SYNOPSIS

Name of Sponsor/Company: LMU Klinikum, AöR Prof. Dr. Dr. Michael Strupp (SDP, Sponsor Delegated Person) Neurologische Klinik und Deutsches Schwindel- und Gleichgewichtszentrum (DSGZ), Studienzentrale Marchioninistr. 15, 81377 München, Germany	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: Timonil®		
Name of Active Ingredient: Carbamazepine		

Title of Study:
Prophylactic treatment of vestibular paroxysmia with carbamazepine: a prospective, randomized, placebo-controlled, cross-over, multi-center trial (VesPa)

Protocol Version 2.1 dated 08-Nov-2017 is Amendment 1 of first positive voted Protocol Version 2.0 dated 03-Apr-2020 which include updated inclusion criteria due to changes of diagnosis of vestibularis paroxysmia and an additional MRI examination for a subgroup of patients

Investigators:
Leiter der Prüfgruppe and their substitutes are listed, if they gave consent.

04 Prof. Dr. med. Dr. h.c. Michael Strupp, FRCP, FANA, FEAN
Dr. med. Nicolina Goldschagg
09 Prof. Dr. med. Wolfgang Heide
06 Prof. Dr. med. Dagny Holle-Lee

Study centre(s): Trial site Hospital of University of Munich and Allgemeines Krankenhaus Celle screened for patients and allocated patients into the trial. The third trial site Essen did not screen or allocate patients.

Trial site 04
Hospital of University of Munich
Department of Neurology and German Center for Vertigo and Balance Disorders
Marchioninistr. 15, D-81377 Munich

Trial site 09
Hospital Celle
Department of Neurology
Siemensplatz 4, 29223 Celle

Trial site 06
University Clinic Essen
Department of Neurology, Clinical Trials
Hufelandstr. 55, D-45147 Essen

Publication (reference)
manuscript not planned yet

Studied period (years): 18-Nov-2016 (FPFV) – 27-Feb-2019 (LPLV)	Phase of development: III

Objectives

Main objective: The primary objective of the comparison of carbamazepine and placebo is to demonstrate that carbamazepine is efficacious in reducing the number of vertigo attacks in patients with vestibular paroxysmia measured by a diary.

Secondary objectives: To demonstrate that carbamazepine is efficacious in
1) reduce days with vertigo
2) improving impairment and quality of life (assessed by the Dizziness Handicap Inventory (DHI, the Vestibular Disorders Activities of Daily Living Scale (VDADL) and the EQ-5D-5L)
3) shorten the average duration of the attacks and median severity of the attacks of vertigo
4) shorten the hyperventilation induced vertigo and/or nystagmus

To assess the side effects, adverse events, SAEs, SUSARs

Methodology

This study was an investigator-initiated (IIT) prospective, randomized, placebo-controlled, cross-over, multi-center trial to demonstrate that carbamazepine is efficacious in reducing the frequency, duration and severity of vertigo attacks, the number of vertigo per month and improving quality of life in patients with vestibular paroxysmia compared to placebo.
Subjects were screened for their eligibility to participate in the study. Each subject gave written informed consent before any study-related procedures were performed.
Subjects satisfying all selection criteria were randomly assigned in a 1:1 ratio to one of the treatment sequences to receive either placebo followed by carbamazepine, or carbamazepine followed by placebo for six weeks in each treatment period.
Study-related procedures included documentation of medical and neurological history, physical, neuro-ophthalmological and neuro-otological examinations, and instrumental testing (MRT, ECG, audiogram, video-oculography with caloric testing). Patients were asked to complete the Dizziness Handicap Inventory, Vestibular Disorders Activities of Daily Living Scale and EQ-5D-5L questionnaire, and diary of the daily attacks while in the treatment phases.

Number of patients (planned):
To be assessed for eligibility: Total number of 204 patients
To be allocated: Total number of 153 patients
To be analyzed: Total number of 153 patients (122 patients completed both treatment periods)

Number of patients:
Assessed for eligibility: 21 patients (16 at trial site 04 and 5 at trial site 09)
Enrolled in the study: 10 patients (8 at trial site 04 and 2 at trial site 09)

Diagnosis and main criteria for inclusion:

The main symptoms of vestibular paroxysmia are brief attacks of rotatory or postural vertigo lasting seconds to a few minutes with or without ear symptoms (tinnitus and hypoacusis). As in trigeminal neuralgia or hemifacial spasm, it is assumed that a neurovascular cross-compression of the eighth cranial nerve is cause of the attacks.

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

- written informed consent
- over 18 years of age
- at least 5 attacks in the three months prior to inclusion
- attacks last less than 5 minutes
- course of attacks is stereotypical of the individual patient
- spontaneous occurrence or provocation due to certain head movements
- symptoms cannot be explained by another disease, in particular Menière disease, vestibular migraine, BPPV or perilymph fistula

- ability to follow study instructions and likely to attend and complete all visits
- female subjects with childbearing potential and fertile men are eligible if they use a medically accepted highly effective contraceptive method

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

- other vestibular disorders such as Menière's disease, BPPV, vestibular migraine or perilymph fistula at the time of inclusion
- Paroxysmal brainstem attacks after stroke or in multiple sclerosis
- Episodic ataxia
- Absence seizures or types of epilepsy, which include absence seizures
- Intake of other antiepileptic drugs
- Serve hepatic, cardiac or renal failure
- Known intolerance to carbamazepine
- Known intolerance to structurally related substances, for example tricyclic antidepressants
- Known damage of the bone marrow or acute and/or previous severe haematological diseases
- Atrioventricular block
- Active pregnancy or breast-feeding
- Known hepatic porphyria
- required therapy with MAO-Inhibitors, voriconazol or stiripentol
- Hypo- or hypernatraemia
- Known myotonic dystrophia
- Known alcoholabuse
- Life expectancy under 12 months
- Participation in another study with an investigational drug or device within the last 30 days before participating of the study

Test product, dose and mode of administration, batch number:
Carbamazepine: patients took 400 mg per day (dose schedule 1-0-1) in week 3 to 8 after a 2-week up-titration (week 1: 200 mg per day, dose schedule: 0-0-1; week 2: 400 mg per day, dose schedule: 1-0-1). Week 9 for down-titration, dose schedule 0-0-1.

Batch numbers:
Package No. 101-108 = Batch No. VESPA/201636
Package No. 109-112 = Batch No. VESPA/201715
Package No. 117-128 = Batch No. VESPA/201748
Package No. 133-144 = Batch No. VESPA/201828
Package No. 149-160 = Batch No. VESPA/201908

Duration of treatment: 2x 6 weeks (treatment phase with carbamazepine and treatment phase with placebo) with 2 weeks for up-titration and a 2 weeks down-titration after the second treatment phase.

Reference therapy, dose and mode of administration, batch number:
Placebo: patients took 2 placebo capsules per day (intake schedule 1-0-1) in week 3 to 8 (week 1 and week 9: dose schedule: 0-0-1; week 2: dose schedule: 1-0-1).

Batch numbers:
Package No. 101-108 = Batch No. VESPA/201636
Package No. 109-112 = Batch No. VESPA/201715
Package No. 117-128 = Batch No. VESPA/201748
Package No. 133-144 = Batch No. VESPA/201828
Package No. 149-160 = Batch No. VESPA/201908

Criteria for evaluation:
Efficacy
Primary Endpoints:
Number of vertigo attacks per month during the 6-week treatment periods

Secondary Endpoints:
1) Days with vertigo during the two treatment periods
2) Change of the Dizziness Handicap Inventory (DHI), the Vestibular Disorders Activities of Daily Living Scale (VDADL and the EQ-5D-5L)
3) Average (per day) duration of the attacks of vertigo and median severity of the attacks of vertigo reported by the patient
4) change of hyperventilation induced vertigo and/or nystagmus

Safety
Adverse events (AE), serious adverse events (SAE), suspected unexpected serious adverse reaction (SUSAR) were collected for the entire study duration.

Statistical methods:
The VesPa trial was conducted to provide evidence for or against the efficacy of carbamazepine compared to placebo in vestibular paroxysmia measured by total number of vertigo attacks during the treatment phases collected via patients diary.

Summary – Conclusions
In October 2019, sponsor delegated person together with responsible Data Safety and Monitoring Board prompted an early termination of the study on the grounds of poor patient accrual after randomization of 10 patients within 2 years and not for any reasons related to safety. Financial resources for the continuation of VesPa trial were no longer available due to lack of funding. To reach the determined target sample size further years and more recruiting site would have been required, which was considered not feasible. Besides, monthly recruitment rates in the participating site were lower than anticipated. All in all an early stopping for feasibility reasons seemed justified.

Efficacy Results
A total of 10 patients could be enrolled in this study. At the time of trail termination, no evidence for a difference in the number of vertigo attacks between both treatment periods was detected.
The mean of vertigo attacks within the placebo phases are 2.3 attacks per day (SD=3; n=5) and 2.0 attacks per day (SD=2.5; n=5). Compared to Carbamazepine treatment phases, there is an insignificant increase, as the average of vertigo attacks is 2.5 attacks per day (increase of 9%; SD=3.1; n=4; p=0.46; α=0.05) and 2.9 attacks per day (increase of 45%; SD=4.5; n=5; p=0.35; α=0.05). In summary, the analysis demonstrate an insignificant increase (p=0.35) of number of vertigo attacks of 2.1 attacks per day (n=10; SD=2.6) to 2.7 attacks per day (n=9; SD=3.7) under carbamazepine treatment.

Key secondary outcome:
1) Patients under placebo had on average at least one vertigo attack every second day (0.51 attacks per day; n=10; SD=0.35), under Carbamazepine average value is 0.52 attacks per day (n=9, SD=0.35), which is insignificant (p=0.47).
2) Patients reported outcome was obtained by several questionnaires (DHI, EQ-5D-5L and VDADL) before each treatment period and at the end of the treatment periods. The Dizziness handicap inventory (DHI) demonstrated an insignificant reduction after each treatment period (p=0.13; α=0.05). The average value after Carbamazepine treatment improved by 0.09 points per question (n=9). The improvement after placebo treatment was 0.34 points per question (n=9). Similar results were assessed by Vestibular Disorders Activities of Daily Living Scale (VDADL). After Carbamazepine treatment patients reported in average an improvement in

daily activities of about 0.6 points per question (n=9) in comparison before carbamazepine treatment. No differences were measured after placebo treatment compared before treatment period (n=10). There is also no significant difference between Carbamazepine and placebo treatment (p=0.31, α=0.05). The EQ-5D-5L questionnaire contains questions about current situation in mobility, self-care, usual activities, pain/discomfort and anxiety/depression and a visual analogue scale (0-100) to record patient's self-rated health. Analysis demonstrate a worsening after Carbamazepine treatment (average= 1.33 points per question; n=9) and placebo treatment (average=0.5 points per question; n=10). The difference between Carbamazepine and placebo treatment is insignificant (p=0.31). Same results were obtained by the visual analogue scale for patient's self-rated health. Average of improvement after Carbamazepine treatment is 5.9 points (n=9) and after placebo treatment average value is 7.25 points (n=10, p=0.35; α=0.05).

3) There is no significant reduction of duration of vertigo attacks (p=0.16) under carbamazepine compared to placebo treatment. Results demonstrated an average duration of attacks of 127 sec per day (n=10; SD=0.35) under placebo treatment and 41 sec per day (n=8; SD=60) under Carbamazepine treatment. Furthermore, no significant limiting of intensity of the attacks could be determined under Carbamazepine treatment compared to placebo (p=0.41; α=0.05). The average intensity of vertigo attacks under placebo treatment is 2.12 points of 5 point scale (n=9; SD=0.5). Under Carbamazepine treatment average intensity of vertigo attacks is 2.19 points of 5 point scale (n=8; SD=0.7).
4) Due to low recruitment rate no evaluation regarding key secondary point 4 could be performed. There are no changes of hyperventilation induced vertigo and/or nystagmus after Carbamazepine treatment or placebo treatment.

Safety Results

27 Adverse Events were documented throughout the course of the trial. Of these, none were assessed as serious. Most AEs were mild (18) or moderate (8), one was assessed as severe. 74% of AE outcomes were classified as recovered or resolved.

In the carbamazepine group there were 14 AEs: 9 classified as mild (64,3%), 4 as moderate (28,6%), 1 as severe (7,1%, Tiredness, depressed mood). This patient discontinued treatment due to AE.

4 were possibly related to the drug (1 tiredness and depressed mood, two times dizziness during fast head movements and 1 accomodation disorder), 3 (21,4%) unlikely and 7 (50%) not related.

In the placebo group there were 13 AEs. 9 classified as mild (69,2%), 4 as moderate (30,8%), none as severe. In table below all adverse events are listed.

Statistic		**Carbamazepin** (N=14)	**Placebo** (N=13)	**All** (N=27)
Akkomodationsstörung	n=	1	0	1
Brustschmerzen intermittierend	n=	1	0	1
Durchfall	n=	1	0	1
Erkältung	n=	1	1	2
Gewichtszunahme bei fehlendem Sättigungsgefühl	n=	1	0	1
Halsschmerzen	n=	1	0	1
Juckreiz	n=	0	1	1
Kopfschmerzen	n=	2	0	2
Kopfschmerzen (während Attacke, zum ersten mal !)	n=	0	1	1
Magendruck	n=	0	1	1
Magenschmerzen	n=	0	1	2
Mandelentzündung	n=	0	1	1
OP Dig. 2+3 rechts (bei Heber-Dehner-Arthrose mit Entfernung eines zuvor eingesetzten Drahtes)	n=	0	1	1
Schwindel bei schneller Kopfbewegung	n=	1	0	1
Schwindel beim nach oben schauen	n=	1	0	1
Tachykardie	n=	0	1	1
akute Bronchitis	n=	0	1	1

akute Exazerbation allergische Rhinitis	n=	0	1	1
bakterielle Infektion	n=	0	1	1
gedrückte Stimmung, Müdigkeit	n=	1	0	1
grüner Urin	n=	1	0	1
leichte und kurze Magenverstimmung nach Mahlzeit (Kaiserschmarrn), auch bei Sohn	n=	0	1	1
schlechte Stimmung, depressiv verstimmt	n=	1	0	1
taube Finger und Zehen (intermittierend)	n=	0	1	1

Date of report: 15. January 2021

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