

Summary of clinical trial results

Date of summary	3 March 2026
Title of the clinical investigation	Enhancement of glymphatic function with electroacoustic therapy Glymfaattisen toiminnan tehostaminen elektroakustisella hoidolla
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Unique identification number	EudraCT number: 2021-000625-27 Fimea KLnro 57/2021 FIMEA/2021/005240 TUKIJA/258/2021
Clinical investigation protocol number	2022102021_v5

Title of the clinical investigation – Summary information	
Short title of the study	Glymf_EAC, EAC01
Full title of the study	Enhancement of glymphatic function with electroacoustic therapy: a clinical investigation evaluating the effects of blood pressure reduction and whole-body vibration therapy in healthy adult volunteers.
Study dates	First posted date on the clinical trial registry: 21.05.2021 Approval date of the clinical investigation (Ethics Committee TUKIJA): 16.08.2021 Approval date of the clinical investigation (Fimea): 01.11.2021 Study start date: 01.11.2021 Start of recruitment: 01.11.2021 First subject first visit: 29.11.2021 Last subject last visit: 10.10. 2023 End of study: 31.12.2023
Study site	Department of Radiology Research Unit and Outpatient Clinic, Oulu University Hospital, Oulu, Finland.
If applicable, reason for study interruption or early termination	The study was not interrupted or terminated prematurely.

Purpose of the clinical investigation
<p>The purpose of the study was to evaluate the effects of the investigational intervention on pulsations associated with the brain clearance system, the transfer of brain-derived proteins into the systemic circulation, fluid dynamics of the brain clearance system, blood pressure regulation, and other physiological parameters. In addition, the study aimed to assess the safety and potential adverse effects of the intervention in healthy adult volunteers.</p> <p>The following devices were used in the study: magnetic resonance imaging (MRI), functional near-infrared spectroscopy (fNIRS), non-invasive blood pressure monitoring (NIBP), electroencephalography (EEG), and a Neurosonic whole-body vibration mattress.</p>

Description of the investigational devices, the clinical investigation, and the methods used	
Description of participants	<p>Participants were healthy adult volunteers aged 18–70 years who were not on regular medication (with the exception of contraceptives and thyroxine).</p> <p>Exclusion criteria included pregnancy or breastfeeding, migraine or recurrent headache, alcohol or substance abuse, smoking, allergy to glyceryl trinitrate or nitrates, current use of erectile dysfunction medication (sildenafil, vardenafil, or tadalafil), or contraindications to magnetic resonance imaging (e.g., metallic foreign bodies, severe claustrophobia, electronic implants).</p> <p>All participants underwent a medical examination prior to study initiation.</p>

Investigational medicinal product	The investigational medicinal product was a commercially available and generally well-tolerated sublingual formulation, Nitroglycerin Orifarm® 0.5 mg resorbable tablet (Phase 4). Its effect is mediated via nitric oxide–induced relaxation of vascular smooth muscle cells, resulting in blood pressure reduction.
Description of devices	<p>Neurosonic Plus Mobile Mattress (Neurosonic NSPLUS4-N, serial number: 18120417) produces variable low-frequency (26–43 Hz) electroacoustic vibration energy applied to the whole body. Its intended purpose in this study was to enhance (g)lymphatic pulsations by stimulating metabolic activity, blood flow, and central nervous system pulsatility.</p> <p>fNIRS (OFNI_fNIRS_v1) is an optical measurement technique emitting light in the wavelength range of 600–1300 nm. Its intended purpose is to measure cerebral blood circulation and lymphatic fluid dynamics in humans.</p> <p>NIBP (OFNI_NIBP_v1) is a non-invasive blood pressure monitoring device. Its sensors detect small skin movements caused by cardiovascular pulsations and are used for continuous blood pressure monitoring.</p>
Description of procedures related to device/medicinal product use	<p>The fNIRS device was developed for use in the fMRI environment and enables continuous measurement of cortical hemodynamic changes and CSF volume fluctuations synchronously with MRI. The measurements were used to assess changes in blood oxygenation and CSF volume. The device was used according to its intended purpose during both MRI and vibration therapy.</p> <p>Continuous blood pressure was measured using an MR-compatible NIBP device. Optical accelerometer sensors placed over the carotid artery and sternum detected microscopic skin movements induced by cardiovascular pulsations, from which blood pressure was estimated. The device was used according to its intended purpose during imaging and vibration therapy.</p> <p>Whole-body vibration therapy was performed outside the MRI room using the commercially available Neurosonic mattress. A 36-minute recovery program was applied, producing variable low-frequency (26–43 Hz) electroacoustic vibration energy across the whole body. Participants lay on the mattress with their head positioned at the foot end, and the manufacturer-provided pillow was not used.</p> <p>The investigational medicinal product was administered according to routine clinical practice, and participants received a maximum of two doses during the study visit. During Study Visit B, the medicinal product was combined with whole-body vibration therapy in accordance with the study protocol. This combination deviates from normal clinical practice and was implemented for research purposes under physician supervision.</p>
Study design	<p>The study was a controlled interventional investigation conducted in a randomized crossover design. Participants were randomly assigned to attend either Study Visit A or Study Visit B first and subsequently participated in the alternate visit.</p> <p>Study Visit A included multimodal imaging and whole-body vibration therapy.</p>

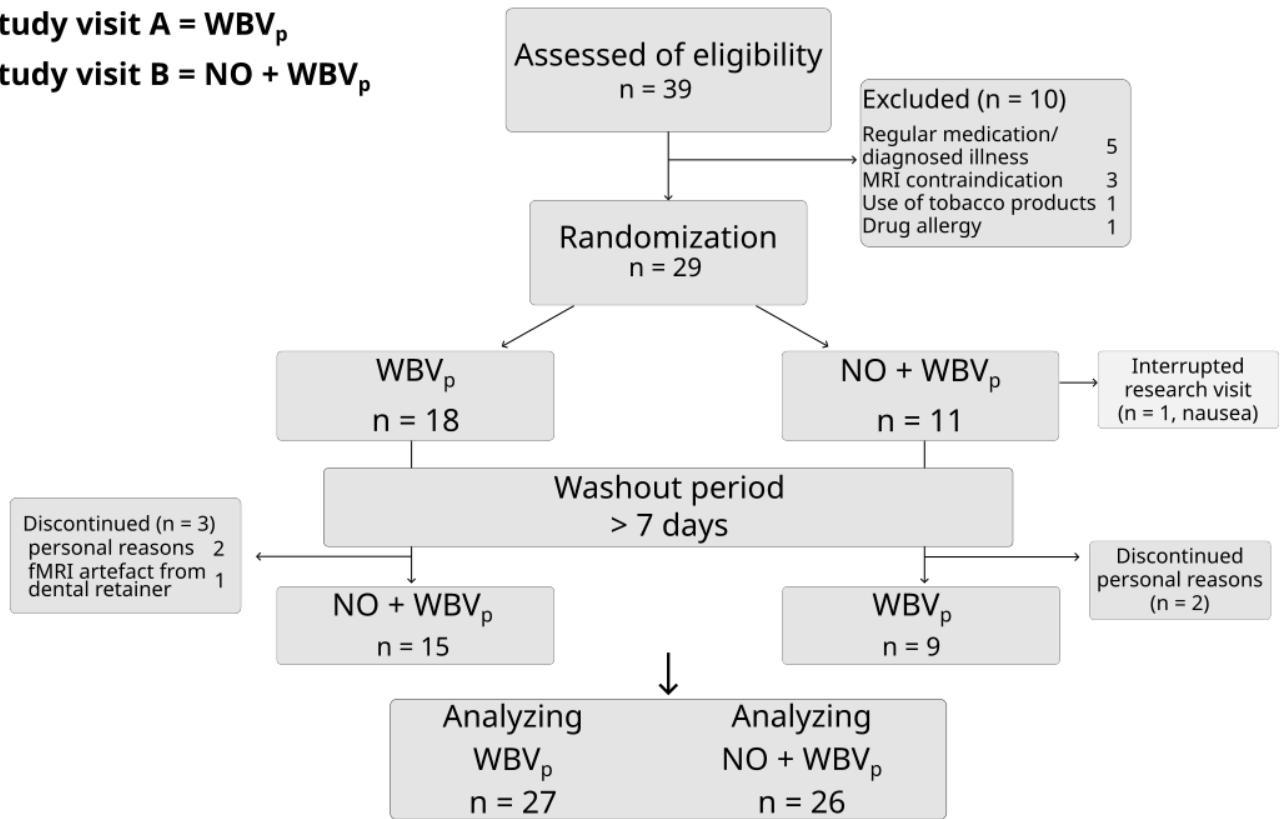
	Study Visit B included multimodal imaging, whole-body vibration therapy, and administration of the investigational medicinal product for blood pressure reduction.
Randomization	Simple randomization was used to determine whether a participant attended Study Visit A or Study Visit B first. All participants subsequently attended the alternate visit, resulting in a randomized crossover design. No blinding was applied.
Objectives and endpoints	<p>The primary hypothesis was that whole-body vibration therapy combined with Nitroglycerin Orifarm® is safe and does not cause major adverse health effects in healthy participants.</p> <p>It was further hypothesized that the intervention activates glymphatic clearance, leading to increased physiological brain pulsations, enhanced brain water dynamics, and increased transfer of brain-derived proteins (amyloid-beta, neurofilament light, glial fibrillary acidic protein, phosphorylated tau) into the systemic circulation.</p> <p>Secondary outcome measures included changes in physiological parameters such as heart rate, heart rate variability, blood pressure, and respiration.</p>
Sample size	The planned sample size was 25–50 voluntary participants. In functional measurement studies, 20–25 participants have been shown to represent the minimum number required to detect physiological effects. As this was a pilot study, no formal sample size calculation was performed.
Duration of follow-up	Participants were followed throughout the study visits. After the medicinal product-containing visit (Study Visit B), participants were followed for at least 30 minutes to ensure that blood pressure had returned to baseline levels and that the participant's condition was stable.
Statistical analysis methods	<p>Statistical analyses of MRI data were performed using FSL randomise permutation testing to assess statistical significance while minimizing multiple comparison errors.</p> <p>Normality of variables was evaluated graphically and using the Shapiro–Wilk test. For normally distributed variables, two-sided paired Student's t-tests were applied. For non-normally distributed data, the paired Wilcoxon signed-rank test was used.</p> <p>The level of statistical significance was set at 0.05. Multiple comparisons were corrected using the False Discovery Rate (FDR) method.</p>
Significant changes	No significant modifications to the study protocol were made.

Results of the study

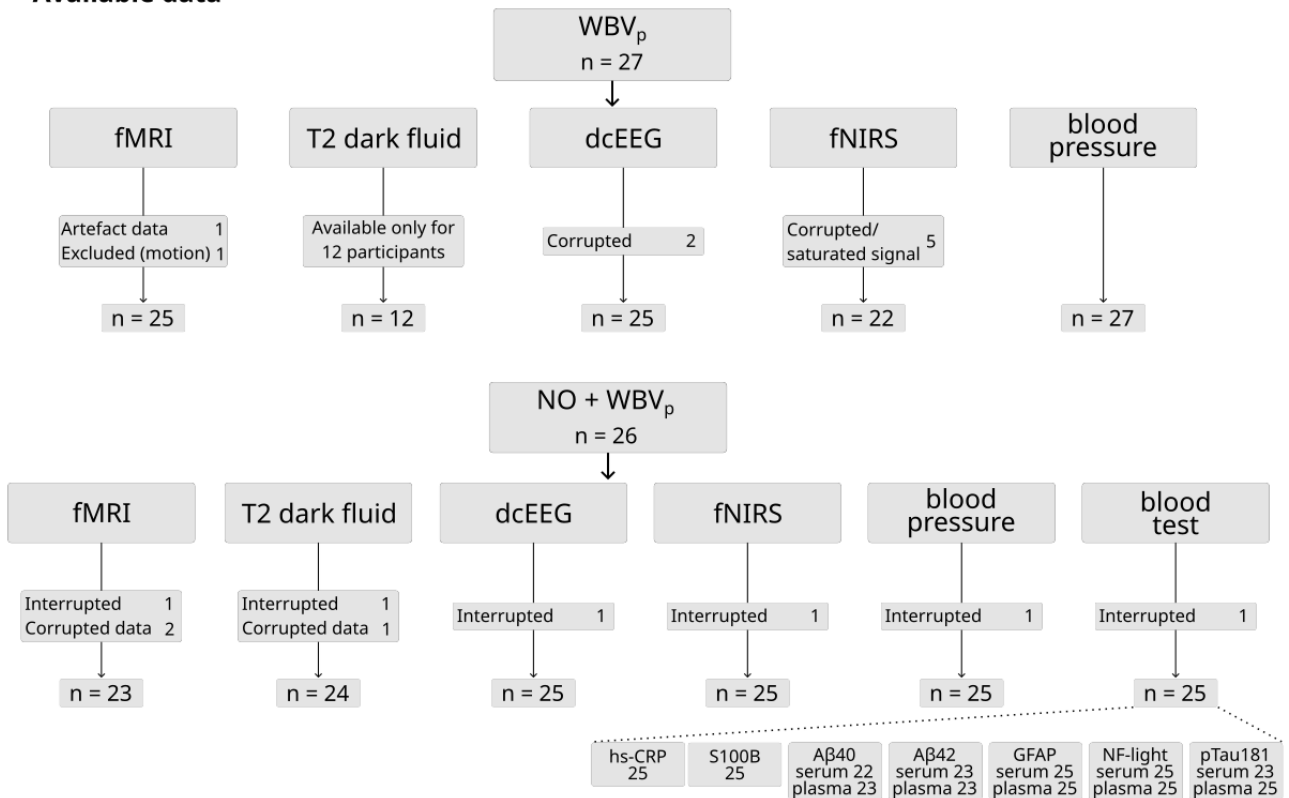
Participant flow

Study visit A = WBV_p

Study visit B = NO + WBV_p



Available data



Demographics information	The study involved 29 healthy Finnish volunteers (mean age: 44 ± 10 years, 15 females, range 27-61 years).
Results of the study	<p>Before treatment, systolic/diastolic blood pressure measured from the left brachium was 134 ± 14 / 79 ± 8 mmHg. During intervention, the pressure fell to a nadir of 114 ± 9 / 67 ± 7 mmHg ($p < 0.0001$), corresponding to 14.9 ± 6.3 % (systolic) and 14.8 ± 9.0 % (diastolic) reductions.</p> <p>Following the treatment, whole-brain T2 dark-fluid MRI signal intensity decreased by a mean of 4.6 ± 6.1 % ($p = 0.008$), indicating a shift in the brain tissue water and/or macromolecule content in the brain, without any detectable change in brain tissue volume. In parallel, the volume of segmented extracerebral free dark CSF fluid increased by 6.5 ± 9.8 ml ($p = 0.02$).</p> <p>At the onset of intervention, there was a rapid rise in oxygenated hemoglobin along with a slower and smaller increase in deoxygenated hemoglobin, consistent with NO-mediated vasodilation. These hemodynamic effects coincided with reductions in mean arterial pressure and brain water content.</p> <p>Following the treatment, respiration-driven brain pulsation power increased in a focal region of the right temporal lobe. Cardiovascular pulsation power was also elevated after the treatment in frontal and parietal cortex.</p> <p>The treatment significantly increased the low molecular weight (< 68 kDa) brain-derived proteins; Aβ40 (pre 38.2 ± 19.0 pg/ml, post-corrected 50.5 ± 25.2 pg/ml $p = 0.03$), Aβ42 (pre 2.6 ± 1.4 pg/ml, post-corrected 3.5 ± 1.8 pg/ml $p = 0.03$), and GFAP (pre 65.2 (56.7 to 83.5) pg/ml (median (interquartile range)), post-corrected 85.1 (69.7 to 113.5) pg/ml, $p < 0.0001$) in systemic circulation. In contrast, the larger neurofilament-light ($p = 0.67$) and phosphorylated tau-181 ($p = 0.75$) proteins were unaltered in serum, suggesting that molecular weight constrains CNS-to-blood efflux efficiency.</p> <p>S100 calcium-binding protein B (S100B, pre: 0.07 ± 0.10 µg/l, post 0.06 ± 0.04 µg/l, $p = 0.4$) and high-sensitivity C-reactive protein (hs-CRP, pre: 1.16 ± 1.26 mg/l, post 1.10 ± 1.12 mg/l, $p = 0.08$) showed no significant changes, suggesting a good margin of clinical safety.</p>
Safety results and adverse events	<p>There were no serious adverse events reported during the study.</p> <p>No device-related or investigational medicinal product-related unexpected or unanticipated adverse events were observed. No device malfunctions occurred that could have led to a serious adverse event.</p> <p>Mild adverse effects were reported by some participants following administration of the investigational medicinal product. Headache was reported by 4/26 participants (15%) and nausea by 3/26 participants (12%); both are known and expected effects of nitroglycerin. In one case, Study Visit B was discontinued due to the severity of nausea (vomiting).</p> <p>No participants reported discomfort related to the whole-body vibration procedure.</p>

	The number of withdrawals and the reasons for withdrawal are presented in the Participant Flow diagram.
Deviations from the clinical investigation plan	No deviations from the clinical investigation plan.

Conclusion of the clinical investigation	
Meaning of the results.	The benefits of the investigation were considered to be significantly greater than the associated risks. The investigational devices and the medicinal product were safe to use in combination, and the devices demonstrated acceptable performance and safety for both participants and study personnel.
Interpretation of the results	<p>The study demonstrated that whole-body vibration therapy combined with pharmacological blood pressure reduction is safe in healthy volunteers and did not result in clinically significant health-related adverse effects. The overall benefits of the investigational devices were considered to outweigh the associated risks.</p> <p>Furthermore, the results indicate that the intervention activated brain glymphatic fluid dynamics, enhanced physiological pulsatility within the brain, and increased the transfer of brain-derived proteins (amyloid-beta 40 and 42, and glial fibrillary acidic protein) into the systemic circulation.</p> <p>We conclude that human brain solute efflux can be safely and significantly enhanced with nitric oxide-mediated vasodilation combined with mechanotransductive stimulation.</p> <p>The findings provide a meaningful contribution to the investigation of disorders associated with impaired glymphatic function.</p>
Limitations	<p>The study was conducted with a relatively small sample size in healthy volunteers, which limits generalizability to patient populations. A randomized crossover design was used to minimize inter-visit variability; however, potential order effects cannot be fully excluded.</p> <p>Some outcome measures were based on indirect physiological markers, which may introduce uncertainty in interpretation. Potential researcher or analysis-related bias was minimized by applying multiple complementary analysis approaches.</p> <p>The intervention was evaluated in a short-term setting, and long-term effects cannot be assessed based on this study.</p>
Potential for future research	The findings demonstrate significant potential for future research in diseases associated with impaired brain solute efflux of protein waste.