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Betahistine therapy in patients with Menière's disease: Primary results of a long-term, multicentre, double-blind, randomized, placebo-controlled, dose-defining trial of efficacy and safety (*BEMED* trial)

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ABSTRACT

Objectives: To compare two different dosages of betahistine-dihydrochloride and placebo with respect to the long-term effect of treatment on the reduction of the frequency and severity of acute episodes of vertigo as well as on the progression or deterioration of signs and symptoms in patients diagnosed with Menière's disease (MD).

Design: Investigator-initiated, multicentre, double-blind, randomized, placebo-controlled, 3-arm, parallel-group, phase III, dose-defining superiority trial over a 9-month treatment period.

Setting: Specialized academic outpatient services within 14 neurology or ENT departments throughout Germany. Examinations were performed in an outpatient setting.

Participants: 221 adults aged 21 to 80 (mean age 55.6 years; 50.7% female) who fulfilled the 1995 American Academy of Otolaryngology Head and Neck Surgery (AAO-HNS) diagnostic criteria for definite MD, with at least two attacks per month for at least three consecutive months before enrolment, were recruited from March 2008 to November 2012.

Interventions: Two dosages of betahistine-dihydrochloride [high dose (HD): 3 × 48 mg per day, (N=74); approved standard dose (LD): 2 × 24 mg per day, (N=73)] and placebo (PL) (N=74) over a period of nine months.

Main outcome measures: The primary efficacy outcome was the number of Menière's attacks per 30 days according to self-reported vertigo assessments obtained from patients' diary entries. The time frame of primary interest to compare attack rates across the three treatment groups was a 3-month long assessment period over month 7, 8, and 9 (day 181 to 270 after start of treatment). Secondary efficacy outcomes included the duration and severity of Menière's attacks, change from baseline to the 9-month visit in three quality of life (QoL) scores (dizziness handicap inventory (DHI), vestibular disorders activities of daily living (VDADL) scale and Mini Tinnitus score (MiniTF12)), as well as several observer-reported parameters to assess the change in audiological and vestibular function.

Results: The mean incidence rate (95% bootstrap confidence interval) per month over the assessment period was 2.380 (1.640 to 3.074) for the PL, 2.000 (1.509 to 2.466) for the LD and 2.111 (1.479 to

2.698) for the HD group. Mixed model analysis revealed no statistically significant difference in the incidence of Menière's attacks between the three intervention arms (P=0.759 for the full analysis set; P=0.493 for the per protocol sample). All three treatment groups showed a significant overall monthly reduction in the mean attack rate by the factor 0.758 (95% CI, 0.705 to 0.816; P<0.0001) over the 9-month treatment period. Hence, no significant additional effect attributable to either dose of betahistine was noted. No significant alleviation of duration and severity of attacks was found in the treatment groups. The results were consistent for all subjective and objective secondary efficacy outcomes. Overall, the treatment was well tolerated. There were no unexpected safety findings in the HD group compared to the established LD or the PL group.

Conclusions: To our knowledge, BEMED is the first long-term, pragmatic, randomized, placebo-controlled trial to quantify the efficacy of betahistine on attack frequencies on the basis of patients' diaries and to explore a well-established drug therapy from the patient's perspective. The study found no beneficial effect of prophylactic betahistine therapy. Positive changes in attack rates were comparable in all three treatment arms. The trial provides information on symptom relief under placebo intervention which is relevant for the design of future studies on potential disease-modifying therapies in patients with MD.

Trial Registration: EudraCT number: 2005-000752-32; ISRCTN number: ISRCTN44359668; Serial number at source: 04T-617.

INTRODUCTION

Menière's disease (MD) is a progressive and incurable disorder of the membranous labyrinth of the inner ear characterized by paroxysmal vertiginous attacks, fluctuating sensorineural hearing loss, aural fullness, and tinnitus.[1] Its histopathological hallmark is endolymphatic hydrops.[2 3] The US-lifetime prevalence of MD is reported as 190 per 100,000 with a female:male ratio of 1.89:1.[4 5] The US incidence rate was 15.3 per 100,000 population (annual age-adjusted).[6] The peak age of onset is during the fifth and sixth decade.[7]

For patients suffering from MD unpredictable vertigo attacks are the most important and unpleasant symptom. Although MD is clinically problematic and the target of several therapeutic interventions, there are so far no validated vertigo-related patient-reported outcome (PRO) instruments for comprehensively evaluating the disease severity in a clinical trial.

Therapy of MD should aim to stop or reduce the number and severity of acute attacks of vertigo, reduce or eliminate tinnitus, and prevent impaired vestibular function and hearing loss. Given the chronic nature of MD and the fluctuating and episodic pattern of the symptoms it is important to investigate the long-term effectiveness of any prophylactic drug therapy.

Numerous therapeutic approaches, such as a low-salt diet and diuretics,[8] intratympanic steroid application[9 10] or minimal invasive interventions like insertion of a ventilation tube into the tympanic membrane,[11 12] endolymphatic sac surgery[13] or pulsed low-pressure delivery (i.e. Meniett device) have been tried.[14-17] In cases that are not responsive to these treatments, destructive procedures like intratympanic application of gentamycin[18 19], plugging of the semicircular canal, labyrinthectomy or neurectomy, can be used.[20-23] However, these interventions are irreversible and the possibility of associated trauma to the cochlear organ cannot be excluded, and a recent Cochrane review could not show any evidence of benefit in a surgical approach.[24 25]

Betahistine is a licensed medication for "Menière's-like symptom complexes" which contains the active ingredient betahistine dihydrochloride (maximum daily dose 48 mg) or betahistine dimesylate (maximum daily dose 36 mg). It was first registered in Europe in the 1970s and has been administered to more than 100 million patients so far. The drug is cheap and well tolerated and one of the most frequently prescribed drugs for MD in Europe.[26 27]

A series of clinical studies that assessed the effect of betahistine on the vestibular and, to a lesser degree, audiological symptoms suggested that it caused an improvement in these symptoms.[28 29] According to a Cochrane systematic review of betahistine for Menière's disease or syndrome, there is, however, insufficient evidence to say whether betahistine has any effect.[28] So far, randomized controlled trials that meet high quality standards are lacking, either due to inadequate diagnostic criteria or methods,[30] or because the effect of betahistine therapy on vertigo was assessed inadequately. Several previous trials have produced contradictory results: some suggested a reduction of vertigo with betahistine, and some suggested a reduction in tinnitus. To summarize, the limitations of the evidence base for preventive treatment strategies for MD include the predominance of trials investigating short-term effects (treatment periods of six months or less), the inclusion criteria of the enrolled patients (for instance, no differentiation between patients with MD and patients with other causes of vertigo), high dropout rates[30] with potential for considerable attrition bias, small trials or few placebo-controlled trials,[31] and the different quality of efficacy outcome measures (including QoL scores, functional impairment, disability and the number and severity of acute attacks of vertigo).[28] The dosage of betahistine in these studies varied between 16 and 72 mg per day which might explain the differences in symptom relief observed. Even higher dosages of up to 480 mg/day have been used with benefit for severe cases in a small case series, suggesting a possible effect of high-dosage regimens in the treatment of MD.[32] The drug appears to retain a good tolerability profile. On the basis of many years' clinical experience, the dosage was successively increased to 48 mg three times a day, pointing towards the role of long-term treatment (up to 12 months). This was supported by an open, uncontrolled, non-masked study without a placebo arm evaluating the therapeutic benefit of the high-dose regimen of 48 mg three times daily compared to the recommended standard dosage of 16 or 24 mg three times daily.[31] This non-interventional study revealed that the higher dosage was superior to the lower dosage, and that the treatment effect of betahistine on the frequency of attacks of vertigo became more prominent over time.

Due to variable methodological rigour and shortcomings in previous trials including the potential risk of bias, the Medical treatment of *ME*nière's *D*isease with *BE*tahistine (*BEMED*) trial was designed. This investigator-initiated, prospective, longitudinal, multicentre, double-blind, randomized, placebo-

controlled, 3-arm, parallel-group, phase III superiority trial aimed to assess the long-term prophylactic effects of betahistine-dihydrochloride in two different dosages and placebo, administered continuously for 9 months, on the frequency, duration and severity of acute Menière's attacks, vertigo-related impairment of quality of life, and vestibular and audiological function.

A further major confirmatory goal was to ascertain the speed of effect, that is, whether the two active agents may be distinguished from each other or from placebo by how quickly reduction in attack frequency is achieved.[33] Additionally, the tolerance and adverse events were examined. We report the pre-specified 9-month efficacy and safety analyses for the BEMED trial.

METHODS

Study population and protocol

Study participants were recruited by the outpatient dizziness services in the neurology or ENT departments of 14 German university hospitals. Patients were enrolled in the study from 31 March 2008 (first subject, first visit) to 5 November 2013 (last subject, last visit), including a 3-month follow-up period.

Patients aged 18 to 80 years were eligible for enrolment if they presented with two or more definitive spontaneous episodes of vertigo of at least 20 minutes duration, had audiometrically documented hearing loss on at least one occasion, and tinnitus or aural fullness in the treated ear (diagnosis of definite uni- or bilateral MD fulfilling the criteria of the 1995 AAO-HNS guideline[34]), excluding other possible causes of vertigo. Furthermore, patients had to be in an active phase of the disease with at least two vertigo attacks in three consecutive months prior to inclusion in the trial. Female patients of childbearing potential were only allowed to be included if they had a negative serum pregnancy test within 7 days before initiation of therapy and were willing to practice acceptable methods of birth control during and for 3 months after therapy.

Exclusion criteria were diagnosis of other central or peripheral vestibular disorders such as vestibular migraine, benign paroxysmal positioning vertigo, paroxysmal brainstem attacks, as well as phobic postural vertigo. Patients suffering from known contraindications or sensitivity to betahistine, such as bronchial asthma, pheochromocytoma, treatment with other antihistaminic drugs, ulcer of the stomach or duodendum, or severe dysfunction of liver or kidney were excluded. Safety-related exclusion criteria were severe coronary heart disease or heart failure, persistent uncontrolled hypertension with systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg, life expectancy <12 months, other serious illness, or a complex disease that might confound treatment assessment. General exclusion criteria were participation in another trial with an investigational drug or device within the last 30 days prior participation in the present study or planned participation in another trial. Pregnant and breast-feeding women and women contemplating pregnancy during the trial were excluded from enrolment.

Written informed consent was obtained from all patients before initiation of the first study-specific procedure. The protocol was approved by local independent ethics committees and was performed in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations.

The study was a dose-defining, phase III, investigator-initiated, longitudinal, multicentre, double-blind, randomized, placebo-controlled, 3-arm, parallel-group trial conducted at 14 academic sites throughout Germany.

The individual study duration was 12 months: 9 months of treatment and 3 months of follow-up. Both the examinations and the study treatment were performed in an outpatient setting. After the baseline visit, subjects returned to the study centre at months 1, 4, 6, and at the end of the treatment period at month 9. In addition to these 4 clinic visits, during the treatment period, 5 standardized telephone interviews were performed at post-baseline months 2, 3, 5, 7 and 8 in order to verify compliance and increase protocol adherence, in particular to remind the subjects to complete their vertigo diary and to record any treatment discontinuation, change in relevant concomitant medication, or side effects they might have experienced in the meantime.

All patients underwent a standardized physical, neurological, and neuro-orthoptic examination, peripheral vestibulo-cochlear testing, assessment of medical history (for the last five years), laboratory examination and measurement of blood pressure and heart rate. Electronystagmography, including bithermal caloric irrigation to measure caloric nystagmus response, and pure-tone audiometry were also performed. Furthermore, patients had to complete 3 different vertigo-related QoL scores at each clinic visit, together with a paper-based vertigo diary on a daily basis. Collection and reporting of concomitant medication and adverse events was performed on a continuous basis.

Randomization and masking

A total of 221 eligible patients at 14 study sites were randomly assigned in a 1:1:1 ratio to receive either high-dose or low-dose betahistine, or placebo for 9 months (Figure 1 CONSORT). Each site received a pool of study medication kits including the treatment assignment in a sealed opaque emergency envelope. If a subject dropped out before receipt of the study medication kit he or she was replaced by the next eligible subject enrolled in the same centre. The concealed allocation was performed by an internet-based randomization schedule (https://wwwapp.ibe.med.uni-

muenchen.de/randoulette) stratified by study site. The fixed random block size was three (starting with six) which was not disclosed during the trial. The random number list was generated by an investigator with no clinical involvement in the trial. Patients, clinicians, core laboratories and trial staff (data analysts, statisticians) were blind to treatment allocation.

Study treatments

Betahistine-dihydrochloride tablets were over-encapsulated using mannitol and aerosil as filling material. Capsules containing the active ingredient were refilled from original pharmacy packaging into vials under sterile conditions and relabelled by the pharmacy of the university hospital of the University of Heidelberg. In the control group, an identically appearing capsule filled with mannitol and aerosil but not containing any active ingredient was administered as placebo.

Patients were instructed to take six capsules per day (two capsules in the morning, two at noon, and two in the evening) with the first drug intake starting as soon as possible after receipt of the study medication kits containing the vials during the baseline visit. In patients assigned to the experimental arms (LD or HD), betahistine-dihydrochloride (VASOMOTAL®, manufactured by Abbott Pharma, Hannover, Germany) in a dosage of 24 mg, which is the highest clinically admitted dosage, was administrated orally 2 times each day (LD group), or 2×24 mg 3 times each day (HD group) for 9 months. In the LD group, patients took one betahistine capsule and one placebo capsule in the morning; two placebo capsules at noon; and one betahistine capsule together with one placebo capsule in the evening.

The 9-month treatment duration was deemed necessary and adequate to reliably assess the long-term prophylactic effect of continuous therapy on the frequency and severity of acute vertigo symptoms caused by MD. There were no disallowed concomitant medications during the study except for antihistaminic drugs since we aimed to assess the efficacy of the assigned prophylactic treatment irrespective of rescue medication use by measuring efficacy conditional on real-life adherence. Hence, rescue medication use for the treatment of acute vertigo-related symptoms such as vomiting or nausea could also be prescribed since a possible effect on the occurrence of vertigo attacks is not known so far.

Study outcomes

Blinded diary assessment

Participants were required to record acute MD-related attacks of vertigo, co-existing symptoms (e.g., aural fullness, changes in tinnitus, changes in hearing) and other characteristics of their vertigo attack, including time of onset, type of vertigo (rotatory and/or postural vertigo, and/or gait unsteadiness, and/or lightheadedness), duration and severity in a paper-based diary for the full 12-month study duration. Additional symptoms that could occur simultaneously with MD attacks but also symptoms of other diseases with vertigo symptoms were monitored with the aim of catching real MD attacks. A template of the vertigo diary is provided as a web supplement.

Typically, attack data were recorded by the patients whenever they experienced vertigo-related symptoms. However, due to the complexity of vertigo symptoms, erroneously documented perseverative or persistent episodes of vertigo and differing individual perceptibility, counting of vertigo attacks caused by MD is challenging.[35] Therefore, all raw patient ratings (i.e. the patient's opinion of the occurrence of vertigo episodes) were evaluated in a blinded manner by trained professionals (CF; CA) at the site of the principal investigator. The decision process was performed according to a consensus document (unpublished standard operating procedure) prior to unblinding in order to define conclusive primary efficacy data from a clinical perspective on the basis of the whole attack information documented in the patient's diary. In particular, since multiple classifications concerning the type of vertigo episode were documented in the original patient diaries, the hierarchy displayed above was used to derive type-specific efficacy outcomes, with rotatory vertigo being the most "severe" of four different types used to characterize an attack.

The primary efficacy outcome was the individual attack rate standardized on a 30-day period (starting from time point 1 defined as the date of first intake with the day of first study drug intake being day 1). The number of evaluated days was defined as the number of days with non-missing information about the patient's vertigo status provided by the daily diary recordings. For example, a patient with 12 attacks during 75 (=2.5×30) documented days has the rate 12/2.5 = 4.8. The 15 undocumented days out of the 90-day assessment period (starting day 181, ending day 270) are handled as missing at random.[36]

Secondary efficacy outcomes

Diary-based secondary efficacy endpoints were the median duration and median severity of evaluated Menière attacks during months 7 to 9 within the 9-month treatment period.

Handicap and impairment of quality of life due to vertigo or tinnitus were measured with the following three well-established self-administered questionnaires: the Dizziness Handicap Inventory (DHI) score based on 25 items,[37] the Vestibular Disorders Activities of Daily Living (VDADL) score,[38] and the Mini-Tinnitus Impairment Questionnaire score based on 12 items (MiniTF12).[39 40] The total score of the VDADL is defined as the median value of answers across all 28 questions and is thus not affected significantly by missing values. To deal with missing items for both the DHI and MiniTF12 questionnaire, we derived the DHI mean total score and the MiniTF mean total score as secondary outcome variables, averaging for the number of available answers. For all three scores, higher values reflect greater perceived disability and impairment of QoL. The definition of the total scores for the dizziness and self-assessment scales can be found in the supplementary materials.

One of the key secondary endpoints measured during clinic visits was peripheral vestibular function determined by electronystagmography (ENG) under caloric irrigation (two test conditions for the right and left ear: 30 °C for the cool, 44 °C for the warm irrigation). The parameter of interest was the peak slow-phase velocity (recorded in °/sec) of the caloric nystagmus response of the "selected ear". The definition of the selected ear is provided in the supplementary material together with the trial protocol available as a web supplement. Furthermore, hearing loss (recorded in decibel; dB) during bone conduction for test conditions 250 Hz, 500 Hz, 1000 Hz, and 2000 Hz, and the tinnitus intensity (in dB) were determined by pure-tone audiometry. Both secondary outcomes were defined for the selected ear.

The three QoL scores as well as the observer-reported secondary efficacy outcomes measured during clinic visits were assessed at baseline and at the 9-month visit.

Explorative, not pre-planned efficacy analyses were performed on specific types of vertigo spells: rotatory and/or postural ("RP-attacks"), and rotatory ("R-attacks").

Safety

Safety was assessed from reports of adverse events as well as laboratory parameters, vital signs (blood pressure, pulse, height, weight and body mass index) and physical or neurological examinations over the entire treatment period at months 1, 4, 6, and 9 (including post-treatment AEs occurring in the first three weeks after cessation of treatment).

Hypotheses and statistical methodology

The BEMED trial was conducted to determine whether treatment with high- or low-dosage betahistine or placebo differed in effectiveness. We assumed the maximal impact would most probably be during the pre-specified 90-day assessment period (months 7 to 9). For the target estimates, the difference in attack incidence over the assessment period, we used a negative binomial mixed effects model (NB GLMM) with normal random intercepts and random slopes associated with time (correlated random effects structure), unstructured covariance pattern, and offset term for the log-transformed number of evaluated days within each 30-day interval.[41] The mixed model with fixed effects for treatment group, time (numerical variable for months 1 to 9), and the treatment-by-time interaction was applied to obtain maximum likelihood estimates of parameters and treatment effects. This model-based approach for longitudinal outcomes not only can yield unbiased parameter estimates when missing observations are missing at random (MAR),[42] but may also provide reasonably stable results even when the assumption of MAR is violated.[43 44] This MAR-based primary efficacy analysis excluding patients who did not provide any diary data (leading to zero evaluable days) was performed according to an "all observed data approach" (as proposed, e.g., in White, et al. [45]) and is statistically efficient without using multiple imputation techniques.[46] Data retrieved after withdrawal of randomized study medication were also included in the analysis.

The pre-specified main model was established by using data from a previous open non-interventional study[31] together with statistical methodology which has been published elsewhere.[41]

Secondary outcomes

Secondary outcomes assessed during clinic visits, i.e. both the observer-reported outcome and the QoL scores, were analysed in a descriptive manner. The absolute change from baseline to 9-month visit was pre-specified as the parameter of interest. Differences between treatment groups were analysed with an ANCOVA for absolute change scores, with factor for treatment group and the baseline value as covariate, by using a closed testing approach to avoid the adjustment of the significance level because of multiple testing.

In case of a high proportion of missing values at baseline or 9-month visit, multiple imputation techniques based on chained equations (MICE method[47 48]) assuming MAR were applied within the ANCOVA.

Both diary-based endpoints (attack duration and severity) were reported on an ordinal scale using predetermined codes (codes for attack duration: "2": 1-20 min, "3": 20-60 min, "4": 60-180 min, "5": >180 min; codes for attack severity: "1": weak, "2": modest, "3": strong, "4": very strong). For each patient the median duration and severity of attacks within interval 7, 8, and 9 (time period of primary interest) was calculated. Hence, only patients with a total number of evaluated days larger than zero across the assessment period were considered for analysis. In order to quantitatively describe treatment effects together with 95% CIs a cumulative logit model (proportional odds model) was applied. According to the consensus document, the variable duration was necessary and sufficient for a Menière's attack to be defined on the basis of the original diary entries. Hence, there were no missing values concerning the duration of an evaluated attack.

Analysis sets

Analyses were based on the intention-to-treat (ITT) principle; safety analyses were done on all patients who received at least one dose of study drug. The full analysis set (FAS) population included all subjects randomized (irrespective of whether they were treated or not), and who did not fail to satisfy a major entry criterion. Subjects who provided neither primary nor secondary efficacy data were excluded from efficacy analyses assuming missingness at random.

The per protocol (PP) set consisted of all subjects who did not substantially deviate from the protocol and could be characterized as follows: (1) all subjects from the FAS for whom no major protocol violations were detected (e.g. poor compliance, errors in treatment assignment etc.), and (2) who were on treatment for at least 8 months, i.e. more than 240 days, counting from day of first intake [completion of a certain pre-specified minimal exposure to the treatment regimen], and (3) who provided diary information within the assessment period [availability of measurements of the primary variable within the time period of interest]. Hence, patients who prematurely discontinued the study or treatment before time interval 7 were excluded from the PP sample.

Determination of sample size, Sample size recalculation

Pilot data from an observational study published in Strupp, et al. [31] supported the assumption that 75% of patients on betahistine show better results than patients on placebo. Hence, a sample size of 21 in each group will have 80% power to detect the difference between groups A and B using a Wilcoxon Mann-Whitney rank-sum test with a two-sided 5% significance level. Initially, a drop-out rate of about 25% was assumed. Thus, a total of 84 patients (28 in each treatment group) had to be enrolled.

The asinh-transformed linear mixed model of Adrion and Mansmann [41] was used to simulate potential study results under more conservative clinical scenarios: based on the results of the observational study[31] we assumed a time effect of -0.06 on the daily attack rate without treatment plus -0.08 with treatment. Using the random intercept variation of Strupp, et al. [31] with a standard deviation of 0.8 and a measurement error of 0.5, we could estimate $P[\Delta_A > \Delta_B]$ for the new scenario (1000 samples) as 0.33. Based on this target parameter, the recalculated sample size of 46 participants per group (i.e. 138 in total) will have 80% power to detect the difference between both groups using a Wilcoxon Mann-Whitney rank-sum test for two independent groups with a two-sided 5% significance level.

We assumed a drop-out rate of approximately 37%. Hence, a total of 220 subjects had to be enrolled in the trial.

Sensitivity analyses and additional efficacy analyses as well as the strategies for multiple testing are described in the supplemental material.

The study database was stored in SAS (Unix Version 9.2, SAS Institute Inc., Cary, NC). Statistical analyses were performed using the statistical software package R version 3.1.1.[49] The R package "`lme4`" (version lme4_1.1-7) was used to fit frequentist generalized linear mixed effects models,[50 51] "`ordinal`" to fit cumulative logit models,[52] and "`mice`" was applied for multiple imputation techniques used for key secondary efficacy outcomes.[47 48]

Previous and concomitant medications were coded using the World Health Organizational-Drug Dictionary (WHO-DD) version 01 MAR 2014. Medical history and adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0.

RESULTS

Enrolment and subject attrition

A total of 1450 subjects were screened for eligibility at 17 sites. 221 subjects were randomized at 14 study sites. The largest site was the sponsor's site located at the Department of Neurology, University Hospital and German Center of Vertigo and Balance Disorders (DSGZ) in Munich which screened 410 and randomized 86 out of 221 patients (i.e. about 40% of all study participants). Altogether, 74 patients were assigned to the PL, 73 to the LD, and 74 to the HD group. Figure 1 shows the flow of participants through the trial together with the completeness of diary information over the entire 9-month treatment period.

1229 of 1450 subjects (84.8%) were screening failures. The most frequent reason was that the subjects did not meet the inclusion criteria regarding attack frequency (255 patients); followed by general refusal to participate for no specific reasons (204 patients); and concerns about the protocol, especially fear of placebo (100 patients). Some did not meet the inclusion criteria of definite MD (123 patients), fulfilled exclusion criteria (173 patients), did not tolerate betahistine or were even allergic to it (31 patients). Others were being treated with betahistine and did not want to change or stop treatment (93 patients). In some cases, the cause of vertigo was not clear (137 patients). Others reasons (e.g. desire for another treatment option such as an operation; or moving abroad) were named in 158 cases. In total, 45 patients were judged ineligible due to fulfilling two of these criteria. No subject prematurely terminated study participation prior to allocation to treatment. One patient in the LD group did not receive the allocated intervention due to fear of placebo. Figure 1 follows the CONSORT PRO reporting guideline[53] and reveals that 78.8% (174 out of 221 patients) provided attack data in the 3-month assessment period for the primary endpoint. In each group, a few patients did not submit any diary at all without giving a specific reason for this. Completeness of the patient diaries did not differ between the three treatment groups.

Participants' baseline characteristics

Table 1 shows the demographic and clinical characteristics as well as three QoL total scores assessed at the baseline visit of all 221 patients randomized. Overall, approximately half of the randomized

patients were female; the total range for age was 21 to 80. The treatment groups were well balanced for demographic, clinical factors, and tinnitus-related, dizziness and self-assessment scores. Pre-randomization attack frequency was not reported although considered as an inclusion criterion. Initial evaluation of the post-treatment frequency of MD attacks within the first 30 days after the start of treatment ("pseudo-baseline") showed the three groups to be comparable at the outset (Table 2).

Dosing and protocol adherence

Treatment compliance based on drug accountability was not calculated due to insufficient data quality and due to a high proportion of missing data. Instead, the treatment duration defined as the difference between the date of the end of treatment and the date of the first intake was used as a measure of treatment adherence. In the FAS sample, the mean (95% CI) treatment duration was 222.54 (201.99 to 243.10) in the PL, 225.77 (204.55 to 246.99) in the LD, and 215.83 (192.63 to 239.04) in the HD group (Table 2). There was no significant difference between the three groups concerning treatment duration (Kruskal-Wallis test used as global testing procedure; FAS: P=0.770; PP: P=0.600).

Figure 2 shows for each treatment group the time to withdrawal and the percentage of patients who stopped treatment before the day indicated on the x-axis. In this figure, an event indicating treatment dropout is defined as end of treatment before day 241 (according to the definition for per-protocol). For example, about 10% of the placebo patients discontinued the assigned treatment before day 50, compared to about 14% of patients under high-dose treatment. The figure also indicates that about 77% (72%; 70%) of LD (HD; PL) patients were on treatment for at least 8 months (241 days). No evidence was found for a differential drop-out (attrition bias) from the administered therapy between the three groups (Log-rank test: P=0.703).

Primary efficacy outcome measures

A negative binomial mixed-effects model assessed a general decline in the incidence of Menière's attacks over the nine 30-day time intervals. The mean attack rate for placebo patients was significantly lowered by the factor 0.758 per additional 30-day interval on treatment (95% CI, 0.705 to 0.816). It was hypothesized that the assigned experimental treatment (LD or HD betahistine) would make this

decay rate even smaller. However, no evidence for a treatment-by-time interaction was found (global testing, Likelihood-Ratio (LR) test: P=0.759 for the FAS sample; P=0.493 for the PP sample), indicating no statistically significant differences in the attack rates across the two betahistine groups or the placebo group. The corresponding estimated factors, representing rate ratios (RR) compared to PL, were 1.036 (95% CI, 0.942 to 1.140) for the LD, and 1.012 (0.919 to 1.114) for the HD group. The mean incidence rate (95% nonparametric bootstrap CI) per month within the 90-day assessment period was 2.380 (1.640 to 3.074) for the PL, 2.000 (1.509 to 2.466) for the LD and 2.111 (1.479 to 2.698) for the HD group.

In figure 3, the upper panel shows the data of the observed individual time course of monthly attack counts during the 9-month treatment period. The lower panel shows the theoretically predicted individual monthly attack counts during the treatment period stratified by treatment group.

For all patients randomized, a total of 5003 episodes of vertigo were evaluated according to the consensus document on the basis of the raw diary entries. 36.64% of all evaluated episodes of vertigo could be classified at least as an attack of postural vertigo ("P-attack"). 52.63% of all evaluated episodes of vertigo were classified as an attack of rotatory vertigo ("R-attack") and were interpreted as the most severe type of vertigo attack. 84.53% of all evaluated episodes of vertigo were classified as an "RP-attack", i.e. vertigo documented as either rotatory or postural, or rotatory and postural combined. (Only 4.74% of all evaluated episodes of vertigo were characterized as both an R- *and* P-attack.)

Table 3 displays the estimated RR if two alternative definitions of a Menière's attack were considered for statistical analysis. Notably, these supportive post-hoc efficacy analyses demonstrated the robustness of the key results with respect to the definition of the primary endpoint. If either rotatory and/or postural attacks of vertigo, or rotatory attacks of vertigo were considered for model-based primary analysis (by leaving out episodes of vertigo which were classified as gait unsteadiness and/or lightheadedness), these supportive post-hoc efficacy analyses reflected no betahistine effect in a consistent way.

The primary analysis considered time courses for each patient in a longitudinal manner, taking patients into account who did not provide attack information for the 3-month assessment period at the end of

the treatment period. In order to check whether early analysis drop-outs influenced the main efficacy results, a pre-planned sensitivity analysis was performed to calculate attack rates across time intervals 7, 8, and 9 by taking into account only patients who provided attack information within this assessment period. The results of the generalized linear model (GLM) approach confirmed the robustness of the longitudinal model applied for primary efficacy analysis (Table 3). For the FAS sample, the estimated mean incidence rate per day in months 7 to 9 was 0.079 (95% CI, 0.053 to 0.124) in the PL, 0.067 (0.044 to 0.101) in the LD, and 0.067 (0.044 to 0.102) in the HD group. There was no evidence for a difference in attack incidence between the three treatment groups for the FAS as well as for the PP set (global LR test, FAS: P=0.850; PP: P=0.808).

Exploratory adjusted efficacy analyses

Pre-planned sensitivity analysis to investigate centre effect also yielded no significant treatment-by-time interaction (P>0.100) for the number of attacks per 30 days. Pooling of sites within the catchment area of the DSGZ in Munich, which recruited about 40% of all randomized patients, revealed no evidence of a centre effect (P=0.542, global LR test to compare the main model with the adjusted one (pooled pseudo-site Munich yes vs. no)). The overall decline of attacks over time in the three treatment groups was not significantly affected by whether a patient was recruited in a study centre outside of Munich or not. This finding was confirmed when pooling of small investigator sites with fewer than 15 randomized patients was performed (P=0.080, global LR test).

Adjusting for gender effect did not significantly improve the model used for the primary efficacy analysis (P=0.202, global LR test). Hence, gender did not have an impact on the time course of Menière's attacks, nor does gender affect the decline in attack rates. The main result of no treatment-induced changes in attack rates was therefore confirmed.

A second pre-specified adjusted analysis explored whether estimated treatment effects varied significantly between age subcategories of trial participants. However, adjusting for age (using age categories defined in the supplemental materials) did not significantly improve the model used for primary efficacy analysis (P=0.771, global LR test), indicating that age did not affect the decline in attack rates as was seen in the model used for primary efficacy analysis.

Attack duration and severity

The duration and severity of an attack for those patients with at least one evaluated Menière's attack within the assessment period (months 7, 8 and 9) was analysed by using a cumulative logit modelling approach in order to compare ordinal duration and severity data across the treatment groups PL, LD and HD. It was of interest to examine whether the percentages of patients suffering from attacks of a longer duration and a higher severity respectively were reduced by the assigned treatment. For the FAS as well as the PP sample, the percentages of patients suffering from long-lasting attacks or more severe attacks did not significantly differ across treatment groups (duration: P=0.348 (FAS), P=0.515 (PP); severity: P=0.390 (FAS), P=0.438 (PP)). The data showed that the experimental treatment LD or HD did not lead to higher probabilities of attacks in the low categories of duration and severity respectively, as compared to PL.

Subject questionnaires, and vestibular and audiological parameters

The three tinnitus-related or vertigo-specific QoL scores remained fairly stable at the end of the treatment period as compared to the score measured at the baseline visit prior to the start of therapy. Table 4 displays the results of the ANCOVA, indicating that no evidence for between-treatment differences in mean change scores was found.

As regards changes in vestibular and audiological function, no therapeutic gain of drug treatment was found: the efficacy of placebo treatment-induced change in tinnitus intensity, peak slow phase velocity during caloric irrigation with water at 30°C and 44°C, and pure-tone audiometrically assessed hearing level was not significantly better than the efficacy of low-dose or high-dose betahistine (P>0.05, global F-test for FAS as well as for PP, ANCOVA for absolute change values applied).

Clinical safety events

Table 5 summarizes adverse events deemed clinically important. The majority (over 85%) of subjects in the safety set reported one or more treatment-emergent adverse event (TEAEs) within the 9-month treatment period with no clinically relevant difference between the three treatment groups. The most commonly reported TEAEs were headache, balance disorder, nausea, nasopharyngitis, feeling hot, eye irritation and palpitations. Balance disorder and nausea were more commonly reported in the betahistine groups than with placebo. Eye irritation and palpitations were more commonly reported with HD compared to LD and placebo. Differences were, however, small and probably not clinically relevant.

Between 54.1% and 63.9% of subjects in each treatment group had one or more TEAEs that were considered treatment-related by the investigator: most of these were reported with low-dose betahistine treatment (see Table 5). Most TEAEs were of mild or moderate intensity. TEAEs of severe intensity were reported for 20 (27.0%) subjects in the PL, 20 (27.8%) subjects in the LD, and 19 (25.7%) subjects in the HD group. The only AE of severe intensity that was reported by more than 5% of subjects in any treatment group was headache. There were no deaths during the study.

56 treatment-emergent SAEs were reported for 14.9% subjects with placebo, 13.9% with LD and 13.5% subjects with HD treatment. Treatment-emergent SAEs reported by more than 1 subject during the study were vertigo (4.1% of subjects in the PL and the HD group) and inguinal hernia and intervertebral disc protrusion (both 2.8% of subjects in the LD group). These events were all considered not related to study treatment. Notable is the higher incidence of drug discontinuations due to AEs in the HD group (14.9% compared to 6.8% with placebo and 5.6% with LD). The most commonly reported AEs leading to drug discontinuation were tinnitus, vertigo, ear discomfort and nervous system disorders, which were all more commonly reported with high-dose betahistine than with low-dose betahistine treatment and placebo.

DISCUSSION

For patients suffering from MD, unpredictable vertigo attacks are the most unpleasant symptom, leading to not just physical but also psychological strain. Clinical experience and several studies have supported a potential beneficial effect of prophylactic drug treatment with betahistine on the attacks of vertigo as well as on vestibular and, to a lesser degree, audiological symptoms.[29] However, according to a Cochrane review of betahistine for MD or Menière's syndrome[28] there is insufficient evidence to say whether betahistine has any effect.

The key findings of the BEMED trial are as follows: first, in each arm a significant decline of attack rates was observed over the 9-month treatment period. Second, the effects of two different dosages of betahistine could not be distinguished from a patient-reported effect caused by placebo intervention in terms of the frequency of attacks as well as vestibular and audiological function and QoL. This means the results do not give clear evidence that MD patients experience a relevant clinical reduction in the number of attacks after a 9 month-long treatment with betahistine compared to placebo intervention. Third, there were no safety concerns and betahistine was well tolerated even in the high dose group of 144 mg betahistine per day.

MD is a disease with inter-individual differences in a complex mixture of Menière's-specific symptoms represented by vertigo attacks, hearing loss, tinnitus, pressure on the affected ear, and accompanying symptoms such as nausea or vomiting. The clinical course of MD is cyclical and unpredictable.[54] Further, knowledge about the natural history and the underlying progression of episodes of vertigo in the long term is limited so far. The spectrum of symptoms tends to reflect the stage of the disorder. Some patients develop bilateral disease and non-relapsing symptoms. Variability also exists in the length of time required before symptoms improve. Perez-Garrigues, et al. [55] provide data that even without therapeutic intervention the vertigo spells subside with time as vestibular function "burns out".

It might be the case that for some participants in the BEMED trial a degree of compensation had already occurred. Separating the effect of therapy from the cyclical natural history of the disorder poses difficulties for all studies of MD. Because the natural history is one of remission and recurrence,

and because participants must have active vertigo in order to enrol in a study, spontaneous improvement through regression to the mean in terms of symptom frequency and severity is expected, creating the illusion of a therapeutic efficacy.[56 57] Thus, a control group is vital to contrast the long-term treatment effect against spontaneous improvement. The possibility of experiencing an episode-free year increases as the disease progresses.[55] Therefore, assessing the efficacy of treatments for MD needs a randomized approach including a *placebo* or *no-treatment* ("wait and see") control group. Following the concept of Perez-Garrigues, et al. [55] the BEMED population consisted of patients at different stages of MD which may be reflected by individual baseline rates as well as individual time slopes for decay rate of attacks as displayed in Figure 3 (left panel). This consideration also influenced the choice of our statistical model.

The BEMED trial is, to our knowledge, the first randomized controlled trial with a specific focus on how betahistine prevents Menière's attacks taking into account different types of vertigo. It was designed as an investigator-initiated, prospective, longitudinal, multicentre, double-blind, randomized, placebo-controlled, 3-arm, parallel-group, phase III superiority trial. It specifically assessed the frequency, duration and severity of acute MD attacks during a 9-month treatment period. It also studied as secondary endpoints the treatment effect on vertigo-related impairment in QoL as well as on vestibular and audiological function. It is the only trial which ascertains the *speed of effect*, that is whether the two active agents may be distinguished from each other or from placebo by how quickly reduction in attack frequency is achieved.[33] A series of sensitivity analyses supports the consistency and robustness of the BEMED efficacy results.

Studies which support the beneficial effect of betahistine on MD are mostly observational. On the one hand, nonrandomized studies tend to show larger treatment effects compared to RCTs and tend to overestimate the magnitude of a potential treatment effect.[58] On the other hand, there is the question of whether bias alone can explain the large effect differences between observational and experimental studies. There may also be the problem of external validity for the RCT under consideration. Below, we will reconsider these aspects using the PICO approach (Patient-Intervention-Comparison-Outcome) to discuss the strengths and limitations of the BEMED trial.

Population: The BEMED trial population of 221 patients was selected from 1450 screened patients. Patients were diagnosed with MD according to the criteria of the AAO-HNS guideline[34] and the new schema for diagnosis of MD previously ratified by the Bárány Society,[59] which are widely accepted and provide sufficient diagnostic accuracy.[28] The mean monthly attack rate during the first study month is about 5.7 which is considered as representative for MD patients treated with betahistine. The population may be contaminated by patients suffering from vestibular migraine, benign paroxysmal positional vertigo, and secondary functional dizziness, which is typical for many MD studies.[60]

Intervention: The duration of exposure to study treatment was similar across the three treatment groups and ranged between a mean of 214 and 227 days. About 75% of the subjects completed the 9-month treatment period.

Control group: The BEMED trial decided to implement a placebo arm for ethical and compliance reasons. Our placebo results may not fully reflect MD's natural history.

Outcome: Electing the "(number of) Menière's attacks in a given time period" as the efficacy endpoint, documented by patient diaries at home (PRO), runs the risk of there being some missing or inaccurate information compared to objective measurements such as audiogram or questionnaires. In previous trials the frequency of vertigo spells (gold standard) was mainly documented by a symptom report card using a Likert scale of 0 ("no vertigo") to 4 ("worst vertigo attack ever") to characterize a vertigo symptom and to perform a vertigo control categorization as a simple and convenient summary statistic of a patient's vertigo experience.[15] The BEMED trial used a more complex vertigo symptom diary as an instrument to enable the patient to differentiate between several types of vertigo feelings. In order to establish efficacy or effectiveness from a patient's perspective there are no reasonable alternatives to patient diaries which might be superior to alternative patient-reported outcomes such as self-assessment scales or more or less disease-specific and validated QoL scores in reflecting fluctuations in the disease severity over time. Derivation of definite or probable Menière attacks based on the original patient recordings documented by paper-based vertigo diaries is methodologically challenging.

Other studies used QoL scores, functional impairment, and disability instruments. We implemented these patient-reported outcomes as secondary endpoints. A wide spectrum of different efficacy

endpoints is needed to measure any treatment-related effect since it is not known how the complex symptom clusters are modified by the treatment.

Preliminary Implications and Recommendations for Clinical Practice

We presented the primary results of the BEMED trial and articulated open questions that might guide future studies on therapeutic options in MD (e.g. planning figures for sample size calculation). Several aspects of our design and experiences during the trial might also be relevant for clinical trials of other vertigo diseases that cause recurring attacks of spontaneous vertigo, such as vestibular migraine or vestibular paroxysmia, as well as for treatment of acute episodes of vertigo.

Further long-term randomized, placebo-controlled trials with higher dosages of betahistine are warranted to confirm or disprove the findings of the BEMED trial. Clinical research should also focus more specifically on identifying predictors for betahistine therapy success, which will hopefully lead to broader knowledge of this challenging field and ultimately to an improvement of the patients' quality of life. In conclusion, therapeutic options for MD will remain a challenge for both patients and physicians.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Acute vertigo attacks caused by Menière's disease (MD) have a major impact on quality of life and play a major role in the patient's perceived wellbeing.

The natural history of MD is one of remission and recurrence, and because participants must have active vertigo in order to enrol in a study, spontaneous improvement through regression to the mean is expected.

There are no state-of-the-art therapeutic confirmatory drug trials in the complex chronic condition of MD. Observational studies or low-quality RCTs of low- and moderately-dosed betahistine have produced contradictory efficacy results and did not investigate the effect of an experimental intervention from the patient's perspective with respect to vertigo attack prophylaxis.

WHAT THIS STUDY ADDS

Long-term prophylactic treatment with betahistine-dihydrochloride does not change the time course of episodes of vertigo compared to placebo intervention.

Placebo intervention as well as betahistine treatment show the same reduction of attack rates over time during the 9-month treatment period.

Reliable and valid instruments for the measurement of subjective vertigo symptoms, in particular vertigo attacks caused by MD, are lacking. Derivation of definite or probable Menière's attacks based on the raw patient recordings documented by vertigo diaries is methodologically challenging and requires pre-specified rules.

Contributors:

MS, JW, CF, CA, and UM contributed to the design of the trial, wrote the study protocol and subsequent amendments, and interpreted the work. As coordinating investigator, MS initiated the collaborative clinical trial project and is the guarantor. MS, CF, and all investigators of the 14 study sites acquired the data. CA and UM wrote the statistical analysis plan, performed the statistical analyses, interpreted the results, wrote the first draft and substantially contributed to the writing of all subsequent versions of the manuscript. CF and CA evaluated the original patient ratings provided by paper-based vertigo diaries.

All authors revised the work critically for important intellectual content, approved submission of the final report for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

This article is published on behalf of the BEMED investigators, a full list of whom is provided in the Web Supplement.

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Ethical approval:

All participants provided written informed consent according to the procedures approved by the ethics committee of the University Hospital Munich.

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Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare:

Michael Strupp is Joint Chief Editor of the Journal of Neurology, Editor in Chief of Frontiers of Neuro-otology and Section Editor of F1000. He has received speaker's honoraria from Abbott, Actelion, UCB, GSK, TEVA, Biogen Idec, Pierre-Fabre, Eisai and Hennig Pharma.

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Data sharing:

Data to reproduce the ITT analyses of the primary and secondary efficacy endpoints together with the used R-code will be available from the corresponding author (Michael.Strupp@med.uni-muenchen.de) or biostatistician (mansmann@ibe.med.uni-muenchen.de). Informed consent for data sharing was not obtained from participants, but the data presented are anonymised and the risk of identification is very low.

TABLES

Table 1. Baseline characteristics of the intention-to-treat (ITT) sample.*

Characteristics	PL (N = 74)	LD (N = 73)	HD (N = 74)	*P* value
Demography				
Age – yr				
Mean ± SD	54.5 ± 12.834	56.1 ± 11.118	56.1 ± 12.606	0.657
Median [Min; Max]	55.0 [22.0; 76.0]	57.0 [22.0; 80.0]	58.0 [21.0; 79.0]	
Male sex – N (%)	35 (47.30%)	39 (53.42%)	35 (47.30%)	0.693
Ethnicity: Caucasian – N (%)	71 (95.95%) (3 Asian)	72 (98.63%) (1 Asian)	74 (100%)	0.400
Baseline NRO/ ENT characteristics				
Audiometrically documented hearing loss (inclusion criteria) – N (%)				0.836
both ears	20 (27.03%)	24 (32.88%)	25 (33.78%)	
left ear	25 (33.78%)	21 (28.77%)	25 (33.78%)	
right ear	28 (37.84%)	28 (38.35%)	24 (32.43%)	
	Missing: 1 (1.35%) §			
Documented tinnitus/ aural fullness (inclusion criteria) – N (%)				0.855
both ears	15 (20.27%)	16 (21.92%)	17 (22.97%)	
left ear	32 (43.24%)	27 (36.99%)	32 (43.24%)	
right ear	27 (36.49%)	30 (41.10%)	24 (32.43%)	
			Missing: 1 (1.35%) §§	
Tinnitus intensity [dB], selected ear				
Mean ± SD	42.84 ± 22.00	44.45 ± 22.75	53.98 ± 19.75	0.031#
Median [Min; Max]	42.50 [0; 83.00]	46.00 [0; 103.00]	59.00 [5.00; 83.00]	
Missing	24	33	29	
Peak slow-phase velocity [°/sec], selected ear				
cool water irrigation (30°C)				
Mean ± SD	8.76 ± 8.25	9.84 ± 11.23	7.37 ± 7.29	0.501
Median [Min; Max]	6.00 [1.00; 40.00]	6.90 [0; 73.00]	5.30 [0; 45.00]	
Missing	9	7	10	
warm water irrigation (44°C)				
Mean ± SD	9.42 ± 8.07	11.68 ± 12.96	9.65 ± 11.94	0.503
Median [Min; Max]	6.90 [1.00; 36.00]	8.00 [0; 72.00]	5.50 [0; 71.00]	
Missing	7	5	7	
Pure tone audiometry [dB hearing level], selected ear				

250 Hz				
Mean ± SD	29.39 ± 18.19	32.84 ± 16.03	29.56 ± 15.99	0.543
Median [Min; Max]	31.50 [0; 80]	40.0 [0; 70]	30.0 [0; 75]	
Missing	20	22	19	
500 Hz				
Mean ± SD	33.63 ± 19.95	36.53 ± 19.24	35.44 ± 19.89	0.678
Median [Min; Max]	37 [0; 75]	41 [0; 70]	37.5 [0; 75]	
Missing	14	15	10	
1000 Hz				
Mean ± SD	35.27 ± 20.74	37.57 ± 19.74	34.40 ± 21.30	0.645
Median [Min; Max]	39 [2; 80]	40 [0; 70]	30 [0; 75]	
Missing	11	8	9	
2000 Hz				
Mean ± SD	35.77 ± 19.87	38.69 ± 19.27	37.92 ± 18.52	0.598
Median [Min; Max]	36 [0; 75]	43 [0; 70]	40 [5; 70]	
Missing	12	8	10	
QoL Scores				
MiniTF *mean* score				
Mean ± SD	0.765 ± 0.564	0.807 ± 0.531	0.733 ± 0.482	0.718
Median [Min; Max]	0.667 [0; 2.000]	0.750 [0; 2.000]	0.750 [0; 1.833]	
Missing	2	4	0	
VDADL total score				
Mean ± SD	1.767 ± 1.352	1.754 ± 1.531	1.777 ± 1.070	0.521
Median [Min; Max]	1.000 [1.000; 7.000]	1.000 [1.000; 10.000]	1.000 [1.000; 6.000]	
Missing	1	4	0	
DHI *mean* total score				
Mean ± SD	1.693 ± 0.899	1.777 ± 1.007	1.765 ± 0.906	0.760
Median [Min; Max]	1.560 [0; 3.840]	1.760 [0; 4.000]	1.920 [0; 3.583]	
Missing	2	5	0	

* Means ± standard deviation (SD) together with Median [Min; Max] are depicted for quantitative, absolute numbers and proportions for categorical variables.
Categorical variables were compared by using the Chi² test or Fisher's exact test as appropriate. To compare continuous variables between the three treatment groups, an ANOVA or Kruskal-Wallis test was applied.

[#] This significance is a consequence of the imbalance between treatment groups at baseline and not contributed to a treatment effect.

[§] Inclusion criteria not fulfilled. This patient was not included in the FAS.

[§§] Inclusion criteria not fulfilled. This patient was included in the FAS, and in the PP set. This patient completed the trial regularly (treatment duration 267 days, study duration 12 months).

Table 2. Postrandomization data regarding initial attack frequency and treatment compliance (FAS sample).

Characteristics	PL (N = 74)	LD (N = 73)	HD (N = 74)	*P* value
***Pseudo-baseline** **				0.625
Number of attacks/ 30 days				(KW test)
Mean ± SD	6.152 ± 6.927	5.779 ± 4.590	5.101 ± 4.531	
Median [Min; Max]	4.500 [0; 37]	5.000 [0; 19]	4.000 [0; 23]	
Follow-up				
Treatment duration [days]				0.824 (ANOVA)
Mean ± SD	222.5 ± 87.48	225.8 ± 89.00	215.8 ± 98.75	
Median [Min; Max]	266.5 [2.0; 348.0]	269.0 [0.0; 317.0]	269.0 [2.0; 311.0]	

***** "Pseudo-baseline" defines data documented during the first treatment month (with the day of first study drug intake being day 1). Pre-treatment attack data were not available.

KW test: Kruskal-Wallis rank sum test. ANOVA = Analysis of variance.

Table 3. Results of the primary efficacy analysis (FAS sample) together with two varying definitions of a Menière's attack used as supportive efficacy analyses.

Outcome measure	Decay rate (95% CI) of attacks over time	RR (95% CI) for LD vs. PL	RR (95% CI) for HD vs. PL	Global *P* value[#]
Menière's attacks evaluated[*] (pre-specified primary outcome)	0.758 (0.705 to 0.816)	1.036 (0.942 to 1.140)	1.012 (0.919 to 1.114)	0.759
Attacks of rotatory and/or postural vertigo	0.766 (0.711 to 0.826)	1.032 (0.936 to 1.138)	0.974 (0.882 to 1.076)	0.511
Attacks of rotatory vertigo	0.741 (0.675 to 0.813)	1.050 (0.937 to 1.177)	0.991 (0.882 to 1.115)	0.575
Menière's attacks evaluated in months 7 to 9 (GLM)	n.a. [§]	0.846 (0.465 to 1.533)	0.887 (0.485 to 1.625)	0.850

RR: rate ratio resulting from the model-based primary efficacy analysis (NB GLMM); CI: confidence interval (reference category: PL group).

[*] "evaluated" means evaluated according to the pre-specified decision rules described in a consensus document. *Rotatory and/or postural vertigo***:** considers episodes of vertigo classified as rotatory and/or postural. This restriction implies that evaluated episodes of vertigo classified as gait unsteadiness and/or lightheadedness were ignored. *Rotatory vertigo***:** Only evaluated episodes of vertigo classified as rotatory − ignoring attacks classified as postural and/or gait unsteadiness and/or lightheadedness – were considered for statistical analysis.

[§] n.a.: not applicable since the generalized linear model (GLM) used as sensitivity analysis does not include a time effect. The GLM is based upon attacks experienced across 30-day time intervals 7 to 9 only.

[#] LR test used as global test.

Table 4. Mean absolute change (95% CI) for secondary efficacy outcome measures (FAS sample) together with the number of patients with measurements at baseline and month 9 visit.

Absolute change (Month 9 – BL)	PL (N = 72)	LD (N = 70)	HD (N = 72)	*P* value[#]
Quality of life scores				
MiniTF *mean* score	-0.121 (-0.223 to -0.019)	-0.113 (-0.212 to -0.014)	-0.140 (-0.240 to -0.039)	0.929
N	54	58	56	
VDADL total score	-0.202 (-0.405 to 0.000)	-0.261 (-0.461 to -0.060)	-0.360 (-0.560 to -0.159)	0.547
N	57	58	58	
DHI *mean* total score	-0.497 (-0.689 to -0.305)	-0.364 (-0.554 to -0.173)	-0.515 (-0.705 to -0.325)	0.482
N	56	57	57	
***Tinnitus intensity* [dB]**	-0.558 (-6.024 to 4.9078)	7.066 (0.533 to 13.598)	-1.823 (-7.957 to 4.311)	0.107
N	35	24	28	
***Peak slow-phase velocity* [°/sec]**				
cool water irrigation (30°C)	-0.126 (-1.605 to 1.353)	-0.892 (-2.401 to 0.616)	0.489 (-1.020 to 1.999)	0.442
N	52	50	50	
warm water irrigation (44°C)	-0.107 (-1.824 to 1.611)	-1.676 (-3.443 to 0.090)	-1.044 (-2.811 to 0.722)	0.449
N	54	51	51	
***Pure tone audiometry (bone conduction): hearing loss* [dB]**				
250 Hz	-5.533 (-9.010 to -2.057)	-1.986 (-5.195 to 1.224)	-2.883 (-6.119 to 0.352)	0.316
N	34	40	39	
500 Hz	-4.372 (-8.386 to -0.358)	0.288 (-3.636 to 4.212)	-3.268 (-7.099 to 0.563)	0.231
N	44	46	48	
1000 Hz	-5.441 (-9.206 to -1.677)	-0.600 (-4.287 to 3.088)	-2.956 (-6.680 to 0.769)	0.196
N	47	49	48	
2000 Hz	-1.534 (-4.937 to 1.869)	0.612 (-2.575 to 3.798)	-1.840 (-5.098 to 1.418)	0.513
N	45	51	49	

[#] Complete case ANCOVA for absolute change, with factor for treatment group, and baseline value of the dependent variable used as a covariate. P-value resulting from global testing (F-test).
Absolute change means difference of 9-month value minus baseline value.

For VDADL Total Score: summary statistics for absolute change in median score was analyzed.
Tinnitus intensity [dB] in the "selected ear" assessed by audiometry.
QoL scores, tinnitus intensity, hearing loss: higher values at time point BL or 9-month visit indicate more severe impairment; a negative value in absolute change means that impairment improved over time.

Table 5. Safety assessment (safety sample): Frequency of clinically important adverse events occurring in the 9-month treatment period (plus post-treatment AEs occurring within a 3-week gap period). Values are number of subjects (percentages) together with number of events.

	PL (N = 74)		LD (N = 72)		HD (N = 74)	
Number of Deaths	0		0		0	
Number of Subjects With at Least One SAE	11 (14.9%)	21	12 (16.7%)	14	14 (18.9%)	21
Number of Subjects With at Least One TESAE	11 (14.9%)	16	10 (13.9%)	12	10 (13.5%)	12
Number of Subjects who Prematurely Terminated the Study Due to a TEAE	5 (6.8%)	23	4 (5.6%)	19	11 (14.9%)	65
Number of Subjects With at Least One TEAE	65 (87.8%)	426	65 (90.3%)	429	63 (85.1%)	427
Number of Subjects With at Least One Severe TEAE	20 (27.0%)	41	20 (27.8%)	39	19 (25.7%)	32
Number of Subjects With at Least One Related TEAE	41 (55.4%)	150	46 (63.9%)	138	40 (54.1%)	132
Number of Subjects Without Any TEAE	9 (12.2%)		7 (9.7%)		11 (14.9%)	

Percentages are based on the number of subjects in the Safety Subject Sample.
A treatment-emergent adverse event (TEAE) is defined as an AE that started or worsened in severity on or after the first study drug administration and within 21 days of last study drug administration.
TEAEs leading to study termination are TEAEs reported on the Adverse Event CRF with 'Led to Study Termination' = 'yes'.
A treatment-emergent SAE (TESAE) is an AE that was judged to be serious by the investigator and started at or after the first administration of study drug and within the gap period (21 days) after the last study drug administration or an AE that already existed before the start of that treatment but worsened during the treatment and within the gap period including any subsequent wash-out or post-treatment period.

Severe = severity reported as 'severe' or missing.
Reasonable possibility for a causal relationship = drug-event relationship reported as 'possible', 'probable', or missing.

FIGURES

Legends for Figures:

Figure 1. Study flow chart, according to the Consolidated Standards for Reporting of Trials (CONSORT). Enrolment and primary efficacy endpoints based on patient diaries (patient-reported outcome; PROs). The steps lead from prescreening to collection of the data used in the efficacy analyses. The diagram shows the extent of exclusions, loss to follow-up and completeness of diary documentation available across time intervals 1 to 9.

Figure 2. Proportion and timing of patient withdrawal for all 221 patients randomized. Time to withdrawal in the three treatment groups (PL, LD, HD). 270 days is the pre-planned treatment duration according to the protocol. An event is defined as end of treatment before day 241 (first vertical grey line) according to the pre-specified minimal exposure to the treatment regimen defined as "per protocol" and the corresponding definition of a major protocol deviation.

Figure 3. Profile plot. Left panel: Individual trajectory plot for observed *daily* incidence of Menière's attacks over the 9-month treatment period (divided into nine 30-day intervals).

Right panel: Conditional posterior mean trajectories for the incidence rates per day depending upon fixed and random effects after fitting a Negative Binomial GLMM (i.e. estimates resulting from the longitudinal model used for primary efficacy analysis). 10 patients (PL: N=5; LD: N=2; HD: N=3) submitted no diary for the whole individual study period for no specific reasons (N=1), loss-to-FU (N=3), IC withdrawn (N=4), analysis dropout due to AEs (N=2).

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SUPPLEMENTARY MATERIALS

Betahistine therapy in patients with Menière's disease:
Primary results of a long-term, multicentre, double-blind, randomized, placebo-controlled, dose-defining trial of efficacy and safety (*BEMED* trial)

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The PDF file includes:

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17 centres (Neurology or ENT departments of university hospitals) screened for eligible patients.

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S2. Procedural and Statistical Methods

2.1 Sensitivity analysis

To deal with missing values a sensitivity analysis of the primary efficacy outcome was performed which only used patients with a total number of evaluated days larger than 0 within the 90-day assessment period (months 7, 8 and 9). This particular MAR-based analysis examined whether patients who withdrew before time interval 7 showed comparable efficacy results with respect to the overall primary analysis. Marked differences would indicate a strong selection process and informative missingness. This pre-planned sensitivity analysis excluded patients who withdrew totally from the study before time interval 7. The simple negative binomial model (NB GLM) was based on an aggregated version of the longitudinal approach used for the main model by summarizing the number of Menière's attacks and the number of evaluated days within time intervals 7, 8, and 9 only (should be 90 days according to the protocol). The linear predictor for the generalized linear model was defined according to the mixed effects model chosen for the primary analysis, leaving out the random effects part and time effects.

As supportive primary efficacy analyses and in order to substantiate the robustness of the estimated treatment effect, we explored two alternative definitions of a *Menière's attack* derived from the original patient-reported vertigo symptoms. This restriction implied that rather mild types of patient-reported vertigo symptoms classified as gait unsteadiness and/or lightheadedness (hence without the criteria rotatory and/or postural documented on the original patient diary) were ignored, because they were assumed to have a potential diluting effect.

The incidence of episodes of vertigo classified as rotatory and/or postural ("*RP-attacks*"), and rotatory ("*R-attacks*") were analyzed in an exploratory fashion to investigate the diminishment over time and its relation to intervention by using exactly the same definition concerning time units (30-day intervals) and the time at risk for attacks (number of evaluated days per 30-day interval). Therefore, the methodological concept applied for the primary efficacy analysis was adopted for these two derived efficacy endpoints in an analogous manner.

2.2 Additional efficacy analyses: adjusting for centre effects, subgroup analyses

Study site was used as the variable in the allocation process. Since the BEMED trial was not explicitly designed with enough power to detect centre effects, the primary efficacy analysis was performed unadjusted. Centre was studied as one of the exploratory adjusted analyses by pooling of small sites with fewer than 15 randomized patients (based on geographical considerations), and, additionally, pooling of sites located in Munich within the catchment area of the German Center for Vertigo and Balance Disorders (DSGZ), which recruited the largest number of patients.

According to the main efficacy analysis, pre-specified subgroup effects were explored by including interaction terms between treatment group and the baseline covariates gender and age, the latter with pre-specified cut-off points ≤45, (45, 55], (55, 65], >65 years. These exploratory subgroup analyses focused on the evidence for a difference in treatment effects, investigating for potential interaction effects.

2.3 Multiplicity Issues

All null hypotheses were tested at the nominal two-sided 5% significance level.

HD, LD and PL groups were compared in terms of the primary endpoint by using a formal closed-testing procedure that examines the three hypotheses with respect to the three comparisons HD vs. LD, HD vs. PL, and LD vs. PL by preserving the overall 5% significance level of the confirmatory efficacy analyses. The closed-testing procedure (Marcus et al., 1976; Bauer 1991) consisted of overall global test testing of whether there is any treatment effect at all (referring to the omnibus treatment-by-time interaction), followed by three pairwise comparisons using the same significance level of 5%. If the global test for the global null hypothesis was not significant no pairwise comparisons would be valid. The likelihood ratio test was performed as a global test.

The secondary outcomes were analyzed in an exploratory manner and the results are only interpreted as supportive evidence related to the primary efficacy outcome.

S3. Secondary Efficacy Outcomes

3.1 Definition of the Selected Ear

According to the inclusion criteria, a study participant suffers from audiometrically documented hearing loss in either the left or right ear, or both ears. Additionally, tinnitus or aural fullness in the treated ear has to be diagnosed prior to enrolment. The *selected ear* chosen for statistical analyses was defined as follows:

- For patients with audiometrically documented hearing loss either in the left or right ear, the selected ear is the ear with hearing loss.
- For patients with audiometrically documented hearing loss in both ears and documented tinnitus/aural fullness in either the left or right ear, the selected ear is the ear affected by tinnitus/aural fullness.
- For patients with audiometrically documented hearing loss in both ears and documented tinnitus/aural fullness in both ears, the selected ear will be chosen randomly.

This strategy avoids bias-away-from-null which would be the case if the 'most affected' ear had been defined, as in many MD trials.

3.2 Quality of life (QoL): Dizziness and self-assessment questionnaires − Definition of Total Scores

3.2.1 VDADL score

To determine how well patients judged their functional compensation, they completed self-administered questionnaires designed for vestibular patients that included the vestibular disorders activities of daily living (VDADL) scale. The VDADL consists of 28 questions that assess subjects' comfort and ability to perform activities categorized as *functional (F), ambulatory (A),* and *instrumental (I)*, as well as a "total scale" that summarizes all three categories. In the original

definition of the VDADL, subjects score their responses to each question using integer numbers ranging from 1 ("`best`") to 10 ("`worst`").

According to Cohen & Kimball (2000) the parameter to summarize the three subscales and the total score is the median score. In this way, if the patient fails to answer a question, the VDADL score is not affected significantly by missing values. Unlike the mean, the median is not unduly influenced by extreme answers that do not agree with the remainder of the subject's assessment, and avoids the bias that would be introduced into a sum if a subject omits an answer or uses the non-applicable rating ("`NA`").

The *VDADL total score*, i.e. the median value of answers across all 28 questions, was used as secondary efficacy outcome.

3.2.2 DHI score

To assess the impact of impairment the patients were asked to fill out the 25-item DHI questionnaire. The original DHI total score (range: 0 to 100 points) consists of three subscales: *functional subscale (F), emotional subscale (E) and a physical subscale (P)*. The top score is 100 (maximum perceived disability), the bottom score is 0 (no perceived disability).

The subjective measure of the patient's perception of handicap due to the dizziness can be categorized as follows (Jacobson & Newman, 1990):

- 16−34 points (mild handicap)
- 36−52 points (moderate handicap)
- 54+ points (severe handicap)

For reach of the 25 items, a "`yes/always`" response is scored 4 points, a "`sometimes`" response 2 points, and a "`no`" response 0 points.

To deal with missing items, we used the derived *DHI mean total score* (DHI $\text{Total}_{\text{mean}}$) as outcome variable averaging for the number of answered questions:

$$\text{DHI Total}_{\text{mean}} = \left(1/\sum_i item_i \neq NA\right) \sum_{i=1}^{25} item_i$$

where *NA* denotes a missing answer. In R code this means: `mean(., na.rm = T)`.

3.2.3 MiniTF12 score

The full tinnitus questionnaire (TF) of Goebel and Hiller (1994) measures the impairment due to tinnitus with six partially correlating factors and is a standardized instrument for grading the severity of tinnitus.

Instead of using the full TF global score (in which 40 of the 52 items are needed for computation of the total score), the *MiniTF12 score* according to Hiller & Goebel (2004) as an abridged and more compact measure was analyzed to assess tinnitus-related psychological distress. The following selected 12 items reflect most central and characteristic aspects and are used to calculate the MiniTF12 score:

- [5] I am aware of the noises from the moment I get up to the moment I sleep.
- [16] Because of the noises I worry that there is something seriously wrong with my body.
- [17] If the noises continue my life will not be worth living.
- [24] I am more irritable with my family and friends because of the noises.
- [28] I worry that the noises might damage my physical health.
- [34] I find it harder to relax because of the noises.
- [35] My noises are often so bad that I cannot ignore them.
- [36] It takes me longer to get sleep because of the noises.
- [39] I am more liable to feel low because of the noises.
- [43] I often think about whether the noises will ever go away.
- [47] I am a victim of my noises.
- [48] The noises have affected my concentration.

Each item can be answered as either "`true`" (= 2 points), "`partly true`" (= 1 point) or "`not true`" (= 0 points). The crude MiniTF12 score is the sum of all points, ranging from 0 to 24.

As described in section 3.2.2, we used the derived *MiniTF mean score* ($\text{MiniTF}_{\text{mean}}$) as an outcome variable, averaging for the number of answered questions defined above (item number #5, 16, 17, 24, 28, 34, 35, 36, 39, 43, 47, 48) and ignoring the missing values

$$\text{MiniTF}_{\text{mean}} = \left(1/\sum_i item_i \neq NA\right) \sum_{i \in \{5,16,17,24,28,34,35,36,39,43,47,48\}} item_i$$

where *NA* denotes a missing answer. In `R` code this means: `mean(., na.rm = T)`.

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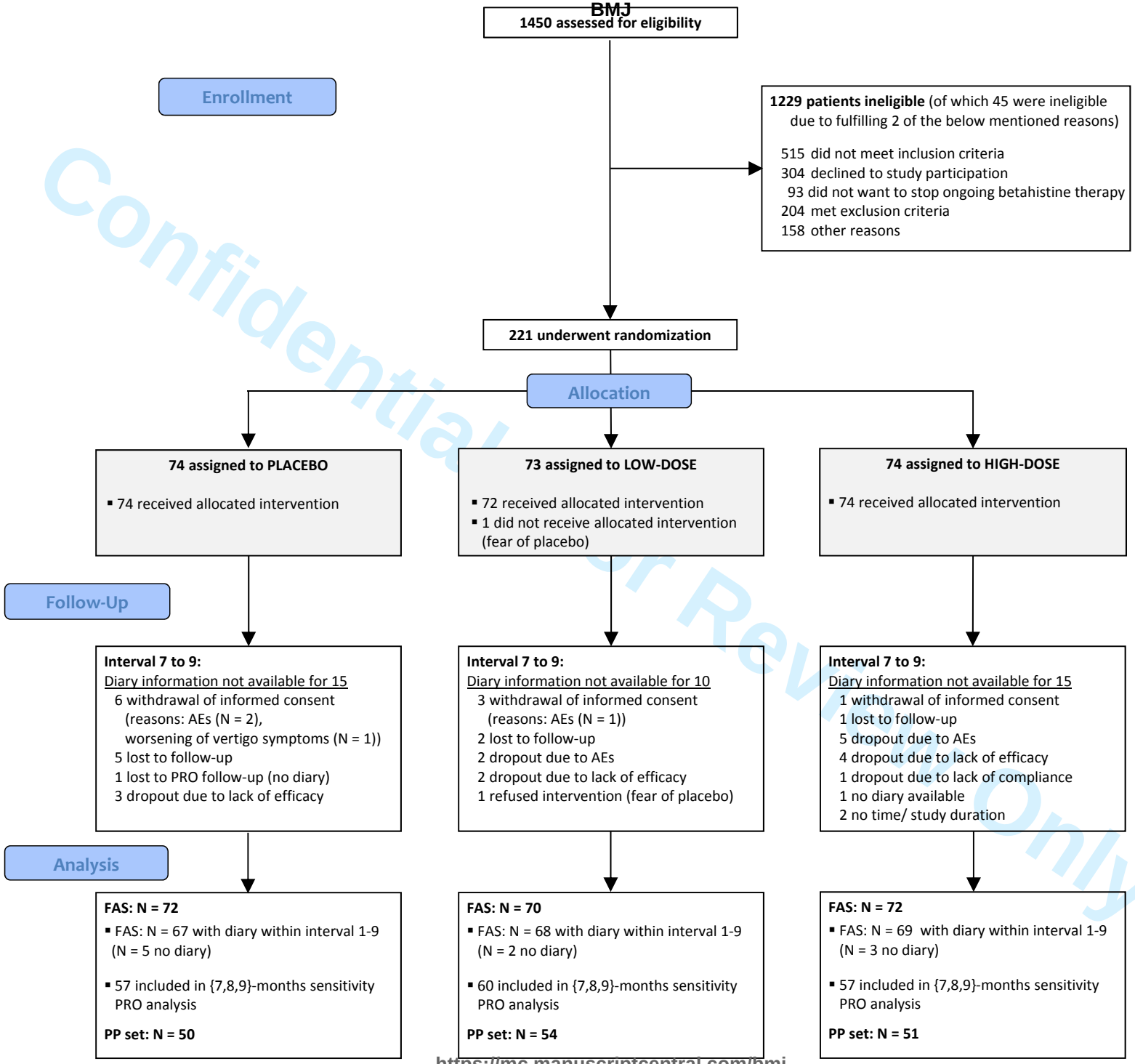

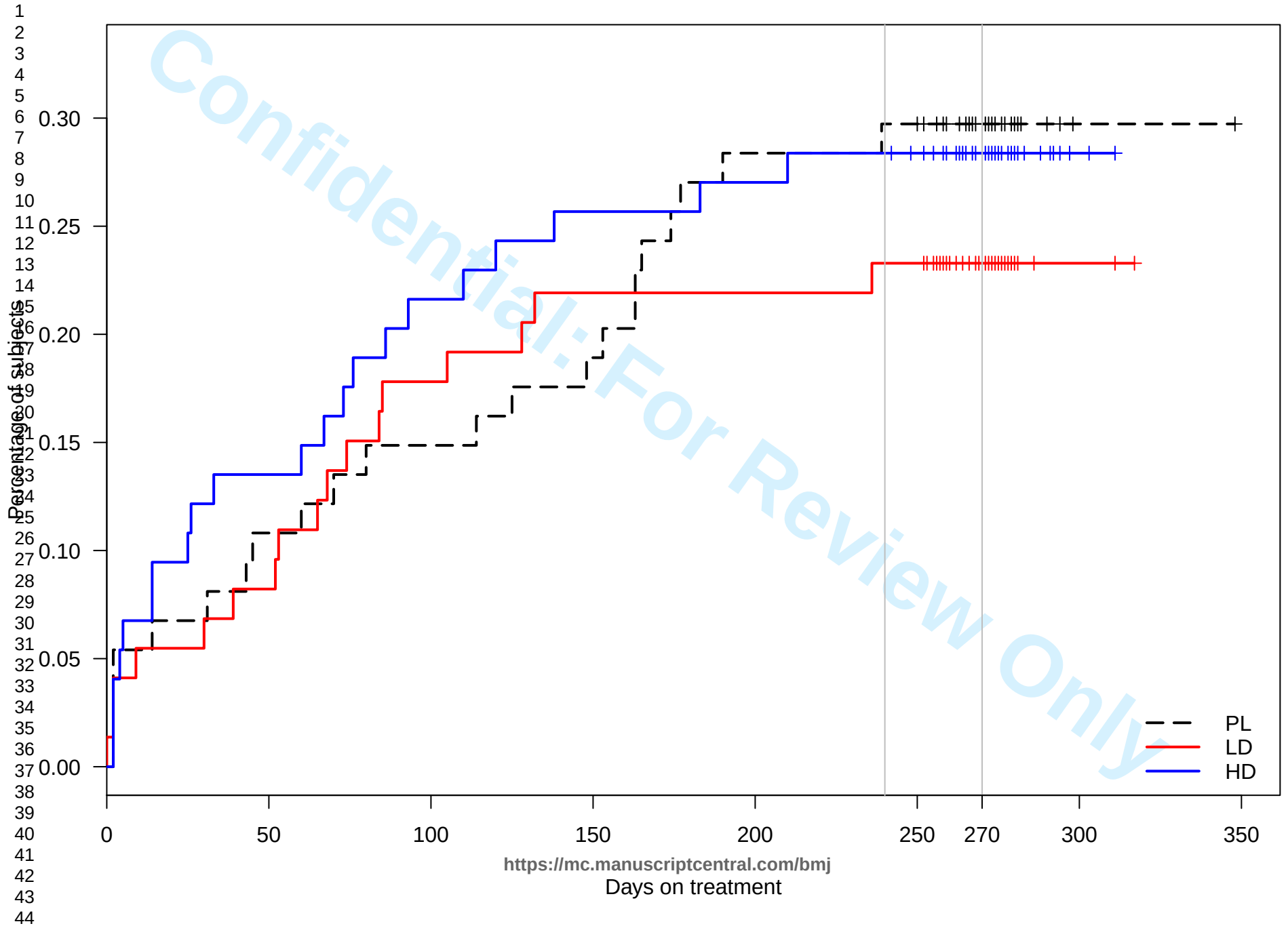

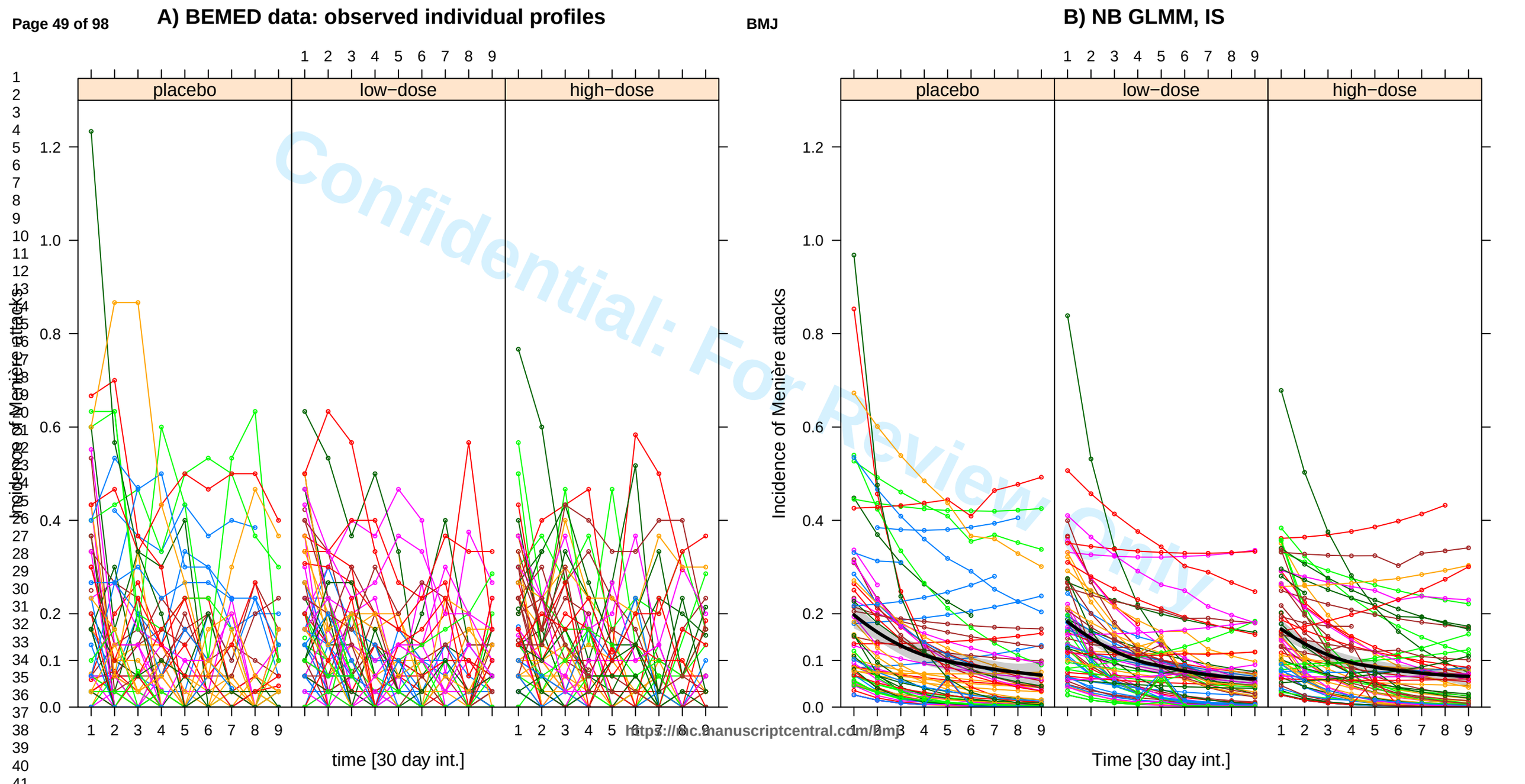

VERTIGO DIARY

PATIENT-IDENTIFICATION-NUMBER: _____ MONTH: _____ YEAR: _____

Date		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Attack 1	Time																															
	Type																															
	Duration																															
	Severity																															
	Change in tinnitus																															
	Aural Fullness																															
	Change in hearing																															
	Additional Symptoms																															
Attack 2	Time																															
	Type																															
	Duration																															
	Severity																															
	Change in tinnitus																															
	Aural Fullness																															
	Change in hearing																															
	Additional Symptoms																															
Attack 3	Time																															
	Type																															
	Duration																															
	Severity																															
	Change in tinnitus																															
	Aural Fullness																															
	Change in hearing																															
	Additional Symptoms																															

BEMED trial

Time:	**Type:**	**Duration:**	**Severity:**	**Tinnitus:**	**Aural fullness:**	**Change in hearing:**
Enter time of onset of attack	P: postural R: rotatory G: gait unsteadiness L: lightheadedness	(1) <30 Min (2) 30 – 60 Min (3) 60 – 120 Min (4) >120 Min	(1) mild (2) moderate (3) mod-severe (4) severe	Enter R or L for presence of tinnitus in right or left ear during attack	Enter R or L for presence of aural fullness in right or left ear during attack	Enter R or L for change of hearing in right or left ear during attack

Klinikum der Universität München

Neurologische Klinik und Poliklinik – Großhadern
Direktor: Prof. Dr. med. Dr. h. c. Thomas Brandt FRCP

In Assoziation mit dem
Institut für Klinische Neuroimmunologie
und dem
Friedrich-Baur-Institut

Ludwig Maximilians Universität München

CLINICAL TRIAL PROTOCOL

1. General Information

Study name:

Medical treatment of Menière's disease with betahistine: a placebo-controlled, dose-finding study

EudraCT-Nr.: 2005-000752-32
Prüfplan-Code: 04T-617
Version and date: **Ver. 6, Oktober 07, 2011**

Coordinating Investigator / Sponsor:
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SUMMARY

APPLICANT/ COORDINATING INVESTIGATOR	*Prof. Dr. Michael Strupp* *Date of birth: September 26th, 1961* *Nationality: German* *Consultant of the Dept of Neurology, University of Munich, Klinikum Grosshadern,* *Marchioninistr. 15, 81377 Munich* *Tel: 004989 70953678;* *Fax: 004989 70956673* *Michael.Strupp@med.uni-muenchen.de* *private address and telephone: Sonnenblumenstrasse 42, D-81377 Munich* *Tel: ++49(0)89 7144181*
TITLE OF STUDY	*Medical treatment of Menière's disease with betahistine: a placebo-controlled, dose-finding study*
CONDITION	*Ménière's disease.*
OBJECTIVE(S)	*Medical treatment of Menière's disease with betahistine-dihydrochloride in a placebo-controlled, dose-finding study.* *There is a plethora of treatment strategies for Menière's disease, including endolymphatic sac decompression, restriction of salt and fluid intake, diuretics, intratympanic injections of gentamycin, administration of corticosteroids, and medical treatment with betahistine-dihydrochloride. There are, however, no state-of-the-art treatment studies in this field. The aim of this trial is to evaluate the effects of betahistine-dihydrochloride in a dosage of 24 mg, 2 x day vs. 48 mg, 3 x day vs. placebo on the occurrence of vertigo attacks. Secondary objectives are to assess the median duration and severity of attacks as well as vestibular and audiological functions. The clinical aims of this study are to stop vertigo, reduce or abolish tinnitus, and preserve or even reverse hearing loss.*
INTERVENTION (S)	*Multicenter, national, randomized, double-blind, Placebo-controlled, three-arm parallel-group dose-finding study* *Experimental intervention: betahistine dihydrochloride 24 mg, 2 x per day and betahistine dihydrochloride 48 mg, 3 x per day* *Control intervention: placebo* *Duration of intervention per patient: 9 months, further 3 months follow-up* *Experimental and/or control off label or on label in Germany: the trial drug is licensed for treatment of Ménières's disease in Germany, but not the high dosage regimen that will be evaluated (3x48mg)*
KEY INCLUSION AND EXCLUSION CRITERIA	*Key inclusion criteria: definite Ménière's disease according to the American Academy of Ophthalmology and Otolaryngology, Head and Neck Surgery (1): Two or more attacks of vertigo, each lasting more than 20 minutes; audiometrically documented hearing loss in at least one examination;* *tinnitus or aural fullness in the affected ear; other causes excluded. Further: at least two attacks of Ménière's disease per month for at least 3 subsequent months. Age: 18 to 80 yrs; written informed consent to all protocol-specified procedures.* *Key exclusion criteria: other vestibular disorders such as vestibular migraine or phobic postural vertigo; contraindications for treatment with betahistine-dihydrochloride, such as asthma bronchiale, pheochromacytoma, pregnancy or breast-feeding, severe dysfunction of kidneys or liver, ulcer of the stomach or duodenum, tumors, severe coronary heart disease, treatment with other antihistamines.*

OUTCOME(S)	*Primary efficacy endpoint: number of attacks in the three treatment arms during the last 3 months of the treatment period.* *Secondary efficacy endpoints: Number of vertigo attacks during the last 3 months of the total follow-up period; median duration of vertigo attacks, median severity of vertigo attacks during the last 3 months of the treatment period and the last 3 months of the total follow-up period; change of peripheral vestibular function, tinnitus intensity, subjective hearing loss, objective hearing loss – determined by acoustic evoked potentials, change of handicap / impairment due to vertigo or tinnitus – assessed by the Dizziness Handicap Inventory (DHI), the Vestibular Disorders Activities of Daily Living (VADL) and the Minor TBF12 score – between baseline, 9-month and 12-month follow-up visit.* *Assessment of safety: occurrence of flush, novel/severe vertigo or dizziness, tachycardia, bronchial spasm, edema of the upper respiratoy tract or the mucosa (Quincke's edema), severe persisting headache, hypotonia (systolic blood pressure < 100 mmHg), increase of alanine aminotransferase level (> two times the upper limit of the normal range of higher) at any time of the entire study period.*
STUDY TYPE	*Multicenter, national, randomised, double-blind, placebo-controlled, double-blind, three arm parallel-group, dose-finding study*
STATISTICAL ANALYSIS	*Efficacy: Primary efficacy endpoint is the number of vertigo attacks in the three treatment arms during the last 3 months of the 9-month treatment period.* *Description of the primary efficacy analysis: The statistical analysis fo this three armed study uses the closed testing principle to avoid the adjustment of the significance level because of multiple testing: in a first step a Kruskall-Wallis test will be used to reject the global Null-Hypothesis that all three arms show an equal response on treatment. If the global Null-Hypothesis is rejected on the significance level alpha = 5%, it is possible to perform three pair wise comparisons between the three study arms again on the significance level of alpha = 5%.*
SAMPLE SIZE	*To be assessed for eligibility (n = **440** patients)* *To be allocated to trial (n = **220** patients)* *To be analysed (n = 138 patients)*
TRIAL DURATION	*First patient in to last patient out: 5 years* *Duration of the entire trial: 6 years*
PARTICIPATING CENTERS DURATION	*Department of Neurology, University of Munich* *Department of Neurology, Schlosspark-Klinik, Berlin* *Department of Neurology, Park-Klinik Weißensee, Berlin* *Department of Neurology, University of Essen* *Department of Neurology, Kreisklinik Altötting* *ENT Department, Technical University of Munich* *ENT Department, University of Munich* *ENT Department, University of Aachen* ~~*ENT Department, Charite, University of Berlin*~~ ~~*ENT Department, University of Erlangen*~~ *ENT Department, University of Tübingen* *ENT Department, MHH Hannover* *ENT Department, University of Regensburg* *ENT Department, University of Mannheim* *ENT Department, University of Münster* *ENT Department, University of Cologne* *ENT Department, University of Jena*

STUDY FLOWCHART:

	Day 1 / randomisation	1st month: study visit	2nd month: Telephone-interview	3rd month: Telephone-interview	4th month: study visit	5th month: Telephone-interview	6th month: study visit	7th month: Telephone-interview	8th month: Telephone-interview	9th month: study visit
Informed consent signed	*									
Medical history	*									
Vertigo / dizziness diary		*	*	*	*	*	*	*	*	*
Physical / neurological examination	*	*			*		*			*
Dizziness/Tinnitus Self-assessment- scales	*	*			*		*			*
Blood sample	*	*			*		*			*
Electronystagmography	*						*			*
Neuro-orthoptic examination	*						*			*
Audiometry	*						*			*
Acoustic evoked potentials	*						*			*
Randomisation	*									
Delivery of trial medication	*									
Treatment compliance		*	*	*	*	*	*	*	*	*
Concomitant / additional medication	*	*	*	*	*	*	*	*	*	*
Assessment of adverse events / serious adverse events		*	*	*	*	*	*	*	*	*

LIST OF ABBREVIATIONS

AE	Adverse Event
BMBF	(Bundesministerium für Forschung und Bildung) Federal Ministry of Education and Research
CRF	Case Report File
CRO	Contract Research Organization
DAC	German Pharmaceutical Code (Deutscher Arzneimittel-Codex)
DHI	Dizziness Handicap Inventory
DSMB	Data Safety Monitorin Board
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IBE	Institute for Biometrics and Epidemiology
IEC	Independent Ethics Committee
IMP	Interventional Medicinal Product
L	liter
LKP	"Leiter der klinischen Studie" according to the German drug law; in this study: principal investigator
mmHg	Millimeters mercury
Mol	Moles
MRI	Magnetic Resonance Imaging
SAE	Serious Adverse Event
SOP	Standard Operation Procedure
SUSAR	Suspected Unexpected Serious Adverse drug Reaction
VADL	Vestibular Disorder Activities of Daily Living Score
VAS	Visual Analogue Scale

2. *Background Information, Introduction and Rationale*

2.1. Epidemiology, Clinical Features and Pathophysiology of Ménière's Disease

Ménière's disease is a disorder of the inner ear membranous labyrinth characterized by paroxysmal vertiginous attacks, fluctuating sensorineural hearing loss, aural fullness, and tinnitus (for review see Minor et al. (2)). With an incidence of 7.4% it ranks 6th in frequency of all disorders diagnosed at our specialized vertigo unit (3). The incidence of Ménière's disease in a general population has been estimated as 157 per 100000 persons in the United Kingdom (4) with a slight female preponderance (1.3:1). The peak age of onset is during the fifth and sixth decade (5).

The defining symptoms of Ménière's disease according to the American Academy of Otolaryngology – Head and Neck Surgery consist of two or more spontaneous episodes of rotational vertigo each lasting 20 minutes or longer, hearing loss documented by audiograms on at least one occasion and tinnitus or aural fullness in the affected ear (1). Especially in the early phase of the disease, however, patients may display only a subset of these symptoms, vertigo being the most common one (96.2% according to Paparella et al. (5)), followed by tinnitus (91,1%) and ipsilateral hearing loss (87,7%). The latter typically affects low frequencies but becomes more generalized as the disease progresses. In about one third of patients, the attack is preceded by an "aura" of aural fullness, worsening tinnitus or hypacusis (2). In the remainder, the attacks occur spontaneously, at times in unrelenting clusters. Although spontaneous remissions are observed, most patients develop one or more persistent deficits, i.e. hypacusis, tinnitus or vestibular imbalance. Patients suffering from Ménière's disease have been shown to suffer serious impairments in quality of life and to have an above-average risk of developing depression and anxiety disorders (6, 7).

The underlying pathophysiology of Ménière's disease is commonly seen in a hydrops of the endolymphatic space of the membranous labyrinth, resulting in recurrent ruptures of the endolymphatic sac and spillage of potassium-rich fluid into the perilymphatic space (8-11). This change of the ionic environment leads to depolarization of the vestibular nerve, thereby causing attacks of severe vertigo. The chronic deterioration of inner ear function with progressive hypacusis and tinnitus is thought to be caused by repeated exposure of the eighth nerve to high-concentration potassium (12). A variety of possible causative factors have been associated with the evolution of Ménière's disease. Among these are hypoplasia of the endolymphatic sac (13, 14), inflammation of the endolymphatic sac (15, 16), autoantibodies (17, 18), viral infection (10, 19) and vascular pathology (20).

2.2. Current therapeutic strategies

Therapy of Ménière's disease should aim at stopping vertigo, reducing or abolishing tinnitus, and preventing or even reversing hearing loss. Traditionally, medical treatments for Ménière's disease aim at decreasing production and increasing absorption of endolymph. Approaches used for this purpose include salt-restriction and diuretic agents (eg hydrochlorothiazide). However, although several studies report relief of vestibular symptoms in many patients undergoing diuretic therapy (21-23), few data exist to support an effect on auditory acuity or tinnitus.

In the light of a possible inflammatory aetiology of Ménière's disease, antiinflammatory agents such as corticosteroids have been used. However, few data from clinical trials exist and a recent double-blind placebo-controlled study did not show any superior effect of intratympanically injected dexamethasone over placebo (24).

Effective control of vertigo can be expected by destruction of vestibular hair cells via intratympanic injection of gentamicin (2, 25). Although low-dose regimens have been shown to reduce the frequency of hearing loss, this invasive therapeutic approach should be considered as a last resort. The same pertains to destructive operative approaches such as vestibular neurectomy or labyrinthectomy (26).

More recently, betahistine has come to be used as an alternative medical treatment in Ménière's disease. Clinical studies have demonstrated its beneficial effects on the vestibular and to a lesser degree on the audiological symptoms. To our knowledge, all these trials feature low to moderate doses of betahistine. With clinical evidence pointing towards a role of high-dosage regimens in the treatment of Ménière's disease, we aim at conducting a prospective randomized double-blind placebo-controlled dose-finding clinical trial.

2.3. Betahistine: Pharmacological and Toxicological Properties

Betahistine belongs to the group of β-2-Pyridylalkylamines and is structurally related to the endogenous amine histamine. In the course of animal studies, the response to betahistine following intravenous administration and its action on a variety of isolated and intact tissues resembled some of the responses to histamine. Intravenous administration produced a transient rise in blood flow through the labyrinthine artery in dogs, preceded by a fall in pulse pressure reflecting a systemic response. It is assumed that betahistine could act by decreasing endolymphatic pressure as a result of increased vascularization. Additional modes of action that have been proposed include modification of the neuronal activity of the vestibular nuclei and the labyrinthine ampullar hair cells (27-31).

The lethal dose of betahistine hydrochloride for the albino rat is 30-40 mg/kg by the oral route. By the intravenous route, the lethal dose for the rabbit is 5.1 mg/kg. The main signs of toxicity observed are ataxia, salivation, inactivity, hyperpnea, tremors, cyanosis and acute gastroenteritis. A two-litter reproductive study with rats revealed no adverse effects. Chronic toxicity studies in dogs given doses up to 25 mg/kg/day for eighteen months revealed no significant abnormalities in the parameters measured. So far no data concerning reproduction toxicity and mutagenic potential in humans are available. Increased embroyfetal losses were observed in rabbits. Therefore, the Fachinformation (June 2005) recommends the special measure for women with childbearing potential.

2.4. Betahistine: Risks and Benefits Established in Clinical Studies

Most placebo-controlled clinical studies investigating the effect of betahistine in Ménière's disease have established a significant reduction of vertiginous symptoms in the verum group (32-36) (for review see James and Burton(37)). No significant alleviation of vertigo was seen in the study conducted by Okamato et al (38). The study by Ricci et al. (39) revealed a beneficial effect of betahistine, which however did not reach significance. Concerning tinnitus, the currently available studies generated equivocal results. Elia et al.(33) and Salami et al.(32) found significant improvement of tinnitus in the betahistine group, whereas Okamato et al.(38), Ricci et al.(39) and Schmidt et al.(35) did not. None of the studies revealed a significant beneficial effect of betahistine on hearing loss.
The dosage of betahistine in these trials varied between 16 and 72mg per day. This may partially account for the differences in symptom relief observed by the various investigators.
Betahistine was first registered in Europe in 1970 for the treatment of Ménière's disease. Since then it has been used as a therapeutic in more than 100 million patients. The side effects of betahistine according to the package leaflet include gastrointestinal symptoms such as nausea, vomiting, pyrosis, flatulence and diarrhoea, as well as palpitations, drowsiness, exanthema and rarely tightness of chest. However, none of the above mentioned studies revealed significant differences in side effects between betahistine and placebo. Furthermore, a recent clinical study on betahistine as a prophylactic agent of antipsychotic drug-weight gain used bethahistine in the same dosage as proposed for this study (48 mg t.i.d.). According to the authors, the drug was safe and well tolerated (40). These results from clinical trials conform with the high doses needed to produce toxic and lethal effects in animal experiments as outlined above.

2.5. Betahistine: Description and Justification of this Trial Design

The proposed trial is a prospective, randomized, placebo-controlled, double-blind, dose-finding clinical study of the efficacy of betahistine in reducing the frequency of vertigo attacks in Ménière's disease. It will be conducted over a treatment period of nine months and a subsequent follow-up period of three months. This trial period seems necessary and adequate to judge the efficacy of betahistine on attack frequency.
Betahistine will be administered in oral form, tablets being the common form of application in an ambulant setting.
Two dosage regimens of betahistine (2x24mg/day vs. 3x48mg/day) will be compared with placebo. In our clinical experience, many patients do not profit from betahistine administered at conventional doses of 18 to 48mg per day, but do so from higher doses. Concordantly, clinical studies of low- and moderatly-dosed betahistine in Ménière's disease have brought forth controversial results, especially concerning the audiological symptoms. To our knowledge, there is no study investigating the efficacy of betahistine given in doses higher than 3x24mg/day (the latter dosage used in the trial by Schmidt et al.(35)). As the current scientific data suggest a very low rate of adverse events secondary to betahistine, increasing the daily intake to 3x48mg/day should not compromise the safety of the study participants.
The majority of patients suffering from Ménière's disease are middle-aged and acutely threatened in their capacity to work and to run a motorized vehicle due to the paroxysmal character of this disorder. Therefore, it is of utmost importance to provide them with a safe and efficient therapeutic. Betahistine seems to be a promising agent. Not only has it been shown to exceed the potential of other drugs regarding alleviation of symptoms in Ménière's disease (41-43), review of literature and clinical experience have also shown it to be very safe. The proposed trial aims at generating further information as to the efficacy and safety of high-dosage betahistine compared to the currently employed regimen.

2.6. Statement

The study will be conducted in accordance with the current version of the "Arzneimittelgesetz" (AMG) and the standards of Good Clinical Practice (GCP). It is in keeping with the declaration of Helsinki with its modifications of Tokio (1975), Hong Kong (1989) and Sommerset West (1996). The trial has been approved by the "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM).

2.7. Population to be studied

The population to be studied includes patients in the age range of 18 to 80 years diagnosed with Ménière's disease according to the criteria of the American Academy of Otolaryngolgoy - Head and Neck Surgery: two or more attacks of vertigo, each lasting more than 20 minutes; audiometrically documented hearing loss in at least one examination; tinnitus or aural fullness in the affected ear and exclusion of other causes. These criteria are widely accepted as providing high diagnostic accuracy (37). Excluded are patients who suffer from other central or peripheral vestibular disorders such as vestibular migraine as these may confound the rate and severity of vertiginous symptoms. Furthermore not eligible are patients suffering from known contraindications for treatment with betahistine such as pheochromocytoma, severe renal or hepatic dysfunction, asthma or pregnancy. The participants will be recruited from our vertigo outpatient service at the Department of Neurology, Klinikum Großhadern, Munich as well as the Department of ENT, Klinikum Grosshadern, Munich, the Department of Neurology of the Schlosspark-Klinik Berlin and the ENT Departments of the Technical University of Munich, the University of Munich, the University of Aachen, the Charite (University of Berlin), the University of Tübingen and the University of Erlangen.

3. Trial Objectives and Purpose

3.1. PRIMARY OBJECTIVE

The aim of this trial is to evaluate the effect of betahistine-dihydrochloride in a dosage of 48mg three times per day (high-dose betahistine-dihydrocholoride) compared to a standard dosage of 24mg two times per day and to placebo on the frequency of attacks during the last three months of nine months continuous administration. It shall be analysed whether there is a positive effect of betahistine-dihydrochloride on meniere's disease at all and the appropriate dosage shall be determined.

3.2. SECONDARY OBJECTIVES

To evaluate the tolerance and side effects of the novel high dosage of betahistine-dihydrochloride, the effect of different dosages on severity of vertigo attacks, vestibular and audiological function or deficits like hearing loss and tinnitus as well as on the handicap in daily living activities due to vertigo.

4. Trial Design

4.1. ENDPOINTS

4.1.1. Primary endpoint

Primary efficacy endpoint is the number of vertigo attacks in the three treatment arms during the last three months of the nine months treatment period.

4.1.2. Secondary endpoints

Secondary efficacy endpoints:

- Number of vertigo attacks during the 3 month follow-up period
- Median duration of vertigo attacks during the last 3 months of the treatment period and the 3 month follow-up period
- Median severity of vertigo attacks during the last 3 months of the treatment period and the 3 month follow-up period
- Change of peripheral vestibular function between baseline, 9 months visit and 12-mont follow-up visit
- Audiometrically assessed hearing loss and tinnitus intensity between baseline, 9 months visit and 12-mont follow-up visit
- Objective hearing loss – determined by acoustic evoked potentials - between baseline, 9 months visit and 12-mont follow-up visit
- Change of handicap / impairment due to vertigo or tinnitus between baseline, 9 months visit and 12-mont follow-up visit, assessed by the Dizziness Handicap Inventory (DHI), the Vestibular Disorders Activities of Daily Living (VADL), and the Minor TBF 12 score (Appendix)

4.1.3. Safety endpoints:

Occurrence of

- flush
- novel/severe vertigo or dizziness
- tachycardia
- severe persisting headache
- hypotonia (systolic blood pressure < 100mmHg)
- increase of alalnine aminotransferase level > two times the upper limit of the normal range or higher
- bronchospasm
- Quincke's edema (edema of the upper respiratory tract or the mucosa)

at any time of the entire study period.

4.2. DESIGN OF THE TRIAL

The study is designed as a multicenter, national, randomized, double-blind, placebo-controlled, three-arm parallel-group trial in patients suffering from Meniere's disease. To evaluate the effect of a high-dosage betahistine-dihydrochloride treatment of 144 mg per day with a standard dosage of 48mg betahistine-dihydrochloride per day and placebo a total of **220 patients** will be enrolled in **15 centres** in Germany. Adult female and male patients presenting, both as in- or outpatients, at one of the involved centres with the definite diagnosis of Meniere's disease – according to the Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Meniere's disease (1) – will be screened for eligibility. Informed consent will be obtained by one of the investigators or their authorized representatives as defined by German laws before any protocol-specific procedures are performed. Eligible patients will be randomly assigned to one of the three treatment groups (in a 1:1:1 ratio) to receive either betahistine-dihydrochloride in the above given dosage groups, or an identically appearing placebo. Trial medication shall be taken according to the same scheme (two capsules at a time, three times daily) over a period of nine month. No hospitalisation is required for the conduction of the study, but treatment can in exceptional cases also be administered to inpatients of the involved medical centres.

4.3. METHODS AGAINST BIAS

4.3.1. Randomisation

Randomisation to three treatment arms in the ratio of 1:1:1 will be performed by the IBE of the University of Munich. According to a pre-specified randomisation list the study kits - consisting of identically appearing boxes containing equal amounts of either placebo, standard-dose or high-dose betahistine-dihydrochloride in randomised sequence - will be signed out with continuous identification numbers, and a sealed envelope containing the respective treatment group for unblinding in case of emergency will be attached. Each study center receives a pool of study kits, the identification numbers fo the kits stored at each center will be registered at the IBE. The IBE will provide an internet-based randomization tool, which chooses one of the study kits stored at the respective center when a new patient fulfills the inclusion criteria and has signed the informed consent. In this way an immediate registration of each new subject is guaranteed. The coordinating investigator can thus provide an unblinding of the treatment group for a single patient at any time. Furthermore the amount of study kits stored at the centers can be checked continuously, and redistribution can be arranged if centers enroll different numbers of patients.

4.3.2. Blinding

This study is designed as a double-blind trial. Randomisation will be performed by the IBE and neither the investigators nor the patients will be informed to which treatment arm a patient is allocated and neither can get access to the randomisation list. Unblinding happens regularly when the study databse is closed. In cases of a medical emergency with the need to unblind the trial drug, the emergency envelope – stored at the repective study center by the principal investigator – can be opened or the IBE of the University of Munich as well as the coordinating investigator can unblind a single case by the next working day. Emergency envelopes will be sent back to the coordinating investigator and checked for integrity when the respective patient has completed follow-up.

Whenever a patient does not receive any study treatment after randomisation, he will be regarded as drop-out. He will not be part of the collective analyzed for safety. Neither will an event which would normally be dose-limiting be used to decide over termination of the trial. If a patient drops out before receipt of the study kit he will be replaced by the next eligible patient enrolled in the same centre. In this case, a treatment arm will not be complete until a substitute patient enters the trial at the appropriate centre.

4.4. DOSE-LIMITING EVENTS

Any of the following events are considered dose-limiting, if SAE is highly probably related to drug treatment:

- death
- a life-threatening adverse event
- inpatient hospitalisation or prolongation of existing hospitalisation
- persistent or significant disability / incapacity

The reported SAEs will be reviewed by the DSMB and the LKP (“Leiter der klinischen Prüfung” according to the German drug law) and judged for causality.
If any dose-limiting event occurs during the treatment or the follow-up period of a patient, treatment will be unblinded for this patient. If treatment is placebo, the study continues as normal. If treatment is high-dose betahistine-dihydrochloride, the trial will stop and the low-dose treatment will be defined as the maximum tolerable dose.

4.5. TRIAL TREATMENTS

4.5.1. Investigational Products

Betahistine-dihydrochloride is a drug that has been marketed and used primarily for the treatment of Meniere’s disease since many years in Europe as well as in USA and other countries. It is manufactured by Solvay Arzneimittel GmbH, D-30002 Hannover (Vasomotal®) according to all regulations and standards. Betahistin will be encapsulated using mannitol and aerosile as filling material. The modification will be performed by the Pharmacy of the University Hospital Heidelberg (Im Neuenheimer Feld 670, D-69120 Heidelberg). Betahsitine-dihydrochloride is refilled from original pharmacy packaging to vials under sterile conditions and relabelled by the Pharmacy of the university hospital of the University of Heidelberg.

Placebo will be an identically appearing capsule filled with manitole and aerosil according to DAC. It will be manufactured by the pharmacy of the University of Heidelberg, Im Neuenheimer Feld 670, 69120 Heidelberg. Placebo will also be refilled to vials.

The bottles will be labelled as follows:

- Name of the drug (it will be mentioned that the bottle contains either placebo or verum), pharmaceutical formula, amount: “Vasomotal® bzw. Placebo Tabletten 180 bzw. 90 Stück”
- Patient-identification-No.
- Bottle-No.
- Purpose of use:
- Code of the trial protocol
- Ingredients
- Date of expiry
- Batch-No
- Instructions for storage

Label for drug bottles:

Sponsor: Prof. Dr. Strupp, Neurologische Klinik, Klinikum der Universität München
Hersteller: Apotheke der Universität Heidelberg, Im Neuenheimer Feld 670, 69120 Heidelberg
Vasomotal® 24mg bzw. Plazebo Kapseln 180 (bzw. 90) Stück
Dose:_____(von 2) - Patienten-Nr.:_____
Zur klinischen Prüfung bestimmt, unzugänglich für Kinder aufbewahren!
Nach Anweisung des Arztes oral einnehmen.
Prüfplancode: O4T 617 EudraCT Nr.:2005-00251925
Inhaltsstoffe: 24mg Betahistindihydrochlorid und/oder Aerosil; Hilfsstoffe: Mikrokristalline Cellulose, D-Mannitol, Cirtronensäure Monohydrat, hochdisperses Siliciumdioxid, Talkum, Magnesiumstearat

Haltbar bis: nicht über 25°C lagern Ch.B.:VASO_____

4.5.2. Administration

Both betahistine-dihydrochloride and placebo are appointed to oral administration and no further preparation is required. Trial medication can be stored at room ambient temperature and is durable for the whole duration of the trial.
The drug should be administered in 3 dosages per day, each consisting of two capsules (2-2-2). To achieve compliance concerning the intended ratio of verum and placebo in the low-dose betahistine-dihydrochloride treatment arm, all patients are instructed to take one capsule out of the vials No. 1 and 2 (3 and 4, 5 and 6) in the morning and evening and two capsules out of vial 2 (4,6) at mid-day. Whereas in the placebo (A) and the high-dose betahistine-dihydrochloride (C) treatment arm all vials contain either placebo or verum, in the low-dose (B) arm only every other vial (3) contains verum, the other vial (4) placebo.

The first study drug intake should take place as soon as possible after receipt under supervision of an investigator. Each kit will contain the total amount of capsules for the entire treatment period. If patients temporarily discontinue study medication, they should resume taking it as soon as possible.

4.5.3. Concomitant medications

In case of simultaneous administration of betahistin-dihydrochloride and other antihistminergic drugs a mutual attenuation of the effect has to reckoned with.
Otherwise there is no known limitation for concomitant medication. There is no contraindication for the use of any other medication during the treatment period.

4.5.4. Contraindications

Several patients with a history of peptic ulcer have experienced an exacerbation of symptoms while using betahistine-dihydrochloride. Although no causal relation has been established betahistine-dihydrochloride is contraindicated in the presence of peptic ulcer and in patients with a history of this condition. Betahistine-dihydrochloride is also contraindicated in patients with pheochromocytoma.

4.6. Duration of subject participation and trial duration

Duration of the treatment period will be nine months. The subsequent follow-up period will last three months.

4.7. Based on our experience concerning the frequency of Meniere's disease in our dizziness outpatient unit and in the other participating centres we expect to enrol 84 patients within two years. As total follow-up is 12 months a total duration of the clinical phase of this study is expected to be three years. Discontinuation criteria for individual patients and / or parts of the trial

Discontinuation of study agent
Study medication should be discontinued if any of the following occur:

- severe headache
- flush
- novel/ severe vertigo or dizziness
- tachycardia
- hypotension (systolic blood pressure < 100mmHg)
- increase of alanine aminotransferase level > two times the upper limit of the normal range or higher
- bronchial spasm
- oedema of the upper respiratory tract or the mucosa (Quincke's oedema)

5. Selection and Withdrawal of Subjects

5.1. NUMBER OF SUBJECTS

220 subjects will be treated in **15 German centers**. This number was calculated on the basis of experience with the efficacy of betahistine-dihydrochloride obtained in our own open trial (see 9.2), on the basis of baseline data for the primary outcome measured for study patients allocated to the BEMED trial (19 patients) **and on the basis of the current drop-out rate.**

5.2. SUBJECT INCLUSION CRITERIA

Patients may be enrolled only if they meet all of the following inclusion criteria:

- Diagnosis of definte Meniere's disease (1):
  - Two or more definitive spontaneous episodes of vertigo of 20 minutes duration or longer
  - Audiometrically documented hearing loss on at least one occasion
  - Tinnitus or aural fullness in the treated ear
  - Other causes excluded
- At least two attacks per months for at least three subsequent months
- Age 18 to 80 years
- Written informed consent, signed and dated by the patient (or patient's authorized representative) and by the person obtaining the consent, indicating agreement to comply with all protocol-specified procedures.
- Female patients of childbearing potential must havea negative pregnancy test within 7 days before intiation of therapy. Postmenopausal woman must be amenorrahic for atleats twelfe months

5.3. SUBJECT EXCLUSION CRITERIA

5.3.1. General

- Participation in another study with an investigational drug or device within the last 30 days, prior participation in the present study or planned participation in another trial
- Women known to be pregnant or lactating
- Woman of childbearing potential who are not willing to practice acceptable methods of birth control (during and for three months after therapy) to prevent pregnancy .

5.3.2. Concerning vertigo / dizziness

- Other vestibular disorder such as
  - vestibular migraine
  - phobic postural vertigo
  - benign paroxysmal positioning vertigo
  - paroxysmal brainstem attacks
- Contraindications for the 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

5.3.3. Safety related

- severe coronary heart disease or heart failure
- Persistent hypertension with systolic blood pressure > 180 mmHg or diastolic BP > 110 mmHg (mean of 3 consecutive arm cuff readings over 20-30 minutes) that cannot be controlled by antihypertensive therapy

5.3.4. Potentially interfering with outcome assessment

- life expectancy < 12 months
- other serious illness, eg. severe hepatic, cardiac or renal failure, acute myocardial infarction, neoplasm or a complex disease that may confound treatment assessment

5.3.5. Comedication

- treatment with other antihistaminic drugs

5.4. SUBJECT WITHDRAWAL CRITERIA

5.4.1. General

Subjects may be withdrawn from the trial for the following reasons: at their own request or at the request of their legally authorized representative; if, in the investigator's opinion, continuation in the clinical trial would be detrimental for the subject's well-being; at the specific request of the sponsor.

Follow-up data will be collected for all randomized patients except those who specifically withdraw consent for release of such information. All patients randomized into this trial will be included in analysis of safety and efficacy (principle intention to treat, i.e. every subject is analyzed in the group he was randomized to at the beginning of the trial). Thus, it is imperative to obtain complete follow-up data for all patients whether or not they receive study agent. All procedure requested for evaluation of follow-up should be carried out as per protocol whether or not a patient receives treatment according to the protocol or is transferred to another facility.

5.4.2. Deviations from the Protocol

The investigators will not deviate from the protocol without the prior written approval of the principle investigator except in medical emergencies. In medical emergencies, prior approval for protocol deviations will not be required, but the principal investigator and the DSMB must be notified as soon as possible. The name of the principal investigator and the chairman of the DSMB, with telephone number, is provided in the Study Reference Manual. All other protocol deviations require prior written approval from the principal investigator or designee. The principle investigator will not assume any resulting responsibility or liability.

The Ethics Committee will be informed of all protocol changes by the investigator in accordance with the Ethics Committee's established procedures. No deviations from the protocol of any type will be made without complying with all the Ethics Committee's established procedures.

6. Treatment of Subjects

6.1. General

Patients will be recruited by the centres' outpatient services and both, examinations and treatment will be performed in an ambulant setting. The choice of other ancillary care measures will be at the discretion of the treating general practitioner. Due to the strict inclusion criteria only patients without other severe diseases should be enrolled, but efforts should be taken to maintain subjects normothermic, normotensive and normoglycemic.

6.2. Pre-randomization procedures

Written informed consent will be obtained for this study by the principal investigator or his designee from each patient (or patient's authorized representative) prior to the performance of any protocol-specific procedure. The study will be conducted in accordance with the provisions of the Declaration of Helsinki, last amended in Somerset, South Africa (1996).

The following assessments and laboratory tests will be performed routinely with all patients of the centre's dizziness outpatient services with suspected Meniere's disease:

- Medical history and physical examination
- Electronystagmography with caloric irrigation
- Neuro-orthoptic examination
- Audiometry
- Acoustic evoked potentials

In case of definite diagnosis of Meniere's disease, conformance with all other inclusion criteria and if no exclusion criterion is fulfilled and written informed consent is signed, the following procedures will be performed:

- Assessment of the handicap concerning daily living activities due to vertigo attacks and tinnitus by means of three self-assessment scales (see Appendices)
- Routine blood-sample to exclude liver or kidney failure

All patients who meet inclusion criteria but are not enrolled in the trial must be entered on the Screening Log, indicating the reason(s) for exclusion.

6.3. Trial drug and placebo

6.3.1. Betahistine-dihydrochloride

Betahistine-dihydrochloride is a drug that is marketed and used primarily for the treatment of Meniere's disease since many years in Europe as well as in USA and other countries. It is manufactured by Solvay Arzneimittel GmbH, D-30002 Hannover (Vasomotal®) according to all regulations and standards. Betahsitine-dihydrochloride is encapuslated and refilled from original pharmacy packaging to vials under sterile conditions and relabelled by the Pharmacy of the university hospital of the University of Heidelberg.

6.3.2. Placebo

Placebo will be an identically appearing capsule filled with manitole and aerosil according to DAC. It will be manufactured by the pharmacy of the University of Heidelberg, Im Neuenheimer Feld 670, 69120 Heidelberg. Placebo will also be refilled to vials.

6.3.3. Storage

All investigational drug supplies in the study will be stored in a secure, safe place, under the responsibility of the Investigator or other authorized individuals.

6.4. Treatment arms / dosage and administration

The drug should be administered in 2 dosages per day, each consisting of two capsules (2-2-2). To achieve compliance concerning the intended ratio of verum and placebo in the low-dose betahistine-dihydrochloride treatment arm, all patients are instructed to take one capsule out of the vials No. 1 and 2 (3 and 4, 5 and 6 respectively) at a time. Whereas in the placebo (A) and the high-dose betahistine-dihydrochloride (C) treatment arm all vials contain either placebo or verum, in the low-dose (B) arm only every other vial (3) contains verum, the other vial (4) placebo. The resulting dose will thus be:

- 3*2 tbl. placebo in arm (A)
- 2*24 mg betahistine-dihydrochloride per day + 1*2 tbl. placebo + 2*1 tbl placebo in arm (B), and
- 3*48 mg betahistine-dihydrochloride per day in arm (C)

The first study drug intake should take place as soon as possible after receipt under supervision of an investigator. Each kit will contain the total amount of capsules for the entire treatment period. If patients temporarily discontinue study medication, they should resume taking it as soon as possible.

6.5. POST-RANDOMIZATION PROCEDURES AND ASSESSMENTS

- the study trial as well as the vertigo diary and a form for acquisition of and naming all known side effects will be handed out
- a standardised telephone interview (Appendix) will be conducted after the second, third, fifth, seventh and eighth month of treatment to remind subjects to protocol their complaints in the vertigo diary and to acquire the treatment's effect as well as side-effects.
- Study visits are performed after the 1st, 4th, 6th and 9th month of treatment, comprising the following examinations / procedures:
    - Acquisition of vertigo attacks and further complaints by means of the standardised vertigo diary
    - Physical / neurological examination, in all study visits
    - Dizziness- and Tinnitus-self-assessment scores will in all study visits
    - Blood samples (after 1st month, 4th month, 6th month, 9th month)
    - Electronystagmography after 9th month
    - Neuro-orthoptic examination after 9th month
    - Audiometry after 9th month
    - Acoustic evoked potentials after 9th month

6.6. FOLLOW-UP

Patients will be instructed to inform their physician about participation in the trial and will receive a medical report providing detailed information about the intervention. In case they develope any new symptom they should contact their general practitioner or the respective study centre's outpatient or emergency service, which will be available at any time and can provide all necessary ambulant or inpatient treatment.
Duration of the treatment period is 9 months and there will be a further follow-up after another 3 months. During the post-treatment follow-up patients should preferably receive no treatment for Meniere's disease. Thus, the long-term effect of the drug can be evaluated. In cases of further severe complaints, however, administration of betahistine-dihydrochloride in the standard dose (up to 48mg per day) can be considered.

6.6.1. 12 months follow-up visit

Three months after completion of treatment a follow-up visit will be arranged. The following measures will be assessed:

- Vertigo diary
- Physical / neurological examination
- Dizziness and tinnitus self-assessment scores
- Electronystagmography under caloric irrigation
- Neuro-orthoptic examination
- Audiometry
- Acoustic evoked potentials

Patients are considered enrolled in this trial until completion of the 3-months follow-up visit and are not to be entered into any other trial during this period.

6.7. PRIOR AND CONCOMITANT ILLNESSES

Prior and past illnesses should be documented for the last five years, especially vestibular or other neurological disorders.

6.8. PRIOR AND CONOMITAND TREATMENTS

All present medication should be noted in all study visits and telephone interviews, especially any antihistaminic or antacid medication. Furthermore patients will be instructed to record any treatment like antivertiginous agents in their vertigo diary.

6.9. COMPLIANCE

Patients are instructed to bring all study agent bottles the 9-month study vistit.. Capsules will be counted to assess compliance. A remainder exceeding 15% of the total amount of capsules a patient had to take during the treatment period will not be tolerated.

7. Assessment of Efficacy

7.1. PRIMARY ENDPOINT

Primary efficacy endpoint is the number of vertigo attacks in the three treatment arms during the last three months of the nine months treatment period. The frequency of attacks will be documented by the subjects by means of the standardized dizziness and vertigo diary (Appendix). Patients will be asked concerning the frequency of attacks at all telephone interviews and the diaries will be checked in all study visits.

7.2. SECONDARY ENDPOINTS

- Number of vertigo attacks during the 3 month follow-up period
- Median duration of vertigo attacks during the last 3 months of the treatment period and the 3 month follow-up period
- Median severity of vertigo attacks during the last 3 months of the treatment period and the 3 month follow-up period
- Change of peripheral vestibular function and postural stability between baseline, 9 months visit and 12-mont follow-up visit
- Audiometrically assessed hearing loss and tinnitus intensity between baseline, 9 months visit and 12-mont follow-up visit
- Objective hearing loss – determined by acoustic evoked potentials - between baseline, 9 months visit and 12-mont follow-up visit
- Change of handicap / impairment due to vertigo or dizziness between baseline, 9 months visit and 12-mont follow-up visit, assessed by the Dizziness Handicap Inventory (DHI), the Vestibular Disorders Activities of Daily Living (VADL), and the Minor TBF12 score (Appendix)

8. Assessment of Safety

8.1. GENERAL

The safety profile will be supervised by the safety board (DSMB) and all adverse events will be noted.

8.2. SAFETY PARAMETERS

The number of occurrences of any AEs, SAEs, or SUSARs, which are classified as certainly, probably, or possibly related to the treatment, will serve as safety measures. Especially the following signs and symptoms are considered to be improtant:

- flush
- novel/severe vertigo or dizziness
- tachycardia
- severe persisting headache
- hypotonia (systolic blood pressure < 100mmHg)
- increase of alalnine aminotransferase level > two times the upper limit of the normal range or higher
- bronchospasm
- Quincke's edema (edema of the upper respiratory tract or the mucosa)

at any time of the entire study period.

8.3. DEFINITIONS

8.3.1. Adverse event (AE)

An adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject participating in a clinical trial and which does not necessarily has a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE may be:

- New symptoms/medical conditions
- New diagnosis
- Changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening of medical conditions/diseases existing before clinical trial start
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.

8.3.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose

- results in death
- is life-threatening
- requires subject hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect.

8.3.3. Suspected Unexpected Serious Adverse Drug Reaction (SUSAR)

All suspected adverse reactions related to the study drug (investigational medicinal product and comparators) which occur in the trial, and are both unexpected and serious are subject to expedited reporting (see 8.4.). Unexpected is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (see appendix).
The following safety issues (SAEs regarded as SUSARs) also qualify for expedited reporting where they might materially alter the current benefit-risk assessment of an IMP (investigational medicinal product) or that would be sufficient to consider changes in the IMP administration or in the overall conduct of the trial, for instance:

- single case reports of an expected serious adverse reactions with an unexpected outcome (e.g.: a fatal outcome)
- an increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important,
- post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor

8.4. Period of observation and documentation

All AEs reported by the subject or detected by the investigator, will be collected during the trial and must be documented on the appropriate pages of the CRF. AEs must also be documented in the subject's medical records.

All AEs that occur after the subject has signed the informed consent document until the individual end of the trial will be documented on the pages provided in the CRF. The intensity of an AE should be assessed by the investigator as follows:

mild:	temporary event which is tolerated well by the subject.
moderate:	event which results in discomfort for the subject and impairs his/her normal activity
severe:	event which results in substantial impairment of normal activities of subject.

The investigator will evaluate each AE regarding the relationship with the trial treatment as follows:

certain:	if there is a reasonable possibility that the event may have been caused by trial treatment. A certain event has a **strong temporal relationship** and an alternative cause is unlikely.
probable:	An AE that has a reasonable possibility that the event is likely to have been caused by trial treatment. The AE has a **timely relationship** to the trial treatment(s) and **follows a known pattern of response**, but a potential alternative cause may be present.
possible:	An AE that has a reasonable possibility that the event may have been caused by trial treatment. The AE has a **timely relationship** to the trial treatment(s); **however, follows no known pattern of response**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.
unlikely:	Only a remote connection exists between the trial treatment and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.
unrelated:	An AE that does not follow a reasonable temporal sequence from trial treatment and that is likely to have been produced by the subject's clinical state, other modes of therapy or other known aetiology.
not assessable:	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship to the trial treatment.

8.5. Reporting of SAEs and SUSARs by the investigator

All SAEs (including SUSARs) have to be reported immediately by the investigator to the sponsor within 24 hours after the SAE/SUSAR becomes known using the "Serious Adverse Event" form (Appendix) and fax for transmission. The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal

relationship between the event and the trial treatment.

Please use the following contact:

CSC$_{LMU}$,
Max-Lebsche-Platz 32
81377 München
Tel: +49(89)7095-7308
Fax: +49(89)7095-8848

The sponsor is responsible for the notification of SUSARs and special SAEs (see 8.2.3) to the responsible Ethics Committee (IEC), the Data and Safety Monitoring Board (DSMB) and the competent authorities (BfArM in Germany) in the defined time frame (seven respectively 15 days).

On a yearly basis or if requested all SAEs will be reported to the above mentioned authorities. Each SAE will be followed up by the site monitor during the study on a regular basis until complete recovery or the reasons for AE are identified. The investigator is expected to follow-up any SAE which occurred during the study.

8.6. MONITORING OF ADVERSE EVENTS

The independent DSMB will be responsible for reviewing subject safety during the trial.
The major function of this committee will be to monitor the safety and efficacy of the study and to provide recommendations regarding further enrolment and conduct of the trial. The DSMB will periodically review tabulated safety summaries and additional safety data which the DSMB may request during the conduct of the trial. The DSMB is responsible for making recommendations to a Steering Committee regarding modifications or stopping of the trial based on observed safety. Particular attention will be paid to the incidence of particular AEs, including death, headache, flush, vertigo or dizziness, tachycardia, hypotension, bronchial spasm, oedema of the upper respiratory tract or the mucosa (Quincke's oedema).

9. Statistics

9.1. STATISTICAL METHODS

Primary efficacy endpoint is the number of vertigo attacks in the three treatment arms during the last 3 months of the treatment period. Neither the primary endpoint nor the secondary and safety endpoints are considered to be normally distributed. Thus, non-parametric testing has to be applied and values will be described at all time points by median, minimum, and maximum separately for placebo and both dose groups.
The statistical analysis of this three-armed study uses the closed testing principle to avoid the adjustment of the significance level because of multiple testing:
In a first step a Kruskall-Wallis test will be used to reject the global Null-Hypothesis that all three arms show an equal response on treatment. If the global Null-Hypothesis is rejected on the significance level alpha = 5% it is possible to perform three pair wise comparisons between the three study arms (placebo versus low-dose, placebo versus high-dose, low-dose versus high-dose again on the significance level of alpha = 5%).

9.2. SAMPLE SIZE CALCULATION

Primary efficacy endpoint is the number of vertigo attacks in the three treatment arms during the last 3 months of the 9 month treatment period. This outcome variable is skewed and therefore cannot be considered to be normally distributed.
Thus, an overall effect of treatment is analysed with a longitudinal approach based on a linear random intercept model for the arcus-sinus-hyperbolicus transformed frequency measurements. We used data from an open, non-masked trial published recently (Strupp M, Hupert D, Frenzel C, Wagner J, Hahn A, Jahn K, Zingler VC, Mansmann U, Brandt T. Long-term prophylactic treatment of attacks of vertigo in Menière's disease − comparison of a high with a low dosage of betahistine in an open trial. *Acta Otolaryngol*. 2008 May;128(5):520-4.), and, additionally, baseline data for the primary outcome measured for study patients allocated to the BEMED trial (19 patients).

Based on these two data sources, the mixed modelling approach identified a time effect of -0.06 and an effect of medication on the number of attacks in the course of time of about -0.08 (transformed scale). The individual variation of baseline level (i.e. standard deviation of predicted random intercepts) was estimated to be 0.8, the within-error to be 0.5.

Using the combination between model and observed baseline variation it was possible to determine the new planning figures for a sample size re-estimation by simulation. The protocol performs the sample size calculation for a Mann-Whitney test between the differences of baseline and final attack frequency in treatment groups (Δ_A , Δ_B). Based on the scenario described above it was possible to determine the relevant parameter ($P[\Delta_A > \Delta_B]$) as 0.33.

Based on this parameter, a sample size of 46 in each group (i.e. a total of 138 patients in the whole study) will have 80% power to detect the difference between both groups using a Wilcoxon (Mann-Whitney) rank-sum test for two independent groups with a 0.050 two-sided significance level. [Software used: nQuery Advisor Version 7.0]

On the basis of the current drop-out rate of 37%, a total of 220 patients have to be enrolled to the trial. It has to be taken into consideration that about 50% of patients fulfilling the inclusion criteria for this trial might refuse to give their consent to participate in this trial, because the frequency of study visits is high and the medication might consist of placebo for an entire 9 months. We therefore expect to screen about 440 patients for eligibility.

9.3. THE LEVEL OF SIGNIFICANCE

Analysis will be based on a two-sided level of significance of 0.05.

9.4. CRITERIA FOR TERMINATION OF THE TRIAL

Premature termination of the trial may occur under the following conditions:

- recruitment rate is too low, so that it is not realistic to consider completion of the trial within an acceptable period of time
- the number of drop-outs in a center is too high and the situation cannot be approved
- occurrence of unknown or increase of known AEs that render the risks/benefit ratio unacceptable
- an unacceptably high number of SAEs
- a relevant superiority of one group (treatment) in a comparable clinical trial
- a novel therapy developed in the meantime, superior to the investigational therapy modalities
- other reasons reducing ethical justification
- decision of authorities

9.5. HANDLING OF MISSING DATA

Every effort will be made to keep the number of missing values for all parameters to a minimum. This effort is also directed to avoid the drop-out of patients and their loss to follow-up. The scores and measures for efficacy will be recorded by examinations (during study visits) and telephone interviews. The structure of a telephone interview is given in Appendix h. It is not unlikely that some patients will refuse to provide any information by telephone or will fail to attend study visits. If a patient will refuse to have follow-up examinations we will apply the principle “last value observed carried forward” (LVOCF) to replace the missing data for the scheduled examinations.

The LVOCF principle represents a conservative approach to the analysis: (1) In case of a placebo patient who drops out because his situation did not change, the procedure does not introduce a bias. (2) In case of a placebo patient who drops out because his situation worsened, the procedure underestimates the true treatment effect and gives a conservative effect estimate. (3) In case of a placebo patient who drops out because of adverse events in the active group, the procedure results in a less optimistic estimate of the treatment effect and as in point 2 gives a conservative effect estimate.
Detailed measures on how to deal with missing values will be laid out in the statistical analysis plan.

9.6. Sensitivity Analyses

We will use „pattern-mixture models“ to handle possible non-ignorable missing data. (Little RJ, Wang Y, 1996, Pattern-mixture models for multivariate incomplete data with covariates, Biometrics, 52: 98-111; Chapter 8 in Fairclough DL (2002) Design and analysis of quality of life studies in clinical trials: Interdisciplinary, Boca Raton, Chapmann & Hall / CRC Press). We assume a monotone dropout which results in six strata corresponding to patients who drop out at one of the six study examinations. In each stratum there are three strategies to analyse the data: (1) The complete-case missing variable restriction (CCMV) which assumes the distribution of the missing values is equal to the distribution of the complete cases. (2) The available case missing value restriction (ACMV) which uses data from subjects in all the patterns to impute the value for a missing observation. (3) The neighbouring case missing value restriction (NCMV) which uses data from subjects in the neighbouring pattern to impute the missing observations. All three analyses will be performed in order to get an objective picture of the underlying process.

Gender specific analyses will be done

10. Direct Access to Source Data/ Documents

Regulatory authorities, the independent ethics committee, the monitors and the safety board may request access to all source documents, CRFs, and other trial documentation for on-site audit or inspection. The investigator must provide direct access to these documents and must support these activities at all times.

11. Qualtiy Control and Quality Assurance

11.1. MONITORING

The trial will be monitored by CRO Winicker Norimed, D-90429 Nürnberg, according to the monitoring Standard Operation Procedures (SOPs) of Winicker Norimed GmbH, which are based on ICH guidelines for Good Clinical Practice. Monitoring will be performed to verify that

- the rights and well-being of human subjects are protected,
- the documented trial data are accurate, complete and verifiable from source documents
- the conduct of the trial is in accordance with the currently approved protocol / amendment(s), with GCP and with local regulatory requirements.

Monitoring will be done by personal visits from a representative of Winicker Norimed GmbH who will check the CRFs and source documents. Source data verification of all study data will be performed for all randomized subjects. All study sites will be visited by the monitor, six regular visits are planned. Depending on number of subjects at study site, an adaption can be carried out – including a close out visit at each study site. Monitoring will be performed according to SOPs based on GCP principles. By frequent communication (letter, telephone, fax email), the monitor will check the current status and the progress of the trial.

12. Ethics

12.1. ETHICAL PRINCIPLES

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies and the ICH guidelines for Good Clinical Practice (GCP). The investigators participating in this trial will not receive any financial profit from their activities related to this trial.

12.2. LAWS AND PRINICPLES

This clinical trial will be conducted in compliance with all international laws and regulations and national laws and regulations of the country in which the trial is performed, as well as any applicable guidelines. This trial is registered on http://eudract.emea.eu.int.

12.3. INFORMED CONSENT

Before being admitted to the clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. The person who informs the subject must be a physician. An informed consent document that includes both information about the trial and the consent form will be given to the subject. This document complies with all the requirements set out in ICH GCP and has been approved by the independent ethics committee. The document must be in a language understandable to the subject and must specify who informed the subject.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject. A copy of the signed consent document must be given to the subject. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical trial until valid consent has been obtained.

12.4. INDEPENDENT ETHICS COMMITTEE (IEC)

This clinical trial protocol, the informed consent document and any other required document have been submitted to the appropriate Independent Ethics Committee. The Independent Ethics Committee must be informed of all subsequent protocol amendments. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised. All updates of the Investigator's Brochure will also be sent to the Independent Ethics Committee. The investigator must keep a record of all communications with the Independent Ethics Committee. The investigator must submit information on serious or unexpected adverse events as soon as possible to the Independent Ethics Committee. Periodic reports on the progress of the trial should also be provided to the Independent Ethics Committee.

13. Data Handling and Record Keeping

Collection and encoding of data will be performed by the respective investigator, the monitor, and her / his authorized co-workers. Only these persons will have access to documents containing uncoded patient data. Patient data will be encoded using consecutive numbering. All findings including clinical and laboratory data will be documented in the subject's CRF. The subject randomisation number is to be entered onto each CRF page. The responsible investigator has to ensure that an identification of a given subject is possible at any time based on the subject's randomisation number. He therefore has to keep an identification list assigning the subjects identification code to the subject's full name. Should it become necessary to reveal the patient identity in the course of the study for medical reasons, all persons involved will be bound to patient / physician confidentiality.

The investigator is responsible for ensuring that all sections of the CRF are completed correctly and that entries can be verified against source data. Any errors should have a single line drawn through them so that the original entry remains legible and the correct data should be entered at the side with the investigator's signature, date and reason for change. In order to facilitate further handling, CRFs should preferably be completed with a black ball-point. The trial monitor will review the CRFs and check them for completeness. Each individual CRF has to be dated and signed by the responsible investigator upon completion.

For data processing, all data will be entered in a database as recorded. After completion of data entry, checks for plausibility, consistency and completeness of the data will be performed. All missing data or inconsistencies will be reported back to and clarified by the responsible investigator. If corrections of the data have to be performed, the changes will be documented and the original data will not be erased. If no further corrections are to be made in the database, it will be declared closed and used for statistical analysis. Statistical analysis will be performed by the Department of Epidemiology and Biometrics, University of Munich. All data management activities will be done according to ICH-Good Clinical Practice (GCP) as required by regulatory agencies.

The Dept. of Epidemiology and Biometrics, University of Munich, will archive the original trial protocol, the original CRFs and the final trial report and retain all documents including certificates that satisfactory audit and inspection procedures have been carried out pertaining to the trial according to the requirements of the ICH-GCP guidelines.

14. Financing and Insurance

Financing and insurance will be addressed in a separate agreement. Insurance will be provided for all patients by Gehrling GmbH insurance company, D-80339 Munich (for details, refer to full application for funding to the BMBF)

15. Publication Policy

The investigators are committed to the publication and widespread disemination of the results of this study. This study represents a joint effort between the participating neurological and ENT centers (listed above). The investigators, and as such, the parties agree that the recommendation of any party on manuscripts or texts shall be taken into consideration in the preparation of the final scientific doucments for publication or presentation. All proposed publications and presentations by the investigaros or their personnel and associates resulting from or relating to this study must be submitted to the coordinating investigar for review 60 days before submission for publication or presentation.

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Appendices

COMMITTEES OF THIS STUDY

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VERTIGO DIARY

PATIENT-IDENTIFICATION-NUMBER: _____ MONTH: _____ YEAR: _____

Date		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**
Attack 1	Time																															
	Type																															
	Duration																															
	Severity																															
	Change in tinnitus																															
	Aural Fullness																															
	Change in hearing																															
	Additional Symptoms																															
Attack 2	Time																															
	Type																															
	Duration																															
	Severity																															
	Change in tinnitus																															
	Aural Fullness																															
	Change in hearing																															
	Additional Symptoms																															
Attack 3	Time																															
	Type																															
	Duration																															
	Severity																															
	Change in tinnitus																															
	Aural Fullness																															
	Change in hearing																															
	Additional Symptoms																															

Time:	Type:	Duration:	Severity:	Tinnitus:	Aural fullness:	Change in hearing:
Enter time of onset of attack	P: postural R: rotatory G: gait unsteadiness L: lightheadedness	(1) <30 Min (2) 30 – 60 Min (3) 60 – 120 Min (4) >120 Min	(1) mild (2) moderate (3) mod-severe (4) severe	Enter R or L for presence of tinnitus in right or left ear during attack	Enter R or L for presence of aural fullness in right or left ear during attack	Enter R or L for change of hearing in right or left ear during attack

DIZZINESS HANDICAP INVENTORY DHI

Instructions: The purpose of this scale is to identify difficulties that you may be experiencing beause of your dizziness or unsteadiness. Please answer "yes", "no", or "sometimes" to each question. Answer each question as it pertains to your dizziness or unsteadiness problem only.

P1. Does looking up increase your problem?
E2. Because of your problem, do you fell frustrated?
F3. Because of your problem, do you restrict your travel for business or recreation?
P4. Does walking down the aisle of a supermarket increase your problem?
F5. Because of your problem, do you have difficulty getting into or out of bed?
F6. Does your problem significantly restrict your participation in social activities such as going out to dinner, going to movies, dancing, or to parties?
F7. Because of your problem, do you have difficulty reading?
P8. Does performing more ambitious activities like sports, dancing, household chores such as sweeping or putting dishes away increase your problem?
E9. Because of your problem, are you afraid to leave your home without having someone accompany you?
E10. Because of your problem, have you been embarrassed in front of others?
P11. Do quick movements of your head increase your problem?
F12. Because of your problem, do you avoid heights?
P13. Does turning over in bed increase your problem?
F14. Because of your problem, is it difficult for you to do strenuous housework or yard work?
E15. Because of your problem, are you afraid people may think you are intoxicated?
F16. Because of your problem, is it difficult for you to go for a walk by yourself?
P17. Does walking down a sidewalk increase your problem?
E18. Because of your problem, is it difficult for you to concentrate?
F19. Because of your problem, is it difficult for you to walk around your house in the dark?
E20. Because of your problem, are you afraid to stay home alone?
E21. Because of your problem, do you feel handicapped?
E22. Has your problem placed stress on your relationships with members of your family or friends?
E23. Because of your problem, are you depressed?
F24. Dos your problem interfere with your job or household responsibilities?
P25. Does bending over increase your problem?

A "yes" response is scored 4 points, a "sometimes" response 2 points and a "no" response 0 points. F indicates functional subscale, E emotional subscale and P physical subscale.

VESTIBULAR DISORDERS ACTIVITIES OF DAILY LIVING SCALE (VADL)

Task	Independent	Uncomfortable, No change in ability	Decreased Ability, no change in manner of performance	Slower, cautious, more careful	Prefer using an object for help	Must use an object for help	Must use special equipment	Need Physical assistance	Dependent	Too difficult, No longer perform	
	1	2	3	4	5	6	7	8	9	10	NA
F-1 Sitting up from lying down											
F-2 Standing up from sitting on the bed or chair											
F-3 Dressing the upper body											
F-4 Dressing the lower body											
F-5 Putting on socks or stockings											
F-6 Putting on shoes											
F-7 Moving in or out of the bathtub or shower											
F-8 Bathing yourself in the bathtub or shower											
F-9 Reaching overhead											
F-10 Reaching down											
F-11 Meal preparation											
F-12 Intimate activity (eg foreplay, sexual activity)											
A-13 Walking on level surfaces											
A-14 Walking on uneven surfaces											
A-15 Going up steps											
A-16 Going down steps											
A-17 Walking in narrow spaces											
A-18 Waling in open spaces											
A-19 Walking in crowds											
A-20 Using an elevator											
A-21 Using an escalator											
I-22 Driving a car											
I-23 Carrying thins while walking											
I-24 Light household chores (eg dusting, putting items away)											
I-25 Heavy household chores (eg vacuuming, moving furniture)											
I-26 Active recreation (eg sports, gardening)											
I-27 Occupational role (eg. job, child care, homemaking, student)											
I-28 Travelling around the community (car, bus)											

Explanation of Independence Rating Scale

This scale will help us to determine how inner ear problems affect your ability to perform each task. Please indicate your current performance on each task, as compared to your performance before developing an inner ear problem by checking one of the columns in the centre of the page. Pick the answer that most accurately describes how you perform the task.

1. I am not disabled, perceive no change in performance from before developing an inner ear impairment
2. I am uncomfortable performing the activity but perceive no difference in the quality of my performance
3. I perceive a decrement in the quality of my performance, but have not changed the manner of my performance
4. I have changed the manner of my performance, eg I do things more slowly or carefully than before, or I do things without bending
5. I prefer using an ordinary object in the environment for assistance (eg stair railing) but I am not dependent on the object or device to do the activity
6. I must use an ordinary object in the environment for assistance, but I have not acquired a device specifically designed for the particular activity
7. I must use adaptive equipment designed for the particular activity (eg grab bars, cane, reachers, bus with lift, wedge pillow)
8. I require another person for physical assistance or, for an activity involving 2 people, I need unusual physical assistance
9. I am dependent on another person to perform the activity
10. I no longer perform the activity due to vertigo or a balance problem

NA I do not usually perform this task or I prefer not to answer this question

The tinnitus questionnaire (minor TBF12, Goebel et al):

- I notice the tinnitus from waking up until going to bed	**O right O partial O wrong**
- Due to the tinnitus I am worried about my physical constitution	**O right O partial O wrong**
- If the tinnitus stays like that my life is not worth living	**O right O partial O wrong**
- Due to the tinnitus I am more on edge with my family and friends	**O right O partial O wrong**
- I am worried that the tinnitus can affect my physical constitution	**O right O partial O wrong**
- Due to the tinnitus I have problems to relax	**O right O partial O wrong**
- Sometimes the tinnitus is so strong that I cannot ignore it	**O right O partial O wrong**
- Due to my tinnitus I feel low	**O right O partial O wrong**
- I often wonder if the tinnitus will go away sometime	**O right O partial O wrong**
- I fall prey to the tinnitus	**O right O partial O wrong**
- The tinnitus has diminished my concentration	**O right O partial O wrong**

ENG

Bithermal Caloric Test

The test is performed with the patient in the supine position with the head flexed 30 degrees, so that the horizontal canal is in the vertical plane. Four irrigations are performed separately (2 for each ear) with at least 5 minutes of rest between irrigations to avoid additive effects. The temperatures of the standard caloric stimuli are equally above and below body temperature. Water irrigation is done with 250 mL of water irrigated for 30 seconds at 30°C for the cool irrigation and 44°C for the warm irrigation. Caloric testing with water may be performed with direct irrigation and wetting the ear canal and eardrum or with a closed loop system (usually a small latex balloon), through which the water circulates but does not wet the ear. Closed loop and air irrigation systems have the advantage of being safe for use in patients with eardrum perforations. Closed loop systems do carry the risk of eardrum perforation if the balloon suddenly ruptures during irrigation. Air irrigation is done with 8 L of air irrigated for 60 seconds at 24°C and at 50°C for the cool and warm irrigations, respectively. With these values both water and air produce about equivalent stimuli that can be reliably reproduced. If the nystagmus response is weak or absent, additional irrigation with ice water is warranted. The standard ice-water test consists of 2 mL of water, equilibrated with ice, placed in the ear canal for 30 seconds and then dumped out. The patient is then immediately positioned in the standard supine position, and nystagmus is recorded for 2 minutes. If a response is not obtained in the supine position, if the reading is in doubt, or if a spontaneous nystagmus exists, ice-water irrigation should be done in the prone position, inverting the body and the head 180 degrees. When a cold stimulus is applied to the ear in the prone position, endolymph flow is ampullopetal (toward the ampulla), and according to Ewald's law, ampullopetal deviation of the cupula of the lateral semicircular canal evokes a stronger response than ampullofugal deviation (cold stimulus in the supine position). Thus, in cases of bilateral weakness, in total 4 additional ice-water caloric irrigations are performed. Because the caloric stimulus delivered to each ear is the same, the assumption is that if the ears are normal, the responses should be about equal. A unilateral weakness is therefore determined by comparing the response strength from each side with Jongkees' formula:

$$\frac{(RW + RC) - (LW + LC)}{RW + RC + LW + LC} \times 100 = \%UW$$

where RW, RC, LW, and LC are the peak SPVs of the responses to right warm, right cool, left warm, and left cool irrigations, respectively, and UW is unilateral weakness. The accepted normal limits should be determined by each testing laboratory. Published values from some laboratories are shown in Table 1 (Barber HO, Wright G, Unpublished data Bilateral vestibular weakness is usually considered to be present if the sum of the peak caloric responses (warm plus cool) of each ear falls below 10°/second because the range of caloric responses can be as low as 5°/second and still be within the 95% confidence interval for normal subjects. Such a finding usually indicates
bilateral peripheral vestibular dysfunction. This finding is most commonly seen in ototoxicity and bilateral Meniere's disease. CNS disorders may also produce such a finding, but bilateral weakness of CNS origin is usually accompanied by other signs of CNS dysfunction.

Table 1. Normal caloric values

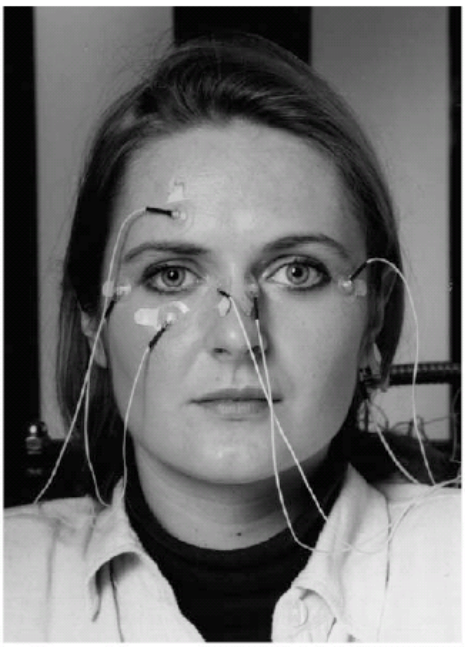
		Water (SPV (°/sec))					Air (SPV (°/sec))				
		Warm		Cool			Warm		Cool		
Source	N	Mean	Range	Mean	Range	UW (%)	Mean	Range	Mean	Range	UW (%)
Barber and Wright*	114	35	11-80	28	6-50	25	—	—	—	—	—
Barber and Wright*	24	—	—	—	—	—	37	11-85	30	10-46	25
Custer et al[27]	20	15	—	15	—	20	—	—	—	—	—
Ford and Stockwell[24]	8	22	16-28	17	11-23	—	20	15-25	15	10-20	—
Baloh and Honrubia[2]	44	21	6-68	15	5-40	22	—	—	—	—	—
Hammersma[28]; Jongkees & Philipszoon[26]	47	23	8-52	22	9-46	15	—	—	—	—	—
Mehra[29]	31	26	10-52	21	3-39	—	—	—	—	—	—
Henriksson[30]	25	29	8-65	29	8-45	—	—	—	—	—	—
Capps et al[31]	10	16	6-26	18	8-28	—	15	3-27	17	7-27	—
Benitez et al[32]	30	—	—	—	—	—	22	6-38	21	5-37	16

Adapted from Barber HO, Stockwell CW. Manual of electronystagmography. St Louis: Mosby; 1980.
*Barber HO, Wright G, Unpublished data.

Abridged from Bhansali et Honrubia "Current status of electronystagmography testing", Otolaryngology – Head and Neck Surgery, March 1999, Volume 120 Number 3, pp. 419-426

Placement of electrodes

The electrophysiological basis of the ENG is the corneo-retinal dipole (a potential difference of about 1 mV). The dipole is parallel to the longitudinal axis of the eye, with the retina or the cornea having a negative potential. Changes in this dipole between the horizontal or vertical electrodes are DC-amplified. The ENG allows non-invasive horizontal recordings of +/-40° with an accuracy of about 1° and vertical recordings of +/-20°.



Text and picture from Brandt et Strupp "General Vestibular Testing", Clinical Neurophysiology 116 (2005): 406-426

SAEPs

[...]

III. Stimulus

It is recommended that "broad-band" clicks, the acoustic energy of which is spread over a wide range of audio frequencies, be used for the neurologic applications of auditory evoked potentials. These clicks should be generated by driving with a 100 µsec rectangular pulse (single monophasic square wave), a standard audiometric earspeaker having a relative flat frequency spectrum. For special purposes, such as intraoperative recording, the clicks can be delivered through ear inserts. The sound pressure waves so produced consist of a first and major wave, followed by smaller, highly damped oscillations of alternating polarity that may last up to 2 msec or longer. The waveform of the driving pulse, to be referred to as the click's *"electrical waveform,"* can be viewed by displaying on an oscilloscope screen, the output of the pulse generator (Fig. 6, top waveforms). The sound pressure waves, to be designated the click's *"acoustical waveform,"* can be examined by coupling the earspeaker to the microphone of a "sound level meter' via a standard "earphone coupler" or "artificial ear" and displaying the meter's electrical output on an oscilloscope screen (Fig. 6, bottom waveforms). To the extent that the artificial ear approximates the acoustic transfer characteristics of the human external auditory meatus, this acoustic waveform resembles the stimulus applied to the tympanic membrane.

[...]

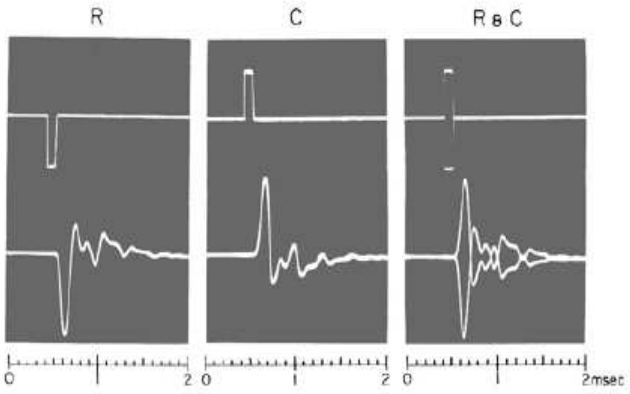


FIG. 6. Electrical (**top**) and acoustic (**bottom**) waveforms of rarefaction (R), condensation (C), and alternating (R and C) clicks (1).

Stimulus Polarity

The polarity of the first and most prominent wave of the acoustic waveform of the click (as distinct from that of the electrical pulse driving the earspeaker) determines whether a negative or positive pressure is applied in front of the earspeaker diaphragm. Those clicks in which the first and major acoustic wave applies negative pressure in front of the earspeaker diaphragm are referred to as *rarefaction* clicks (Fig. 6, R). Those clicks in which the first and most prominent acoustic wave applies a positive pressure in front of the earspeaker diaphragm are referred to as *condensation* clicks (Fig. 6, C). It should be recognized that these polarity designations are, to some degree, arbitrary, since acoustical polarity is sometimes reversed during transfer through the ear canal. Click generators must be capable of delivering rarefaction only, condensation only, and alternating rarefaction and condensation (Fig. 6, R and C) clicks. For tone pips, a polarity designation is meaningless.

[...]

Stimulus Rate

Stimulus rates employed vary widely from 5 to 200/s. depending on test applications. Waves I, II, VI, and VII are particularly reduced in amplitude at rates higher than 10/s. Thus, stimulus rates of 8—10/s are especially suited to resolve these peaks.

Stimulus Intensity

It is recommended that click intensity be acoustically *calibrated* in "decibels peak-equivalent

sound pressure level" (dB pe SPL). Sound pressure level measurements use as a reference level (0 dB) 20 micropascals (Pa), which equal 0.0002 dyne2/cm2. A click's pe SPL is the SPL of a pure tone, the peak-to-peak amplitude of which matches the peak-to-peak amplitude of the click's acoustic waveform (Chatrian et al., 1982). The calibration of the stimulus delivery system should be repeated at least every 6 months. Each laboratory should be capable of converting its intensity measures into equivalent values obtained with other methods, i.e., expressed in "decibels above normal hearing level" or dB HL (dB above the average hearing threshold of a group of normal young adults tested by the same laboratory under conditions identical to those used for recording BAEPs clinically) or in "decibels above sensation level" or dB SL (dB above the subject's individual hearing threshold in the ear tested). Stimulus intensities employed generally range between 40 and 120 dB pe SPL.

Monaural Versus Binaural Stimulation
Click should be delivered monaurally, i.e., to one ear at a time (Stockard et al., 1978).

Contralateral Masking
It is recommended that the contralateral (nonstimulated) ear be masked by white noise at 60 dB SPL to eliminate "crossover" responses, i.e., bone-conducted responses originating in this ear. Although not necessary in every situation, it is recommended that contralateral masking be included in the routine test protocol to avoid its inadvertent omission when it is required. For a description of the instrumentation and procedure for calibrating the masking noise as well as the click stimulus, see Chatrian et al. (1982).

IV. Recording
System Bandpass
The recommended system bandpass for BAEP recording is 10-30 to 2,500-3,000 Hz (—3 dB) with a filter rolloff not exceeding 12 dB/octave for the low frequencies and 24 dB/octave for the high frequencies. Whenever this test is performed in the presence of irreducible EMG and mechanical artifacts, the low-frequency cutoff may be raised to 100-200 Hz. However, this last cutoff is not advisable for testing children (Stapells, 1989). A high-frequency cutoff of 1,500 Hz is acceptable for intraoperative BAEP (but not ECochG) monitoring.

Stimulus Artifact
The use of properly electrostatically and electromagnetically shielded stimulus delivery systems is suggested to attenuate or eliminate the stimulus artifact, especially when using rarefaction-only or condensation-only clicks.

Analysis Time
An analysis time of 10-15 ms from stimulus onset is suggested. An analysis time of no less than 15 ms is sometimes required to demonstrate extremely delayed responses in certain pathologic conditions. Analysis times of 15 ms are also essential for neonatal and intraoperative recordings.

Number of Trials to be Averaged
It is suggested that about 1,000-4,000 individual trials be averaged until good waveform resolution has been achieved. Two or more responses must be obtained and superimposed to demonstrate replicability or lack of replicability of their components.

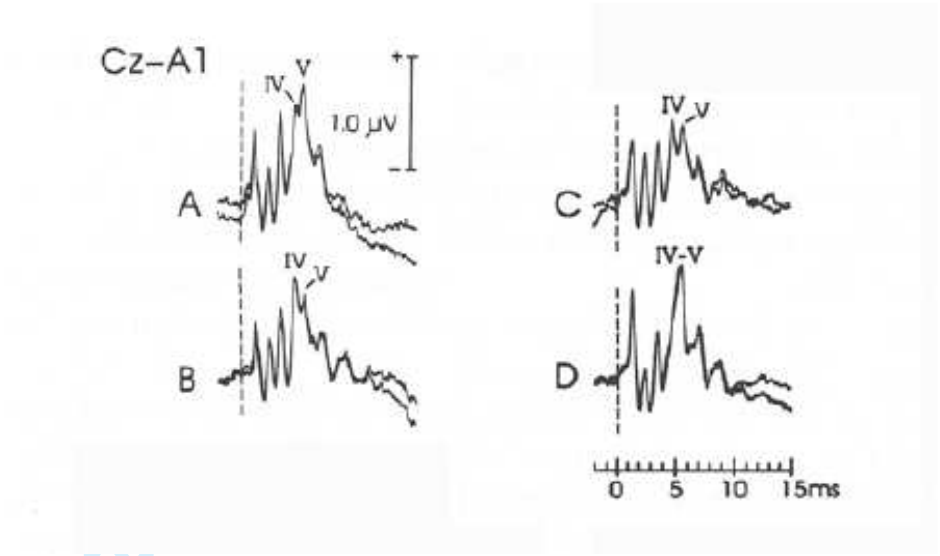


FIG. 7. BAEPs of four audiometrically normal volunteers. Monaural click stimulation at 8/s and 120 dB pe SPL and recording between vertex and ipsilateral earlobe (Cz—Ai). Note variable relationship between waves IV and V. (From G. E. Chatrian, unpublished data.)

Electrode Placement

It is recommended that recording electrodes be placed as follows: (1) on the scalp at the vertex (Cz position of the 10-20 International System of EEG electrode placement) and (2) over the left and right earlobes (auricular) A1 and A2 positions of the 10-20 System) or the left and right mastoid processes (M1 and M2).

The ground electrode may be placed anywhere on the body. For convenience, it is recommended that it be placed on the head, for instance, on the scalp in a midline frontal location (position Fz of the 10-20 System). Electrode impedances must be < 5 KOhms.

Montage

A montage consisting of the following derivations is suggested for BAEP recording:

Channel 1: Vertex-ipsilateral earlobe or mastoid (Cz-Ai or Mi)

Channel 2: Vertex-contralateral earlobe or mastoid (Cz-Ac or Mc)

In vertex-ipsilateral earlobe derivations, the relationships of waves IV and V (the "IV-V complex") are very variable even in normal subjects (Chiappa and Gladstone, 1979). Wave IV may appear as a wavelet on the ascending limb of wave V (Fig. 7, A). Less commonly, wave V may consist of a wavelet on the descending limb of wave IV (Fig. 7, B). In some subjects, both waves IV and V may be well developed (Fig. 7, C). In other individuals, wave IV may be absent (Fig. 7, D). Vertex-contralateral earlobe or mastoid derivations generally demonstrate better separation of waves IV and V (Fig. 8). Thus, they are helpful in confirming the identity of waves IV and V detected in vertex-ipsilateral earlobe or mastoid reference derivations and are sometimes essential to identify them (Stockard et al., 1978; Chiappa and Gladstone, 1979).

[...]

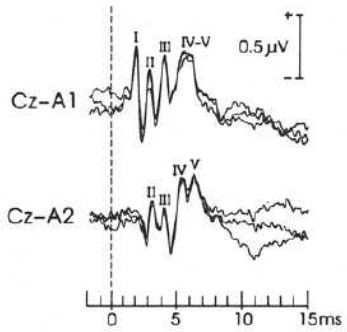


FIG. 8. BAEPs of audiometrically normal volunteer. Monaural click stimulation of 8/s and 120 dB pe SPL and recording between vertex and ipsilateral earlobe (top trace) and vertex and contra-lateral earlobe (bottom trace). (From G. E. Chatrian, unpublished data.)

V. Analysis of Results

Records are analyzed primarily for the presence of waves I, III, and V.

Measurements

Measurements must include the following: (1) wave I peak latency; (2) wave III peak latency; (3) wave V peak latency; (4)I-III interpeak interval; (5) III-V interpeak interval; (6) I-V interpeak interval; (7) wave I amplitude; (8) wave V amplitude; and (9) wave IV-V/I amplitude ratio. Peak latencies, i.e., absolute latencies, must be measured from the leading edge of the driving pulse (electrical waveform of the click) indicated in the recording by the onset of the artifact, if any. Peak amplitudes are measured from the prestimulus baseline (when one is available) or from the immediately preceding or following peak of opposite "polarity."

VI. Criteria for Clinically Significant Abnormality

In most laboratories, it is customary to interpret as abnormal peak latencies, interpeak intervals, and amplitude ratios that are beyond 2.5 or 3 standard deviations from the mean of an age-matched control sample from the normal population.

[...]

Abnormal BAEP measures do not necessarily imply altered retrocochlear function. At present, criteria for *retrocochlear dysfunction* include the following.

1. Absence of all BAEP waves I through V. unexplained by extreme hearing loss determined by formal audiometric testing.
2. Absence of all waves following waves I, II, or III.
3. Abnormal prolongation of I-III, III-V. and I-V interpeak intervals. I-III or III-V intervals can sometimes be abnormally prolonged even in the face of a normal I-V interval.
4. Abnormal diminution of the IV-V/I amplitude ratio, especially when accompanied by other abnormalities.
5. Abnormally increased differences between the two ears (interaural differences) as regards the I-III, III-V, and I-V interpeak intervals, when not explained by unilateral or asymmetric middle and/or ear dysfunction determined by appropriate audiometric tests.

[...]

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Abridged from American Clinical Neurophysiology Society "Guideline 9C: Guidelines on Short-Latency Auditory Evoked Potentials"

Orthoptic Examination

4.1. Eye position and nystagmus

Clinical examination of patients with suspected vestibular disorders should begin with the examination of the eyes in 9 different positions (i.e. looking straight ahead, to the right, left, up, down as well as diagonally right up, right down, left up, and left down) to determine ocular alignment (…), fixation deficits, spontaneous or fixation nystagmus (Serra and Leigh, 2002), range of movement, and disorders of gaze-holding abilities (Büttner and Grundei, 1995). The examination can be performed with an object for fixation or a small rod-shaped flashlight. In primary position one should look for periodic eye movements, such as nystagmus (e.g. horizontal-rotatory, suppressed by fixation as in peripheral vestibular dysfunction), vertically upward (upbeat nystagmus) (Baloh and Yee, 1989; Fisher et al., 1983) or downward (downbeat nystagmus syndrome) (Baloh and Spooner, 1981; Böhmer and Straumann, 1998; Glasauer et al., 2003), or horizontal or torsional movements with only slight suppression (or increase) of intensity during fixation as in a central vestibular dysfunction.

[…]

The examination of the eyes with Frenzel's glasses is a sensitive method for detecting spontaneous nystagmus. This can also be achieved by examining one eye with an ophthalmoscope (while the other eye is covered) and simultaneously checking for movements of the optic papilla or retinal vessels (Zee, 1978) even with low, slow-phase velocities/frequencies or square-wave jerks (small saccades [0.5–58] that are often observed in progressive supranuclear palsy or certain cerebellar syndromes) (Leigh and Zee, 1999). Since the retina is behind the axis of rotation of the eyeball, the direction of any observed vertical or horizontal movement is opposite to that of the nystagmus detected with this method, i.e. a downbeat nystagmus causes a rapid, upward movement of the optic papilla or retinal vessels. After checking for possible eye movements in primary position and the misalignment of the axes of the eyes, the examiner should then establish the range of eye movements monocularly and binocularly in the 8 endpositions; deficits found here can indicate, e.g. extraocular muscle or nerve palsy. Gaze-holding deficits (Büttner and Grundei, 1995; Leigh and Zee, 1999) can also be determined by examining eccentric gaze position. Use of a small rod-shaped flashlight has the advantage that the corneal reflex images can be observed and thus ocular misalignments can be easily detected (note: it is important to observe the corneal reflex images from the direction of the illumination and to ensure that the patient attentively fixates the object of gaze.) The flashlight also allows one to determine whether the patient can fixate with one or both eyes in the end-positions. This is important for detecting a defect of gaze holding.

[…]

4.2. Smooth pursuit

The patient is asked to visually track an object moving slowly in horizontal and vertical directions (10–208/s) while keeping his head stationary. Corrective (catch-up or backup) saccades are looked for; they indicate a smooth pursuit gain that is too low or too high (ratio of eye movement velocity and object velocity).

[…]

4.3. Saccades

First, it is necessary to observe spontaneous saccades triggered by visual or auditory stimuli. Then the patient is asked to glance back and forth between two horizontal or two vertical targets. The velocity, accuracy, and the conjugacy of the saccades should be noted. Normal individuals can immediately reach the target with a fast single movement or one small corrective saccade (Botzel et al., 1993).

[…]

4.4. Vestibulo-ocular reflex

One bedside test is of special clinical importance: the head-impulse test of Halmagyi and Curthoys (Halmagyi and Curthoys, 1988; Halmagyi et al., 1992); it allows the examination of the horizontal VOR. This test is closely related to the purpose and special properties of the VOR.

Fig. 5 summarizes how to do this test and how to interpret the findings. The test also allows examination not only of the horizontal, but also of the vertical canals, because they can be stimulated in specific planes and sides, e.g. the left anterior semicircular canal can be stimulated by moving the head in the plane of this canal downward and observing the induced eye movements.

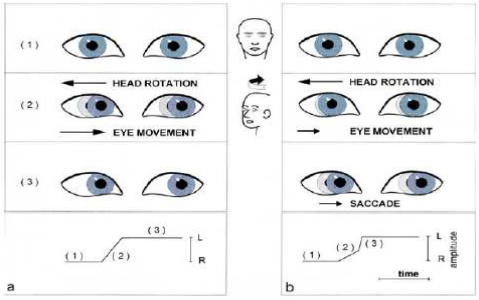

Fig. 5. Clinical examination of the *horizontal vestibulo-ocular reflex* (VOR) by the *head-impulse test* (Halmagyi and Curthoys, 1988). To test the horizontal VOR, the examiner holds the patient's head between both hands, asks him to fixate a target in front of his eyes, and rapidly and arbitrarily turns the patient's head horizontally to the left and then to the right. This rotation of the head in a healthy subject causes rapid compensatory eye movements in the opposite direction (a). In cases of unilateral labyrinthine loss the patient is not able to generate the VOR-driven fast contraversive eye movement and has to perform a corrective (catch up) saccade to re-fixate the target. Part b explains the findings in a patient with a loss of the right horizontal canal. During rapid head rotations toward the affected right ear, the eyes move with the head to the right and the patient has to perform a refixation saccade to the left; the latter can be easily detected by the examiner.

[…]

4.6. Positioning/positional maneuvers

All patients should also be examined with the so-called Dix-Hallpike maneuver in order not to overlook the most common form of vertigo, benign paroxysmal positioning vertigo (BPPV) (Brandt and Steddin, 1993; Schuknecht, 1969) of the posterior as well as central positioning/positional nystagmus or vertigo (Bertholon et al., 2002; Brandt, 1990; Büttner et al., 1999a,b). In addition, the 'barbecuespit maneuvers' should be performed to look for a BPPV of the horizontal canal (Baloh et al., 1993; McClure, 1985; Pagnini et al., 1989; Strupp et al., 1995), which is characterized by a linear horizontal nystagmus beating in most cases to the undermost ear ('geotropic'), but in some cases to the uppermost ear (Bisdorff and Debatisse, 2001).

4.7. Miscellaneous

4.7.1. Visual fixation suppression of the VOR

A disorder of visual fixation suppression of the VOR (which as a rule occurs with smooth pursuit abnormalities, as these two functions are mediated by common neural pathways) (Takemori, 1983) is often observed in lesions of the cerebellum (flocculus or paraflocculus) or of the cerebellar pathways and in progressive supranuclear palsy (see above). Anticonvulsants and sedatives can also impair visual fixation of the VOR. Before testing visual fixation suppression of the VOR, it is necessary to confirm that the VOR is intact.

4.7.2. Head-shaking nystagmus

To test for head-shaking nystagmus (HSN), the examiner turns the subject's head by about +/-45° horizontally about 30 times within about 15 s or the patient does it by himself. HSN is defined as the occurrence of at least 5 beats of nystagmus immediately after the head-shaking maneuver, which should be performed with Frenzel's glasses. There is good evidence that HSN reflects a dynamic (peripheral
and/or central vestibular) asymmetry of the velocity-storage mechanism (Hain and Spindler, 1993; Hain et al., 1987).

[…]

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Abridged from Brandt et Strupp “General Vestibular Testing”, Clinical Neurophysiology 116 (2005): 406-426

Subjective Visual Vertical

During the measurement of SVV, the patient sits with the chin resting on a fixed pad looking into a half-spherical dome of 60-cm diameter which can be rotated around their line of sight. The surface of the dome extendes over the entire visual field and is covered with a random pattern of colored dots providing no cues to gravitational orientation. Thirty centimeters in front of the subject is a linear target whose center was fixed on the shaft of a servo motor. The target can be rotated in the subject’s frontal plane. After target and dome are rotated to a randomized offset position, the patient is instructed to align the target with thr perceived vertical by using a joystick-device. A PC recordes the difference between the adjusted orientation and the true spatial vertical and calculates the average of ten readjustments. Determination of the SVV is done mono- and biocularly. The normal range is within 0° +/- 2,5°.

Modified from “Klinische Neuroophthalmologie”, Huber A et Kömpf D, Thieme 1998

AUDIOMETRIC TESTING

Audiometric testing will be performed according to the international standard ISO 8253.

Telephone Interview – M. Ménière

A. Dizziness Diary

1. Number of attacks during the last month ☐

2. Number of attacks
   a. with rotatory dizziness ☐
   b. with postural dizziness ☐
   c. with gait unsteadiness ☐
   d. with lightheadedness ☐

3. Number of attacks lasting
   a. less than 30 min ☐
   b. 30 – 60 min ☐
   c. 60 – 120 min ☐
   d. more than 120 min ☐

4. Number of attacks of severity rated
   a. 1 ☐
   b. 2 ☐
   c. 3 ☐
   d. 4 ☐

5. Number of attacks accompanied by

	R	L
a. change in tinnitus	☐	☐
b. change in hearing	☐	☐
c. aural fullness	☐	☐

6. Other accompanying symptoms noted

_____

_____

B. Treatment Compliance

	Yes	No
1. Did you take your medication on a daily basis?	☐	☐
2. Did you take your medication three times a day?	☐	☐
3. Did you take one capsule out of every bottle / two capsules out of bottle 2 (4/6)?	☐	☐

4. On how many times since the last visit / interview did you fail to take your medication? _____

C. Concomitant / additional medication / new diseases

1. Have you been prescribed any new regular medication? ☐ ☐
2. If yes, specify

Name: _____ Dose:_____

3. Have you been diagnosed with any new diseases? ☐ ☐
4. If yes, specify

Diagnosis: _____ ICD10: _____

D. Assessment of adverse events / serious adverse events

1. Does the patient relate any adverse events or serious adverse events?
2. If yes, fill out AE / SAE - report

PATIENT INFORMATION LEAFLET

Betaserc 8 mg, 16 mg and 24 mg tablets

This instruction leaflet contains important information about Betaserc. Please read the leaflet carefully before using Betaserc.
After reading, keep it with the product until the treatment is completed.

What does Betaserc contain?
One tablet contains either 8 mg, 16 mg or 24 mg of betahistine dihydrochloride as active substance. In addition the preparation contains the following excipients:
microcrystalline cellulose, mannitol, citric acid anhydrous, colloidal silicium dioxide and talc.

How does Betaserc work?
The exact method of action of the product is not known. It has shown to minimize dizziness by improving the blood flow in the inner ear. Your sense of balance originates from an organ in your inner ear. Dizziness may be caused by disturbances in the pressure of the liquids inside the ear, or, in the case of Ménière's disease, by damage to the balance organ.

Holder of the marketing authorization / additional information is given by
Holder of the marketing authorization and manufacturer:
Solvay Pharmaceuticals B.V., C.J. van Houtenlaan 36, 1381 CP Weesp, Holland

Additional information is given by:
Algol Pharma Oy
Karapellontie 6, 02610 Espoo
Tel. (09) 50 991

Indications
Betaserc tablets are used in the treatment of Ménière's disease. The preparation is also used in the treatment of dizziness with origin in the inner ear.

When should you not take the preparation?
The preparation should neither be used if hypersensitivity to any of the components has been observed nor if you suffer from pheochromocytoma (a rare abnormality of the adrenal gland).

What should you know before using the medicine?
The physician shall observe closely patients with bronchial asthma or peptic ulcer.

Pregnancy and breast feeding
You should discuss with your doctor before using this medicine.

Effect on driving skill and use of machines
No effects.

What should you avoid when you are taking this medicine?
Before using this medicine the patient should discuss the use of other concurrent medicines with the attending doctor.

How is the medicine used?
The daily dosage varies between 24 and 48 mg and should be divided into two or three doses. The doctor prescribes the dosage to the individual patient. The doctor's instructions shall be followed carefully. The drug should be taken during or after the meals with liquid. The tablets/halves are swallowed as a whole.

What happens if the medicine is taken inappropriately?
Overdose does not normally cause any symptoms, but in case of a clear overdose or if a child has taken Betaserc you should contact a doctor.

Which side effects can the medicine cause?
Mild nausea, stomach upset and cutaneous hypersensitivity reactions, especially rash, pruritus and urticaria may occur. By taking the drug during meals or lowering the dosages (according to the doctors prescription), these effects should disappear.

Should other than the above mentioned side effects occur you should contact a doctor.

How is the preparation stored?
Store below 25℃.
The expire date is printed on the package.
Keep out of the reach of children.

Last revision: 06.04.2010

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