

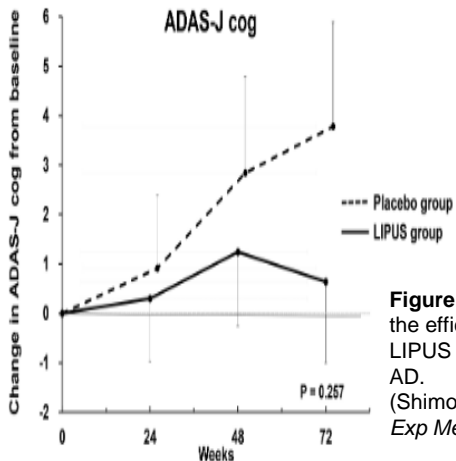
# Pivotal Trial of Low-intensity Pulsed Ultrasound Therapy for Early Stage of Alzheimer’s Disease (LIPUS-AD) –Rationale and Design-

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## Background (Rationale)

- Cerebral microvascular dysfunction has been suggested as an important pathology of Alzheimer’s disease (AD).
- We found that low-intensity pulsed ultrasound (LIPUS) therapy upregulates endothelial NO synthase (eNOS) with resultant angiogenesis and suppression of chronic inflammation (Shindo T, Shimokawa H. *Ann Vasc Dis.* 2020;13:116-125.)
- We demonstrated that the LIPUS therapy ameliorates cognitive declines in a mouse model of AD. (Eguchi K, Shimokawa H, *Brain Stimul.* 2018.)
- We have performed a pilot study, suggesting the efficacy and safety of the LIPUS therapy in patients with early stage of AD (Shimokawa H, et al. *Tohoku J Exp Med.* 2022;258:167-175.) (Figure 1)



**Figure 1.** The pilot trial suggests the efficacy and safety of the LIPUS therapy for early stage of AD. (Shimokawa H, et al. *Tohoku J Exp Med.* 2022;258:167-175.)

Placebo group (N)	8	8	5	5
LIPUS group (N)	11	10	10	10

## Purpose

A randomized, double-blind, placebo-controlled trial to address the efficacy and safety of the LIPUS therapy in early stage of AD.

## Design

### Trial design

- Target sample size: 220, Number of sites: 17 (Japan)
- Randomization: 1:1 fashion (LIPUS: Placebo)
- Enrollment period: August 2023~July 2024
- Trial period: August 2023~October 2026

### Inclusion criteria

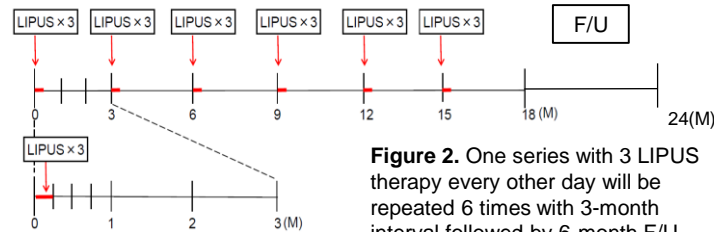
- Mild AD or MCI due to AD (NIA/aa 2018), Age: 50~90, Both sex
- Positive Aβ PET (within 48 weeks)
- At screening: CDR global score 0.5~1.0, MMSE-J>20
- No symptomatic cerebral hemorrhage or infarct on MRI
- Informed consent from a patient or reliable partner/supporter

## Endpoints

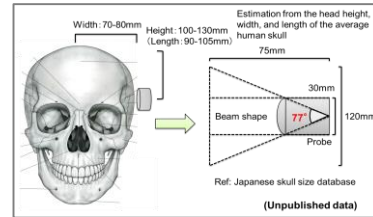
- **Primary EP:** Changes in ADAS-J-cog-14 at week 72
- **Secondary EPs:** Changes in the following items at week 24, 48, and 72 ADAS-J-cog-14, CDR sum boxes, NPIQ-J, J-ZBI, MMSE-J, etc.
- **Safety EPs:** Any adverse effects that cannot be ruled out for LIPUS Tx.
- **Pilot EPs:** Changes in Aβ PET and brain MRI at week 72

## LIPUS therapy

### A. Protocol



### B. Whole-brain irradiation



**Figure 3.** In a preliminary Study, we confirmed that 77° is the best angle for whole-brain irradiation.

### C. LIPUS irradiation conditions

- Frequency: 0.5 MHz
- Intensity: 0.25W/cm<sup>2</sup>
- Cyclic number: 32 cycles
- PRF (Pulse repetition frequency): 7.1 kHz

### D. LIPUS machine and treatment scene



**Figure 4.** The LIPUS therapy consists 3 times of 20-min irradiation with a 5-min interval. It is quite less invasive.

## Conclusion

The LIPUS-AD trial finally addresses the efficacy and safety of the LIPUS therapy in patients with early stage of AD. (This pivotal trial is conducted as a corporate clinical trial by Sound Wave Innovation, Inc.) (ClinicalTrials.gov: NCT05983575, jRCT2032230125)