Report Synopsis of Study: PROVEMIG

EudraCT No.: 2009-013701-34
Sponsor's Protocol Code Number: VMMET009

<table>
<tr>
<td>Name of Sponsor/Company:
Klinikum der Universität München, AöR
Prof. Dr. med. Dr. h.c. Michael Strupp, FRCP, FANA, FEAN (Sponsor delegated person, SDP)
Deutsches Schwindel- und Gleichgewichtszentrum (DSGZ), Studienzentrale
Marchioninistr. 15, 81377 München, Germany</td>
<td rowspan="3">Individual Study Table Referring to Part of the Dossier:
n/a

Volume: n/a

Page: n/a</td>
<td rowspan="3">(For National Authority Use only)</td>
</tr>
<tr>
<td>Name of Finished Product:
Beloc-Zok® mite 47.5 mg Retardtabletten (Manufacturer: AstraZeneca GmbH, Wedel, Germany)</td>
</tr>
<tr>
<td>Name of Active Ingredient:
Metoprolol Succinate</td>
</tr>
<tr>
<td colspan="3">Title of Study:
Prophylactic treatment of vestibular migraine with Metoprolol: a double-blind, placebo-controlled trial
Short Title: PROVEMIG

Latest Protocol Version V2.1, dated 19 Dec 2011
(Amendment 1 after protocol version V 2.0, 13 Jul 2011), approved before trial commencement, i.e. start of recruitment. Summary of changes:

▪ changes of key inclusion criterion (diagnosis of “definite vestibular migraine”, replaced with diagnosis of “definite” or “probable vestibular migraine”)
▪ changes in the production process of IMP
▪ addition of rescue/escape/salvage therapy</td>
</tr>
</table>

Principal Investigators:

Leiter der Prüfgruppe (according to German Drug Law) and their substitutes are listed, if they gave consent:

Prof. Dr. med. Dr. h.c. Michael Strupp, FRCP, FANA, FEAN (SDP, Coordinating Investigator)
Prof. Dr. med. Hans-Christoph Diener
Prof. Dr. med. Hubert Löwenheim
Prof. Dr. med. Thomas Lempert
Prof. Dr. med. Wolfgang Heide
Prof. Dr. Holger Rambold

Study centre(s): Before trial commencement, 8 centres in Germany gave consent to participate in the recruitment process. In the end, 6 centres were initiated and screened for eligible patients (LMU Munich, Celle, Altötting-Burghausen, Parkklinik Berlin-Weißensee, Tübingen, Essen), 4 of them (LMU Munich, Celle, Altötting-Burghausen, Essen) allocated patients to the trial.

Hospital of the University of Munich
Clinic for Neurology and German Center for Vertigo and Balance Disorders
Marchioninistr. 15, D-81377 Munich

Hospital of the University of Essen
Department of Neurology
Hufelandstr. 55, D-45130 Essen

Hospital of the University of Tübingen
Department of ENT
Elfriede-Aulhorn-Str. 5, D-72076 Tübingen

Schlosspark-Klinik
Department of Neurology
Heubnerweg 2, D-14059 Berlin

Allgemeines Krankenhaus
Neurology
Siemensplatz 4, D-29223 Celle

Kreiskliniken Altötting-Burghausen
Neurologische Klinik
Vinzenz-von-Paul-Str. 10, D-84503 Altötting

Publication (reference)
Not applicable (manuscript submitted, under review)

Studied period (years): 06/2012 (first patient first visit) – 01/2018 (last patient last visit); last patient in: 10/04/2017 In 07/2017, recruitment was prematurely stopped due to poor patient accrual	Phase of development: III

Objectives

Primary Objective:
To demonstrate the superiority of Metoprolol Succinate treatment regarding the number of vertigo attacks per month compared to placebo

Secondary Objectives:

- To quantitatively describe and compare the number of vertigo days;
- To quantitatively describe and compare the median duration and severity of vertigo attacks;
- To quantitatively describe and compare the number of headache days;
- To quantitatively describe and compare change from baseline to 6-months visit in neurological and neuro-orthoptic assessments between both groups;
- To quantitatively describe and compare the change from baseline to 6-months visit in impairment due to vertigo or dizziness between both groups;
- To analyze whether the superiority of Metoprolol Succinate treatment is kept up to three months after the last drug intake;
- To check for the occurrence of the adverse effects reported in the summary of product characteristics (SmPC) of the drug.

Methodology
This study was an investigator-initiated, national, multicenter, randomized, double-blind, placebo-controlled, 2-arm parallel-group, phase III trial aiming to establish superiority of Metoprolol (maintenance dosage of 95mg per day) compared to placebo treatment on vestibular and headache-related symptoms in patients with diagnosed vestibular migraine (VM).

Patients were screened for their eligibility to participate in the study. Each patient gave written informed consent before any study-related procedures were performed. Patients satisfying all eligibility criteria were randomly assigned in a 1:1 ratio to one of the two treatment arms to receive either placebo or Metoprolol Succinate continuously for six months.

Study-related procedures included documentation of relevant medical and neurological history, laboratory testing at screening visit, physical and neurological examinations (general, cranial nerves, oculomotor system, motor function and reflexes, sensibility, coordination) at baseline and

at follow-up visit scheduled 3 months after end of treatment; oculography, neuro-orthoptic examinations (including subjective visual vertical (SVV), smooth pursuit eye movements), concomitant medication, and documentation of adverse events. Besides, study participants were provided a paper-based dizziness diary, and they were instructed to document vestibular symptoms (items: type, duration and severity, time of occurrence) together with accompanying symptoms including migraine-related events (headache or related free text) on a daily basis over the whole 9-month study period.
At clinical visits scheduled at the screening visit/ baseline, after 1 and 3 month, at the end of the treatment period after 6 months and after a 3-month post-treatment follow-up period scheduled after 9 months, trial participants were additionally asked to complete a self-administered paper-based questionnaire (Dizziness Handicap Inventory, DHI) to evaluate their impairment due to vertigo. Furthermore, telephone visits were scheduled 2, 4 and 5 months after enrolment to increase protocol adherence.

Number of patients (planned; randomized and analysed):
Planned (according to the initial fixed sample size calculation): Total number of 266 patients to be allocated (133 in each treatment group).

Randomized: Total number of 130 patients, 65 assigned to Metoprolol, 65 to placebo treatment. The trial was prematurely ended due to insufficient recruiting**.**

Analysed (intention-to-treat): Total number of 130 subjects;
Full analysis set sample (FAS): 127 subjects (Metoprolol: n=64, placebo: n=63).

Diagnosis and main criteria for inclusion:
Adult male and female subjects with vestibular migraine (VM).
Subjects meeting all of the following requirements could be included:

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

- Patients aged 18 years or above,
- Patients with diagnosis of probable (criteria no. 1., 4., 5., see below) or definite (criteria no. 1., 2., 3., 5.) vestibular migraine according to the criteria of Neuhauser *et al*. 2001:
    1. episodic vestibular symptoms of at least moderate severity (rotational vertigo, other illusory self or object motion, positional vertigo, head motion intolerance, i.e., sensation of imbalance or illusory self or object motion that is provoked by head motion);
    2. migraine according to the IHS criteria (Olesen et al. 1988);
    3. at least one of the following migrainous symptoms during at least two vertiginous attacks: migrainous headache, photophobia, phonophobia, visual or other auras;

4. at least one of the following: migraine according to the IHS criteria; migrainous symptoms during vertigo as specified in 3; migraine-specific precipitants of vertigo, e. g. specific foods, sleep irregularities, hormonal changes; response to antimigraine drugs
5. other causes ruled out by appropriate investigations;

- Between 6 and 30 attacks per 3 subsequent months before enrolment;
- Subjects with the ability to follow study instructions and likely to attend and complete all required visits;
- Written informed consent of the subject.

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

- Patients not able to give consent;
- Other vestibular disorders such as Menière's disease, phobic postural vertigo, benign paroxysmal positioning vertigo, vestibular paroxysmia;
- Central disorders such as paroxysmal brainstem attacks, transient ischemic attacks;
- 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 SA-block, AV-block;
  - Bradycardia < 50 bpm at rest, systolic blood pressure < 100 mmHg, end-grade peripheral arterial disease;
  - known severe coronary heart disease or heart failure;
  - concurrent treatment with MAO-inhibitors, sympathomimetic drugs, Catecholamine-depleting drugs, digitalis glycosides;
- Poorly controlled diabetes mellitus;
- Pheochromocytoma;
- Suspicion of developing thyrotoxicosis;
- Disorders of hemostasis;
- Porphyria;
- Psoriasis;
- Pregnancy or breast-feeding;
- 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;
- Life expectancy < 12 months;

- Other serious illness, e.g., severe hepatic, cardiac, or renal failure, acute myocardial infarction, neoplasm or a complex disease that may confound treatment assessment;
- Treatment with beta-blockers
- The patient has received any investigational medication within 30 days prior to administration of study medication or is scheduled to receive an investigational drug up to 30 days after end of study;
- The patient was previously admitted to this trial or simultaneous participation in another clinical trial or participation in any clinical trial involving an administration of investigational medicinal product.

Test product, dose and mode of administration, batch number:
Metoprolol Succinate 47.5 mg once daily during the first week (up-titration); 95 mg after the first week until the end of the 6-month treatment period (maintenance dosage); plus tapering with 47.5 mg per day for two weeks before stopping therapy (down-titration).
Each capsule contained 47.5 mg and 95 mg Metoprolol Succinate, respectively.

Batch numbers:
VMMET009/201221
VMMET009/201311
VMMET009/201332
VMMET009/201432
VMMET009/201519
VMMET009/201640

Duration of treatment: 6 months of study medication (placebo or Metoprolol), followed up with 3 months off-treatment after the end of the treatment period (after completion of the treatment period daily administration of 47.5 mg Metoprolol or placebo for two weeks before final treatment stop); maximum individual study duration 9 months

Reference therapy, dose and mode of administration, batch number:
Placebo; 1 placebo capsule was administered orally.

Batch numbers: not applicable

Criteria for evaluation:
Note: Any changes to the latest protocol version concerning efficacy evaluation were made before unblinding.

Efficacy

Primary efficacy endpoint:

Number of vertigo attacks*) per 30 days during the last three months of the six month treatment

period. [*Co-primary endpoint 'number of headache attacks per 30 days' skipped due to quality issues concerning the raw patient ratings provided by the dizziness diary*]
*) main criterion for evaluation: vertigo episode with a duration of at least 5 minutes and no longer than 72 hours, irrespective of vertigo type and severity; otherwise, documented vertigo episodes were not evaluated.

Secondary endpoints:

- Number of vertigo days per 30 days during the last three months of the 6-month treatment period [*secondary efficacy outcome not pre-planned in the protocol, added for supplementary analyses*];
- Median duration and severity of vertigo attacks during the last 3 months of the 6 months treatment period and the last 3 months of the total follow-up period [*statistical analyses not possible due to data quality*];
- Number of migraine days per 30 days during the last 3 months of the 6 months treatment period days [*outcome definition changed*];
- Absolute change from baseline to month 6 in the DHI mean total score;

Further secondary endpoints concerning changes in the neurological and neuro-orthoptic examination:

- Proportion of patients achieving an improvement from baseline to 6-month visit in pursuit eye movement (positive change defined as change from status 'saccadic (of any direction)' to 'smooth'; vs. negative change defined as change from status 'smooth' to 'saccadic' or no change)
- Proportion of patients achieving an improvement in subjective visual vertical (change from status 'abnormal' to 'normal' vs. change from 'normal' to 'abnormal' or no change; status 'abnormal' was defined as the absolute deviation of more than 2.5° from normal range)

Safety
Adverse events were collected from the first intake of the investigational medical product until the last visit of the subject (scheduled 3 months after the treatment period according to the protocol, i.e. 9 months after randomization).

Statistical methods:

Analysis of the primary efficacy endpoint:

The *PROVEMIG* phase III trial was conducted to provide evidence for or against the effectiveness of Metoprolol compared to placebo. The primary efficacy endpoint was the incidence of vertigo attacks per 30 days relative to the number of evaluated days, i.e. the number of days with non-missing information with respect to the patient's vertigo status provided by the daily diary recordings. Assuming that the maximal impact would most probably be starting month 4 (i.e. after more than 90 day on treatment ending month 6), a pre-specified 90-day assessment period at the end of the 180 day treatment period was defined to derive target estimates and to compare between

Metoprolol and placebo.
In order to deal with the missing data structure over time a Poisson mixed effects model (Poi GLMM) was applied as principal analysis for the primary efficacy endpoint. For this longitudinal approach, the log-transformed number of evaluated days per 30 days was considered as offset term in order to reflect missing diary information and to standardize the monthly incidence of vertigo attacks to 30 days for that month. Time (discrete variable, 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. The target estimates (together with 95% confidence intervals) consist of the decay rate for the placebo group (fixed effect for time) as well as the incidence rate ratios (RR) for the Metoprolol group (treatment-by-time interaction) to assess if the magnitude of the difference between treatment groups varies over time.

Analyses of secondary endpoints:

For the secondary efficacy outcome vertigo days per 30-day interval the same longitudinal model approach was applied serving as supplementary analysis to demonstrate robustness of the principal analysis.

Migraine headache days per 30 days were analyzed with a negative binomial model (with offset term for the corresponding patient-specific number of evaluated days during the pre-specified 90-day assessment period across month 4 to 6) considering the aggregated number of migraine-associated symptoms reported 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 using a factor variable for treatment group and the baseline score value as covariate.
For the binary-response measures, change status from baseline in SVV and pursuit eye movement measure at month 6, a logistic regression analysis was conducted (response coded as 1, from abnormal to normal; 0, otherwise).

Adverse events were analyzed descriptively stratified by group.

Summary – Conclusions

In June 2017, the sponsor delegated person together with the responsible biometrician and the Data Safety and Monitoring Board 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. Besides, monthly recruitment rates in the participating sites were lower than anticipated and decreasing over time. All in all, an early stopping for feasibility reasons at the risk of generating an underpowered trial providing inconclusive data seemed justified.

Efficacy Results:

At the time of trial termination, no evidence for a difference in the monthly incidence of vertigo

attacks (according to the definition used in this trial) between both treatment groups was detected. For the FAS sample, the rate ratio (RR) was 0.983 (95% confidence interval (CI), 0.902 to 1.071; *P*=0.696, global likelihood ratio test) for Metoprolol vs. placebo. There was a significant reduction of the overall monthly vertigo attack rate by the factor 0.830 (95% CI, 0.776 to 0.887; *P*<0.001).

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 supplementary analysis for vertigo days confirmed that there was no treatment benefit for patients on metoprolol: For the FAS sample, the RR was 0.940 (0.869 to 1.017; P=0.125) for Metoprolol vs. placebo, and the overall decay rate for vertigo days was estimated to be 0.870 (0.821 to 0.923; P<0.001).

Results were consistent for all subjective secondary efficacy outcomes, i.e. incidence in monthly migraine days and absolute change in DHI mean total score:

Migraine days:
The negative binomial modelling approach for migraine days confirmed the robustness of the longitudinal model used for primary efficacy analysis. There was no evidence (no significant *P*-value) for a difference in the number of migraine days during the assessment period between Metoprolol and placebo (FAS sample: Estimated mean incidence rate per day on placebo was 0.079 (0.047 to 0.147), the RR (95% CIs) for Metoprolol vs. placebo during months 4 to 6 was 1.048 (0.482 to 2.250; *P*= 0.904).

DHI total score:
The respective mean difference between both groups in absolute change in DHI mean total score was Δ= -0.079 points (-0.360 to 0.201).

Clinician-reported secondary outcomes:
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.

Safety Results:

Metoprolol can be considered as a safe and well tolerated drug for a symptomatic treatment of

vestibular migraine according to the Neuhauser diagnostic criteria 2001.

Adverse Events (AEs) and Serious Adverse Events (SAEs):
Since Metoprolol Succinate is a well-established drug used for many years in common diagnoses such as hypertension and 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).

Conclusion

A 6-month prophylactic treatment with Metoprolol Succinate did not diminish the incidence of evaluated vertigo attacks (according to the definition used in this study, i.e. lasting between 5 minutes and no longer than 72 hours) compared to placebo. Neither in the patient-reported secondary efficacy outcomes including the DHI total score nor in the clinician-reported efficacy outcomes a beneficial therapeutic effect of Metoprolol could be established.
The investigational and placebo treatment were approximately equally safe and well tolerated with no unexpected safety findings.
The *PROVEMIG* trial did not achieve its planned recruitment goal. So far, there is no evidence from randomized placebo-controlled trials to support or refute the Metoprolol treatment in patients diagnosed with VM according to the Neuhauser criteria 2001. Faced with persisting recruitment difficulties, future studies should aim to follow patient retention strategies and involve more participating study sites.

Date of report: 11 January 2019

Signature:

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

References:

Neuhauser H, Leopold M, von Brevern M, et al. The interrelations of migraine, vertigo, and migrainous vertigo. *Neurology* 2001;56(4):436–41.

Olesen J. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;8(suppl 7):9–96.