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: Dekristol®		
Name of Active Ingredient: Vitamin D		

Title of Study:
Vitamin D in secondary prevention of benign paroxysmal positional vertigo: a prospective, multicentre, randomized, placebo-controlled, double-blind study (VitD@BPPV)

Protocol version 2.0 dated 02-Nov-2016 is first positive voted and approved version. Addition of barbeque manoeuvre for treatment therapy of BPPV, additional information material for patients and changes in the analysis of trial parameter were requested in Amendment 1 (version 2.01 dated 02-May-2017) and positive vote by EC 14-Jun-2017 and approved by BfArM 06-Jun-2017. Amendment 2 (protocol version 2.02 dated 25-Jul-2017) contains analysis process of trial blood parameters and change of deputy at trial site Munich. Amendment 2 was approved by BfArM 29-Aug-2017 and positive voted 30-Aug-2017.

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

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Publication (reference)
manuscript not planned yet

Studied period (years): 24-Feb-2017 (FPFV) – 14-May-2020 (LPLV)	Phase of development: II/III

Main objectives

- Proof of efficacy of vitamin D to the reduction of the number of patients with one or more relapses of BPPV

Secondary objectives

- Quantification of the limitation due to vertigo (investigation by means of "Dizziness Handicap Inventory" (DHI) and "Vestibular Disorders Activities of Daily Living Scale" (VDADL)
- Proof of efficacy of vitamin D to the reduction of frequency of relapses of every single patient
- Group analysis: vitamin D

1) within reference range at time point of study inclusion and treatment within placebo group
2) below reference range at time point of study inclusion and treatment within placebo group
3) within reference range at time point of study inclusion and treatment within verum group
4) below reference range at time point of study inclusion and treatment within verum group

Methodology

This study was an investigator-initiated (IIT) prospective, multicentre, randomized, placebo-controlled, double-blind trial to demonstrate that vitamin D is efficacious in reducing the number of patients with relapses of BPPV. 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 or vitamin D for 14 months.
Study-related procedures included documentation of medical and neurological history, physical and neurological examination and positioning manoeuvre. Patients were asked to complete the Dizziness Handicap Inventory, Vestibular Disorders Activities of Daily Living Scale and document the number of relapses of BPPV.

Number of patients (planned):
To be assessed for eligibility: Total number of 300 patients
To be allocated: Total number of 219 patients
To be analyzed: Total number of 208 patients

Number of patients:
Assessed for eligibility: 95 patients (75 at site 04; 5 at site 06 and 15 at trial site 08)
Enrolled in the study: 59 patients (39 at site 04; 5 at site 06 and 15 at site 08)

Diagnosis and main criteria for inclusion:
The main symptoms of benign paroxysmal positional vertigo (BPPV) are brief in part strong attacks of rotatory vertigo lasting seconds. These attacks can be provoked by reclination of the head or turning of the head/the body toward the affected ear. The pathophysiology of BPPV is related to a displacement of the otoconia toward the semicircular canals, which may remain floating in the endolymph of the semicircular canal (canalolithiasis) or adhere to the cupula (cupulithiasis).

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

- written informed consent to participation in the study
- age $\geq$ 18 years
- patients with BPPV of the posterior, horizontal or anterior semicircular canal (confirmed by diagnostic maneurvers) of different etiologies (idiopathic, traumatic, other vestibular diseases)
- ability to follow study instructions and likely to attend and complete all visit

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

- Osteoporosis
- Hyper-/Hypocalcemia
- Hyper-/Hypophosphatemia
- Hypercalcuria
- Uro-/Nephrolithiasis in medical history
- Intake of vitamin D-metabolites/-analogues
- Intake of cardiac glycoside
- Sarkoidosis
- Active or intended pregnancy
- Hereditary fructose intolerance, glucose-galactose malabsorption, sucrose-isomaltase deficiency, congenital galactose intolerance, congenital lactase deficiency
- pseudohypoparathyreodism
- life threatening disease with statistical life expectancy < 12 months
- Former participation in this study or participation in a clinical trial with intake of an investigational drug within the last 30 days before participation in this study

Test product, dose and mode of administration, batch number:
Vitamin D: patients took 1000 I.E. per day (dose schedule 1-0-0) for 14 months

Batch numbers:
BPPV/201703, BPPV/201707, . BPPV/201710, BPPV/201804, BPPV/201812, BPPV/201824

Duration of treatment: 14 month treatment with vitamin D or placebo. No up-titration or wash-out is needed.

Reference therapy, dose and mode of administration, batch number:
Placebo: patients took 1 placebo capsules per day (intake schedule 1-0-0) for 14 month

Batch numbers:
BPPV/201703, BPPV/201707, . BPPV/201710, BPPV/201804, BPPV/201812, BPPV/201824

Criteria for evaluation:
Efficacy
Primary Endpoints:
Number of patients with relapse(s) of BPPV between visit 2 and final visit (corresponding observation period of 12 months

Secondary Endpoints:

- Absolute changes of DHI and VDADL measured before (V1), 2 months (V2) and 7 months (V3 after beginning of the therapy and at the end of treatment period (14 months after beginning of therapy (V4)); DHI and VDADL will also be measured at supplementary visits (taking place in case of relapse(s) of BPPV
- Number of relapses per patient from visit 2 to final visit
- Group analysis: vitamin D
    - Within reference range at timepoint of study inclusion and treatment within placebo group
    - Below reference range at timepoint of study inclusion and treatment within placebo group
    - Within reference range at timepoint of study inclusion and treatment within verum group
    - Below reference range at timepoint of study inclusion and treatment within verum group
- Correlation of the levels of vitamin D to the number of patients with relapses and to the number of relapses of the single patient (independent of treatment group)

Statistical methods:
The VitD@BPPV trial was conducted to provide evidence for or against the efficacy of vitamin D compared to placebo in BPPV patients measured by number of patients with relapses of BPPV the treatment phase.

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 59 patients within 2 years and not for any reasons related to safety. Financial resources for the continuation of VitD@BPPV 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 59 patients could be enrolled in this study, but 14 patients were drop outs, so only data of 45 patients could be analysed. At the time of trail termination, no evidence for a difference in the number of patient with relapses between both treatment arms was detected. 20 patients were enrolled to the placebo group and 20% (5 patients) had relapses of BPPV. To the verum group 25 patients were enrolled and 44% (11 patients) had relapses. These results demonstrate no advantage of treatment with vitamin D regarding the reduction of relapses of BPPV.

Key secondary outcome:

Dizziness Handicap Inventory (DHI)

The absolute changes of dizziness handicap inventory (DHI) scores between vitamin D and placebo group is 0.1 after 2 month treatment compared to beginning of treatment (95 % CI; -0.441; 0.641); p-value = 0.711, which is insignificant. Same statistical insignificant result was analysed for absolute change of DHI values after 7 month compared to beginning of treatment. The absolute change of vitamin D minus placebo is 0.2 (95% CI; -0.358; 0.758); p-value = 0.473. Tendency continues also for the end of treatment period (14 months) compared to beginning of treatment. The absolute change of DHI scores of verum and placebo group is -0.1 (95 % CI; -0.729; 0.529); p-value = 0.749, which is statistically insignificant.

Vestibular Disorders Activities of Daily Living Scale (VDADL)

The analysis of the scores of the VDADL questionnaire demonstrates following statistical values within the treatment arms verum and placebo. Absolute change of VDADL scores after 2 month treatment compared to beginning of treatment is 0.2 (95% CI; -0.664; 1.064); p-value = 0.643. Score difference of absolute change of both groups after 7 month of treatment compared to beginning of treatment is 0.6 (95% CI; -0.169; 1.369); p-value = 0.123. And after 14 month of treatment the absolute change is 0.2 (95% CI; -0.538; 0.938); p-value = 0.586. All changes between verum and placebo group are statistical insignificant.

Relapses of BPPV

Patients reported relapses of placebo group after 2 month treatment were 0.3 relapses of BPPV per patient, whereas in the verum group the value is 0.36 relapses of BPPV. This is a statistical insignificant difference of 0.06 (95% CI; -0.498; 0.387); p-value = 0.801. After 7 month treatment, patients in the placebo group reported 0.11 relapses of BPPV per patient, patients in the verum group reported 1 relapse of BPPV per patient. The mean difference is -0.9 (95% CI; -1.919; 0.129); p-value = 0.085. Same results were analysed after 14 month of treatment. Patients of the placebo group reported in average 0.7 relapses of BPPV per patient less compared to patients of verum group (95% CI; -0.465; 1,844); p-value = 0.234.

Safety Results

96 Adverse Events were documented throughout the course of the trial. Of these, 14 were assessed as serious but also as "not related" to the treatment, so no SUSAR was observed. 10 SAEs were documented in the verum group, where 1 SAE was assessed as mild (anxiety and depressive disorder), 5 as moderate (perinal bleeding, orthostatic syncope, acute hyperthyreosis, hip luxation, tonsillectomy) and 4 SAE as severe (angina pectoris, coronary artery disease with stent placement, excision basal cell carcinoma, excision squamous cell carcinoma). 4 SAEs were documented in the placebo group, where 1 SAE was assessed as mild (surgery hallux valgus), 2 as moderate (basal cell carcinoma, myocardial infarction) and 1 as severe (complete thyroidectomy). All SAE outcomes were classified as recovered or recovered with sequelae (anxiety and depressive disorder, orthostatic syncope).

Of 82 non-serious Adverse Events, 37 were assessed as mild, 43 as moderate and 2 as severe. 78% of AE outcomes were classified as recovered or resolved. In the vitamin D group there were 44 AEs: 19 classified as mild (43.2%), 24 as moderate (54.5%), 1 as severe (2.3%, worsening sore throat). 2 were possibly related to the IMP (worsening of gastro-oesophageal reflux and hypercalciuria). In the placebo group there were 38 AEs; 18 classified as mild (47.4%), 19 as moderate (50%), 1 as severe (2.6%, ischialgia). In table below all adverse events are listed.

Statistic of non-serious SAEs		**Vitamin D** (n=44)	**Placebo** (n=38)	**All** (n=82)	**SAE** (n=14)
Pollinosis	n=	0	1	1	
Protein deficiency	n=	0	1	1	
Hypocalciuria	n=	0	1	1	
Hypercalciuria	n=	1	0	1	
Hypothyreosis	n=	0	1	1	
Hyperthyreosis	n=	2	0	1	1
complete thyroidectomy	n=	0	1	1	1
Bursitis	n=	2	0	2	
Synovitis	n=	0	1	1	
Epicondylitis	n=	0	1	1	
Laryngitis	n=	2	1	3	
Tonsillectomy	n=	1	0	1	1
Excision basal cell carcinoma	n=	1	1	2	2
Excision squamous cell carcinoma	n=	1	0	1	1
Infection (flue-like, common cold)	n=	10	10	20	
Migraine	n=	1	2	3	
Headache	n=	2	0	2	
Cystitis	n=	1	1	2	
Diarrhea	n=	3	3	6	
Perinal bleeding	n=	1	0	1	1
Nausea	n=	1	2	3	
Gastro-oesophageal reflux	n=	1	1	2	
Oesophagogastroduodenoscopy	n=	1	0	1	
Gastritis	n=	1	0	1	
Shingles	n=	1	0	1	
Ischalgia	n=	0	1	1	
Fibromyalgia	n=	1	0	1	
Mal de debarquement	n=	1	0	1	
Aneurysm	n=	1	0	1	
Orthostatic syncope	n=	1	0	1	1
Myocardial infaction	n=	0	1	1	1
Coronary artery disease with stent placement	n=	1	0	1	1
Angina pectoris	n=	1	0	1	1
Vertigo	n=	1	1	2	
Knee-TEP surgery	n=	1	0	1	
Hip luxation	n=	1	0	0	1
surgery hallux valgus	n=	0	1	1	1
Tooth extraction	n=	0	1	1	
Fall	n=	1	2	3	

Anxiety and depressive disorder	n=	1	0	1	1
Disorientation	n=	2	0	2	
Sleeping disorder	n=	0	2	2	
Musculoskeletal pain	n=	7	1	8	
Hyposphagma	n=	0	1	1	
Otalgia	n=	0	1	1	
Hearing loss	n=	1	0	1	
Tubal ventilation disorder	n=	0	1	1	
Tinnitus	n=	0	1	1	

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