

Results and lessons learnt from a randomized controlled trial: Prophylactic treatment of vestibular migraine with metoprolol (PROVEMIG)

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Abstract

BACKGROUND Vestibular migraine (VM) is the most frequent cause of recurrent spontaneous attacks of vertigo causally related to migraine. The objective of the PROVEMIG trial was to demonstrate that metoprolol succinate is superior to placebo treatment in the prevention of episodic vertigo- and migraine-related symptoms in patients with VM. **METHODS** This phase 3, two-arm parallel-group, double-blind, randomized placebo-controlled trial was designed to be conducted at tertiary referral centres at neurology and ENT departments of eight German university hospitals. The planned sample size was a total of 266 patients to be allocated. Adults aged 18 years or above diagnosed with probable or definitive VM according to the Neuhauser criteria 2001 were randomly assigned 1:1 to six months blinded metoprolol (maintenance dosage of 95 mg daily) versus placebo treatment policy. The primary efficacy outcome was the self-reported number of vertiginous attacks per 30 days documented by means of a paper-based daily symptom diary. The pre-specified time period of primary interest was defined within month 4 to 6. Secondary outcomes included the patient-reported number of migraine days and vertigo days, the Dizziness Handicap Inventory and clinical assessments. Adverse events were reported throughout the whole 9-month study period. **RESULTS** At the time of trial termination, no evidence for a difference in the incidence of vertiginous attacks between both treatment groups was detected. For the full analysis set, the incidence rate ratio (IRR) was 0.983 (95% confidence interval (CI), 0.902 to 1.071) for metoprolol vs. placebo. There was a significant decline in the overall monthly vertigo attacks by the factor 0.830 (95% CI, 0.776 to 0.887). Results were consistent for all subjective and objective key measures of efficacy. The treatment was well tolerated with no unexpected safety findings. **CONCLUSIONS** Due to poor participant accrual not related to the tolerability of the study medication or safety concerns PROVEMIG had to be discontinued after randomizing 130 patients. Additional preparatory work is much-needed in the development, psychometric evaluation and interpretation of clinically meaningful endpoints in trials on episodic syndromes like VM taking into consideration the two-dimensional aspect of this disease entity. **TRIAL REGISTRATION** EudraCT no 2009-013701-34, prospectively registered on 08 April 2011, <https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-013701-34/DE>.

Background

During the past decades vestibular migraine (VM) has been identified as a type of migraine with the leading symptom of vertigo. Recently, it has been accepted as a distinct diagnostic entity by the Bárány Society and the International Headache Society (IHS) [1]. Since vertigo frequently occurs isolated, not always being accompanied by headache or other migrainous symptoms, there is a strong need for accepted diagnostic criteria, which were first published 2001 by Neuhauser and colleagues [2] and later refined by the Bárány Society [3]. Based on validated neuro-otologic interviews [4, 5] the prevalence of migrainous vertigo in the general adult population was estimated in a large German neuro-otologic survey: its lifetime prevalence was 0.98% and the 12-month prevalence 0.89% [6]. The similarity of these two numbers suggests that these patients suffer chronically from this condition. A more recent survey from the US found a prevalence of 2.7% in adults [7]. In a specialized dizziness clinic VM is the most

frequent cause of spontaneous recurrent attacks of vertigo and accounts for approximately 10% of the patients [8]. The majority of patients with VM are middle-aged and in the middle of their working lives.

With double-blind randomized controlled clinical trials missing [9], recommendations for treatment are aligned to those of migraine [10, 11]. The following drugs have been recommended as *prophylactic* treatment for VM: beta-blockers, valproic acid, lamotrigine [12], tricyclic antidepressants and topiramate [13]. In an observational study on 81 patients the effects of tricyclic antidepressants, beta-blockers, or calcium-channel blockers in combination with diet were evaluated. Seventy-two percent of the patients showed a good response [14]. More recently, flunarizine [15], propranolol and venlafaxine [16] have been investigated in active-controlled open-label trials. Metoprolol is listed as group 1 medication (drugs of first choice) in a dose of 50 to 200 mg and has shown efficacy in prophylactic treatment of migraine [17, 18]. Due to absence of consensus guidelines for the treatment of VM, beta-blockers such as metoprolol are commonly prescribed as off-label preventive pharmacologic treatment in VM. For this reason, the PROphylactic treatment of VEstibular MIGraine with metoprolol (PROVEMIG) trial was conducted. This investigator-initiated, prospective, longitudinal, national, multicentre, double-blind, randomised, placebo controlled, two-arm parallel group, phase 3, pragmatic, superiority trial aimed to evaluate the effectiveness, safety and tolerability of metoprolol succinate versus placebo treatment for the preventive treatment of VM. Treatment duration in both arms was 6 months, with a 3-month post-treatment follow-up period. The primary objective was to demonstrate the superiority of metoprolol with respect to the incidence rate of vertiginous attacks. Further secondary objectives included to compare both treatment regimens with respect to vertigo and headache characteristics, to investigate changes in neurological and neuro-ophthalmological assessments, and vertigo-related impairment of quality of life, and to further establish the safety profile of the drug. We report the pre-specified efficacy and safety analyses for the 6-month treatment period following reporting guidelines for trials describing patient-reported outcomes and related extensions (Checklist for CONSORT 2010 Statement provided in Additional file 1) [19-21].

Methods

Study oversight

The study was investigator initiated and conducted in accordance with the principles of the Declaration of Helsinki, International Conference for Harmonisation Guidelines for Good Clinical Practice and relevant national regulations. The protocol (Additional file 2) was approved by the ethics committees of each participating centre. Furthermore, the efficacy, safety, integrity and feasibility of the trial was monitored by a data safety monitoring board (DSMB) consisting of three independent, non-participating clinicians. All patients provided written informed consent before any study procedures or assessments were done.

Study population and procedures

Subjects were screened at 6 German academic outpatient clinics, 4 of these investigational sites (German Center for Vertigo and Balance Disorders at the university hospital Munich; Department of Neurology of the general hospital Celle, University of Essen, and community hospital Altötting-Burghausen) allocated patients between June 20, 2012 (first patient in) and April 10, 2017; last patient last visit was on January 3, 2018.

The patient population consisted of male or female patients aged 18 years and above diagnosed as having probable or definite vestibular migraine according to the Neuhauser criteria [2] (see Additional file 2 for details). For enrolment, patients had to experience a frequency of 6 to 30 VM-related attacks per 3 subsequent months prior to screening visit (information retrospectively collected at in-person interviews), be capable to follow the study instructions and likely to complete study visits.

Exclusion criteria were a diagnosis of other co-existing vestibular disorders such as Menière's disease, phobic postural vertigo, benign paroxysmal positional vertigo (BPPV) and vestibular paroxysmia. Patients were also excluded if they had central disorders such as paroxysmal brainstem attacks and transient ischemic attacks. Other exclusion criteria were given by contraindications for the treatment with metoprolol such as known allergic reaction to the trial drug or other beta receptor blockers, shock, acidosis, any bronchospastic disease (e.g. bronchial asthma), sick sinus syndrome, known sino-atrial- or atrio-ventricular block, bradycardia of less than 50 bpm at rest, systolic blood pressure less than 100 mmHg, end grade peripheral arterial disease, known severe coronary heart disease or heart failure and concurrent treatment with monoamine oxidase inhibitors, sympathomimetic drugs, catecholamine-depleting drugs, digitalis glycosides. Other patient factors leading to exclusion included poorly controlled diabetes mellitus, pheochromocytoma, suspicion of developing thyrotoxicosis, disorders of homeostasis, porphyria, psoriasis; pregnancy or breastfeeding; persistent hypertension with systolic blood pressure higher than 180 mmHg or diastolic blood pressure higher than 110 mmHg (mean of 3 consecutive arm-cuff readings over 20 to 30 minutes) that cannot be controlled by antihypertensive therapy; life expectancy of less than 12 months; other serious illness that may confound treatment assessment; currently receiving beta-blockers; enrolment in another clinical trial; exposure to any investigational medication within 30 days prior to baseline visit.

Study procedures

This study consisted of a screening visit, a 6-month treatment period, and a final evaluation at month 9 after a 3-month post-treatment follow-up period. Both the study examinations and treatment were performed in an outpatient setting. Based on the information from the screening visit patients were randomized or were excluded if they did not meet eligibility criteria. At the day of inclusion, patients received their study medication together with a paper-based diary to document VM-related symptoms on a daily basis over the 9 month observation period. Patients were seen at 5 scheduled clinic visits for protocol-specified evaluations at screening, baseline (day of inclusion), and at months 1, 3, and 6 (end of treatment period); 3 standardized telephone visits were performed after 2, 4, and 5 months post-

randomization for compliance checks with respect to treatment and diary documentation, and safety assessment.

All enrolled patients underwent a physical examination at baseline visit, and at every clinic visit post-randomization non-invasive neurological and neuro-otological and -ophthalmological examinations such as video-oculography including bithermal caloric testing, assessment of pursuit eye movement, gaze-holding, saccades and subjective visual vertical (SVV). For more details refer to the original protocol in the Additional file 2 and Additional file 4. Further, they had to complete the paper-based self-administered Dizziness Handicap Inventory (DHI), a 25-item validated questionnaire with a 3-point response scale to rate the self-perceived impact of dizziness on health-related quality of life [22, 23]. Possible DHI total scores range from 0 to 100 points, with higher values reflecting greater impairment. Results from the trial assessments were recorded in paper-based case report forms filled by the study personnel at each clinical site.

Event-driven diary documentation

Dizziness event data were captured by means of the patient's diary with entries made whenever symptoms associated with migrainous vertigo occurred. Patients were instructed to document the following items: time of onset, duration, severity and type of the vertigo symptom (rotatory or postural vertigo, gait unsteadiness, or light-headedness); occurrence of accompanying symptoms (headache; nausea, vomiting, photo- or phonophobia, diplopia, other visual symptoms, tendency to fall); any action taken including any medication use. A diary template (original German version together with an English translation) is provided in Additional file 3.

Randomization, concealment, and blinding

Patients who met the eligibility criteria for enrolment were randomized in a 1:1 ratio to receive either metoprolol succinate or placebo for six months (Figure 1 CONSORT). Each study site received a pool of study medication including the treatment assignment in an opaque, sealed emergency envelope. If an eligible patient dropped out before the study medication had been delivered he or she was replaced by the next eligible patient enrolled at the same site. The concealed allocation was performed by an internet-based randomization schedule stratified by study site (<https://wwwapp.ibe.med.uni-muenchen.de/randoulette>). The fixed block size was four (starting with 6) which was not disclosed during the trial. The random number list was generated by a person with no clinical involvement in the trial. Patients and site personnel including outcome assessors, data analysts and statisticians remained blinded to treatment allocation.

Study treatments

Metoprolol-succinate sustained-release tablets (Beloc-Zok® mite 47.5 mg) manufactured by AstraZeneca, Wedel, Germany) were encapsulated for blinding purposes. Hard gelatine capsules containing the active ingredient were refilled from original pharmacy packaging into relabelled blisters by the pharmacy of the university hospital in Heidelberg, Germany. Placebo was an identically appearing inactive capsule filled with mannitol and aerosil but not containing any active ingredient, and was packed in identically appearing blisters as the investigational drug. Randomized patients were instructed to take one capsule per day starting as soon as possible after the receipt of the trial medication kit dispensed at baseline visit. The treatment procedure included a one week run-in period of 47.5 mg metoprolol succinate or placebo once a day (up-titration), a six month maintenance dosage with 95 mg metoprolol succinate or placebo once a day, plus tapering with 47.5 mg metoprolol succinate or placebo once a day for two weeks before stopping the prophylactic therapy (down-titration). Placebo treatment was justified due to lack of well-designed placebo-controlled trials for any drug therapy in VM. The six month treatment duration was deemed necessary to reliably assess a long-term prophylactic effect of the drug treatment on the incidence of VM-related vertigo attacks. If the patient was on prophylactic drug treatment of migraine, a washout period of at least one month was required before enrolment. Topiramate, valproic acid, lamotrigine, tricyclic antidepressants and other beta-blockers were considered as prohibited concomitant medication and thus, a protocol violation. Acute medical treatment of VM-related attacks like in episodic migraine with aura using non-opioid analgesics, non-steroidal anti-inflammatory drugs or triptans was allowed serving as added rescue medication. We aimed to assess the comparative effectiveness of the assigned prophylactic treatment regardless of whether or not switching to rescue medication had occurred which can be denoted as *'treatment policy estimand'* according to the ICH E9 addendum [24].

Statistical methodology and planned analyses

Protocol-defined efficacy outcomes, and changes after trial commencement

The primary objective was to assess whether metoprolol was superior to placebo with respect to both disease domains 'vertigo' and 'headache'. For the purpose of the study, the target estimate was based on the overall monthly mean incidence of vertigo and headache attacks during a 3-month long assessment period at the end of the double-blind 6-month treatment period, i.e., month 4 to 6 (day 91 to day 180) was defined as the time period of primary interest assuming that the maximum treatment effect emerges after being on study medication for more than 3 months. The pre-specified primary efficacy outcomes were the patient-reported number of vertigo attacks and the number of headache attacks per 30 day interval (starting from time point 1 defined as the date of first intake of the study medication). According to the protocol, superiority was to be claimed based on the vertigo outcome domain alone. Thus, the incidence of headache attacks per 30 days was defined as a co-primary outcome. In case of claimed superiority with respect to the outcome domain 'vertigo', the comparison of the monthly incidence of

headache attacks between both groups was to be considered next important. However, due to the poor documentation concerning headache-related symptoms and the diary focussing on the vestibular symptoms, derivation of a measurable variable for headache attacks was considered impossible and the co-primary efficacy endpoint had to be omitted. Further, the initially planned secondary outcomes duration and severity of vertigo episodes were omitted due to insufficient data quality. Instead, the number of *vertigo days* per 30 days (which was not preregistered in the protocol) was defined as a clinically meaningful key secondary efficacy outcome to assess the disease burden with respect to the outcome domain vertigo. A vertigo day was defined as a calendar day (0:00 to 23:59) demonstrating at least one documented vertigo episode of at least 5 minutes (regardless of severity and type). Derivation of this efficacy variable relies on fewer assumptions compared to a vertigo attack and also enables handling missing diary items.

On the contrary, a *vertigo attack* was endorsed applying the following decision rules: duration of at least 5 minutes and no longer than 72 hours, irrespective of vertigo type and severity; if time data (start and stop time) for a vestibular symptom were absent a duration of 24 hours was assumed; a vertigo episode which was interrupted by sleep or temporarily remits, was classified as one single attack, and not two; if applicable, patient-reported vertigo symptoms reported on two or more consecutive calendar days were summarized to one single vertigo episode lasting over consecutive calendar days (however, if the resulting duration extends 72 hours, these calendar days were considered free of vertigo attacks but counted as vertigo day).

A pre-specified diary-based secondary efficacy outcome was the number of monthly headache days (a calendar day where headache of any severity occurred according to the patient ratings). During the blind data review, this patient-reported outcome was refined to a *migraine headache day* (MHD), requiring at least one additional migraine-associated symptom such as nausea, vomiting, phono- or photophobia, disturbance of vision, or “migraine” provided as free text on the diary. However, features such as duration and severity of migraine headache or criteria as proposed by the International Classification of Headache Disorders-3 (ICHD-3) from 2018 [1] were not considered in order to derive definite MHD since these items were not requested on the diary.

All these changes to the latest protocol version concerning efficacy evaluation were made before breaking the treatment blind minimizing outcome reporting bias. Owing to the complexity of vestibular and migraine-associated symptoms, inaccurately documented episodes of vertigo (e.g. missing outcome items) and different individual perceptibility of both domains of the disease, the assessment of vertigo attacks, days and migraine headache days based on the raw daily diary recordings was very challenging. Therefore, a computer algorithm programmed in SAS was developed for the process of outcome adjudication and to derive all diary-based efficacy variables.

Protocol-defined observer-reported secondary efficacy endpoints included the proportion of patients achieving an improvement from baseline to month 6 in pursuit eye movement (change from state ‘saccadic (of any direction)’ to ‘smooth’ vs. change from state ‘smooth’ to ‘saccadic’, or no change); the

proportion of patients achieving an improvement in SVV (change from state 'abnormal' to 'normal' vs. change from 'normal' to 'abnormal' or no change; state 'abnormal' was defined as the absolute deviation of more than 2.5° from vertical). Further, the absolute change from baseline to month 6 in the DHI mean total score was assessed.

Statistical efficacy analyses (including changes to protocol-specified analyses)

Efficacy analyses were conducted for the full analysis set (FAS) which included all randomized patients (ITT, intention-to-treat population) who did not fail to satisfy a major entry criterion, irrespective whether they were treated or not. Subjects who provided neither primary nor secondary efficacy data were excluded from efficacy analyses assuming missingness at random (MAR). The per protocol (PP) sample consisted of all subjects part of the FAS who did not substantially deviate from the protocol and who were on treatment for more than 90 days, counting from day of first intake. Safety analyses were done on all patients who received at least one dose of study drug.

According to the protocol, the principal analysis for the primary endpoint incidence of vertigo attack per 30 days during the 3-month time period of primary interest (month 4 to 6) was a robust nonparametric comparison between both treatment groups by means of the Wilcoxon rank-sum test. However, in the course of the trial it was evident that dropouts and incomplete diary documentation creating missing data could not be adequately handled by the intended test-based approach. In order to deal with the missing data structure over time we used a Poisson mixed effects model (Poi GLMM) which not only yields unbiased parameter estimates when missing observations are missing at random (MAR), but also provides reasonably stable results even when the assumption of MAR is violated [25-27].

For this longitudinal model-based approach, the log-transformed number of *evaluated days* per 30 days (defined as the number of calendar days with assessments recorded in the diary within a 30-day interval) was considered as offset term in order to reflect missing diary information (e.g. for withdrawals) and to standardize the monthly incidence of vertigo attacks to 30 days for that month. Time (range 1 to 6) and treatment-by-linear time-interaction was used as fixed effects, together with patient-specific intercepts and slopes for time as normally distributed random effects. Assuming no rapid onset of effect staying stable over time, the main fixed effect for treatment group was omitted. The target estimates consist of the decay rate for the placebo group (fixed effect for time) as well as the incidence rate ratios (IRR) for the metoprolol group (treatment-by-time interaction) to assess if the magnitude of the difference between treatment groups varies over time. The latter can be interpreted as 'speed of efficacy' [28], that is, whether the active agent may be distinguished from placebo by how quickly reduction in incidence of attacks was achieved. The same longitudinal model approach was applied for vertigo days serving as supplementary analysis.

Migraine headache days per 30 days were analysed with a negative binomial model (with offset term for the corresponding number of evaluated days during the 90-day assessment period) using self-reported

symptoms documented within month 4 to 6 only. An analysis of covariance (ANCOVA) for absolute change from baseline in DHI mean total score at month 6 was performed which used a factor for treatment group and the baseline value as covariate. For the binary response measures, change state from baseline in SVV and pursuit eye movement at month 6, a logistic regression analysis was conducted (1, from abnormal to normal; 0, otherwise).

Safety and tolerability

Adverse events (AEs) and tolerability were systematically assessed by evaluating reported AEs, physical examinations and concomitant medication use. The safety population included data from all randomized patients who received at least one dose of the investigational medicinal product during the double-blind treatment phase. Serious AEs (SAEs) were coded and summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. For some AEs, the exact starting date (day and or month) was partially or completely missing. In order to deal with this different input accuracy or partial date issues, AEs were classified with respect to their occurrence (AEs emerging while on treatment vs post-treatment AEs) assuming the AE was experienced at the earliest possible date.

Sample size considerations

A fixed sample size calculation was performed for the primary efficacy outcome (number of vertigo attacks). A sample size of 106 patients in each group will have 80% power to detect a probability of 0.389 that an observation XM is less than an observation XP using a Mann-Whitney test with a 5% two-sided significance level. The probability of $P(XM < XP)=0.611$ was calculated with a presumed normal distribution and difference in means of 1 and a standard deviation of 2.5 (nQuery Advisor 7.0). On the basis of our experience with patient compliance in previous studies and routine treatment, we assumed a drop-out rate of about 20%. Thus, the fixed target sample size was a total of 266 patients (133 in each treatment group) to be allocated. Further detailed descriptions on how the sample size was calculated are provided in the Additional file 2.

The study database was stored in SAS (Unix Version 9.2, SAS Institute, Cary, NC). Statistical analyses were performed using the statistical software package R version 3.5.1 [29]. For the efficacy analyses we used the R package lme4 (version lme4_1.1-18-1) to fit frequentist generalized linear mixed effects models [30, 31]. All statistical tests were 2-sided, with a significance level of 0.05.

Results

Premature termination of the trial

In June 2017, the sponsor delegated person together with the responsible biometrician and the DSMB prompted an early termination of the study on the grounds of poor patient accrual after randomization of

130 patients, and not for any reasons related to safety.

Financial resources for the continuation of the PROVEMIG trial were no longer available due to lack of funding. To reach the a priori determined target sample size of 266 patients in total, further years and more recruiting sites would have been required, which was considered not feasible. Further concerns were the fact that the monthly recruitment rates in the participating sites were lower than anticipated and decreasing over time (Figure S1, Additional file 4). All in all, an early stopping for feasibility reasons at the risk of generating an underpowered trial providing inconclusive data seemed justified.

Patient disposition and baseline characteristics

At the time of the study termination, 527 patients were screened for eligibility at six sites. Despite constant attempts to increase recruitment rates at the participating sites, randomization was stopped after 130 patients were enrolled, 109 (84%) of them at the sponsor delegated person's site in Munich. The most common reasons for screen failure were failure to meet criteria for enrolment such as low baseline severity level with respect to VM-related attack incidence prior to enrolment, refusal to provide informed consent, excluded comorbidities, and ongoing beta-blocker therapy due to indications not necessarily associated with VM.

Figure 1 illustrates the patients' flow through the trial together with PRO specific information [20]. In total, 130 patients were allocated to either metoprolol or placebo and were included in the ITT population. The FAS population consisted of 127 patients with 3 patients being excluded after randomization: 2 patients allocated to placebo (concomitant diagnosis BPPV causing inability to discriminate episodes caused by VM from the ones caused by BPPV; did not fulfil the major entry criterion with respect to baseline attack severity); 1 patient allocated to metoprolol fulfilled a major exclusion criterion (concomitant diagnosis vestibular paroxysmia with no diary information provided). In the placebo group, 9 patients did not provide any diary information compared to 4 patients in the metoprolol group. Within the 3-month assessment period, diary data were available for 91 out of 127 patients of the FAS sample (42 patients in the placebo vs. 49 patients in the metoprolol group). The proportion of intermittent missing was rather low for both treatment groups whereas the proportion of monotone missing diary information, e.g. due to treatment adherence or non-compliance, was rather high. Besides, the proportion of missing diary data was higher in the placebo than in the metoprolol group (Figure S2, Additional file 4).

Table 1 gives the demographic and important clinical characteristics including vertigo-specific QoL score DHI of all randomized patients assessed at baseline visit. Overall, 60.8% of the randomized patients were female; the median age was 44 years. The proportion of patients diagnosed with definite (as opposed to probable) VM was 61.5%, with 64.6% in the metoprolol slightly higher compared to 58.5% in the placebo group. All in all, both groups were similar to each other with respect to demographics and baseline clinical patient characteristics. Pre-randomization attack frequency with respect to the domains vertigo and migraine was not documented although considered as key inclusion criterion. No information with regard to disease duration or age at onset was available.

Dosing and adherence to initial treatments

In total, 121 patients received at least one dose of the study medication. In the FAS, the median treatment duration (range) was 177 (0 to 203) days in the placebo, and 178 (0 to 236) days in the metoprolol group (difference in location of median duration (95% CI) was -1.999 (-6.000 to 2.999; P -value=0.451). A considerable amount of patients took rescue medication on an as needed basis. However the proportion was comparable in both randomized groups (data not shown).

Primary and key secondary efficacy analyses

For the FAS sample, 114 patients (54 on placebo, 60 on metoprolol) contributed data to the Poisson mixed-effects model which revealed an overall relief in vertigo-related symptoms over time in both treatment groups. The mean incidence rate of vertigo attacks on placebo was significantly reduced by the factor 0.830 per additional month while on treatment (95% CI, 0.776 to 0.887; P <0.001). It was hypothesized that the assigned active treatment would make this overall decay rate even smaller. The corresponding estimated factor, representing incidence rate ratio (IRR) compared to placebo, was 0.983 (95% CI, 0.902 to 1.071) on metoprolol; no evidence for a treatment-by-time interaction was found (global testing, Likelihood-Ratio (LR) test, P =0.696) indicating no statistically significant difference in the monthly incidence rates for vertigo attacks between both treatment policies. Table 2 displays the results for month 4, 5 and 6, representing the pre-specified 3-month time period of primary interest to assess treatment effectiveness. Within month 6, the marginal mean incidence rate per 30 days for vertigo attacks was 3.097 (1.914 to 4.281) for patients on placebo vs. 2.796 (1.792 to 3.800) on metoprolol. Similarly, for the PP sample (comprising of 89 patients; 41 of these on placebo), the overall decay rate was 0.848 (0.795 to 0.904; P <0.001) and the IRR was estimated to be 0.978 (0.901 to 1.061; P =0.593) indicating a lack of a beneficial treatment effect.

Considering the robustness of the primary result, a supplementary analysis for vertigo days was conducted in line with the primary efficacy analysis. For the FAS sample, the mean monthly incidence of vertigo days was reduced by 13% per additional month on placebo treatment (factor 0.870 (0.821 to 0.923); P <0.001). However, no superiority of metoprolol compared to placebo was found (IRR 0.940 (0.869 to 1.017); P =0.125). In figure 2, the left panel depicts the estimated monthly incidence rates for vertigo attacks during the whole 6-month treatment period for placebo and metoprolol treatment policy. The right panel shows the estimated monthly incidence rates over time for the key secondary outcome vertigo days. During the 3-month assessment period (month 4 to 6) the mean monthly incidence for MHD was similar in the placebo and metoprolol group. The corresponding IRR defining the treatment effect estimate was 1.048 (0.482 to 2.250; P =0.904).

Table 3 summarizes the results for planned key secondary efficacy outcome analyses at the pre-specified time point month 6. The DHI mean total score evaluating the self-perceived handicapping effects imposed by VM remained fairly stable at the end of the treatment period as compared to the score

measured at baseline visit. The complete case ANCOVA revealed no evidence for a between-treatment difference in mean change scores ($\Delta = -0.079$ (-0.360 to 0.201; $P=0.577$)). As regards smooth pursuit eye movement and SVV assessments, no statistically significant and clinically meaningful difference between placebo and metoprolol could be detected. For both clinician-reported endpoints, the chance of achieving treatment response, i.e. a change from state 'abnormal' at baseline to 'normal' at month 6, did not differ between both groups. For smooth pursuit eye movement, the estimated OR was estimated to be 1.483 (0.454 to 5.277; $P=0.520$), for SVV the OR was 0.413 (0.055 to 2.235; $P=0.322$) on metoprolol compared with placebo. Hence, patients assigned to metoprolol did not achieve superior patient- and clinician-reported outcomes compared to those assigned to placebo treatment suggesting the robustness of the principal result.

Safety and tolerability

Since metoprolol succinate is a well-established drug used for many years in common diagnoses such as hypertension and episodic or chronic migraine it was expected to be generally well tolerated. Hence, there were no protocol-defined adverse events of special interest. No deaths or SUSARs occurred during the trial. 18 patients (9 in the placebo, and 9 in the metoprolol group) reported a total of 21 SAEs in the whole 9-month study period. Within the maximum treatment duration of six months, a total of 348 AEs occurred (174 in each group) for the safety population; 18.6% (11/59) of patients on placebo were not affected by AEs compared to 16.1% (10/62) on metoprolol. With respect to AE severity, the incidence was similar for both groups (AEs on placebo: 45.1% mild, 16.2% severe; on metoprolol: 42.2% mild, 14.5% severe). In both treatment groups, at least three AEs occurred for 50% of patients (placebo: 49.2% (29/59); metoprolol: 50.0% (31/62)). 15 patients (9 in the placebo vs. 6 in the metoprolol group) were affected by a total of 17 SAEs while on study treatment. Two severe treatment-emergent SAEs, one in each group (placebo: hospitalization due to diverticulitis; metoprolol: hospitalization due to migraine; both recovered) were suspected by the investigator to be causally related to treatment. One patient on metoprolol discontinued owing to a SAE, seven because of non-serious AEs, compared to two (two) patients on placebo owing to SAEs (non-serious AEs). Detailed information of the frequency of AEs which occurred within the 6 months of intervention is displayed in Table 4.

Discussion

Vestibular migraine is considered the most common neurologic cause of recurrent spontaneous vertigo episodes [32]. The main reason for the diagnostic challenges is the broad spectrum of its manifestations, e.g. episodic vestibular symptoms without typical migraine headaches, and the wide variety of ictal and interictal symptoms [33].

Principal findings

The PROVEMIG trial proved not to be feasible in patient recruitment and was early terminated after randomization of 130 patients, i.e. after achieving of about 50% of the target enrolment. Nevertheless, there are several important findings and lessons that can be learnt from it to inform future interventional drug trials in this patient population and to apply methods of quantitative evidence synthesis in terms of meta-analyses.

The key finding of the trial are as follows: First, in both randomized groups, patients experienced a significant reduction in the monthly incidence of vertigo attacks (according to the definition used in this study, i.e. lasting between 5 minutes and no longer than 72 hours) of 17.0% (11.3% to 22.4%) over the whole double-blind 6-month treatment period. However, prophylactic treatment with beta-blocker metoprolol was not superior to placebo in diminishing the monthly incidence of vertigo attacks over time (IRR 0.983 (0.902 to 1.071)). Though the trial was prematurely ended, the 95% confidence intervals for the estimated decay rate and IRR are rather narrow; apparently, large treatment effects are not very likely given the present results. Second, neither in the patient-reported efficacy outcomes including the DHI total score measured by a psychometrically validated questionnaire, nor in the clinical assessments a beneficial therapeutic effect of metoprolol could be established. Third, the investigational and placebo treatment regimens were approximately equally safe and well tolerated in the participating patients, with no unexpected safety findings. In summary, there is no evidence from randomised controlled trials to support or refute the metoprolol treatment in patients diagnosed with VM.

Comparison with previous literature

To our knowledge, this is the first report of a pragmatic, double-blind, randomized, placebo-controlled trial investigating the effectiveness, tolerability and safety of a prophylactic symptomatic treatment with metoprolol compared to placebo in VM patients. The first Cochrane systematic review on this topic published in 2015 aimed to assess the effects of pharmacological agents (including beta-blockers) used in the prophylactic treatment of VM-associated symptoms against placebo or no treatment (“wait-and-see”). However, the authors did not find any evidence from completed RCTs using the Bárány Society/ IHS diagnostic criteria, while identifying PROVEMIG as the only ongoing trial fulfilling the inclusion criteria with respect to trial design [9].

Strengths and weaknesses

The trial population consisted of 130 patients (with 121 patients commencing the allocated intervention) selected from 527 patients screened for eligibility. Patients were diagnosed according to the established Neuhauser criteria 2001. The current IHS criteria for VM were not available at that time, which are mostly similar to “definite VM” according to Neuhauser. Investigators at the participating trial sites were clinical experts in the diagnosis and treatment of vestibular disorders. Due to the complexity of the disease entity expert knowledge with respect to diagnosis is essential in order to differentiate between VM and other diseases with spontaneous recurrent vertigo, most notably Menière’s disease [34-36]. Baseline

assessments (Table 1) provide neuro-otological and ophthalmological data systematically collected from a well-defined sample of VM patients. The female preponderance in the study population was found to be 1.5:1 which is consistent with the 1.5 to 5:1 female-to-male ratio reported in other studies [2, 37]. The six month duration of treatment allowed to ascertain whether the active agent may be distinguished from placebo by how quickly patients achieve a reduction in monthly vertigo attacks ('speed of effect'). Since the target was comparing the benefit of two treatment policies (i.e. the drug as actually taken), all patients were allowed to take rescue medication if necessary. About 68% of patients comprising the per-protocol population were at least three months on treatment. Altogether, the proportion of missings with respect to the diary-based efficacy outcomes was not higher than expected for symptomatic trials assessing the ability of an intervention to provide symptom relief from the condition.

In this trial, the specific experimental treatment with beta-blocker metoprolol was compared in a blinded manner with an unspecific treatment, i.e. placebo, which is assumed to cover all the unspecific effects of an intervention (e.g., patients' expectations, natural course or regression-to-the-mean) [38]. The findings for patients on placebo may not fully reflect the natural course of VM which has been reported to vary over time.

Our study has certain limitations: Faced with persisting recruitment difficulties, the trial was not successful in reaching the target sample size. Therefore, we cannot perform confirmatory analyses, but provide 95% confidence intervals for estimators of treatment effectiveness. One factor that led to delays and early trial closure was the number of screening failures being higher than expected. Reasons for the poor participant accrual were multifactorial and included unwillingness to accept the underlying intervention and failure to meet eligibility criteria (in particular, low baseline frequency with respect to attacks of VM, or comorbidities being contraindications for metoprolol). Further, the number of participating trial sites was lower than anticipated. With 84% of 130 randomized patients recruited at a single site, the highly specialized dizziness unit at the LMU Munich, our findings may not be applicable to all German VM patients. Due to the considerable overlap of the two disorders VM and Menière's disease, the study population might be contaminated.

Since VM is a complex and relatively new single disease entity, clinically meaningful patient-centred primary efficacy outcomes are still debated. In this trial, a patient dizziness diary routinely used in clinical practice for diagnosis at the site of the principal investigator was adapted for the clinical trial setting. Paper-based daily diaries are prone to errors or being lost and have no simple methods for backup and reconstruction of information. If symptom diaries are applied for tracking recurrent events and to understand longitudinal relationships over time in confirmatory clinical trials, patient recordings have to be reviewed for accuracy and interpretability of reported symptoms in order to derive rigidly defined primary efficacy endpoints. To face this dilemma, further research is warranted to define responsive patients-centred outcomes for both outcome domains (vertigo and migraine headache) that have been shown to be important to patients and clinicians to allow informed decision making. Since VM patients experience a wide variety of ictal and interictal symptoms, more effort should be considered in investigating whether established outcome measurement instruments for both domains are appropriate

for this target population, and in evaluating the quality of these instruments (primarily with respect to responsiveness to change) [39]. As such, the validated scores derived from the self-reported questionnaire DHI together with self-administered migraine-specific quality-of-life questionnaires such as the Migraine Disability Assessment (MIDAS) or the Headache Impact Test (HIT) might be used to evaluate the treatment benefit while reducing the documentation burden for the patient compared to a diary-based measurement of disability which could be essential for long-term comparative effectiveness trials [40-44].

Conclusions

It is of utmost importance to develop a core outcome set for this complex vestibular disease comprising of symptoms attributable to two both vertigo and migraine headache aiming to reduce the documentation burden for the trial participants in the case of long-term trials and to define clinically meaningful, patient-centered efficacy endpoints being sensitive to change and reproducible [45]. For future phase 3 trials, a more efficient site set-up and improved recruitment methods seem appropriate. Besides, study site personnel should aim to follow patient retention strategies to ensure that participants, once recruited, were engaged clinically and followed up as completely as possible to avoid particularly non-compliance with diary maintenance. Additional multicentre, randomized, placebo-controlled trials are needed to replicate these findings and to explore subgroups for patients reporting response to antihypertensive drugs.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants before initiation of the first study specific procedure. The study protocol, including the patient information and consent form, was approved by the local ethics committee of each participating institution (leading ethics committee: ethics committee of the Medical Faculty of the Ludwig-Maximilians-Universität, Munich, Germany; reference number: 152-11 fed) and by Germany's Federal Institute for Drugs and Medical Devices (BfArM). Clinical trial authorisation was granted on 01 Sept. 2011 (sponsor's protocol code number: VMMET009). The trial was performed in accordance with the Declaration of Helsinki and other applicable guidelines, laws, and regulations.

Consent for publication

Consent forms for the trial included consent for publication of results in peer-reviewed journals.

Availability of data and materials

Data cannot be shared publicly because participants did not explicitly consent to the sharing of their data as per European Union's General Data Protection Regulation and the corresponding German privacy laws.

Data are available through the Research Ethics Board of the Ludwig-Maximilians-Universität, Munich, Germany, for researchers who meet the criteria for access to confidential data. Please address requests to ethikkommission@med.uni-muenchen.de (ethics committee of the LMU Munich) and to biostatistician mansmann@ibe.med.uni-muenchen.de.

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: OB, CA, AT, and UM declare that they have no competing interests.

MS 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, Auris Medical, Biogen, Eisai, Grünenthal, GSK, Henning Pharma, Interacoustics, MSD Sharp & Dohme, Otometrics, Pierre-Fabre, TEVA GmbH, and UCB. He is a shareholder in IntraBio. He acts as a consultant for Abbott, Actelion, AurisMedical, Heel, IntraBio and Sensorion.

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Authors' contributions

OB and CA have shared first authorship. MS, OB, CA and UM contributed to the design of the trial, wrote the study protocol or preceding research proposals leading to the funding of the trial, and interpreted the work. As coordinating investigator, MS initiated the collaborative clinical trial project and is the guarantor. MS, OB, and all investigators of the recruiting study sites acquired the data. OB developed the rules to derive efficacy outcomes based on the raw daily diary recordings and is responsible for the corresponding SAS algorithm. AT wrote the statistical analysis plan; AT and CA performed the statistical analyses. AT, CA and UM interpreted the results. CA and OB wrote the first draft and all subsequent versions of the manuscript. All authors revised the work critically for important intellectual content 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. The corresponding author attests that

all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors read and approved the final manuscript.

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List Of Abbreviations

AE: Adverse events; **BPPV:** benign paroxysmal positional vertigo; **CI:** confidence interval; **CONSORT:** CONSORT Consolidated Standards of Reporting Trials; **CRF:** Case Report Form; **DHI:** Dizziness Handicap Inventory; **FAS:** full analysis set; **GLMM:** generalized linear mixed model; **ICH:** International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; **ICHD-3:** International Classification of Headache Disorders-3; **IHS:** International Headache Society; **IRR:** incidence rate ratio; **ITT:** Intention-To-Treat; **MAR:** missingness at random; **MHD:** migraine headache day; **OR:** Odds Ratio; **PP:** per

protocol; **PRO**: patient reported outcome; **RCT**: Randomized controlled trial; **SAE**: Serious AE; **SVV**: subjective visual vertical; **VM**: vestibular migraine.

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Tables

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

Characteristics	Placebo (n=65)	Metoprolol (n=65)
Demographics		
Age (years)		
Mean (standard deviation)	42.8 (14.3)	44.4 (14.2)
Median (range)	44.0 (19 – 70)	45.0(19 – 75)
Male sex		
No. (%)	29 (44.6)	22 (33.8)
VM Diagnostic Criteria		
Probable VM, No. (%)	27 (41.5)	23 (35.4)
Definite VM, No. (%)	38 (58.5)	42 (64.6)
General physical examination		
Body mass index (BMI)		
Mean (standard deviation)	26.4 (5.5)	25.9 (3.9)
Median (range)	25.3 (17.6 – 46.6)	26.0 (17.5 – 38.1)
Missing No. (%)	5 (7.7)	6 (9.2)
Systolic blood pressure (mmHg)		
Mean (standard deviation)	134.1 (18.6)	136.8 (16.3)
Median (range)	130.0 (100.0 – 188.0)	136.0 (109.0 – 180.0)
Missing No. (%)	9 (13.8)	6 (9.2)
Diastolic blood pressure (mmHg)		
Mean (standard deviation)	85.8 (10.1)	85.5 (9.7)
Median (range)	86.0 (66.0 – 108.0)	84.0 (68.0 – 107.0)
Missing No. (%)	9 (13.8)	6 (9.2)
Heart rate (pulse/min)		
Mean (standard deviation)	74.8 (10.0)	72.4 (10.3)
Median (range)	73.0 (60.0 – 100.0)	73.0 (54.0 – 100.0)
Missing No. (%)	8 (12.3)	6 (9.2)

DHI, mean total score *		
Mean (standard deviation)	1.7 (0.8)	1.6 (0.7)
Median (range)	1.7 (0.4 – 3.5)	1.5 (0.4 – 3.1)
Missing No. (%)	1 (1.5)	2 (3.1)
Physical examination – Cranial nerves: Head-Shaking Nystagmus		
No. of patients with nystagmus (%)	4 (6.2)	4 (6.2)
Missing No. (%)	5 (7.7)	6 (9.2)
Physical examination – Coordination: Romberg's Test		
No. of patients with instability (%)	3 (4.6)	4 (6.2)
Missing No. (%)	2 (3.1)	0 (0.0)
Neuro-orthoptic Examinations		
Smooth Pursuit Eye Movement		
No. saccaded (%)	25(41.5)	29 (44.6)
Missing No. (%)	2 (1.5)	0 (0.0)
Absolute Subjective Visual Vertical (SVV), deviation in degrees		
Mean (standard deviation)	0.5 (1.2)	0.4(1.2)
Median (range)	0.0 (0.0 – 5.0)	0.0 (0.0 – 6.0)
Missing No. (%)	3 (4.6)	0 (0.0)
Gaze-evoked nystagmus		
No. (%)	7 (10.8)	14 (21.5)
Missing No. (%)	2 (3.1)	0 (0.0)
Nystagmus in the scanning laser ophthalmoscope		
No. (%)	8 (12.3)	3 (4.6)
Missing No. (%)	12 (18.5)	9 (13.8)
Disturbed fixation suppression		
No. (%)	6 (9.2)	3 (4.6)
Missing No. (%)	4 (6.2)	1 (1.5)
Oculography		

Spontaneous nystagmus (°/sec.)		
Velocity = 0, No. (%)	47 (72.3)	48 (73.8)
Velocity ≥ 1, No. (%)	16 (24.5)	16 (24.5)
Velocity ≥ 3, No. (%)	1 (1.5)	1 (1.5)
Missing No. (%)	2 (3.1)	1 (1.5)
Gaze-evoked nystagmus (°/sec.)		
Velocity = 0, No. (%)	14 (21.5)	7 (10.8)
Velocity ≥ 1, No. (%)	43 (66.1)	49 (75.3)
Velocity ≥ 3, No. (%)	6 (9.2)	10 (15.3)
Missing No. (%)	8 (12.3)	9 (13.8)
Bithermal Caloric testing		
(normalized right-left-difference according to Jongkees' formula†)		
Mean (standard deviation)	-8.5 (20.5)	-6.9 (21.9)
Median (range)	-10.8 (-58.3 - 73.0)	-5.9 (-82.9 - 71.4)
Missing No. (%)	6 (9.2)	5 (7.7)

* DHI, dizziness handicap inventory: High score indicates high impairment. Range of possible total scores, 0 to 100. Mean total score (range 0 to 4) indicates averaging for the number of answered questions (Additional file 4).

† Jongkees' formula = $(|RC| + |RW| - (|LC| + |LW|)) / (|RC| + |LC| + |RW| + |LW|)$; with RW: right warm rinse (44°C water), LW: left warm rinse, RC: right cold rinse, LC: right cold rinse. The condition "warm" means irrigation with 44°C water; "cold" means irrigation with 30°C water.

Table 2. Summary of diary-based primary and secondary endpoints for the FAS population.

	N †	Placebo	Metoprolol
Primary End point			
Vertigo attacks , monthly* incidence rates (95% CI)†	114	4.499 (3.295 to 5.704)	4.202 (3.138 to 5.267)
Month 4		3.733 (2.527 to 4.939)	3.428 (2.384 to 4.471)
Month 5		3.097 (1.914 to 4.281)	2.796 (1.792 to 3.800)
Month 6			
Decay rate (95% CI), <i>P</i> value		0.830 (0.776 to 0.887), <0.001	
IRR (95% CI), <i>P</i> value		0.983 (0.902 to 1.071), 0.696	
Secondary End points			
Vertigo days , monthly* incidence rates (95% CI)†	114	6.757 (5.067 to 8.447)	5.278 (3.999 to 6.557)
Month 4		5.881 (4.126 to 7.637)	4.319 (3.070 to 5.569)
Month 5		5.119 (3.326 to 6.912)	3.534 (2.334 to 4.735)
Month 6			
Decay rate (95% CI), <i>P</i> value		0.870 (0.821 to 0.923), <0.001	
IRR (95% CI), <i>P</i> value		0.940 (0.869 to 1.017), 0.125	
Mean monthly* MHDs ‡			
Month 4 to 6	91	2.400 (1.410 to 4.410)	2.505 (1.488 to 4.215)
IRR (95% CI), <i>P</i> value		1.048 (0.482 to 2.250), 0.904	

IRR, Incidence Rate Ratio; MHD, migraine headache day (of any severity).

* mean incidence rates per 30 days derived by a model-based approach assuming missingness at random; pre-specified time period of primary interest month 4 to 6; reference group = placebo.

† Primary efficacy analysis, by a Poisson GLMM based on the whole 6-month treatment period. Assumption: maximal effect of intervention during the pre-specified 90-days assessment period months 4 to 6. Analysis of vertigo day rates as supplementary analysis.

‡ MHD: Rates and IRR are estimated from a negative binomial GLM based on the aggregated MHD data reported within months 4 to 6 only (91 patients contributing MHD-related diary documentation).

Table 3. Key secondary outcome results (least square mean change difference or Odds Ratio): Analysis of absolute change from baseline at month 6 for DHI, by ANCOVA; for change state from baseline at month 6 in eye movement and SVV, by logistic regression for FAS sample

Secondary End points	N ‡	Placebo	Metoprolol
DHI mean total score	91		
LS mean change* (95% CI)		0.159 (-0.252 to 0.570)	0.080 (-0.310 to 0.470)
Difference vs Placebo (95% CI) <i>P</i> value		-0.079 (-0.360 to 0.201) 0.577	
Pursuit eye movement	92		
Patients achieving responset, No. (%)		5 (11.6)	8 (16.3)
Odds (95%)		0.132 (0.045 to 0.305)	0.195 (0.092 to 0.416)
Difference vs. placebo (95% CI), OR (95%) <i>P</i> value		1.483 (0.454 to 5.277) 0.520	
SVV	90		
Patients achieving responset, No. (%)		4 (9.5)	2 (4.2)
Odds (95%)		0.105 (0.032 to 0.262)	0.043 (0.012 to 0.179)
Difference vs. placebo (95% CI), OR (95%) <i>P</i> value		0.413 (0.055 to 2.235) 0.322	

DHI, dizziness handicap inventory; LS, least square (estimates derived by complete case ANCOVA for absolute change scores); OR, odds ratio (estimates derived by logistic regression (unadjusted)); SVV, Subjective visual vertical. * Change score means difference between post-intervention score at month 6 vs baseline score. See Table 1 for description of DHI score ranges.

† Logistic regression for the change state in smooth pursuit eye movement or SVV between baseline and month 6 (1, change from abnormal to normal; 0, otherwise). Pursuit eye movement: treatment response means change from state ‘saccadic’ to ‘smooth’. ‡ Numbers of patients with non-missing observations for both baseline and 6 month visit (FAS population: n=127, Placebo: 63, Metoprolol: 64).

Table 4: Safety assessment by study treatment group (safety sample) during the 6-month treatment period.

Safety Assessment	Placebo (n= 59)	Metoprolol (n= 62)
No. of deaths	0	0
No. of patients with SUSARs	0	0
No. (%) of patients with early termination from the study due to SAEs *	2 (3.4)	1 (1.6)
No. (%) of treatment related SAEs	1 (1.7)	1 (1.6)
No. (%) of patients with at least one SAE; total number of SAEs	8 (13.5); 10	6 (9.7); 7
No. (%) of patients with early termination due to adverse events *	4 (6.7)	8(12.9)

SUSARs: Suspected unexpected serious adverse reactions; SAEs: serious adverse events.

Percentages (%) are based on the number of patients in the safety sample.

Reasonable possibility for a causal relationship= drug-event relation reported as “possible”, “probable”, or missing according to the adverse event case report form (CRF).

* Adverse events or SAE leading to treatment discontinuation according to the adverse event case report form (CRF).

Figures

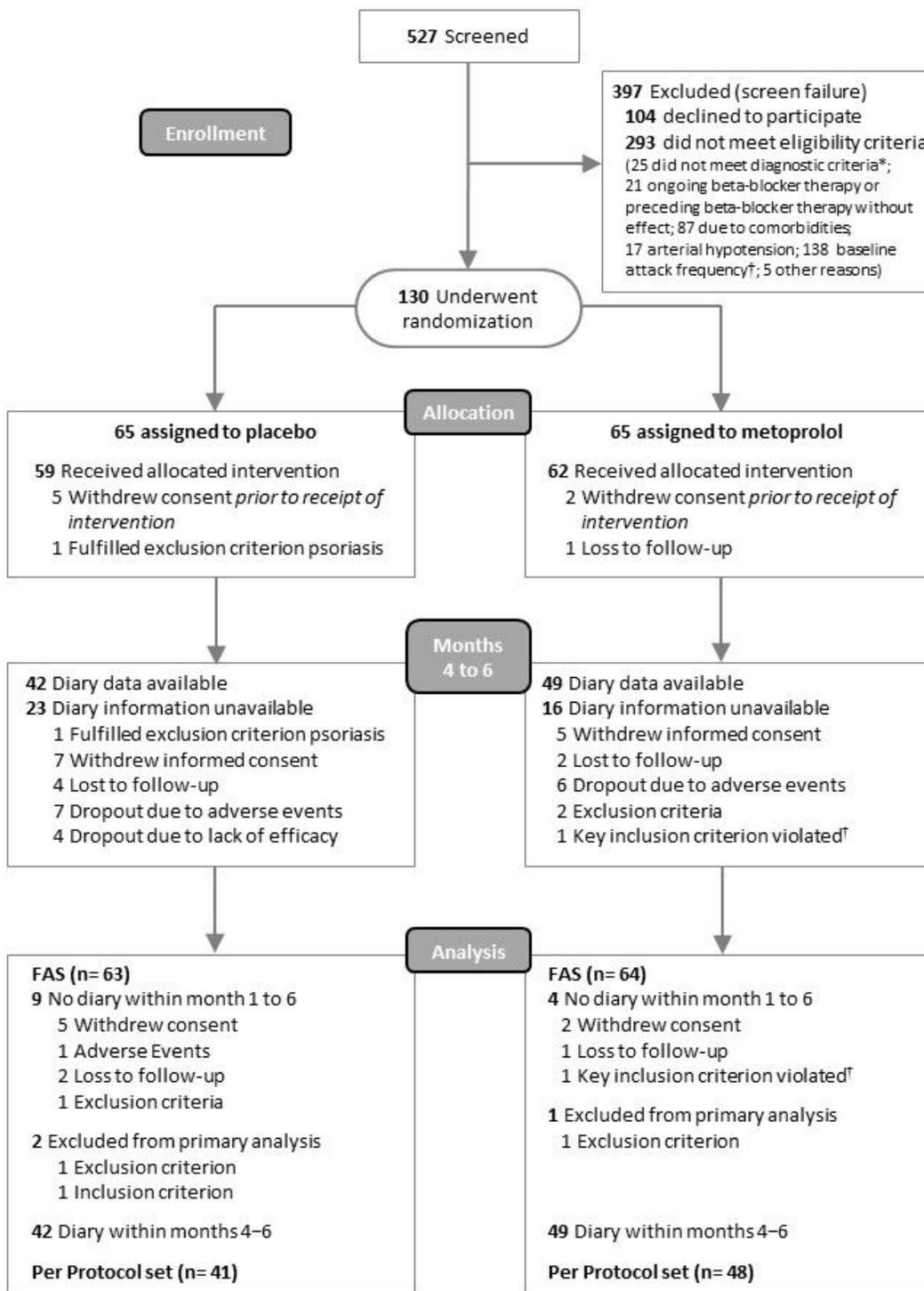


Figure 1

Study flow chart together with PRO specific information. 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 missing data within the 6-month treatment period (diary information unavailable means no diary at all within the time period of primary interest, day 91 to day 180). * Diagnostic criteria according to

Neuhauser (2001). † Baseline frequency of vertigo attacks in the last 3 subsequent months prior to enrolment. Per protocol: treatment duration >90 days, counting from day of first intake.

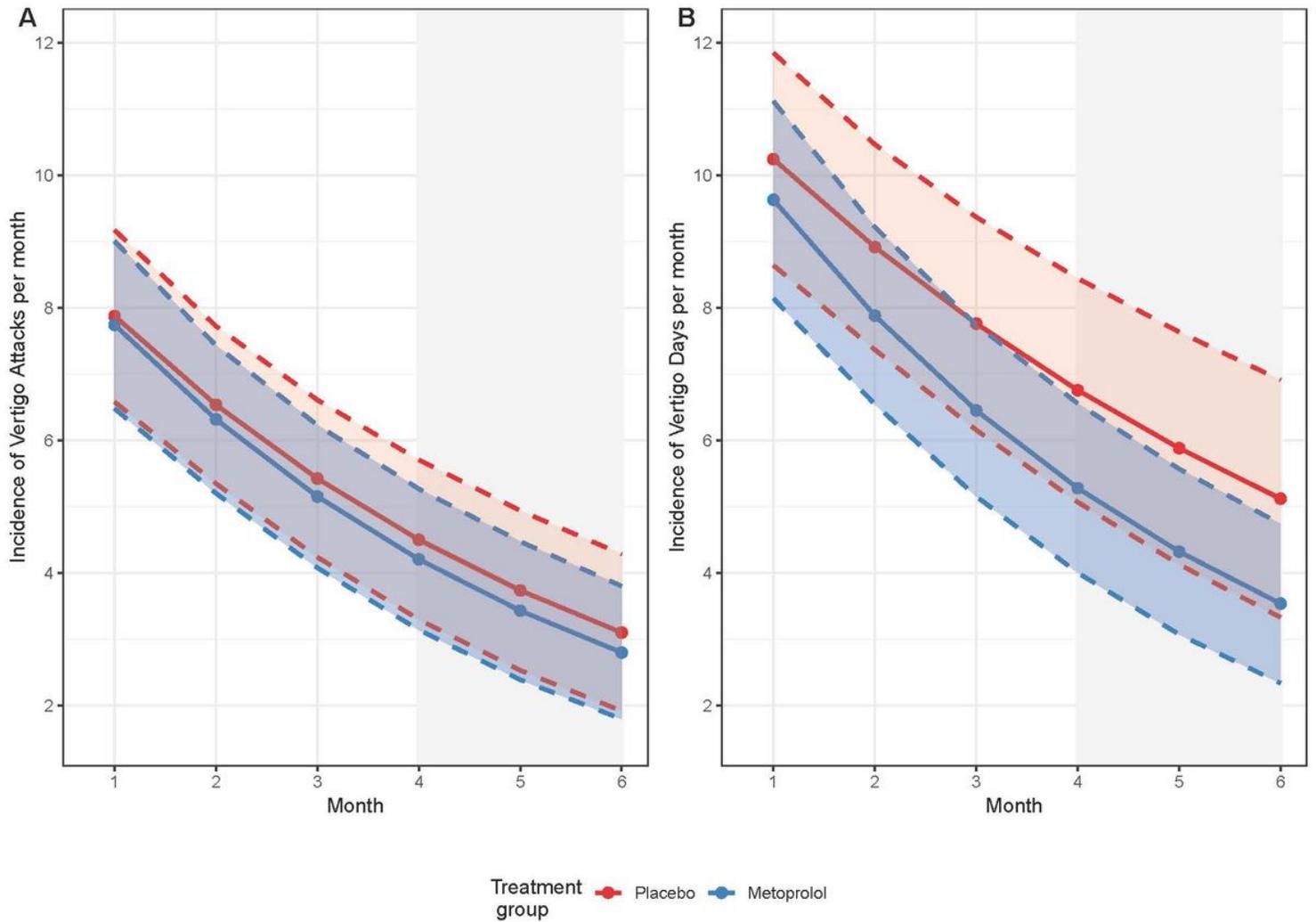


Figure 2

Predicted marginal means (with pointwise 95% CI) for the incidence of vertigo attacks (primary efficacy outcome, panel A) and vertigo days (panel B) per 30 days during the 6-month treatment period (FAS population). A Poisson random intercept and slope model was applied for the principal analysis. The grey shaded area represents the 90-day time period of primary interest comprising of estimated monthly incidences rates for month 4 to 6.

Supplementary Files

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- [supplement1.docx](#)
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