

Digital vertigo therapy: efficacy results of the confirmatory randomized controlled multicenter GEVE II trial

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Abstract

Vertigo is one of the most common clinical complaints that severely impairs quality of life, but no evidence-based causal drug therapy is available for chronic peripheral vertigo. The recently developed non-invasive, training-based, sensorimotor and optokinetic brain stimulation program VH90D (Vertidisan®) is a CE-marked digital therapeutic that induces central vestibular compensation. We treated 259 patients with peripheral vertigo in a randomized, controlled, single blinded, confirmatory, multicenter clinical trial. VH90D reduced the Vertigo Symptom Score an average 65.36% ($p < 0.0001$), compared with a reduction of 22.91% in the physiotherapy control group. The confirmatory group comparison showed a highly significant treatment effect (least squares mean [LSMean] difference: -6.3 ; $p < 0.0001$; Cohen's $d = 1.1$). The Dizziness Handicap Inventory also significantly improved in the VH90D group (39.99% vs. 18.11% in the control group; $p < 0.0001$; Cohen's $d = 0.87$). The results demonstrate a significant clinical benefit of VH90D for patients with peripheral vestibular vertigo.

Study registration: WHO International Clinical Trials Registry Platform (ICTRP), DRKS00028026

INTRODUCTION

Vestibular (peripheral) vertigo, especially in its nonspecific form, is a common and clinically relevant symptom. Vertigo is one of the most common reasons for consultations with general practitioners and specialists^{1,2}, with chronic peripheral vertigo accounting for the vast majority of cases. The lifetime prevalence of vertigo of any cause in adults is an estimated 23.2%³, and the lifetime prevalence of vestibular vertigo with functional impairment is reported to be as high as 29.5%¹. The 1-year prevalence of dizziness in adults is 59.2%⁴.

Dizziness and vertigo significantly impair quality of life, which is reflected in lower scores in various areas of health, including physical function, role limitations due to physical problems, general health, and vitality. However, current guidelines and systematic reviews from both the United States and Europe consistently state that scientific evidence is lacking for the efficacy of drugs in the treatment of chronic vertigo or dizziness⁵⁻¹². To address this underserved need, a digital therapeutic, VH90D (Vertidisan®), was developed that includes a non-invasive, training-based sensorimotor and optokinetic brain stimulation program. The goal of this approach is to induce central vestibular compensation (CVC)^{2,3}. Initial data on the efficacy of VH90D was recently collected in a single-center study¹².

The present study was designed as a prospective, multicenter, randomized, controlled, single-blind, confirmatory clinical trial. The aim was to evaluate the clinical efficacy and safety of VH90D under active safety monitoring. The central hypothesis of the study was that the severity of vertigo would be significantly reduced over the observation period with the use of VH90D compared to standard therapy.

RESULTS

Demographics

A total of 259 patients (124 males, 48% and 135 females, 52%) were included in the intention-to-treat (ITT) analysis and randomly assigned to treatment with VH90D (N = 130) or therapy as usual (TAU; N = 129). Participants in the TAU control group received standardized physiotherapy treatment in line with standard care. The average age was comparable in both study arms. However, there was a relative excess of younger patients (age ≤ 65 years) in the VH90D group compared to the control group (Table 1).

The most common diagnostic entities within the study population were unilateral or bilateral vestibulopathy, presbyvertigo, benign paroxysmal positional vertigo (BPPV), persistent postural-perceptual dizziness (PPPD), vestibular neuropathy, and vestibular migraine (Table 2).

Table 1
Demographic distribution of the study groups. APP =, TAU = treatment as usual, SD = standard deviation.

			APP (N = 130)	TAU (N = 129)	Total (N = 259)
Age, years	Mean		60.58	63.64	62.10
	SD		14.53	16.19	15.43
	≤ 65	n (%)	82 (63.1)	72 (55.8)	154 (59.46)
	> 65	n (%)	48 (36.9)	57 (44.2)	105 (40.05)
Sex	male	n (%)	64 (49.2)	60 (46.5)	124 (47.89)
	female	n (%)	66 (50.8)	69 (53.5)	135 (52.12)

Table 2

Diagnoses. The total number of diagnoses is higher than the population because patients could be assigned more than one diagnosis. Values are given as n or n (%).

Diagnosis	APP (N = 130) n (%)	TAU (N = 129) n (%)	Total (N = 259) n (%)
Acute vestibular syndrome	1 (0.77)	2 (1.55)	3 (1.16)
Senile vertigo, presbyvertigo ^a	12 (9.23)	11 (8.53)	23 (8.88)
Bilateral vestibulopathy	26 (20.0)	32 (24.81)	58 (22.39)
Benign paroxysmal positional nystagmus (BPPN)	18 (13.85)	16 (12.40)	34 (13.13)
Arcuate dehiscence	1 (0.77)	0 (0)	1 (0.39)
Unilateral vestibulopathy	21 (16.15)	19 (14.73)	40 (15.44)
Functional vertigo, persistent postural-perceptual dizziness (PPPD), ^b phobic vertigo, chronic vestibular syndrome, and vestibular syndrome (as secondary diagnosis)	17 (13.08)	19 (14.73)	36 (13.89)
Sudden hearing loss with vertigo (acute idiopathic sensorineural hearing loss with vestibular involvement)	2 (1.54)	2 (1.55)	4 (1.54)
Idiopathic vertigo	3 (2.31)	15 (11.63)	18 (6.95)
Cholesteatoma	0 (0)	0 (0)	0 (0)
Labyrinthitis	3 (2.31)	0 (0)	3 (1.16)
Meniere's disease	9 (6.92)	10 (7.69)	19 (7.34)
Vestibular neuronitis	18 (13.85)	14 (10.85)	32 (12.36)
Toxic vestibulopathy	1 (0.77)	1 (0.77)	2 (0.77)
Trauma	1 (0.77)	3 (2.32)	4 (1.54)
Tumors of skull base and cerebellopontine angle, acoustic neuroma	1 (0.77)	1 (0.77)	2 (0.77)
Vestibular migraine ^c	20 (15.38)	10 (7.69)	30 (11.58)
Vestibular paroxysmia	0 (0)	2 (1.55)	2 (0.77)

^a Patients with bilateral vestibulopathy (hypoexcitability) aged ≥ 60 years.

^bPPPD was a secondary diagnosis. All patients with PPPD had an additional diagnosis as their main diagnosis.

^cVestibular migraine patients showed objective findings of peripheral vestibulopathy, as well as the typical migraine symptoms.

Dropouts

A total of 30 participants discontinued the study prematurely (Table 3). Two of these patients were excluded due to acute, non-vestibular-related surgeries.

Table 3
Dropouts and exclusions. APP=VH90D; TAU (Therapy as usual)=physiotherapy

Group	Last completed visit	Reason	Description
APP (N = 16)			
APP	T0	Personal reasons	"It is currently impossible for me to participate in the study or attend the appointment."
APP	T0	Patient no longer interested in the study	Patient did not want to continue
APP	T0	Unknown	Patient could no longer be reached
APP	T0	Unknown	Patient could no longer be reached
APP	T0	Patient no longer interested in the study	Patient did not want to continue
APP	T0	Unknown	Patient could no longer be reached
APP	T1	Unknown	Patient could no longer be reached
APP	T1	Unknown	Patient could no longer be reached
APP	T1	Unknown	Patient could no longer be reached
APP	T1	Unknown	Patient could no longer be reached
APP	T1	Patient no longer interested in the study	Patient did not want to continue
APP	T2	Surgery	Excluded from study due to acute surgery
APP	T2	Intermittent other disease	The patient discontinued the study due to intermittent other disease but the exact diagnosis was not communicated
APP	T2	Personal reasons	Family problems
APP	T2	Unknown	Patient could no longer be reached
APP	T2	Unknown	Patient could no longer be reached
TAU (N = 14)			
TAU	T0	Personal reasons	Family problems
TAU	T0	Unknown	Patient could no longer be reached
TAU	T0	Unknown	Patient could no longer be reached
TAU	T1	Surgery	Excluded from study due to acute surgery
TAU	T1	Surgery	Patient discontinued study due to upcoming knee surgery

Group	Last completed visit	Reason	Description
TAU	T1	Intermittent other disease	Patient discontinued study due to newly diagnosed psychiatric disease
TAU	T1	Unknown	Patient could no longer be reached
TAU	T1	Dizziness disappeared	"I am ending my participation in the vertigo study. I no longer experience vertigo."

TAU	T1	Unknown	Patient withdrew consent without explanation
TAU	T1	Other	Patient moved abroad
TAU	T1	Patient no longer interested in the study	Patient withdrew consent
TAU	T2	Unknown	Patient withdrew consent without explanation
TAU	T2	Patient no longer interested in the study	Patient withdrew consent
TAU	T2	Unknown	Patient could no longer be reached

Primary endpoint: Vertigo intensity

The intensity of vertigo was assessed using the validated Vertigo Subscale of the Vertigo Symptom Scale – short form (VSS-sf-VER). The score ranges from 0 to 32 points, with lower scores indicating a lower symptom burden and, thus, better clinical condition.

The primary endpoint defined a priori was the difference in the mean change (Δ) in the VSS-sf-VER score between baseline (T0) and week 12 (T3) in the two treatment groups (VH90D vs. TAU) within the ITT population. Statistical analysis was performed using analysis of covariance (ANCOVA) with the treatment group as a fixed factor and the baseline value as a covariate included in the model.

Table 4 and Fig. 1a show the time courses of the mean VSS-sf-VER scores in both groups. Using jump-to-reference (JTR) imputation for missing values, the VH90D group had a significant reduction in the mean VSS-sf-VER score over the observation period with an average change of – 65.36% (–12.04 points; $p < 0.0001$). In comparison, the TAU group had a mean change of – 22.91% (–3.63 points; $p < 0.0001$). Figure 1a also illustrates a clear dose-dependent effect in the VH90D group.

As no minimal clinically important difference in the VSS-sf-VER has been published to date, a conservative clinically important difference of 15% (i.e., 5/32 score points) was used to assess clinical relevance¹³. On this basis, the observed intragroup change of – 12.04 points is both significant and a sufficient clinical effect size. Thus, the results demonstrate the efficacy of VH90D in reducing the intensity of vertigo in patients with peripheral vestibular vertigo.

The corresponding group comparison showed a mean treatment difference (least squares mean) of – 6.3 points in favor of the VH90D group compared to the TAU group (95% confidence interval [CI]: – 7.9 to – 4.7; $p < 0.0001$). This difference was highly significant and indicates a significant superiority of the intervention (Table 4 and Fig. 1a). This observed intergroup difference also meets the previously defined clinically important difference of at least 5 points on the 32-point scale.

The calculated effect size (Cohen's d) was 1.10, which is considered a large effect size according to current interpretation guidelines (Cohen, 1992: $d \geq 0.80$ = large effect size). Therefore, the VH90D group had a clinically and statistically significant advantage. Overall, the proven difference shows both a significant and clinically relevant effect strength, indicating the superiority of VH90D over conventional physiotherapy.

Table 4

VSS-sf-VER scores (ITT). SD = standard deviation, SE = Standard Error, CI = confidence interval. APP = VH90D Group, TAU = Physiotherapy Group, ITT = Intention To treat. .

							LS Mean Difference		
Visit	Treatment	n	Mean	S.D.	Median	Range	Estimate (S.E.)	(95% CI)	P-value
Total score									
Baseline	APP	130	18.42	4.53	18.00	6–32			
	TAU	129	15.84	4.65	15.00	7–32			
Week 02	APP	130	10.81	6.46	9.50	0–28			
	TAU	129	13.61	6.44	13.00	0–32			
Week 06	APP	130	7.53	5.98	6.00	0–25			
	TAU	129	11.67	6.08	12.00	0–31			
Week 12	APP	130	6.38	6.37	4.00	0–28			
	TAU	129	12.22	6.40	12.00	0–31			
Change from baseline									
Week 02	APP	130	-7.61	6.82	-8.00	-27-16	-3.8 (0.8)	(-5.3, -2.2)	< 0.0001
	TAU	129	-2.24	6.90	-1.00	-32-16			
Week 06	APP	130	-10.89	7.06	-12.00	-30- 9	-4.7 (0.8)	(-6.3, -3.2)	< 0.0001
	TAU	129	-4.17	6.73	-3.30	-31-15			
Week 12	APP	130	-12.04	7.47	-13.00	-31-13	-6.3 (0.8)	(-7.9, -4.7)	< 0.0001
	TAU	129	-3.63	7.29	-2.01	-30-16			
Cohen's d for change from baseline to week 12							d = 1.10		

The Dizziness Handicap Inventory (DHI) adds extra dimensions to the assessment of how well VH90D and TAU work. Instead of merely recording dizziness symptoms, the DHI quantifies the impairment of everyday life and the dizziness-related limitation of health-related quality of life (QoL). The scale ranges from 0 to 100 points, with higher scores indicating a greater subjective burden from vertigo (0 = no handicap, 100 = maximum handicap). At the start of the study, the mean DHI total score was slightly higher in the VH90D

group than in the TAU group. These baseline differences were statistically controlled for using the ANCOVA approach, with the baseline value included as a covariate in the model.

In both groups, there was a significant reduction in the mean DHI total score over the 12-week treatment period. In the VH90D group, the DHI decreased by 25.63 points (– 39.99%), from 64.08 (SD = 19.64) to 38.44 (SD = 21.81) ($p < 0.0001$; Table 5 and Fig. 1b). The median change was – 27 points, which significantly exceeds the minimal clinically important difference of 3 points on the ROC-based scale defined by¹⁴.

A smaller decrease in the total DHI score was observed in the TAU group, from 52.88 (SD = 19.07) at the start of the study to 43.29 (SD = 20.07) in week 12, corresponding to an average improvement of only 9.58 points.

The confirmatory intergroup comparison revealed a significant mean difference of – 11.9 points (SE = 2.2; 95% CI: – 16.3 to – 7.5; $p < 0.0001$) in favor of the VH90D group (Table 5 and Fig. 1b). The calculated effect size was $d = 0.87$, which corresponds to a large effect size according to the current classification¹⁵.

Thus, VH90D leads to a significant and clinically relevant reduction in functional and QoL limitations caused by vertigo compared to standard physical therapy.

Table 5

Dizziness Handicap Inventory (DHI) scores (ITT). SD = standard deviation, SE = Standard Error, CI = confidence interval, APP = VH90D Group, TAU = Physiotherapy Group, ITT = Intention To treat.

							LS Mean Difference		
Visit	Treatment	n	Mean	S.D.	Median	Range	Estimate (S.E.)	(95% CI)	P-value
Total score									
Baseline	APP	130	64.08	19.64	64.00	12–100			
	TAU	128	52.88	19.07	52.00	20–94			
Week 02	APP	130	45.29	21.26	45.00	8–90			
	TAU	128	46.98	21.19	48.00	8–94			
Week 06	APP	130	40.25	21.53	37.00	8–90			
	TAU	128	45.02	19.49	44.00	8–94			
Week 12	APP	130	38.44	21.81	31.02	8–86			
	TAU	128	43.29	20.07	42.00	8–90			
Change from baseline									
Week 02	APP	130	-18.79	16.52	-21.00	-74-16	-10.3 (2.0)	(-14.2, -6.4)	< 0.0001
	TAU	128	-5.89	15.00	-8.00	-32-46			
Week 06	APP	130	-23.83	17.74	-26.00	-80-14	-12.6 (2.0)	(-16.6, -8.7)	< 0.0001
	TAU	128	-7.86	14.97	-10.00	-50-40			
Week 12	APP	130	-25.63	19.94	-27.00	-82-18	-11.9 (2.2)	(-16.3, -7.5)	< 0.0001
	TAU	128	-9.58	16.91	-12.00	-50-46			
Cohen's d for change from baseline to week 12							d = 0.87		

Sensitivity analyses

The results of the per-protocol analysis for the primary efficacy variable were consistent with the results of the ITT analysis, confirming the robustness of the main results. In addition to the primarily used JTR imputation, alternative imputation methods for missing values were also used in the sensitivity analyses. Regardless of the chosen method, the ANCOVA-based evaluations yielded consistent results with the JTR results. Supplementary non-parametric Wilcoxon-Mann-Whitney tests also confirmed the results with identical p-values ($p < 0.0001$), further underpinning the statistical robustness of the primary analysis.

External validity

The demographic characteristics and the distribution of diagnoses and clinical findings within the study population largely corresponded to the epidemiological patterns observed in patients with vestibular vertigo in outpatient and inpatient standard care. This is consistent with clinical experience in neurology and ENT medicine^{16,17}. Only the relative proportion of patients with bilateral vestibulopathy was slightly higher in the present study than in comparable publications. Overall, the study population is largely representative of the underlying target population, suggesting that the study results have high external validity.

Safety/adverse reactions

As part of active safety monitoring, reversible adverse drug reactions (ARs) associated with the use of VH90D were identified in this study.

Dizziness	Tinnitus
Nausea	Musculoskeletal pain
Balance problems	Back tension
Neck pain	Muscle tension
Headaches	Fatigue
Blurred vision	Knee pain
Tunnel vision	Loss of appetite

No serious ARs were observed. All ARs were acceptable in relation to the benefits.

DISCUSSION

Summary of the method

This multicenter, randomized, group-controlled, single blinded, confirmatory study investigated the efficacy and safety of digital intervention VH90D (Vertidisan®) in patients with chronic peripheral vestibular vertigo. A total of 259 participants were included in the ITT population. The study groups were comparable in terms of age and clinical characteristics, and there was a homogeneous distribution of peripheral vestibular

diagnoses, including unilateral and bilateral vestibulopathies, presbyvertigo, BPPV, PPPD, vestibular neuropathy, and vestibular migraine. Diagnostic heterogeneity was deliberately accepted in order to adequately reflect the clinical reality of peripheral vestibular vertigo syndromes. The VSS-sf-VER was used as the primary endpoint to assess vertigo intensity, and the DHI was used as the secondary endpoint to assess functional limitations and QoL.

Summary of results

The study showed a significant and clinically relevant superiority of the digital intervention over standard physiotherapy treatment. In the VH90D group, we observed an average reduction in the VSS-sf-VER score of 65.36%, whereas a reduction of only 22.91% was observed in the TAU group. The confirmatory group comparison revealed a highly significant difference in favor of VH90D with a large effect size (Cohen's $d = 1.1$; $p < 0.0001$). The pronounced effect size could be explained, among other things, by the high frequency of exercises, standardized implementation of the intervention, and close adherence of patients to the therapeutic process.

The secondary endpoint also confirmed the clinical benefit of the digital intervention with a 39.99% reduction in vertigo-related impairment compared to an 18.11% reduction in the TAU group (Cohen's $d = 0.87$; $p < 0.0001$). Furthermore, the safety analysis showed a favorable tolerability profile with non-serious adverse reactions occurring at a frequency comparable to that of conventional physical therapy.

Comparison with the literature

The observed effects are consistent with growing evidence of the effectiveness of digitally supported vestibular rehabilitation. Meta-analyses have shown that virtual reality- and augmented reality-supported interventions can lead to significant improvements in vertigo-related impairment in patients with peripheral vestibular disorders, particularly when measured using the DHI^{18,19}. Telemedicine approaches to vestibular rehabilitation have also been associated with a significant reduction in vertigo-related disability, albeit with some heterogeneity²⁰.

The mechanism of action of digital interventions can be explained by established principles of CVC^{21–25}. Repeated optokinetic and sensorimotor stimuli promote neuroplastic adaptations in vestibular core areas, the cerebellum, and multisensory cortical networks^{26,27}. Functional reorganization can be achieved through recalibration of vestibulo-ocular and vestibulospinal reflexes, recruitment of visual and proprioceptive compensation mechanisms, and habituation to vertigo-inducing stimuli^{22,23,28}. The present results extend this evidence by showing that a structured digital intervention may be superior to conventional physical therapy.

Comparison with other therapeutic approaches for vertigo

Current guidelines and systematic reviews from both the United States and Europe consistently state that there is no scientific evidence for the efficacy of drugs in the treatment of chronic vertigo or dizziness^{5–10}. Thus, vestibular suppressants (including dimenhydrinate, meclizine, and benzodiazepines) may provide short-term relief of severe vertigo, nausea, or vomiting, but have not been shown to improve long-term

outcomes or symptom resolution in BPPV. Thus, their use should be limited to the acute phase and avoided in chronic management, as they may impede central compensation^{29,30}. This includes Betahistine that is frequently prescribed for Menière's disease and other chronic peripheral vestibular disorders, with its efficacy remaining controversial, and low-quality evidence supporting its benefit.^{31,32}

A further therapeutic approach are canalith repositioning maneuvers (CRMs), such as the Epley and Semont maneuvers. They represent the most effective acute treatment for benign paroxysmal positional vertigo (BPPV), with immediate symptom resolution rates approaching 80–92% after a single application and higher with repeated maneuvers^{33–35}. These maneuvers are included in the VH90D subprogram for BPPV. This notwithstanding, following successful maneuvers persistent residual imbalance symptoms may remain. These may be overcome by digital sensorimotor vestibular rehabilitation exercises, such as those in the VH90D BPPV subprogram. Thus, VH90D can play a complementary role in promoting central adaptation for longer-term recovery or when maneuvers are not feasible³⁵.

Invasive therapeutic approaches, such as vestibular implants, have had promising results in highly selected patients^{33–36} but these approaches are still in the experimental stage and involve considerable invasive effort. In comparison, VH90D represents a non-invasive, low risk, and widely applicable therapeutic option.

Strengths and limitations

The strengths of this study include its randomized, controlled, and multicenter study design, large sample size, use of validated endpoints, and active comparison group, which allows for a realistic assessment of the results. The conservative statistical approach with JTR imputation further strengthens the robustness of the findings. In addition, the study population included various peripheral vestibular disorders. This diagnostic heterogeneity increases the generalizability of the results but does not allow for disease-specific subgroup analyses.

Limitations include the efficacy assessment being based primarily on patient-reported endpoints and not including objective peripheral vestibular function parameters, such as measurements of caloric responses or cranio-corpography. However, these were also not appropriate because the therapy targets CVC, which by its nature does not affect peripheral vestibular findings. Nonetheless, patient-reported endpoints are considered clinically relevant in vertigo disorders, as they directly reflect the subjective symptom burden and functional limitations in everyday life^{37–45}.

In addition, the actual intensity of use of the digital intervention could not be fully objectified, which may have influenced the individual effect size. Yet, at the same time, this approach reflects the real care situation and increases external validity. Furthermore, participation in the study required a certain level of digital literacy, which could limit its transferability to less tech-savvy populations. Finally, the limited observation period does not allow any conclusions to be drawn about the long-term persistence of the therapeutic effects, so future studies should include longer follow-up periods.

In summary, the results of this randomized controlled trial show that digital vestibular rehabilitation using VH90D is an effective, non-invasive, and practical addition to the established treatment of peripheral

vestibular disorders. Future studies should validate the effects observed here using objective vestibular measurements and investigate disease-specific efficacy profiles.

ONLINE METHODS

Material

VH90D (Vertidisan®) is manufactured by Digitineers, Tübingen, Germany. It is a Class B (EN 62304) cloud-based software as a medical device (SaaSMD). Vertidisan® is a CE-marked medical device (Class I according to the European Medical Device Regulation, 2017) and available on the EU market. Users stream exercise demonstrations.

Methods

The detailed study protocol for this randomized controlled trial was published elsewhere¹¹. This study focused on the efficacy results using the VSS-sf-VER and DHI. The hypothesis that the randomized controlled trial is suitable for distinguishing the efficacy of the digital intervention from the efficacy of standard physiotherapy was tested. All other secondary endpoints are listed in Wirth et al. 2026¹² and, for reasons of space, the results published elsewhere.

Study design and ethical aspects

This study was designed and conducted as a prospective, multicenter, randomized, group-controlled, single-blind, confirmatory clinical trial (GEVE-II study). The study protocol was submitted to the leading ethics committee of the Baden-Württemberg State Medical Association and received a positive evaluation (file number F-2021-157). In addition, positive votes were received from all local ethics committees of the participating study centers.

The study was registered in the German Clinical Trials Registry under registration number DRKS00028026 and included in the International Clinical Trials Registry Platform (ICTRP; 12/12/2023) of the World Health Organization (<https://trialsearch.who.int/Trial2.aspx?TrialID=DRKS00028026>). After receiving verbal information from a study physician, all participants signed a written consent form agreeing to participate in the study and to the use of their data. All participants received written information detailing the purpose and procedure of the study, possible adverse events, the name and address of the insurer, and detailed information on data protection.

An interim analysis was conducted and results were published in advance¹¹. The reason for this was the varying pace of administrative processes (local ethics committees, local hospital administrations) at the individual clinics.

Study centers and setting

The present GEVE-II study was conducted as a national clinical trial at six study centers in Germany (*Department of Otolaryngology, University Hospital Essen, Germany; % Department of Otolaryngology,

University of Tübingen, Germany; [§]Department of Otolaryngology, University of Leipzig, Germany; [&]Department of Otolaryngology, University of Würzburg, Germany, [@] Department of Otolaryngology, Technical University of Munich, Germany; [?]Clinic of Otolaryngology, Kelternturm, Tübingen, Germany) and is the follow-up trial to the single-centre GEVE-I study¹². Primary endpoint data (VSS-sf-VER) of one study center (n=212) have already been published in the singlecenter GEVE-I study¹².

To avoid selection bias, the SBDT (Objective Standard Balance Deficit Test) and the SOT (Sensory Organization Test) posturography were administered to all study participants using the same equipment. To this end, the equipment was transported to each center.

Study population and recruitment

Patients were recruited consecutively as part of standard outpatient and inpatient care at the participating study centers. All potential participants were examined, diagnosed, and systematically assessed by the investigators with regard to the defined inclusion and exclusion criteria.

Adult patients aged 18 years and older with clinically confirmed peripheral vestibular dysfunction and relevant vertigo symptoms were included in this study. A prerequisite for study participation was written informed consent and the ability to use a smartphone or tablet independently in order to properly use the digital intervention.

Patients with indications of central vestibular or other neurological diseases, and those with acute internal medical or surgical conditions requiring immediate medical or surgical intervention were excluded from the study. Individuals with severe psychiatric disorders that impaired their ability to participate in the study as required were also excluded, as were patients with motor or orthopedic limitations that prevented them from safely performing the planned training exercises. Other exclusion criteria included chronic use of anti-vertigo medication, recent vestibular physiotherapy, pregnancy, and substance abuse.

Basic diagnostic examination

Before inclusion in the study, all participants underwent standardized basic otoneurological diagnostics: detailed medical history, ENT examination including ear microscopy, and clinical vestibular function tests, including testing for spontaneous and gaze-evoked nystagmus, the Halmagyi head impulse test, the Romberg and Unterberger tests, the head shake test, and positioning tests to detect or rule out benign paroxysmal positional vertigo. If clinically indicated, a caloric test was also performed. Objective balance tests, such as the Standard Balance Deficit Test or the Sensory Organization Test, could also be used. Only patients with confirmed peripheral vestibular causes of vertigo symptoms were included in the study¹¹.

Randomization and blinding

Randomization was performed 1:1 in blocks using a centrally generated, computer-generated randomization sequence. Allocation was carried out using sealed envelopes that were opened after completion of the baseline examination.

Due to the nature of the intervention, it was not possible to completely blind the participants. However, the primary and secondary endpoints were assessed by blinded investigators.

Intervention: VH90D (Vertidisan®)

The intervention group used VH90D (Vertidisan®), a CE-marked digital health application for vestibular rehabilitation that is used on smartphones or tablets. The intervention consisted of a structured multimodal training program over a period of 90 days with a recommended daily application time of approximately 10 to 25 minutes.

The therapeutic program is based predominantly on diagnosis for adaptive sensorimotor and optokinetic exercises. If benign paroxysmal positional nystagmus (BPPN) is the chosen diagnosis, therapy starts with typical BPPN maneuvers. In case of falls, muscle-strengthening exercises, including those based on the Otago Exercise Program (OEP)⁴⁶, are integrated. In addition, educational content, behavioral therapy elements, progressive muscle relaxation, and autogenic training are provided. The content is conveyed via video- or audio-based demonstrations and structured instructions. The selection and progression of the exercises is based on the specified diagnosis and individual resilience of the patients.

Control intervention: Therapy as usual

Participants in the control group received conventional physiotherapy in line with standard care. The therapy was based on a doctor's prescription and carried out by registered physical therapists. The type, frequency, and duration of the physical therapy corresponded to the specifications of the German Remedies Catalog and generally comprised up to six treatment sessions of 20 minutes each per prescription with the possibility of extending this to up to 18 sessions. No additional standardization or content specifications for the physiotherapy intervention were made within the scope of the study. After completion of the 12-week study phase, participants in the control group were offered the opportunity to also use the VH90D digital intervention. This crossover phase served ethical and practical care considerations and was not included in the primary efficacy analysis.

Study design

Fig. 2 shows the overall design of the study and inclusion of patients. The main steps were recruitment (T0, baseline), allocation (randomization), follow-up (T1, 2 weeks; T2, 6 weeks; and T3, 12 weeks), ITT (JTR imputation), and per-protocol (PP) analysis. The validated VSS-sf-VER was used as the primary efficacy endpoint. The DHI served as a secondary endpoint for assessing functional limitations caused by dizziness. Both instruments were administered at T0 and T3; efficacy analyses were based on the change between these two time points.

Statistical analyses

For descriptive statistics, means, medians, standard deviations, quartiles, and maximum and minimum values were used as quantitative variables. Absolute and relative frequencies were used as qualitative

variables. Where indicated, 95% CIs were calculated. Wilcoxon-Mann-Whitney tests were used in the sensitivity analysis. Primary and secondary endpoints were tested with $\alpha = 5\%$ on both sides.

As part of the confirmatory statistics for the endpoints, a priori hierarchical tests and statistical hypotheses were established. The primary endpoint was a group comparison of the change in the VSS-sf-VER score from T0 to T3. The analysis was performed using ANCOVA with the treatment group as the factor and the baseline as the covariate. The secondary endpoint was a group comparison of changes in the DHI from T0 to T3. ANCOVA was used as for the primary endpoint. Hierarchization was performed to address multiplicity and alpha errors. Testing in the specified a priori order allowed for strong control of the 5% significance level for the above-mentioned primary and secondary efficacy variables. Statistical analyses were performed using SAS statistical analysis software.

Declarations

Conflicts of Interest

The authors declare that they have no personal or financial conflicts of interest related to this study. The sponsor had no influence on the authors' declaration of competing interests.

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Author Contribution

Nadia Sadok: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing – Original Draft, Writing – Review & Editing, Project Administration. Stephan Wolpert: Conceptualization, Methodology, Resources, Writing – Review & Editing. Laura Bühning: Investigation, Data Curation, Writing – Review & Editing. Theresa Wald: Investigation, Data Curation, Writing – Review & Editing. Miriam Bürklein: Investigation, Data Curation, Writing – Review & Editing. Kristen Rak: Investigation, Data Curation, Writing – Review & Editing. Michael Bulitta: Formal Analysis, Software, Validation, Writing – Review & Editing. Daniel Schmitz: Formal Analysis, Software, Validation, Writing – Review & Editing. Walther Lehmacher: Methodology, Formal Analysis, Supervision, Writing – Review & Editing. Hubert Löwenheim: Resources, Supervision, Writing – Review & Editing. Stephan Lang: Conceptualization, Resources, Supervision, Writing – Review & Editing. Andreas Dietz: Resources, Supervision, Writing – Review & Editing. Stephan Hackenberg: Resources, Supervision, Writing – Review & Editing. Barbara Wollenberg: Resources, Supervision, Writing – Review & Editing. Markus Wirth: Conceptualization, Methodology,

Resources, Supervision, Writing – Review & Editing, Project Administration. Moritz Meyer: Conceptualization, Methodology, Formal Analysis, Supervision, Writing – Review & Editing, Project Administration.

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Data Availability

The datasets generated and/or analysed during the current study are not publicly available because they contain potentially identifiable participant information. De-identified data may be made available from the corresponding author on reasonable request, subject to approval by the study sponsor and the participating institutions, and in accordance with applicable ethical, legal, and regulatory requirements.

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Figures

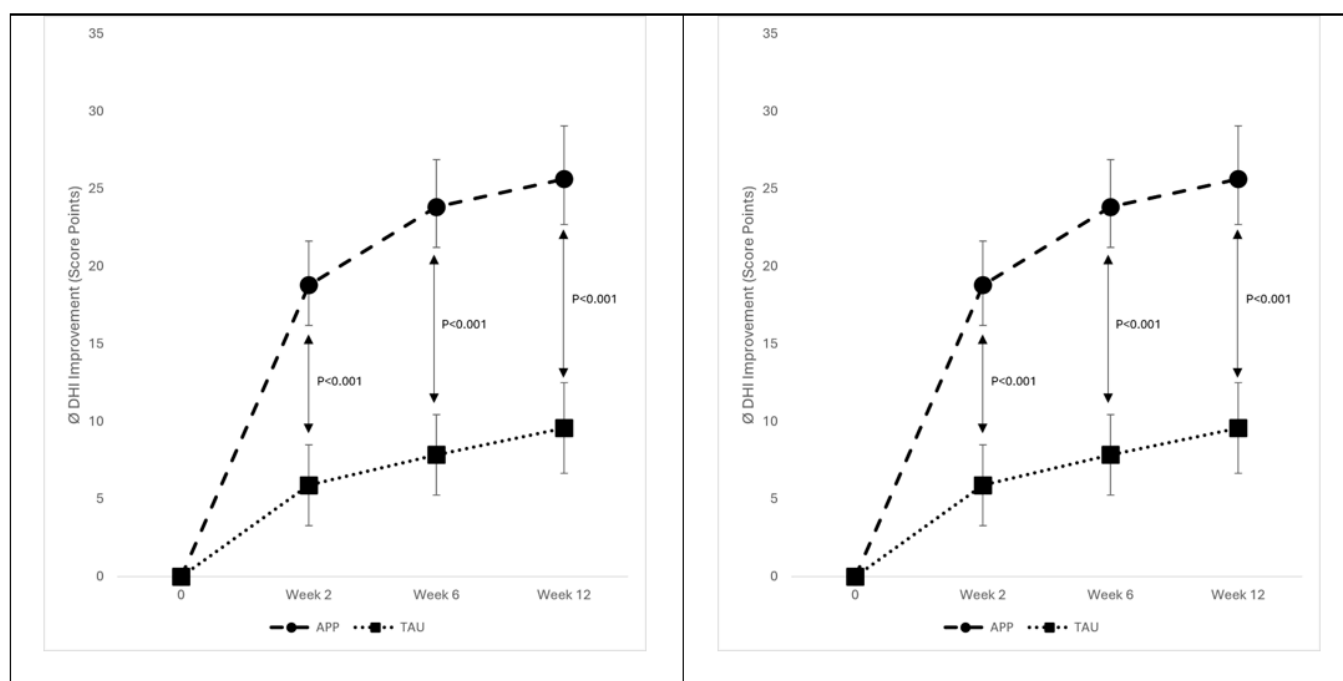


Figure 1

a: Average change in vertigo from baseline (ITT). The VSS-sf-VER score was used as a measure of vertigo.

b: Average change in the Dizziness Handicap Inventory (DHI) from baseline (ITT). Ordinate: Delta of the absolute score. Squares: Intragroup deltas of the VH90D group. Circles: Intragroup deltas of the physiotherapy treatment as usual (TAU) group. Bars indicate confidence intervals. For T3, the final intergroup difference using ANCOVA is given, which is the primary efficacy variable of the study. The confirmatory intergroup delta comparison shows a significant mean treatment difference for both measures (p < 0.0001); ITT = Intention To treat; APP=VH90D; TAU (Therapy as usual)=physiotherapy

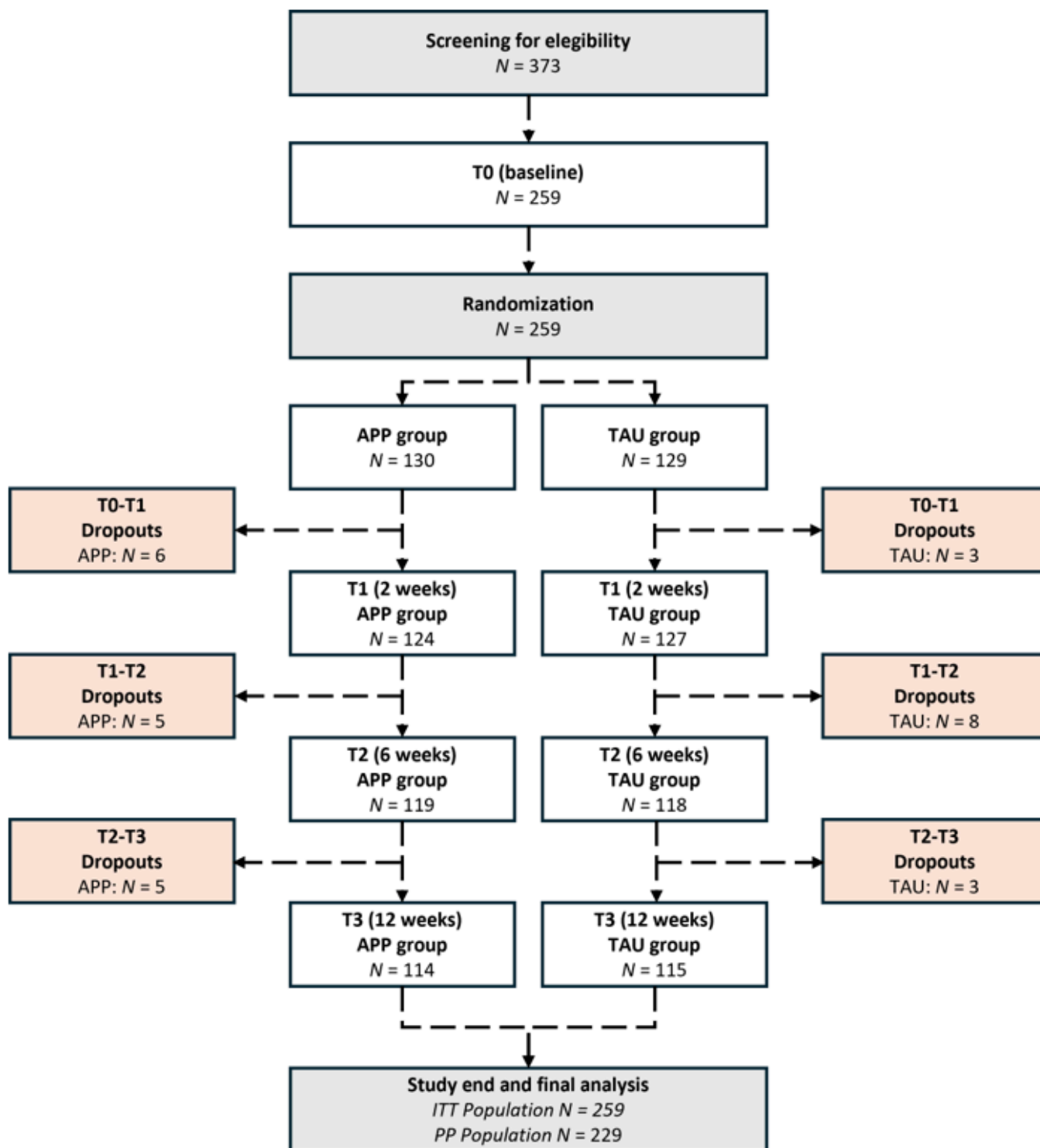


Figure 2

Study diagram of patient inclusion. ITT = Intention To Treat; PP = Per Protocol.