Summary of results

Version 1.0

Clinical Trial to Explore Treatment Effects of Ginkgo biloba Extract EGb 761® in Patients with Chronic Tinnitus and Effect Modification by Etiology, Biological Factors and Concomitant Pathologies

Clinical trial no. 523079.01.113

EudraCT no. 2016-000315-32

Date of report: 28 June 2019

First patient enrolled: 28 October 2016

Last patient completed: 02 October 2017

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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 chronic tinnitus and effect modification by etiology, biological factors and concomitant pathologies

Relevant amendments: Non-substantial changes (clarifications) in the conduct of the trial were implemented before inclusion of the first patient (Clinical Trial Protocol, Version 2.0, 20 October 2016). They all were not relevant.

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 study centres in Poland.

Trial period: First patient enrolled: 28 October 2016
Last patient completed: 02 October 2017

Publications: None

Clinical phase: Phase IIb

Objective: The primary objective of this clinical trial was to explore whether causes, risk factors, chronicity, characteristics of the tinnitus and accompanying features influence the treatment effect of EGb 761® in terms of improvement and response rates.
The secondary objective of this clinical trial was to identify groups of patients that benefit most of EGb 761® treatment.

Methodology: The clinical trial was conducted as a multicentre, uncontrolled, open-label, explorative trial. The trial consisted of a screening phase up to 7 days prior to enrolment at the Baseline visit followed by a 24-week treatment period with EGb 761®. Control visits were performed after 12 (±1) weeks and at the end of the treatment

period (week 24 ±1). Questionnaires (HADS, PSQ, SDS, THI, TQ, 11-point box-scales for tinnitus loudness and annoyance) as basis for the analyses of treatment effects were completed by the patients in the investigator's office at each of these visits.

Abbreviations (alphabetic order):
HADS: Hospital Anxiety and Depression Scale (Zigmond & Snaith 1983, Herrmann 1997)
PSQ: Perceived Stress Questionnaire (Levenstein 1993)
SDS: Sheehan Disability Scale (Sheehan 1996)
THI: Tinnitus Handicap Inventory (Newman et al. 1998)
TQ: Tinnitus Questionnaire (Hallam 2009, Goebel & Hiller 2004)

Number of patients included in the analysis:

	Planned to be treated	Patients taken into account for the analysis of				
				Safety	Treatment effects	
		Screened	Treatment started	Safety set (SES)	Full analysis set (FAS)	Per protocol set (PP)
EGb 761®	175	187	176	176	170	144
Total	175	187	176	176	170	144

Diagnosis and main criteria for inclusion:

Patients included were men and women ≥18 years of age with unilateral or bilateral chronic tinnitus grade 2 or 3 according to Biesinger*, with or without hearing loss and of at least 3 months' duration.

* Grade 2: The tinnitus is mainly perceived in silence and is disturbing under stress and strain.
Grade 3: The tinnitus causes permanent impairment in personal and occupational spheres. Emotional, cognitive and somatic disorders are present.

Test preparation, dose and mode of administration:

Ginkgo biloba special extract EGb 761®
120 mg EGb 761® twice daily
Oral administration

Duration of treatment:

120 mg EGb 761® twice daily for 24 (±1) weeks

Criteria for evaluation:

Main variables to describe treatment effects
(overall analysis of treatment effects):

- Tinnitus Questionnaire (TQ)
- Tinnitus Handicap Inventory (THI)

- 11-point-box-scales for tinnitus loudness and annoyance

Criteria for evaluation (continued)

Further outcome variables (treatment effects):

- Analysis of treatment effects (main variables) by main risk factors:
  - Psychological symptoms (depression, anxiety, by HADS each; stress by PSQ)
  - Cardiovascular disease
  - Idiopathic tinnitus
  - Noise / acoustic trauma
  - Sudden hearing loss
  - Presbyacusis
  - Combinations of anxiety, depression (both by HADS each) and stress (by PSQ)
- Additional analysis of HADS, PSQ, SDS, pure tone audiometry and tinnitus loudness
- Responder analyses
- Responder analyses by main risk factors

Safety variables:

- Adverse events (AEs)
- Vital signs
- Safety laboratory

Statistical methods:

Due to limited information whether causes, risk factors, chronicity, characteristics of tinnitus, and accompanying features influence the treatment effect of EGb 761®, no formal hypotheses were formulated and the data were analysed descriptively.

Continuous variables were described by number of evaluable observations (N_{valid}), number of missing values (N_{miss}), arithmetic mean (mean), standard deviation, minimum, 1st quartile, median, 3rd quartile, and maximum. Furthermore, 95%-confidence intervals were calculated for mean. Categorical variables were described in contingency tables as absolute numbers and percentages.

Results:

Demographic data:

Baseline demographic data for the full analysis set (FAS) show that the patients were about two-third men and about one-third women. Patients were on average 51.6 ± 13.0 years old, had a mean height of 171.8± 8.4 cm, a mean weight of 79.6 ± 13.8 kg.

Demographic data (FAS)

Parameter				**Total (N= 170)**	
Age (years)		Mean	± SD	51.6	± 13.0
		Min	Max	21	82
Height (m)		Mean	± SD	171.8	± 8.4
		Min	Max	151	190
Weight (kg)		Mean	± SD	79.6	± 13.8
		Min	Max	48	115
Gender	female	N	%	62	36.5
	male	N	%	108	63.5

Min = Minimum; Max = Maximum; SD = Standard deviation.

Results of treatment effects:

Summary of the main parameters describing treatment effects

Compared to baseline, in the FAS the mean values of TQ and THI [redacted] till the visit at week 24. [redacted] effects were noted for tinnitus loudness and annoyance. The [redacted] from baseline calculated by ANCOVA models with visit as factor and baseline value as covariate were [redacted] for [redacted] parameters at [redacted] visit at week 12 and visit at week 24.

Similar results of overall treatment effects with respect to TQ, THI and tinnitus loudness and annoyance were obtained for the PP.

Overall treatment effects: TQ, THI, 11-Point Box Scales for tinnitus loudness and annoyance (FAS)

Outcome	Baseline		Difference W12 - baseline (N_{valid}=164)				Difference W24 - baseline (N_{valid}=170)			
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
TQ	[redacted]									
THI	[redacted]									
Loud-ness	[redacted]									
Annoy-ance	[redacted]									

TQ = Tinnitus questionnaire; THI = Tinnitus handicap inventory.
LSMEAN = Least square means; SEM = Standard error of mean.
LSMEAN, SEM and p-value calculated from ANCOVA models with baseline value as covariate.

Summary of further parameters to describe treatment effects

Analysis of treatment effects by main risk factors

The impact of the risk factor depression according to HADS (subscore depression) on the four main variables describing treatment effects was analysed for the subgroups with a depression score ≥8 (borderline abnormal and abnormal) and <8 (normal). In the FAS the scores of TQ, THI, tinnitus loudness and annoyance [redacted] till the visit at week 24 in [redacted]. These [redacted] were [redacted] for [redacted] within [redacted] subgroup. The differences between the [redacted] at week 24 visit in the patient groups with ≥8 and <8 score points in HADS were [redacted] for [redacted] describing treatment effects. This applied also for the PP.

Main variables by risk factor depression according to HADS (FAS)

Out-come	Baseline	Difference W12 - baseline	Difference W24 - baseline	Baseline	Difference W12 - baseline	Difference W24 - baseline	Comp-arison W24
Score points	Mean ± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	Mean ± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	p-value
	≥8			<8			
N_{valid}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TQ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
THI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loud-ness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annoy-ance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W12 = week 12 visit; W24 = week 24 visit; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA models with baseline value as covariate.

The impact of the risk factor anxiety according to HADS on the four variables describing treatment effects was performed for the subgroups with an anxiety score ≥8 (borderline abnormal and abnormal) and <8 (normal). In the FAS the scores of TQ, THI, tinnitus loudness and annoyance [redacted] till week 24 in [redacted] within

[redacted]. The differences between the [redacted] at the visit at week 24 in the patient groups with ≥8 and <8 score points in HADS were [redacted] for [redacted] describing treatment effects. Similar results were obtained for the PP.

Main variables by risk factor anxiety according to HADS (FAS)

Out-come	Baseline	Difference W12 – baseline	Difference W24 - baseline	Baseline	Difference W12 - baseline	Difference W24 - baseline	Comp-arison W24
Score points	Mean ± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	Mean ± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	p-value
	≥8			<8			
N_{valid}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TQ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
THI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loud-ness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annoy-ance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W12 = week 12 visit; W24 = week 24 visit; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA models with baseline value as covariate.

The impact of the risk factor stress on the four variables describing treatment effects according to PSQ was investigated for the subgroups with a stress index ≥0.45 (borderline abnormal and abnormal) and <0.45 (normal). In the FAS the scores of TQ, THI, tinnitus loudness and annoyance [redacted] till the visit at week 24 in [redacted]. These [redacted] were [redacted] for [redacted] within [redacted]. The differences between the [redacted] at week 24 visit in the patient groups with a PSQ stress index ≥0.45 and <0.45 were [redacted] for tinnitus loudness and annoyance with a [redacted] in patients with stress, [redacted] for TQ and THI. Overall, comparable results were obtained for the PP.

Main variables by risk factor stress according to PSQ (FAS)

Out-come	Baseline	Difference W12 – baseline	Difference W24 - baseline	Baseline	Difference W12 - baseline	Difference W24 - baseline	Comp-arison W24
Score points	Mean ± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	Mean ± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	p-value
	Stress index ≥0.45			Stress index <0.45			
N_{valid}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TQ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
THI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loud-ness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annoy-ance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W12 = week 12 visit; W24 = week 24 visit; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA models with baseline value as covariate.

The impact of the risk factor idiopathic tinnitus on the four main variables was analysed with respect to presence or absence of this tinnitus classification. In the FAS the scores of TQ, THI, tinnitus loudness and annoyance [redacted] till the visit at week 24 [redacted]. These [redacted] were [redacted] for [redacted] within [redacted]. The differences between the [redacted] at the visit at week 24 in the patient groups with non-idiopathic and idiopathic tinnitus were [redacted] for tinnitus loudness and annoyance with a [redacted] in patients with idiopathic tinnitus, [redacted] for TQ and THI. Overall, comparable results were obtained for the PP.

Main variables by risk factor idiopathic tinnitus (FAS)

Out-come	Baseline	Difference W12 - baseline	Difference W24 - baseline	Baseline	Difference W12 - baseline	Difference W24 - baseline	Comp-arison W24
	Mean ± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	p-value
	No			Yes			
N_{valid}	[redacted]						
TQ	[redacted]						[redacted]6
THI	[redacted]						[redacted]
Loud-ness	[redacted]						[redacted]
Annoy-ance	[redacted]						[redacted]

W12 = week 12 visit; W24 = week 24 visit; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA models with baseline value as covariate.

The impact of the risk factor presbyacusis on the four main variables was analysed with respect to presence or absence of this risk factor. In the FAS the scores of TQ, THI, tinnitus loudness and annoyance [redacted] till the visit at week 24 in [redacted]. These [redacted] were [redacted] for [redacted]. The patients with presbyacusis developed [redacted] score [redacted] till the visit at week 24 in [redacted]. There was an [redacted] of the TQ [redacted] the [redacted] were [redacted]. The differences between the [redacted] till the visit at week 24 in the patient groups without vs. with presbyacusis were [redacted] for tinnitus loudness and [redacted] for THI and tinnitus annoyance with a [redacted] score [redacted] in patients without presbyacusis.

Comparable results were obtained for the PP whereas the differences between the subgroups till the visit at week 24 were [redacted] in the PP compared to FAS for THI and tinnitus annoyance.

Main variables by risk factor presbyacusis (FAS)

Out-come	Baseline	Difference W12 - baseline	Difference W24 - baseline	Baseline	Difference W12 - baseline	Difference W24 - baseline	Comp-arison W24
	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	p-value
	No			Yes			
N_{valid}	[redacted]						
TQ	[redacted]						
THI	[redacted]						
Loud-ness	[redacted]						
Annoy-ance	[redacted]						

W12 = week 12 visit; W24 = week 24 visit; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA models with baseline value as covariate.

The impact of the risk factor noise / acoustic trauma on the four variables describing treatment effects was analysed with respect to presence or absence of this risk factor. In the FAS the scores of the TQ, THI, tinnitus loudness and annoyance [redacted] till the visit at week 24 [redacted]. These [redacted] were [redacted] for [redacted] within [redacted]. The differences between the [redacted] at week 24 visit in the patient groups with and without noise / acoustic trauma were [redacted] for [redacted] describing treatment effects. Overall, comparable results were obtained for the PP.

Main variables by risk factor noise / acoustic trauma (FAS)

Out-come	Baseline	Difference W12 - baseline	Difference W24 - baseline	Baseline	Difference W12 - baseline	Difference W24 - baseline	Comp-arison W24
	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	p-value
	No			Yes			
N_{valid}	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
TQ	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
THI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Loud-ness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annoy-ance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

W12 = week 12 visit; W24 = week 24 visit; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA models with baseline value as covariate.

The impact of the risk factor sudden hearing loss on the four variables describing treatment effects was analysed with respect to presence or absence of this risk factor. In the FAS the scores of TQ, THI, tinnitus loudness and annoyance [redacted] till the visit at week 24 in [redacted]. [redacted] the [redacted] were [redacted] for [redacted] in patients without this risk factor, they [redacted] in the subgroup of patients with sudden hearing loss. The [redacted] of tinnitus loudness in the subgroup of patients with sudden hearing loss was [redacted] in the subgroup without sudden hearing loss. The differences between the [redacted] till the visit at week 24 in the patient groups without vs. with sudden hearing loss were [redacted] for TQ, tinnitus loudness and annoyance and [redacted] THI with [redacted] for patients without sudden hearing loss. The results in the PP and FAS were similar.

Main variables by risk factor sudden hearing loss (FAS)

Out-come	Baseline	Difference W12 - baseline	Difference W24 - baseline	Baseline	Difference W12 - baseline	Difference W24 - baseline	Comp-arison W24
	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	p-value
	No			Yes			
N_{valid}	[redacted]						
TQ	[redacted]						
THI	[redacted]						
Loud-ness	[redacted]						
Annoy-ance	[redacted]						

W12 = week 12 visit; W24 = week 24 visit; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA models with baseline value as covariate.

The impact of the risk factor cardiovascular disease on the four variables describing treatment effects were analysed with respect to presence or absence of this risk factor. Compared to baseline, in the FAS the scores of TQ, THI, tinnitus loudness and annoyance [redacted] till the visit at week 24 in patients without cardiovascular disease. These [redacted] were [redacted] for [redacted]. In the subgroup of patients with a cardiovascular disease a [redacted] till the visit at week 24 was observed [redacted] variables . The TQ score of patients with cardiovascular disease [redacted] in the other subgroup. [redacted] these [redacted] were [redacted]. The difference between [redacted] till the visit at week 24 in the patient groups without vs. with a cardiovascular disease showed a [redacted] for tinnitus loudness or [redacted] for tinnitus annoyance. Group differences were [redacted] at the visit for TQ and THI. Overall, comparable results were obtained for the PP.

Main variables by risk factor cardiovascular disease (FAS)

Out-come	Baseline	Difference W12 - baseline	Difference W24 - baseline	Baseline	Difference W12 - baseline	Difference W24 - baseline	Comp-arison W24
	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	Mean± SD Median	LSMEAN ± SEM p-value	LSMEAN ± SEM p-value	p-value
	No			Yes			
N_{valid}	[redacted]						
TQ	[redacted]						
THI	[redacted]						
Loud-ness	[redacted]						
Annoy-ance	[redacted]						

W12 = week 12 visit; W24 = week 24 visit; TQ = Tinnitus Questionnaire; THI = Tinnitus Handicap Inventory; LSMEAN = Least square means.
LSMEAN and p-value calculated from ANCOVA models with baseline value as covariate.

The impact of the combination of the risk factors depression, anxiety and stress (i.e. at least one HADS subscore ≥8 or stress index ≥0.45 - borderline abnormal and abnormal) on the four variables describing treatment effects (TQ, THI, tinnitus loudness and annoyance) was analysed with respect to presence or absence of the risk factor. In the FAS the difference of the [redacted] at week 24 visit between the patient groups with and without depression, anxiety and / or stress was [redacted] for [redacted]. Similar results were obtained for the PP.

Additional analyses

Pure tone audiometry: Between Screening and the visit at week 24 visit there were [redacted] in mean volume values per frequency in right and left ear each for air and bone conduction. Similar results were obtained for the PP.

The examination of tinnitus loudness compared to a reference tone did [redacted] in the mean (± SD) value between the Screening and week 24 visit (right ear: [redacted]; left ear: [redacted]). However, [redacted] patients had no longer tinnitus at the visit at week 24. The results for the PP were similar.

Overall responder analysis

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

Overall, there was [redacted] in [redacted] of the four most important variables beyond the visit at week 12 till the visit at week 24. At the end of the treatment with EGb 761® nearly [redacted] of the patients (range: [redacted]% for tinnitus loudness to [redacted]% for TQ) had an [redacted] of the baseline score values by at least 15%. The proportion of patients with an at least 30% improvement varied between [redacted]% for tinnitus loudness and [redacted]% for THI. The mean percentage improvement was [redacted] variables describing treatment effects (range: [redacted]% to [redacted]%). Similar results were obtained for the PP.

Responder analysis by risk and further potential factors

Responder rates were calculated separately for patients with and without risk factors and for patients with and without further exploring potential factors. Subsequently results of the responder analysis are presented if a statistically meaningful difference between the subgroups was observed for at least one of the four most important variables describing treatment effects and if both subgroups consisted of at least [redacted] patients.

For patients with stress (stress index ≥0.45 according to PSQ) a [redacted] mean relative improvement of the TQ ([redacted]%) and a [redacted] rate of patients with an improvement of at least 30% ([redacted]%) compared to patients without this risk factor ([redacted]%, [redacted]%, respectively) was observed. While the average relative THI improvement of patients with stress (stress index ≥0.45, [redacted]%) was [redacted] in the group without this risk factor ([redacted]%) the responder rates (improvement [redacted]%) were [redacted] in the group of patients without stress ([redacted]% vs [redacted]%). Patients with stress (stress index ≥0.45 according to PSQ) demonstrated [redacted] improvement of tinnitus loudness and annoyance ([redacted]% and [redacted]%, respectively) and a [redacted] of patients with improvements of tinnitus loudness and annoyance of at least 30% ([redacted].2%, [redacted]%, respectively) compared to those without this risk factor (relative improvement: [redacted]% and [redacted]%, improvement ≥30%: [redacted], [redacted], respectively).

Patients without an idiopathic tinnitus showed a [redacted] mean improvement of TQ and THI compared to patients with idiopathic tinnitus ([redacted]% and [redacted]% vs. [redacted]% and [redacted]%). The rate of patients with an improvement of at least 30% in the TQ was [redacted] patients without an idiopathic tinnitus [redacted] patients with idiopathic tinnitus ([redacted]% vs

[redacted]%), [redacted] the rate of patients with an improvement of at least 30% in the THI was [redacted] ([redacted]% and [redacted]%). [redacted] an idiopathic tinnitus resulted in [redacted] mean improvement of tinnitus loudness and annoyance ([redacted]% and [redacted]%, respectively) and in [redacted] rates of patients with an improvement of tinnitus loudness and annoyance of at least 30% ([redacted]% and [redacted]%, respectively) compared to non-idiopathic tinnitus (average mean improvement of [redacted]% and [redacted]%, respectively; improvement ≥30% in [redacted]% and [redacted]% of patients, respectively).

Patients without presbyacusis showed [redacted] mean relative improvements of TQ and THI and [redacted] rates of patients with improvements of these variables of at least 30% compared to patients with presbyacusis. The absence of presbyacusis was [redacted] for mean relative improvement of tinnitus loudness and annoyance ([redacted]% and [redacted]%, respectively) and the rate of patients with an improvement of at least 30% ([redacted]% and [redacted]%) compared to presence of such a risk factor (mean relative improvement of [redacted]% and [redacted]%, improvement ≥30% in [redacted]% and [redacted]% of patients, respectively).

For patients with a cardiovascular disease a [redacted] mean improvement ([redacted]% vs. [redacted]%) and a [redacted] rate of patients with an improvement of at least 30% ([redacted]% vs [redacted]%) was observed for the TQ. [redacted] patients without a cardiovascular disease showed [redacted] mean relative improvements of the THI ([redacted]% vs. [redacted]%), tinnitus loudness ([redacted]% vs. [redacted]%) and annoyance ([redacted]% vs. [redacted]%) as well as [redacted] rates of patients with improvements of these variables of at least 30% (THI: [redacted]% vs. [redacted]%, loudness: [redacted]% vs. [redacted]%, annoyance: [redacted] vs.[redacted]%).

The validity of the results in the two last subgroups [redacted] patients with the presence of the risk factor ([redacted]).

Results of safety analysis

Extent of exposure and compliance

The mean exposure to EGb 761® was 154.2 ± 35.54 days with a median of 168.0 days. The mean drug compliance was 97.2 ± 9.26% with a median of 100.0%.

Adverse events of any causality

The subsequent analysis reflects the AEs during both the 24-week treatment phase and the risk phase.

In total, 37 patients (21.0%) experienced a total of 52 AEs. The number of events per observation day (incidence rate) was 0.0018. One SAE was reported by 1 patient (0.6%) [redacted] with no causal relationship to the IMP.

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
	Between begin of trial and active treatment	176	0 (0.0%)	n.a.	n.a.	n.a.
240 mg EGb 761®	During active treatment	176	35 (19.9%)	28071	49	0.0017
	During risk phase	176	3 (1.7%)	352	3	0.0085
	During both active treatment and risk phase	176	37 (21.0%)	28423	52	0.0018
	After risk phase	176	0 (0.0%)	n.a.	n.a.	n.a.

n.a. = not applicable

[redacted] patients with at least one AE reported a [redacted] intensity of their AEs.

Serious adverse events

One serious AE (Urolithiasis) with no suspected causal relationship to EGb761® occurred.

Safety laboratory tests

Overall, there were no relevant changes of mean, minimum, and maximum for any safety laboratory parameter from the Screening visit to the visit at week 24.

Vital signs

The mean values of systolic (SBP) and diastolic blood pressure (DBP) as well as heart rate (HR) were [redacted] before and at the end of treatment with EGb 761®. None of the measured vital signs was reported as an adverse event.

CONCLUSION

Treatment of chronic tinnitus with EGb 761® over 24 weeks was safe and well tolerated. Treatment effects could be shown for the [redacted] for the total trial population under these trial conditions. Analysis of risk factors suggests that patients with stress based on PSQ have [redacted] in [redacted] compared to those without this risk factor. In addition, absence of concomitant chronic organic conditions (e.g. presbyacusis, cardiovascular and neurological diseases), and presence of tinnitus without apparent cause (i.e. idiopathic tinnitus) are associated with [redacted] from treatment with EGb 761® for the [redacted] compared to patients with these risk factors, or tinnitus of known etiology, respectively.

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