SYNOPSIS

Name of Sponsor/Company: Klinikum der Universität München, AöR Prof. Dr. Dr. Michael Strupp, FANA, FEAN (SDP) Deutsches Schwindel- und Gleichgewichtszentrum (DSGZ), Studienzentrale Marchioninistr. 15, 81377 München, Germany	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Vasomotal®		
Name of Active Ingridient: Betahistine-dihydrochloride		
Title of Study: Effects of betahistine on central vestibular compensation in acute unilateral vestibular failure: a double-blind, placebo-controlled trial (BETAVEST) Protocol V3.0, which includes Amendments 1, dated 2011-04-15, and 2, dated 2011-11-18 Amendments contain changes in the inclusion criteria (no limited age), changes in the contact details and new information regarding the IMP. Due to low recruitment and lack of further financial resources and after an interim analysis with blinded sample size review it was decided to stop recruitment at a total number of 141 patients.		
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Publication (reference) manuscript planned		
Studied period (years): 2010 (FPFV) – 2016 (LPLV)	Phase of development: II/III	
Objectives Primary Objective: To demonstrate medium-term and short-term superiority of betahistine treatment regarding recovery of postural control or spontaneous nystagmus as compared to placebo.		

Secondary Objectives:
To establish a patient-oriented endpoint "time to recovery from acute symptoms of acute vestibular neuritis" for phase III trials and to demonstrate faster recovery after betahistine treatment than after placebo. (Key secondary objective).
To analyse whether superiority of betahistine treatment is kept up to the end of treatment. To quantitatively describe/compare recovery over time vs. Placebo and to determine optimal treatment duration. To shed light on the underlying mechanisms (i. e., peripheral vs. central compensation). To check for the occurrence of the adverse effects reported in the summary of the medical product characteristics (SmPC) of the drug.

Methodology
This study was an investigator-initiated (IIT) multicenter, randomized, double-blind, placebo-controlled, 2-arm parallel-group trial to evaluate the effect of betahistine-dihydrochloride (144 mg per day) on central compensation in subjects with acute unilateral vestibular failure.
Subjects were screened for their eligibility to participate in the study. Each subject gave written informed consent before any study-related procedures were performed.
Subjects satisfying all selection criteria were randomly assigned in a 1:1 ratio to one of the treatment arms to receive either betahistine-dihydrochloride 144 mg/day or placebo for four weeks. Study-related procedures included documentation of medical and neurological history, physical examination, and instrumental testing (including posturography, oculography with caloric irrigation, neuro-orthoptic examination). Subjects were asked to complete the Dizziness Handicap Inventory questionnaire, and asked for the time point when they recovered from the disease-related symptoms until day 28 since randomization.

Number of patients (planned and analysed):
To be assessed for eligibility: Total number of 300 patients, i.e. 150 per treatment arm
To be allocated: Total number of 210 patients
To be analysed: Total number of 168 patients
After an interim analysis with blinded sample size review it was decided to stop recruitment at a total number of 141 patients.
Analysed (intention-to-treat): 141 subjects; 73 assigned to placebo (PL), 68 assigned to betahistine-dihydrochloride 144 mg/day (BE).

Diagnosis and main criteria for inclusion:
Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the trial:

- patients male or female who are at least 18 years old;
- patient has a history of acute/sub-acute (i.e., within minutes to hours) onset of severe prolonged rotatory vertigo, nausea, and postural imbalance;
- the clinical examination reveals horizontal-rotatory spontaneous nystagmus (fast phase) toward the unaffected ear without evidence of a central vestibular lesion, and a pathological head-impulse test (i.e., turning the head of the patient rapidly to the right and left while observing provoked compensatory eye movements) that reveals an ipsilateral deficit of the horizontal semicircular canal (Halmagyi & Curthoys 1988);
- caloric irrigation shows hypo-/unresponsiveness of the horizontal canal of the affected ear, i.e., the maximum slow phase velocity during caloric irrigation with 30°C and 44°C water should be less than 3°/ s on the affected side and the asymmetry between the two sides is >25 percent according to "Jongkees's vestibular paresis formula" (Jongkees et al. 1962; Fife et al. 2000); and
- there is a displacement of the subjective visual vertical toward the affected ear without any vertical divergence of the eyes, i.e., without vertical deviation of one eye above the other (Cnyrim et al. 2008).
- Patient's written informed consent is obtained.

Subjects presenting with any of the following exclusion criteria will not be included in the trial:

- patient not able to give consent;
- a history of vestibular dysfunction before the acute symptom onset or vestibular symptoms beginning more than 3 days before patients were recruited;
- additional cochlear symptoms, i.e., tinnitus or acute hearing loss before, during, or after the onset of vertigo;
- central ocular motor or central vestibular dysfunction;
- any other brainstem or cerebellar signs or symptoms or abnormal findings on the MRI in the brainstem or cerebellum in diffusion-weighted images or hyperintense lesions in T2-weighted images in combination with contrast enhancement in T1-weighted images. MRI without clinical indication is not mandatory for assessment of exclusion criteria;
- other known vestibular disorders such as vestibular migraine, Menière´s disease/syndrome, phobic postural vertigo, benign paroxysmal positioning vertigo; central disorders such as paroxysmal brainstem attacks;
- contraindications for treatment with betahistine-dihydrochloride as bronchial asthma, pheochromocytoma,
- pregnancy or breast-feeding,
- severe dysfunction of liver or kidney, ulcer of the stomach or duodenum,
- treatment with other antihistaminic drugs;
- known severe coronary heart disease or heart failure;
- persistent hypertension with systolic blood pressure > 180 mmHg or diastolic BP > 110 mmHg that cannot be controlled by antihypertensive therapy;
- life expectancy < 3 months, other serious illness, e.g., severe hepatic, cardiac or renal failure, acute myocardial infarction, neoplasm or a complex disease that may confound treatment assessment.
- The patient has received any investigational medication within 30 days prior to administration of trial medication or is scheduled to receive an investigational drug up to 30 days after end of trial.
- The patient was previously admitted to this trial or simultaneous participation in another clinical trial or participation in any clinical trial involving an administration of investigational medicinal product within 30 days prior to clinical trial beginning.

Test product, dose and mode of administration, batch number:
Betahistine-dihydrochloride 48 mg three times daily; subjects took two capsules in the morning; two capsules at noon; and two capsules in the evening. Each capsule contained 24 mg betahistine-dihydrochloride.
Batch numbers BETVN009/201046, BETVN009/201146, BETVN009/201203, BETVN009/201302, BETVN009/201316, BETVN009/201409, BETVN009/201429, BETVN009/201521

Duration of treatment: 4 weeks of study medication (followed up of 4 weeks off treatment)

Reference therapy, dose and mode of administration, batch number:
Placebo; subjects took two placebo capsules in the morning; two placebo capsules at noon; and two placebo capsules in the evening.

Criteria for evaluation:
Efficacy
Primary Endpoints:
"Total sway path" (length per time) on a compliant foam-padded posturography platform with eyes closed for postural control, and peak slow phase velocity of the spontaneous nystagmus ("Velocity SPN")

Measurements on day 10 (medium-term efficacy) and day 3 (short-term efficacy) after randomization (which is expected to be close to symptom onset). This results in two 2-dimensional primary efficacy endpoints.

Secondary Endpoints:
Time in days from randomization to subjective recovery from acute symptoms of acute vestibular neuritis, assessed up to day 28-visit. (Key secondary endpoint)
"Total sway path" (length per time) on a compliant foam-padded posturography platform with eyes closed for postural control and peak slow phase velocity of the spontaneous nystagmus measured on day 28 after randomization (the latter is expected to be close to symptom onset)

- "subjective visual vertical"
- slow phase velocity of nystagmus provoked by caloric irrigation as a measure of peripheral vestibular function.
- handicap / impairment due to vertigo or dizziness assessed by the Dizziness Handicap Inventory; these parameters were measured on days 1, 3, 10, and 28 after randomization; and
- all these parameters 8 weeks after randomization.

Safety
Adverse events were collected from the first intake of the investigational medical product until the last visit of the subject (scheduled 8 weeks after inclusion according to the protocol).

Statistical methods:
The BETAVEST trial was conducted to provide evidence for or against the efficacy of high-dose betahistine-dihydrochloride (3 times higher than the approved daily dosage) compared to placebo in vestibular neuritis.

Two 2-dimensional primary efficacy endpoints were pre-specified: total sway path (SP) [m/min] and peak slow phase velocity [°/second] of the spontaneous nystagmus – assessed on day 3 and on day 10 after randomization, respectively. We assumed the maximal impact would most be on day 10. A multiple test procedure based on hypotheses which are completely ordered by importance was applied: The first family includes 4 primary tests. The second family includes one hypothesis for the patient-oriented endpoint “time to subjective recovery”. Thus, the four primary endpoints and the key secondary endpoint would be compared between the two treatment groups in a confirmatory analysis applying a two-sided statistical test for detecting differences. Multiple testing with strong control of the familywise error rate at a significance level of alpha = 5% was performed. Based on the five elementary null-hypotheses of no difference with respect to the pre-specific endpoints, a closed testing procedure of a weighted Bonferroni-Holm type was carried out. Thereby, a Bonferroni adjustment for the two dimensions ‘total sway path’ and mean ‘peak slow phase velocity of the spontaneous nystagmus’ was combined with hierarchical testing – first at the 10-day endpoint, followed by the respective 3-day endpoint.
(In case of a statistically significant result in at least one of the 3-day endpoints confirmatory hierarchical testing would be extended to the comparison with respect to the key secondary endpoint.)

Principal analyses concerning endpoints for SP
To estimate treatment differences with respect to the SP endpoints, we used a two-part normal regression model for semicontinuous data (i.e. a continuous nonzero variable with a discrete component). This modeling strategy can be viewed as arising from two distinct stochastic processes: (1.) one governing the occurrence of the event “unable to stand without help on the

platform", i.e. the logistic part; and (2.) the second determining the observed value given a nonzero response (i.e., the SP values given that it could be assessed). Missingness at random in the sense defined by Rubin (1976) was assumed.

Principal analyses concerning endpoints for Velocity SPN
The hypothesis that the distribution functions of the 10-day and 3-day velocity endpoint in the BE and placebo group are equal and were tested non-parametrically with the Mann-Whitney-Wilcoxon test in order to detect directed differences of the distributions.

Prespecified analysis for key secondary outcome "time to recovery"
Time-to-event outcome was analyzed using a univariate Cox regression model (unadjusted for other covariates) to compare between both treatment groups (BE vs. PL). Patients not recovered were censored at the day of V4. In the case of early withdrawal, patients were censored at the date of study termination.

Summary – Conclusions
Efficacy Results
"Total sway path (SP)":

- 10-day endpoint: On a 2.5% significance level, there was no difference in mean SP value between both therapies, and no difference in the risk for being unable to stand on BE compared to PL (p-value = 0.530). On the log-scale, the mean SP values were 0.122 [m/min] higher on BE treatment compared to PL, however not significant. On the original scale, this corresponds to an estimated factor of 1.130 (SP units) for BE treatment compared to PL. The risk for being unable to stand was reduced by 1.50% on BE compared to PL, however not significant.
- 3-day endpoint: On a 2.5% significance level, there was no difference in mean SP value between both therapies, and no difference in the risk for being unable to stand on BE compared to PL (p-value = 0.055). On the log-scale, the mean SP values were 0.270 [m/min] higher on BE treatment compared to PL, however not significant. On the original scale, this corresponds to an estimated factor of 1.310 (SP units) for BE treatment compared to PL. The risk for being unable to stand was reduced by 9.00% on BE compared to PL, however not significant.

"Velocity SPN":
In the full analysis set, there was no statistically significant difference in velocity of the SPN between both treatment groups:

- At the 10-day endpoint, the estimated location shift parameter was 0.000, 95% CI (-0.900 to 0.500), Wilcoxon Mann Whitney-U test: p = 0.909).
- At the 3-day endpoint, the estimated location shift parameter was 0.000, 95% CI (-1.700 to 0.999), Wilcoxon Mann Whitney-U test: p = 0.552).

Key secondary outcome
Besides, there was no treatment effect with respect to the patient-oriented endpoint "Time to subjective recovery from acute symptoms of vestibular neuritis assessed no later than at V4 (scheduled on day 28)": In a univariate Cox model, we found a hazard ratio (HR) of HR = 0.949 (95% CI 0.636 to 1.416), p = 0.798 for the comparison between patients on BE and on PL treatment.

Adverse Events	BE	PL	SAE
headache	9	20	
migraine with aura	0	2	1
suspected vestibular migraine	1	0	1
amyotrophic lateral sclerosis	1	0	1
vertigo	9	2	
BPPV	0	1	
paresis	2	1	
hypesthesia	1	0	
nausea	2	10	
diarrhoea	4	5	
pyrosis	3	1	
abdominal pain	3	7	
obstipation	0	2	
hypertension	1	3	
tachycardia	1	3	
palpitation	1	1	
thoracic pain	1	1	
cold fingers	0	1	
ear pressure	1	4	
tinnitus	5	5	
otalgia	0	4	
flickering of eyes	0	1	
lid edema	1	0	
subconjunctival bleeding	0	1	
epistaxis	0	1	
pruritus	4	0	
rashes	2	1	
alopecia	1	0	
herpes infection	1	1	
flu-like infection	4	7	
blepharoconjunctivitis	1	0	
contusion ankle	1	0	
lumboischialgia	3	1	
cervical pain / omalgie	1	2	
ostealgie	0	1	
brachialgia	1	0	
prostatitis	0	1	
benign prostate hyperplasia	1	0	
altered urine smell	1	0	
hyperhidrosis	1	3	
sleeping disorder	2	3	
fatigue	2	2	
mood alteration	2	5	
menstrual cramps	0	1	
hyponatremia	1	0	
electrolyte imbalances	0	1	

Safety Results
Betahistine-dihydrochloride can be considered as a safe and well tolerated drug in patients with acute unilateral vestibular neuritis.

Adverse Events (AEs) and Serious Adverse Events (SAEs)
179 AEs (BE: n=75, PL: n=104) were documented throughout the course of the trial. Of these, 3 were assessed as serious (BE: 2 SAEs, PL: 1 SAE). In the BE group, 2 SAEs (suspected vestibular migraine; persistent amyotrophic lateral sclerosis), both events with moderate severity, in the PL group, 1 SAE (migraine with aura; multiple frequency, moderate severity) were observed. In the BE group, 43 AEs of 75 (57.33%) were assessed as IMP related; 30.7% with mild severity, 16.0% with moderate severity, 2.7% with severe severity. In the PL group, 104 AEs were documented with 56.7% assessed as mild, 28.8% assessed as moderate and 6.7% with severe severity. In the BE group, 41.2% of the randomized participants reported no adverse events, 47.0 % of participants reported one or two AEs throughout their observation period. In the PL group, the corresponding numbers were as follows: 37.0% no AEs, 41.1% one or two AEs. No SUSARs were observed.

Conclusion
A 4-week treatment with betahistine-dihydrochloride in a dosage of 144 mg/day was not superior to placebo treatment with respect to recovery of postural control or spontaneous nystagmus. Neither a mid-term nor a short-term treatment benefit of the experimental intervention compared to placebo could be found. Besides, there was no difference in time to subjective recovery from acute symptoms of vestibular neuritis between both treatment groups. The investigational and placebo treatment were approximately equally safe and well tolerated with no unexpected safety findings.

Date of report: 23rd July 2020

Christine Adrion, MPH
Responsible Statistician

Prof. Dr. med. Dr. h.c. Michael Strupp, FRCP, FANA, FEAN
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