displayed in Figure 3.

**Figure 2 DHI Sum Score: Change from Baseline by Visit and Treatment Group in the FAS.**

**Figure 3: Disability Caused by Dizziness DHI (Physical Impact, FAS)**
• Hearing ability (audiometry)

Changes (improvements) in hearing ability at visits 4 and 5 were small (between 0 and 2 dB) with all 95% CIs including zero (FAS, NCAS, AAS) and showed the same tendency as the other efficacy parameters with no significant group differences.

• Cognitive performance (Trail Making Test)

Based on expected values of the age group investigated, Test A results of around 40 s and Test B results of about 100 s could be expected. In the FAS, time to Test A completion shortened from (Median) 50 s to 41 s (Visit 4 & 5) in treatment group A and from 53.5 s to 42 s (43 s) in treatment group B. However, there was no difference between the treatment groups.

In the FAS, time to Test B completion shortened from (Median) 118 s to 88 s (Visit 4) and 96 s (Visit 5) in treatment group A and from 106 s to 90.5 s (Visit 4) and 91 s (Visit 5) in treatment group B. However, there was no difference between the treatment groups.

In the FAS, difference between Test B and Test A decreased from (Median) 71 s to 54 s (Visit 5) in treatment group A and from 50.5 s to 49.5 s in treatment group B. However, there was no difference between the treatment groups.

95% CIs of changes from baseline did not include zero for the total sample at visits 4 and 5 (FAS and AAS).

Safety Results:

Overall, 26 patients (44,1%) in treatment group A experienced 40 AEs and 24 patients (39,3%) in the treatment group B 38 adverse events after first drug intake.

Overall, 23 patients (19,2%) reported a total of 31 adverse events that were potentially related to EGb 761® intake. 13 of these events were reported by 11 patients (18,6%) in the treatment group A, and 18 events by 12 patients (19,7%) in the treatment group B.

For one patient in treatment group A and 4 patients in treatment group B a device deficiency without a related incident was reported. No adverse events related to the device or to the procedure, no adverse events in users or other persons, and no incidents were reported during the clinical trial.

Table 1: Overview of Adverse Events

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<th>Patients with at least one….</th>
<th>Group A (N=59)</th>
<th>Group B (N=61)</th>
<th>Total (N=120)</th>
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<td></td>
<td></td>
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<tr>
<td>Patients with Adverse Events</td>
<td>26 (44.1%)</td>
<td>24 (39.3%)</td>
<td>50 (41.7%)</td>
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</table>
Total number of AEs | 40 | 38\(^1\) | 78  
Serious Adverse Event | 4 (6.8\%) | 1 (1.6\%) | 5 (4.2\%)  

**Drug related AE**  
Patients with drug related AEs | 11 (18.6\%) | 12 (19.7\%) | 23 (19.2\%)  
Number of drug related AEs | 13 | 18\(^1\) | 31  
Serious Adverse Event | 1 (1.7\%) | - | 1 (0.8\%)  

**Device related AE**  
Patients with device related AEs | - | - | -  
Number of device related AEs | - | - | -  
Serious Adverse Event | - | - | -  

**Device Deficiencies**  
Deficiency without related incident | 1 (1.7\%) | 4 (6.6\%) | 5 (4.2\%)  

\(^1\) The AE fatigue (PT level) occurred twice in patient 04004 (treatment group B) but was counted as one event according to the SAP.

Overall, 4 AEs from 4 patients (6.8\%) in treatment group A and 1 AE (1.6\%) in the treatment group B were reported as SAEs. No adverse event leading to death of the patient was reported during the clinical trial.

In addition, three patients (5.1\%) of treatment group A reported 3 adverse events prior to their first EGb 761® intake. A summary of AEs is presented in Table 1.

The most common AEs after the first drug intake belonged to the system organ classes infections and infestations, nervous system disorders, gastrointestinal disorders and skin and tissue disorders as displayed in Table 2.

**Table 2: AEs and System Organ Class (SOC) overview at or after the day of first drug intake (Multiple occurrences of the same event are counted only once per patient)**

<table>
<thead>
<tr>
<th>SOC / Cases</th>
<th>Group A (N=59)</th>
<th>Group B (N=61)</th>
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<tr>
<td>Infections and infestations</td>
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<td>18</td>
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<tr>
<td>Nervous system disorders</td>
<td>7</td>
<td>5</td>
<td>12</td>
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<td>Gastrointestinal disorders</td>
<td>5</td>
<td>4</td>
<td>9</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Musculoskeletal &amp; connective tissue disorders</td>
<td>3</td>
<td>4</td>
<td>7</td>
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</table>
Injury, poisoning and procedural complications 2 2 4
Ear and labyrinth disorders 2 2 4
General disorders and administration center conditions 2 1\(\dagger\) 3
Vascular disorders 2 - 2
Blood and lymphatic system disorders 1 - 1
Cardiac disorders 1 1 2
Eye disorders - 1 1
Investigations - 3 3
Neoplasms benign, malignant and unspecified 1 - 1
Renal and urinary disorders 1 - 1
Respiratory, thoracic and mediastinal disorders - 1 1
Surgical and medical procedures - 1 1

* The AE fatigue (PT level) occurred twice in patient 04004 (treatment group B) but was counted as one event according to the SAP.

More patients in the treatment group A experienced infections and infestations compared to group B. More patients in treatment group B experienced skin and subcutaneous tissue disorders compared to treatment group A, both.

Of AEs potentially related to Egb 761®, over 60% were of the following classes:
- N=6: Skin and subcutaneous tissue disorders
- N=4: Nervous system disorders
- N=4: Gastrointestinal disorders
- N=4: Infections and infestations

Most of the AEs potentially related to Egb 761® are known adverse drug reactions of Egb 761®.

Five patients experienced SAEs: 4 patients in treatment group A (circulatory collapse, hypertension, ovarian adenoma and cerebrovascular accident) and 1 patient in treatment group B (fall). All SAEs were asssed to be not related to use of the medical device by the investigator. All but one SAE were assessed to be not related to Egb 761®. The hypertension case was assed as unlikely to be related to Egb 761®.

**Conclusion:**

Aim of this trial was the proof of the efficacy of vibrotactile neurofeedback using VertiGuard® RT in addition to Egb 761® for presbyvertigo. Primary endpoint was the change in fall risk in equilibrium situations from visit 2 to visit 4 as measured by the geriatric Standard Balance Deficit Test (gSBDT) Composite Score.

- There was a tendency in favour of the combination treatment group A showing a difference between the treatment groups of -2.4 (95% CI -5.4; 0.6) in the FAS and -1.6
(95% CI -4.9; 1.8) in the NCAS. With p-values of 0.1092 and 0.3593, a statistically significant difference between the two treatment arms could not be detected.

- In general, secondary efficacy parameters showed the same tendency. In the AAS, the group differences were generally larger, but did not reach statistical significance. The proportion of patients with an gSBDT score > 50% was significantly smaller at visit 5 in the AAS. In addition, subscores of the Dizziness Handicap Inventory (physical impact) showed a significant difference in favour of treatment group A at visit 3 and visit 4 in the FAS. This difference diminished over time.

- Although group differences in the primary endpoint were not statistically significant, combination group A showed more pronounced effects in all variants of the primary analysis and in all secondary analyses of gSBDT and DHI than group B with sham training. This was observed in the FAS, the NCAS and the AAS. Hence, it is assumed that there is no random difference, but there are consistently better results in combination group A, which, however, was not statistically significant due to the small effect size. All secondary endpoints support this interpretation.

- The multicentric clinical trial design induced variability in conduct of vibrotactile neurofeedback training using VertiGuard® RT. The instruction for users was not written clear enough to ensure identical application of the device at all centers. This variability reduced the statistical power of the trial to prove efficacy of the combination treatment when applied as intended.

- 95% CIs of improvements from baseline in both objective (gSBDT) and subjective (DHI) measures of presbyvertigo did not include zero in both treatment groups and in the total sample. This indicates, that in this difficult to treat population significant improvements from baseline were seen with EGb 761® and sham training and even larger improvements with vibrotactile neurofeedback using VertiGuard® RT in addition to EGb 761®.

- These improvements in presbyvertigo were paralleled by a significant improvement of cognitive performance during 12 weeks of intake of EGb 761®.

- The fall incidence observed in this trial was far lower than expected in this population. Although fall risk was no a-priori defined endpoint, this observation might indicate a substantial reduction of fall risk by the combination treatment administered in this trial.

- Second aim of this trial was the description of safety and tolerability of EGb 761® in patients with presbyvertigo, with and without vibrotactile neurofeedback using VertiGuard® RT

- Overall, 50 patients experienced 78 adverse events at or after the day of first intake of EGb 761®. For a total of 31 AEs a potential relationship to EGb 761® could not be excluded. Most of the events are expected in an elderly multimorbid population, or are known adverse drug reactions of EGb 761® or, else, the disease condition under investigation.

- No adverse events related to the medical device or to the procedure were reported during the clinical trial and no adverse events in users or other persons. In total 5
device deficiencies not being related to an incident were reported for 5 patients. No incidences were reported.

- SAEs occurred in 4 patients in treatment group A (circulatory collapse, hypertension, ovarian adenoma and cerebrovascular accident) and in 1 patient in treatment group B (fall). All SAEs were assessed to be not related to the medical device. All but one SAE were assessed to be not related to EGb 761®. The hypertension case was assessed as unlikely to be related to EGb 761®.

- Based on the findings in this clinical trial and based on the SPC of EGb 761® there were no noticeable adverse effects in this clinical trial that might alter the risk profile of EGb 761®. Overall, the favourable safety profile of EGb 761® could be confirmed.

- The device proved to be safe when applied in combination with EGb 761®.

- Based on this clinical trial, no specific safety measures are required for individual patients or risk groups.

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