HealVertigo

Statistical Analysis Plan

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
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A non-interventional, prospective, mono-center, observational study

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SIGNATURES

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LIST OF ABBREVIATIONS

AE	Adverse event
BfArM	"Bundesinstitut für Arzneimittel und Medizinprodukte" (German federal institute for drugs and medical devices)
BVP	Bilateral vestibulopathy
CI	Confidence interval
DHI	Dizziness handicap inventory
EQ-5D-5L	European quality 5 dimensions 5 level
FD	Functional dizziness
GAD-7	Generalized anxiety disorder scale
ITT	Intention to treat
pCRF	Paper case report form
PHQ-9	Patient health questionnaire
PP	Per protocol
QoL	Quality of life
SmPC	Summary of product characteristics
SP	Safety Population
vHIT	Video head impulse test
VOR	Vestibulo-ocular reflex

1 Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the trial objectives.

The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Statistical methods regarding trial drug exposure, effectiveness analysis, concomitant medications, adverse events handling, laboratory data, vital signs and physical examinations
- Tables, Listings, Figures (TLFs)
- This SAP is based on the Observational Plan, Final Version 1, dated 28-JUN-2021 and pCRF Final Version 1, dated 23-NOV-2021.

1.1 Responsibilities

The Sponsor or a delegate will perform the statistical analyses.

2 OBJECTIVES

2.1 Primary Objectives

- To evaluate the change in PRO 2±1 month after baseline versus 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 month of routine Vertigoheel® treatment measured by questionnaires
- To evaluate the change from baseline in postural imbalance after 2±1 month of routine Vertigoheel® treatment for patients suffering from FD and BVP
- To evaluate the change from baseline in psychiatric symptoms after 2±1 month 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 are 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 are observed for 2±1 month under Vertigoheel® treatment.

3.2 Study Population

Patients with BVP and FD are recruited from the Department of Neurology and 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 is 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 as loss of market authorization.

3.3 Study Medication

Vertigoheel® is a natural medicinal product containing four measurable active ingredients for the treatment of vertigo. Vertigoheel® tablets were approved by BfArM as preventive 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 are 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 or FD (according to the current diagnostic criteria of the Bárány Society ~~(2017)~~ ~~FD~~
- 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

3.5 Exclusion Criteria

Patients are not 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
- At the discretion of the investigator

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

4 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, from Visit 1 documentation of changes vs. baseline	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					

5 STATISTICAL ANALYSIS

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.

This is a non-interventional study. It is planned that 20 patients with BVP and 40 patients with FD participate in the observational period for 2-months treatment. Due to the small number of patients enrolled, no interim analysis is planned.

5.1 Sample Size Calculation

Sample size calculations were 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%

5.2 Treatment Assignment and Blinding

A randomization code is not applicable as this is an open-label, prospective, monocenter non-interventional study.

5.3 Effectiveness Endpoints / Measurements

Since this is a non-interventional study, no differentiation between primary and secondary endpoints is made.

5.3.1 Dizziness Handicap Inventory

The DHI is a validated, self-report questionnaire. To assess the impact of impairment, the patients are asked to fill out the 25 item DHI questionnaire. The scale has three sub-domains (physical, functional, and emotional questions).

5.3.2 Posturography

Posturography is used to assess regulation of stance and gait.

5.3.3 EQ-5D-5L

The EQ-5D-5L is a self-administered questionnaire for evaluating QoL.

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

5.3.4 Patient Health Questionnaire Depression 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.

5.3.5 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.

In patients suffering from BVP:

5.3.6 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.

5.3.7 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.

5.3.8 Safety
Safety data will be collected in this study.
Clinical safety will be addressed by assessing AEs, physical examinations and vital signs in a descriptive manner.
As AEs and relevant medical history will not be coded with MedDRA, they will not be grouped by MedDRA preferred terms.
As previous and concomitant medication will not be coded with the World Health Organization Drug Dictionary, they will not be grouped to the Anatomic Therapeutic Chemical index.

5.3.9 Further Endpoints
Product complaints, Vertigoheel administration details (daily dose, change of dose), early termination, alcohol and drug consumption, smoking status.

5.4 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 two-sided 95% confidence interval (CI).

- For categorical variables, the descriptive statistics will include the count and percent of observations in each category along with its Clopper-Pearson two-sided 95% CI. The denominator for the percentage calculation will be based on the number of patients in the analysis population.

This is a non-interventional, observational study, therefore only CI are calculated. 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.

Missing values will not be imputed.

The following subgroups will be defined:
- Patients with FD
- Patients with BVP

It is planned to include 20 patients with BVP and 40 patients with FD.

No further subgroups will be defined.

Shift tables for physical examination, DHI, Posturography, and vHIT will display the number and percentage of patients per baseline value category vs. the worst value category post-baseline

5.5 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 per-protocol 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 (SP) includes all patients who have received at least one dose of Vertigoheel®.

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

5.6 Definitions

5.6.1 Definition of Baseline

Baseline is defined as Screening Visit.

5.6.2 Absolute change from Baseline

Absolute change from baseline = post-baseline value – value at baseline.

5.6.3 Age

Age at baseline is derived as years of baseline – years of birth.

5.6.4 First patient in, last patient out

First patient in is defined as earliest date of Screening Visit.
Last patient out is defined as last date of Visit 1 and Unscheduled Visit.

1. Appendices

Appendix 1: Tables, Listings, Figures

Item No.	Title	Population	Content Description
14.1	**Disposition, Baseline Characteristics, Medication and Further Analyses**		
14.1.1	Patient disposition	All	Descriptive statistics on patients screened, failed screening, treated
14.1.2	Early termination	All	Descriptive statistics for early termination yes/no
14.1.3	Number of patients in each analysis population	All	Descriptive statistics for number and percentage of patients and reason for exclusion
14.1.4	Duration of study	All	Date of first patient in and last patient out of all patients
14.1.5	Duration of observation per patient	SP	Difference of Date of patient in and patient out per patient
14.1.6	Demographics and other baseline characteristics	ITT	Descriptive statistics of age, , height, weight, pregnancy test
14.1.7.1	Vital signs	ITT	Descriptive statistics of heart rate and blood pressure, at Screening Visit and 2±1 month after baseline
14.1.7.2	Physical examination	ITT	Descriptive statistics (normal, abnormal, ncs (not clinically significant), cs (clinically significant)), at Screening Visit and 2±1 month after baseline (shift table)
14.1.8.1	Primary diagnosis	ITT	Descriptive statistics of - FD yes/no (derived from tick box 'NA' for caloric (BVP)) - BVP yes/no (derived from tick box 'NA' for GAD-7 (FD))
14.1.8.2	Medical history - Abuse history	ITT	Descriptive statistics of alcohol and drug consumption, smoking status
14.1.9.1	Treatment with Vertigoheel	SP	Descriptive statistics for - Duration of treatment (date start of study – date start of Vertigoheel treatment - change of Vertigoheel dose yes/no
14.1.9.2	Prior medication	SP	Descriptive statistics for prior medication yes/no
14.1.9.2	Concomitant medication	SP	Descriptive statistics for change of concomitant medication yes/no
14.1.9.3	Product complaints	SP	Descriptive statistics for product complaint yes/no

14.2	**Patient Reported Outcomes (Effectiveness)**		
14.2.1	**Primary Endpoint**		
14.2.1	Dizziness Handicap Inventory	ITT	Descriptive statistics at Screening Visit and 2±1 month after baseline (yes, sometimes, no), and change from baseline to 2 months (shift table)
14.2.2	**Secondary Endpoints**		
14.2.2.1	Posturography	ITT	Descriptive statistics at Screening Visit and 2±1 month after baseline (normal, neuritis vestibularis, PPV), and change from baseline to 2±1 month after baseline (shift table)
14.2.2.2	Quality of Live (EQ-5D-5L)	ITT	Descriptive statistics per question, at Screening Visit and Visit 1, and change from baseline to 2 months
14.2.2.3	Patient Health Questionnaire depression module (PHQ-9)	ITT In patients with FD	Descriptive statistics for total score, at Screening Visit and Visit 1, and change from baseline to 2 months
14.2.2.4	Generalized anxiety disorder scale (GAD-7)	ITT In patients with FD	Descriptive statistics for total score, at Screening Visit and Visit 1, and change from baseline to 2 months
14.2.2.5	Video head impulse test (vHIT)	ITT In patients with BVP	Descriptive statistics at Screening Visit and Visit 1 (not done, normal, pathologic), and change from baseline to 2 months (shift table)
14.2.2.6	Caloric testing	ITT In patients with BVP	Descriptive statistics per parameter, at Screening Visit and Visit 1, and change from baseline to 2 months

14.3	**Safety Analyses**		
14.3.1	**Adverse Events**		
14.3.1.1	Overview of adverse events	SP	Number and percentage of patients with adverse events (yes/no), intensity (mild, moderate, severe), causality (related, not related, unknown)