HealVertigo

Observational Plan
Non-Interventional Study (NIS)

Evaluation of the impact of Vertigoheel® on symptoms and quality of life of patients suffering from bilateral vestibulopathy and functional dizziness in a real-world setting
-
A non-interventional, prospective, mono-center, observational study

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SIGNATURES

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LIST OF ABBREVIATIONS

AE	Adverse event
AMG	"Arzneimittelgesetz" (German Medicinal Act)
AWMF	„Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften" (Working group of scientific medicine societies)
BfArM	"Bundesinstitut für Arzneimittel und Medizinprodukte" (German federal institute for drugs and medical devices)
BL	Baseline
BVP	Bilateral vestibulopathy
CI	Confidence interval
CM	Concomitant medication
CRO	Clinical research organization
CSR	Clinical study report
DBL	Database lock
DHI	Dizziness handicap inventory
eCRF	Electronic case report form
EDC	Electronic data capture
EFPIA	European federation of pharmaceutical industries and associations
EQ-5D-5L	European quality 5 dimensions 5 level
FD	Functional dizziness
FPI	First patient in
GAD-7	Generalized anxiety disorder scale
GCP	Good clinical practice
HIT	Head impulse test
ITT	Intention to treat
KBV	„Kassenärztliche Bundesvereinigung" (National association of statutory health insurance physicians
LPO	Last patient out
NIS	Non-interventional study
MH	Medical history
PHQ-9	Patient health questionnaire
PP	Per protocol
PRO	Patient Reported outcome
QoL	Quality of life
SAE	Serious adverse event
SmPC	Summary of product characteristics
SOP	Standard operational procedure
V	Visit
vfa	"Verband der forschenden Pharmaunternehmen" (Federation of pharmaceutical industries doing research)
vHIT	Video head impulse test
VOR	Vestibulo-ocular reflex

OBSERVATIONAL PLAN SUMMARY

Title of Observational Study	Evaluation of the impact of Vertigoheel® on patients suffering from bilateral vestibulopathy and functional dizziness in a real-world setting, using patient reported outcomes and quality of life of patients
Type of Study	Non-interventional observational study.
Rationale	Vertigo is a common symptom with significant adverse effects on patients' QoL. Regardless of the exact cause of vertigo attacks, it is important to reduce the frequency, intensity, and duration of vertigo attacks with an effective medication that has no or minimal adverse effect. Vertigoheel®, a natural medicinal product consisting of four ponderable active ingredients, is approved in Germany by BfArM as treatment for vertigo of various origins. However, no systematic data is available for Vertigoheel® regarding patient-reported outcomes in bilateral vestibulopathy and functional dizziness as the most accepted endpoint in vertigo studies in which also German health insurance are interested. Therefore, patient-reported outcomes (PRO) as well as quality of life (OoL) assessed during clinical practice, were chosen as primary and secondary objectives respectively, to evaluate symptoms and QoL of Vertigoheel®-patients in Germany.
Exposure and Outcome	Patients treated with Vertigoheel® will occur according to SmPC and will be observed with respect to change in PRO, postural imbalance and QoL.
Duration of Observation	It is planned to observe patients treated with Vertigoheel® for a duration of 2 months.
Primary Objective	• To evaluate the change from baseline in PRO after 2±1 months of routine Vertigoheel® treatment for patients suffering from functional dizziness (FD) and bilateral vestibulopathy (BVP).
Secondary Objectives	• To evaluate the change from baseline in QoL after 2±1 month of routine Vertigoheel® treatment measured by questionnaires. • To evaluate the change from baseline in postural imbalance after 2±1 months of routine Vertigoheel® treatment for patients suffering from FD and BVP. • To evaluate the change from baseline in psychiatric symptoms after 2±1 months of routine Vertigoheel® treatment for patients suffering from FD measured by questionnaires.

Primary Endpoints	• Effect of Vertigoheel® on subjective symptoms of the sensation of vertigo and dizziness as change from baseline to month 2±1 assessed by the Dizziness Handicap Inventory (DHI; total).
Secondary Endpoints	• Effect of Vertigoheel® on QoL as change from baseline to month 2±1 assessed by EQ-5D-5L. • Effect of Vertigoheel® on total sway path as change from baseline to month 2±1 assessed by static posturography. • In FD effect of Vertigoheel® on psychiatric symptoms as change from baseline to month 2±1 assessed by Patient Health Questionnaire Mood Scale (PHQ-9) and Generalized Anxiety Disorder Screener (GAD-7). • In BVP effect of Vertigoheel® on vestibular function as change from baseline to month 2±1 assessed by video head impulse test (vHIT) and/or caloric testing. • Adverse events (AEs). • Other observations related to safety (physical examination and vital signs).
Study Design	Non-interventional, observational, prospective, monocentric study
Study Population	It is planned to include 20 patients with BVP and 40 patients with FD who are going to start Vertigoheel® treatment according to clinical practice at the study center. The decision of treatment is up to the physician's discretion and is to be made independent of this study.
Inclusion / Exclusion Criteria	*Following documentation criteria should be fulfilled* • BVP (according to the diagnostic criteria of the Bárány Society) or FD (according to the diagnostic criteria of the Bárány Society). • Symptoms for > 3 months of moderate to severe intensity according to the DHI [0 (minimum score) -100 (maximum score)] of 30 to 90 points. • ≥18 – 80 years of age. • Legally competent male or female outpatient. • Signed informed consent. • Not pregnant (as proven by negative pregnancy test in case of woman of childbearing potential before first study drug administration) or breast-feeding. *Patients with the following conditions are excluded from the documentation in this NIS* • Ongoing (within the last two months) or recently started Vertigoheel® treatment. • Debilitating acute or chronic illness (e.g. psychiatric illnesses). • History of sensitivity to any component of the study drug

	under observation. • Unwilling or unable to comply with all the requirements of the study protocol. • Any relationship of dependence with the sponsor or with the investigator.
Milestones	Sept 21 FPI, July 22 LPO, DBL Aug 22.
Statistical Methods	*Previous trial with Vertigoheel®* Weiser et al. (1998) The efficacy and safety evaluation of Vertigoheel® vs betahistine hydrochloride demonstrated a reduction of 2 score points of the mean intensity of vertigo attacks with a standard deviation of 0.8 score points and a non-inferiority limit of 20%. Power: 80%. *Current study* • Significance level 0.05 (2-sided) • 95% confidence intervals will be calculated to estimate treatment effects • Standard deviation of 0.8 for both indications • Lost to follow-up 10% (BVP) or 20% to 30% (FD) Power: 80% (Please see 8.1)
Sample Size Calculations and Power Calculations	Sample size calculations have been performed for confidence intervals for different paired means. When the sample size is 20, a two-sided 95% CI for the difference between paired means will extend 0.351 from the observed difference in means. For a smaller CI a higher n is needed, i.e. n=25 (28 with 10% drop-out) distance from mean to limit 0.314, n=30 (33 with 10% drop-out) distance from mean to limit 0.265, n=40 (44) – 0.248.

1 BACKGROUND AND RATIONALE

1.1 BACKGROUND

Non-interventional studies (NIS) are essential instruments for research institutions, regulatory authorities, and reimbursement bodies in Germany. They are conducted to generate real-life data from clinical practice.

Vertigo is a common symptom with significant adverse effects on patients' QoL. It results from abnormal processing of apparently contradicting information in the central nervous system and is often accompanied by auditory symptoms, making it more difficult for the patient to tolerate. Patients with vertigo suffer from nausea, emesis, sweating, collapse, and tinnitus. Disturbances of equilibrium, systematic imbalance or instability can have negative consequences on the social lives of patients and can be truly disabling.

The leading symptoms of BVP are postural imbalance and unsteadiness of gait that worsens in darkness and on uneven ground. There are typically no symptoms while sitting or lying under static conditions. A minority of patients also have movement-induced oscillopsia while walking. The diagnosis of BVP is based on a bilaterally reduced or absent function of the vestibulo-ocular reflex (VOR). This deficit is diagnosed for the high-frequency range of the angular VOR by a bilaterally pathologic bedside head impulse test (HIT) and for the low-frequency range by a bilaterally reduced or absent caloric response. If the results of the bedside HIT are unclear, angular VOR function should be quantified by a video-oculography system (vHIT). In general, in the long term there is no improvement of vestibular function. There are four treatment options: first, detailed patient counseling to explain the cause, etiology, and consequences, as well as the course of the disease; second, daily vestibular exercises and balance training; third, if possible, treatment of the underlying cause; fourth, if possible, prevention.

FD is another general term for somatoform or psychogenic dizziness with some subtypes such as "Persistent Postural-Perceptual Dizziness". The prevalence of FD as a primary cause of vestibular symptoms amounts to 10% in neuro-otology centers. Rates of psychiatric comorbidity in patients with structural vestibular syndromes are much higher with nearly 50% and with highest rates in patients with vestibular migraine, vestibular paroxysmia and Ménière's disease. Pathophysiologic processes seem to include precipitating events that trigger anxiety-related changes in postural strategies with an increased attention to head and body motion and a co-contraction of leg muscles. FD can be determined by normal results in the neurological tests. Treatment plans include patient education, vestibular rehabilitation, cognitive behavioral therapies, and medications substantially reducing morbidity and offering the potential for sustained remission when applied systematically.

According to German law for this observational study only patients are eligible for whom the treating physician has decided to start treatment with Vertigoheel® independently from the study and in agreement with the patient. It is neither allowed nor the intention to motivate any interventions in the patients` treatment by conduction of this study.

Regardless of the exact cause of vertigo attacks, it is important to reduce the frequency, intensity,

and duration of vertigo attacks with an effective medication that has minimal side effects. Vertigoheel® is a natural medicinal product containing four measurable active ingredients for the treatment of vertigo. Vertigoheel® tablets were approved by BfArM as treatment for vertigo of various origins. The efficacy and safety evaluation of Vertigoheel® versus betahistine hydrochloride demonstrated a reduction of 2 score points of the mean intensity of vertigo attacks with a standard deviation of 0.8 score points and a non-inferiority limit of 20% (Weiser et al 1998).

Legal and regulatory aspects of non-interventional studies in Germany
Stringent requirements for non-interventional studies exist in Germany that will all be adhered to in this NIS:

- Regulatory recommendations of the German Federal Institute for Drugs and Medical Devices (BfArM).
- Art. 2 of EU Directive 2001/20/EC.
- Physicians` decision for treatment must be independent of study conduction: The assignment of the patient to a particular therapeutic strategy (Vertigoheel® in this case) is not defined by the observational plan but is made in responsibility of the treating physician.
- Guidelines for good pharmacoepidemiology practice according to ISPE (International Society for Pharmaepidemiology).
- Strictly observational design, no influence on routine medical diagnostic or therapeutic procedures or decisions of physician.
- Real-life setting.

This NIS will be notified according to German Medicines Act (AMG) to BfArM, the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung, KBV), the National Association of Statutory Health Insurance Funds (Central Association of Health Insurance Funds, Spitzenverband der Krankenkassen), and the National Association of Private Health Insurances (Verband der Privaten Krankenversicherungen). The notification includes information on the aims of the non-interventional study, the performance details, data collection, timelines, patient information methods and the names of the participating investigators.
An appropriate Ethics Committee will be consulted regarding the performance of this NIS.
Additionally, this non-interventional study will be conducted in compliance with the sponsor's local SOP that reflects all stated requirements.

1.2 RATIONALE

No systematic data in bilateral vestibulopathy and functional dizziness is available for Vertigoheel® regarding PRO and QoL in a real life setting in Germany. Nowadays, German health insurance is not only interested in direct costs, e.g. hospitalization, but also in patient reported and in clinical practice implemented outcome parameters. Therefore, patient-reported outcomes (PRO) as well as quality of life (OoL) assessed during clinical practice, were chosen as primary and secondary objectives respectively, to evaluate symptoms and QoL of Vertigoheel® treated patients in Germany. The current German AWMF guidelines for vestibular disorders (03/2021) recommend furthermore VOR, caloric testing, DHI and static posturography, as examinations for diagnosis and monitoring of the development for

patients with vertigo or dizziness.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To evaluate the change in PRO 2±1 months from baseline for patients suffering from functional dizziness (FD) and bilateral vestibulopathy (BVP) treated with Vertigoheel® in German clinical practice.

2.2 SECONDARY OBJECTIVES

- To evaluate the change from baseline in QoL after 2±1 months of routine Vertigoheel® treatment measured by questionnaires.
- To evaluate the change from baseline in postural imbalance after 2±1 months of routine Vertigoheel® treatment for patients suffering from FD and BVP.
- To evaluate the change from baseline in psychiatric symptoms after 2±1 months of routine Vertigoheel® treatment for patients suffering from FD measured by questionnaires.

3 METHODOLOGY

3.1 STUDY DESIGN

This study is an open-label, prospective, monocenter non-interventional study. It is set up for descriptive purposes.

All study activities will be consistent with the EU Directive 2001/20/EC section for non-interventional studies as follows:
- The study drug is prescribed in the usual manner in accordance with the terms of the marketing authorization/SmPC.
- The assignment of the patient to a particular therapeutic strategy is not defined by the observational plan but falls into the responsibility of the treating physician.
- No extra means of interventions that would not otherwise be used, will be applied to the patients.

Patients will be observed for 2±1 months under Vertigoheel® treatment.

Planned study timelines are summarized in the following table:

Study Start Date	August 2021
First patient first visit	September 2021
Last patient last visit	July 2022
Data Base Lock	September 2022
CSR	November 2022

3.2 STUDY POPULATION

Patients with BVP and FD will be recruited from the Department of Neurology in the German Center for Vertigo and Balance Disorders at the Hospital of the LMU, Munich.

As this is a prospective, non-interventional study, the study population will be composed of male and female patients, aged between 18 and 80 years old, diagnosed with BVP or FD. There are no specific patient withdrawal criteria for this non-interventional study except for the common ones such as loss of market authorization. A patient who is enrolled but does not complete the observational period may be replaced if study entry by end-April 2022.

3.3 STUDY MEDICATION

Vertigoheel® is a natural medicinal product containing four ponderable active ingredients for the treatment of vertigo. Vertigoheel® tablets were approved by BfArM as treatment for vertigo of various origins. The doses and dates of administration will be recorded throughout the study. Administration of therapy regimens in FD and BVP should follow the approved label. To collect real world data, the treatment intervals and the dosage administered will be documented in this observational study and analyzed descriptively.

3.4 INCLUSION CRITERIA

Patients will be included in the study if they meet all the following criteria:

- Treatment with Vertigoheel® has been chosen by the physician independently of including the patient in this non-interventional study.
- BVP (according to the current diagnostic criteria of the Bárány Society, 2017) or FD (according to the diagnostic criteria of the Bárány Society, 2017)
- Symptoms for > 3 months of moderate to severe intensity according to the DHI [0 (minimum score) -100 (maximum score)] between 30 to 90 points.
- ≥18 – 80 years of age.
- Legally competent male or female outpatient.
- Signed informed consent.

- Not pregnant (as proven by negative pregnancy test in case of woman of childbearing potential before first study drug administration) or breast-feeding.

3.5 EXCLUSION CRITERIA

Patients will not be included in the study if any of the following criteria applies:

- Having taken within the last 2 months or currently taking Vertigoheel®.
- Debilitating acute or chronic illness (i.e. psychiatric illnesses).
- History of sensitivity to any component of the study drug under observation.
- Unwilling or unable to comply with all the requirements of the study protocol.
- Any relationship of dependence with the sponsor or with the investigator.

Patients with contraindications according to current SmPC must not be included, observed, or documented in this non-interventional study.

4 MEASUREMENTS

Since this is a non-interventional study, no stipulations will be made on assessments as well as on study visits. Data collection will be based on routine clinical practice and no testing/evaluations will be done specifically for this protocol.

4.1 DIZZINESS HANDICAP INVENTORY

The DHI is a validated, self-report questionnaire which is widely used as an outcome measure. It assesses precipitating physical factors associated with dizziness/unsteadiness and functional/emotional consequences of symptoms. To assess the impact of impairment, the patients are asked to fill out the 25 item DHI questionnaire, which has been used in previous studies for patients with vertigo of various origin. The scale has three sub-domains (physical, functional, and emotional questions).

4.2 POSTUROGRAPHY

Posturography is used to assess regulation of stance and gait. A platform is used to measure body sway, which can exist in healthy subjects because of inherent physiological postural instability and which is increased in vestibular disorders.

4.3 EQ-5D-5L

The EQ-5D-5L is a self-administered questionnaire for evaluating QoL introduced in 2009 [EuroQol Group, 2017]. It is a multiple-choice questionnaire and a visual analogue scale that takes only few minutes to complete and is a standardized instrument for measuring generic health status. It has been widely used in population health surveys, clinical studies, economic evaluation and in routine outcome measurement in the delivery of operational healthcare.

In patients suffering from FD due to increased rates of psychiatric comorbidities:

4.4 PATIENT HEALTH QUESTIONNAIRE DEPESSION MODULE (PHQ-9)

The Patient Health Questionnaire depression module (PHQ-9) is an established instrument for the

assessment of depression which is often associated with FD and is validated in German language.

4.5 GENERALIZED ANXIETY DISORDER SCALES (GAD-7)

The Generalized Anxiety Disorder Scales GAD-7 is an established instrument for the assessment of anxiety which is often associated with FD and is also validated in German language.

In patients suffering from BVP:

4.6 VIDEO-HEAD IMPULSE TEST

The vHIT is performed to evaluate the function of the VOR in the high frequency range for the horizontal semicircular canals. The test is based on the clinical head impulse test and it is a non-invasive and easy to perform, quick test that does not generate unpleasant vertiginous or nauseating sensation for the patient.

4.7 CALORIC TESTING

Caloric testing is used to quantify the function of the VOR in the low-frequency range of the horizontal semicircular canal on each side. After a lesion of the eardrum has been ruled out, the patient's head is positioned at an angle of 60° so that the horizontal semicircular canal is approximately vertical, thus ensuring maximum caloric excitability. Each external acoustic canal is then irrigated separately under standardized conditions with cool (30°C) and warm (44°C) water, while horizontal and vertical eye movements are recorded using electronystagmography.

4.8 SAFETY

Safety data will be collected in this study. Please refer to Chapter 7 for further details.

5 STUDY FLOW CHART

Procedure	Visit 0 Month 0 Baseline	Visit 1 Month 2 +/- 1 after Baseline					
Evaluations / Recordings							
Patient informed consent	x						
Assignment of patient number	x						
Inclusion/exclusion criteria	x						
Physical examination including vital signs (heart rate, blood pressure)	x	x					
Demographics, from Visit 1 documentation of changes vs. baseline for variable demographic parameters	x	x					
Medical and medication history vertigo-related	x	x					
Concomitant diseases/medications	x	x					
Procedure (continued)							
Evaluations / Recordings							

DHI	x	x					
Posturography	x	x					
FD: PHQ-9, GAD-7	x	x					
BVP: vHIT, caloric testing	x	x					
Quality of life (EQ-5D-5L)	x	x					
Review of Vertigoheel administration	x	x					
Adverse events / Serious Adverse Events		x					
Patients who stopped therapy (reasons for d/c, date of last intake)		x					
		Close Out Documentation					

6 STUDY PROCEDURES

The study will be conducted in accordance with the ICH E6 Guideline for Good Clinical Practice, the relevant national regulations, and the Declaration of Helsinki. This study is a NIS according to German Medicinal Products Act (AMG) §4 (23) and will be conducted in compliance with national and European Union requirements for ensuring the rights of participants in non-interventional studies.

The Study Diagram in Section 5 summarizes the study procedures that may be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety.

Patient Confidentiality
The investigator must ensure the privacy of patients, including their identity and all personal medical information always. In CRFs and other documents, patients will be identified not by their names but by their pseudonymization number. Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the source and transcribed onto the eCRF. This review may be conducted by properly authorized persons on behalf of the sponsor, the quality assurance unit and/or regulatory authorities. Personal medical information will always be treated as confidential. Patients can opt to withdraw their consent for the study at any time without giving a reason and without any consequences for their medical treatment. If a patient wants to terminate the study participation, no further data will be collected. However, the patient will be asked whether s/he agrees that the data collected so far can be used. In case the patient does not agree, his/her data will be deleted from the study database and will not be used for any study-related analysis or publication unless legal obligations require that this data are kept.

6.1 ADMINISTRATIVE PROCEDURES

Data of therapy will be entered into a case report form (CRF).

6.2 GENERAL INFORMED CONSENT

This study is non-interventional, and no additional procedures will be performed on the patient in addition to the normal real-world clinical practice of the treating physician. Informed consent will be obtained from all patients for their clinical data to be recorded pseudonymously and to collect PRO measures. Patients will also be informed of their right to withdraw their consent at any time during the study. The physician or a qualified person designated by the physician, should fully inform the patient of all pertinent aspects of the study. The written informed consent document must be prepared and provided in the language(s) of the potential patient population. Patients must understand that it is their own free will to participate and that they can withdraw consent at any time without giving reasons and without penalty or loss of benefits to which the subject is entitled. The patient will be given ample time and opportunity to obtain answers to any open questions. All questions relating should be answered to the satisfaction of the patient. The written consent form will be personally dated and signed by the patient and the by investigator conducting the informed consent discussion. The informed consent forms will be filed in the patient's record. A copy of the signed and dated

informed consent form will be given to the patient.

6.3 MEDICAL HISTORY

Medical History/Demographics
A medical history will be obtained by the investigator or qualified designee. Alcohol, drug, and any substance abuse history will also be documented. Demographic data will be collected.

6.4 PRIOR AND CONCOMITANT MEDICATIONS REVIEW

Concomitant Medications
All medication taken by the patient within two weeks prior to the start of treatment with Vertigoheel® and all concomitant medications taken by the patient during this study must be recorded in the source documents and in the eCRF.

Medication
Treatment with Vertigoheel® will be documented in detail (dosing, dose adjustments, and dates of administration).

Termination of Vertigoheel® treatment
When a patient discontinues/withdraws prior to the study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation.

6.5 CLINICAL PROCEDURES/ ASSESSMENT

A complete physical examination performed by the principal investigator includes the following assessments: general appearance, head, eyes, ears/nose/throat, head/neck/thyroid gland, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated. The patient's weight and vital signs should be included in the assessment.

6.6 OTHER PROCEDURES

Patient Number
All consented patients will be given a unique depersonalized identification number. The patient number identifies the patient for all procedures occurring during observation. Data protection and other applicable regulatory requirements will be fulfilled.

Patient Reported Outcome
DHI, PHQ-9, GAD-7 and QoL questionnaire EQ-5D-5L will be collected.

Eligibility Criteria Review
The eligibility criteria must be reviewed by the investigator to ensure that the patient qualifies for the study.

Adverse Events
The investigator must document all AE/SAE. He/she must also determine the severity and relationship to study medication of all AE/SAEs. For further instructions please refer to Chapter 9, Assessment and Reporting of Adverse Events.

Unscheduled Visits
Unscheduled visits may be performed at any time at the discretion of the investigator to ensure patient safety.

End of follow-up
Patients will be followed until:

- End of month 2 ±1 observational period for the patient.
- Death.
- Withdrawal of consent.

7 SAFETY REPORTING AND RELATED PROCEDURES

Introduction

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

7.1 ADVERSE EVENT DEFINITIONS AND REPORTING

Definitions

Adverse Event
An Adverse Event/Experience (AE) is any untoward medical occurrence in a patient or in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether related to the treatment.

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

Serious Adverse Event
Any untoward medical occurrence:

- results in death

- is life-threatening
- requires unscheduled inpatient hospitalization or prolongs an existing hospitalization
- results in persistent or significant disability/incapacity
  or
- is a congenital anomaly/birth defect
- is qualified as another medically significant event or condition

Recording Adverse Events
For adverse event recording, the study period is defined for each patient as the time from signing of the informed consent form through the end of the observation period (including the follow-up period). All adverse events, that occur during the defined study period must be recorded in the eCRF on the respective Adverse Event Report Form, regardless of the severity of the event or the relationship to Vertigoheel®. The AEs related to Vertigoheel® should be reported to Heel monthly.

For serious adverse events, related non-serious adverse events, the Adverse Event Form must also be completed, and the adverse event must be recorded and reported within 24 hours of becoming aware to Heel Drug Safety Management (FON 07221 / 501-0 or drugsafety@heel.com). The investigator should evaluate all adverse events according to the criteria and steps mentioned below.

Assessment of Intensity
Any adverse event must be graded regarding its intensity as follows:

MILD	Does not interfere with subject's usual function, easily tolerated.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function, incapacitating with inability to work or carry out usual activity.

Assessment of Seriousness
Determination of the seriousness of the adverse event according to the definitions for a serious adverse event (SAE).

Assessment of Causality
Determination of the relationship of the adverse events to the medicinal product(s) being studied after having evaluated all accessible data according to the following classification:

NOT RELATED	Adverse events for which a reasonable explanation for an alternative cause is considered plausible, e.g. no study drug taken, plausible clinical alternative like accidental injury, pharmacologically incompatible temporal relationship or intercurrent illness.
RELATED	Adverse event for which a reasonably possible clinical and/or pharmacological relationship to study drug cannot be excluded, e.g. lacking plausible alternatives.

When the final causality assessment is unknown and it is uncertain whether the investigational

product caused the event, then the event should be handled as related to the investigational product for reporting purposes.

Collection of Product Name and Batch Number of Medicinal Product
At each visit, the brand name and the batch number of the used medicinal product should be collected and documented in the eCRF.

Pregnancy
All pregnancies of women participating in the study that occur during the study or within 6 months of the last dose of Vertigoheel® are to be reported to Heel by the physician within 24 hours of awareness. This also includes pregnancies without an adverse event. The pregnancy should be followed up to determine the outcome including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defect, congenital abnormalities or maternal, and newborn complications.

Pregnancies in partners of male patients will be recorded and monitored. The pregnant partner will be asked to sign an informed consent form, and the pregnancy will be followed as any other pregnancy would be.

PRODUCT COMPLAINTS
A product complaint is defined as any report indicating a possible deviation from the product specification. These reports may concern packaging, labeling, medical devices, or drug products. Product complaints may include, but are not limited to, the following:
A product complaint is defined as any report indicating a possible deviation from the product specification. These reports may concern packaging, labeling, medical devices, or drug products. Product complaints may include, but are not limited to, the following:

- missing or extra units (e.g., primary container is received with more or less than the designated number of units inside)
- incorrect packaging, or incorrect or missing labeling/label
- unexpected or unanticipated taste, odor, or both
- suspicion of falsified medicines

If a product complaint is identified for a Vertigoheel® during the study, the investigator should contact Biologische Heilmittel GmbH (FON 07221 / 501-0 or complaints@heel.com) within 48 hours of becoming aware of the issue.

8 STATISTICAL ANALYSIS PLAN

Due to the non-interventional design, this study is set-up for descriptive purposes, no a priori hypothesis will be tested, and no comparisons will be made with other products or treatments. Data will be analyzed by a contract CRO.

This is a non-interventional study. It is planned that 20 patients with BVP and 40 patients with FD (larger than in BVP due to inhomogeneity of the disease) participate in the observational period for

2-months treatment ± 1 month. Due to small number of patients enrolled, no interim analysis is planned.

Sample Size Calculation
Sample size calculations have been performed for confidence intervals for different paired means. When the sample size is 20, a two-sided 95% CI for the difference between paired means will extend 0.351 from the observed difference in means. For a smaller CI a higher n is needed, i.e. n=25 (28 with 10% drop-out) distance from mean to limit 0.314, n=30 (33 with 10% drop-out) distance from mean to limit 0.265, n=40 (44) – 0.248.

- Significance level 0.05 (2-sided).
- 95% confidence intervals will be calculated to estimate treatment effects.
- Standard deviation of 0.8 for both indications.
- Lost to follow-up 10%.
- Power: 80%.

Data Analysis
SAS or R software, or an equivalent software package will be used for statistical analysis.

Descriptive statistics will be provided for all parameters. The statistics will be appropriate for the type of data:
- For continuous and count variables, statistics will include the number of observations, mean, standard deviation, median, minimum, maximum, and 95% confidence interval (CI).
- For categorical variables, the descriptive statistics will include the count and percent of observations in each category along with its 95% CI. The denominator for the percentages will also be presented as the number of subjects in the analysis population.

This is a non-interventional, observational study, therefore only CI are calculated. If data transformations are used, they will be specified in the final clinical study report. All endpoints will be analyzed by the appropriate type of descriptive statistic(s) as described above.

All variables will be analyzed in an exploratory manner. No formal statistical hypothesis testing will be performed.

Populations for Data Analysis
The Intention-to-treat (ITT) population includes all patients who have received at least one dose of Vertigoheel® and have at least one post-baseline measurement.
As data collection will be based on routine clinical practice so that no stipulations will be made on assessments as well as on study visits, a PP population will not be defined. Protocol deviations (as far as known), e.g. deviations from the in-/exclusion criteria, will be listed.
The Safety population includes all patients who have received at least one dose of Vertigoheel®. Clinical safety will be addressed by assessing AEs, physical examinations, vital signs in a descriptive manner.

Effectiveness analyses will be performed with the ITT population, safety analyses with the Safety population.

9 DATA MANAGEMENT

Data Source
Data for this study will be obtained from various sources, including treating physicians and source documentation such as questionnaires and examination methods for vertigo. The investigator will record relevant medical data, participation in the study and the occurrence of adverse events. Treatment related data during visits that take place in routine practice will be collected as source data in the respective patient's records. The outcomes will be captured from validated examination methods for vertigo (i.e. posturography, vHIT, caloric testing). The investigator must keep supportive original source documentation for all patient-related data.

Data collection
Data will be collected using an eCRF that is specifically designed for this study and must match the source data. The data will be pseudonymized, processed and stored according to local law. This also allows preservation for future use. The investigator has ultimate responsibility for the accuracy, authenticity, timely collection and reporting of all data entered on the CRFs. For the duration of the study and afterwards, only the patient's treating physician or authorized site personnel can identify the patient based on the patient identification code. All these data may only be entered and updated in the CRFs by authorized study personnel. eCRFs must be completed for each patient, who provided informed consent.

Data Quality Assurance
The EDC system will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture data from this study. Before using the EDC system, all users will receive training on the system and study-specific training. After they are trained, users will be provided with individual system access rights. Data will be reviewed for consistency by data management using both automated logical checks and manual review. All data collected will be approved by the investigator at the investigational center. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

Quality Control/Data Validation
All procedures must follow Good Clinical Practice (GCP), existing standard operating procedures (SOP) and local laws and regulations as applicable. Details concerning data management procedures and query management will be described in a data management and data validation plan. Using an electronic CRF an audit trail will be maintained to provide an electronic record of which data were entered or subsequently changed, by whom and when Checks will be implemented to review the data entered into the clinical database for completeness, and to review the data for completeness, consistency and plausibility. The checks to be programmed will be specified in the data validation plan. After running the check programs, the resulting queries will be sent to the investigator for clarification. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed. At the conclusion of the study, the EDC system and all other study data will be locked to further additions or corrections. Locking the study data represents the acknowledgement that all data have been captured and confirmed as accurate.

10 PUBLICATIONS

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements and regulations for registration and posting of results. The sponsor is responsible for the preparation of a non-interventional study report. The final study report is signed by the sponsor.

Publication of any data, including abstracts, presentations, and manuscripts, will follow Good Publication Practices.

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