A clinical study on the efficacy and safety of the head ultrasonic stimulator Ultra-Ma for patients with clinically diagnosed dementia with Lewy bodies

Clinical study report

Clinical device provider: Kamiyama, Ltd.

Date:2021/Oct/21st

1. Title for clinical study

A clinical study on the efficacy and safety of the head ultrasound stimulator Ultra-Ma for patients with clinically diagnosed dementia with Lewy bodies

2. Purpose of clinical study

We investigated the usefulness of a head ultrasonic stimulator with drug combination therapy for the improvement of dementia-associated behavioral and psychological symptoms (BPSD) and cognitive function in patients with dementia with Lewy bodies.

3. Identification of clinical study device and provider

- Identifying code: Ultra-Ma (Manufacturing code: KMY-01)
- Clinical device provider: Kamiyama, Ltd.
  Address: 2-264 Kamiyamacho, Funabashi City, Chiba. Japan

4. Clinical deign

Multicenter, single-blind, interventional study

5. Clinical study implementation system

5.1. Chief investigator

Kanagawa Dental University Hospital Department of Dementia and Geriatrics, Professor Yuta Manabe

5.2. Research facility

Yokohama Clinic, Kanagawa Dental University Hospital

6. Certified Review Board

KKR Toranomon Hospital Clinical Research Review Board

6.1. Clinical trial registration

The clinical study plan was registered with jRCT and submitted the implementation plan to the Minister of Health, Labor and Welfare.

- Registration number : jRCTs032190012

7. Subject for clinical study

Patients with clinically diagnosed mild and moderate Lewy body dementia and BPSD

7.1. Selection criteria

(1) Patients who can obtain written consent to participate in the clinical study (consent from the patient himself/herself was obtained as much as possible, and consent from the legal representative was required)
(2) Patients aged between 60 and 90 at the time of informed consent
(3) Japanese, male and female
(4) Patients who meet all of the following diagnostic criteria before enrollment
- Patients with a Hachinski cerebral ischemia score of ≤4
- Patients with a CDR-J score of 0.5 or higher who are compatible with mild cognitive impairment and dementia
- Patients with MMSE score of ≤27 or ≥11
- Patients with a score of 1 or higher on any item on the NPI-Q

(5) Patients diagnosed with probable DLB according to the clinical diagnostic criteria for dementia with Lewy bodies (CDLB guidelines 2017)
(6) Home-care patient who meet the following conditions:
- Have a family member who can monitor their condition at all times
- The same caregiver provides care for more than 2/3 of the day

(7) Patients or caregivers who can record symptom diaries
(8) Patients who have been treated with either or both of the following drugs for more than 4 weeks before the start of the clinical study
① Cholinesterase inhibitor ② L-dopa drugs

7.2. Exclusion criteria

(1) Patients with dementia other than Lewy body dementia
(2) Patients who have complications such as musculoskeletal diseases that interfere with the performance of tests when participating in or conducting clinical research
(3) Patients with a history of alcoholism or drug dependence
(4) Patients who are suspected to have cerebrovascular dementia according to MRI or CT imaging findings within 1 year before obtaining consent (localized brain lesions or multiple infarctions considered to be the cause of dementia are observed)
(5) Patients with such as a Cerebrovascular disease, brain tumor, schizophrenia, epilepsy, normal pressure hydrocephalus, mental retardation, head injury with loss of consciousness, serious neurological/psychiatric disorders, and history of brain surgery with residual deficit.
(6) Patients with severe extrapyramidal disorders (Hoehn & Yahr severity classification IV or higher)
(7) Patients with serious or poorly managed disease at the time of informed consent
(8) Patients who cannot perform MMSE and NPI-Q tests (visually or deaf patients, patients with aphasia, etc.)
(9) Patients with serious complications such as serious hepatic/renal/cardiac disease
(10) Patients who are bedridden or living in facilities (special nursing homes, health care facilities for the elderly, etc.)
(11) Patients using implanted medical electrical devices that are susceptible to electromagnetic interference, such as pacemakers and implanted defibrillators
(12) Patients with metal coils etc. placed in the skull
(13) Patients with built-in hearing aids, cochlear implants, or implanted hearing aids
(14) Patients who have participated in other clinical research or trials for dementia with Lewy bodies within 1 year prior to obtaining informed consent
(15) Other patients who are deemed inappropriate by the attending physician

8. Overview of clinical study device

This equipment operates as a weak ultrasonic acoustic vibration device with a frequency of 30 kilohertz, and the ultrasonic intensity is a constant output at the maximum level (1.6 mW/cm2).

The vibration intensity of the sham stimulus is an auditory stimulus that is about 1/8 (1/8±10%) of the actual stimulus intensity.

・Manufacturing code/number : KMY-01 /No.19001～19020

8.1. Usage of the device

Turn the power switch "on" and press the start switch, it will run for 20 minutes and then stop. The monitor counter is incremented by 1 each time it is used (count values are recorded in the case report form at the start, at the end of sham stimulation, and at the end of real stimulation).

・How to connect the massage band to the main unit

① Sham stimulation: Connect to the output terminal No.1 jack.
② During actual stimulation: Connect to the output terminal No.2 jack.

8.2. Period of use

(1) Screening period (fixed drug intake from 4 weeks before)
(2) Clinical study device usage period (4 weeks: sham stimulation period, 8 weeks: actual stimulation period: total 12 weeks)
20 min/a time
2 times/day （1st time: 10:00 am ± 2 hours, 2nd time: 3:00 pm ± 2 hours）
(3) Follow-up period (4 weeks)

9. Combination therapy (non-drug therapy)

Non-pharmacological therapy (rehabilitation, psychotherapy, etc.) from before obtaining informed consent may be continued as is, but as a general rule, the method of use, etc., will not be changed during the clinical research period. During the clinical research period, patients were decided not to concomitantly use additional therapies that would interfere with the evaluation of this clinical research.

10. Concomitant drug

For the following drugs, starting administration or changing dosage/administration during the study period was prohibited.

(1) cholinesterase inhibitors
(2) L-dopa preparations
(3) Dopamine receptor agonist
(4) Yokukansan and Yokukansanka Chenpihanga (herbal medicine)
(5) typical and atypical antipsychotics;
(6) Sleep-inducing drugs and anti-anxiety drugs
(7) Antiepileptic drugs
(8) Central and peripheral muscle relaxants

If it was unavoidable to administer new drugs or change the dosage/dosage, the study was discontinued and treated as a dropout case.

11. Evaluation items

11.1. Primary endpoint

(1) NPI-Q (BPSD : Behavioral/Psychological symptoms)
(2) MMSE (Cognitive function)

11.2. Secondary endpoint

(1) Effectiveness evaluation

- Zarit-8 (Nursing care burden)
- MDS UPDRSIII (motion function)
- MoCA-J (Mild cognitive function)
- CFI (Cognitive function change rating scale)
- BI (ADL : Activities of daily living)

(2) Safety evaluation

- Adverse event
- Defective of the device

12. Observation/examination schedule

Schedule / Implementation items		screening (Within 4 weeks)	Use of clinical trial device				Follow up (4W)
			Before (0W)	4W (±2day)	8W (±2day)	12W (±2day)	
				Sham	Real		
Consent to acquisition		○					
Before Registration	Diagnostic criteria	○					
	Hachinski	○					
	CRD-J	○					
	MMSE	○					
	NPI-Q						
	Zarit-8						
Review selection and exclusion criteria		○					
Registration		○					
Evaluation items	MMSE	○	○	○	○	○	○
	NPI-Q	○	○	○	○	○	○
	MDS UPDRS-III	○	○	○	○	○	○
	MoCA-J	○	○	○	○	○	○
	Zarit-8	○	○	○	○	○	○
	CFI	○*	○	○	○	○	○
	BI	○	○	○	○	○	○
Interview to Patient		○	○	○	○	○	○
Laboratory tests (blood biochemical tests)		○	○			○	○
Physical Examination		○	○			○	○
Electrocardiography		○				○	○
Use of clinical device			Device installation				
Adverse events			investigation				
Clinical equipment malfunctions			investigation				
Medication			Do not change				

○ The same data was used for the pre-enrollment evaluation test and the evaluation at the start of sham.
○ It was decided to be at the end of the sham for head ultrasonic stimulation (Before) and at the end of the actual machine (After).

13. Clinical study period

- Study start date (date of consent for the first subject) ; 2019/Jun/4
- Study completion date/discontinuation date (end date of observation of the 12th case) ; 2020/Nov/18

14. Patient number of clinical study

- Consent acquisition and registration: 12 cases
- Subjects analyzed; 12 subjects for FAS analysis, 11 subjects for PPS analysis, 12 subjects for safety analysis

15. Result of clinical study

15.1. Background of Patients

Table. Background of patients

Sex	Male	4 cases (33.3%)
	Female	8 (66.7%)
Inpatient/Outpatient	Inpatient	2 (16.7%)
	Outpatient	10 (83.3%)
Activities of daily living	self-assisted walking	10 (83.3%)
	Escort walking	1 (8.3%)
	Chair life	1 (8.3%)
Past medical history	Yes	7 (58.3%)
	No	5 (41.7%)
Complications	Yes	12 (100.0%)
	No	0 (0.0%)
Concomitant medication	Yes	12 (100.0%)
	No	0 (0.0%)
Combination therapy for dementia	Yes	0 (0.0%)
	No	12 (100.0%)
Age at consent	Mean±SD	81.4±3.60 age
Hachinski score	Mean±SD	1.2±0.98 score

15.2. Primary endpoint

1) NPI-Q Severity (total score of 10 items)

① Improvement of NPI-Q severity

Table. Improvement of NPI-Q severity

Analysis target population : FAS

Treatment period	(1)	(2)	(3)	(4)	(5)	(6)	(7)	Total
Sham device	1 (8.3%)	3 (25.0%)	3 (25.0%)	1 (8.3%)	2 (16.7%)	2 (16.7%)	0 (0.0%)	12 (100.0%)
Actual device	4 (33.3%)	1 (8.3%)	2 (16.7%)	3 (25.0%)	1 (8.3%)	1 (8.3%)	0 (0.0%)	12 (100.0%)

Wilcoxon Signed Rank Test p=0.03125

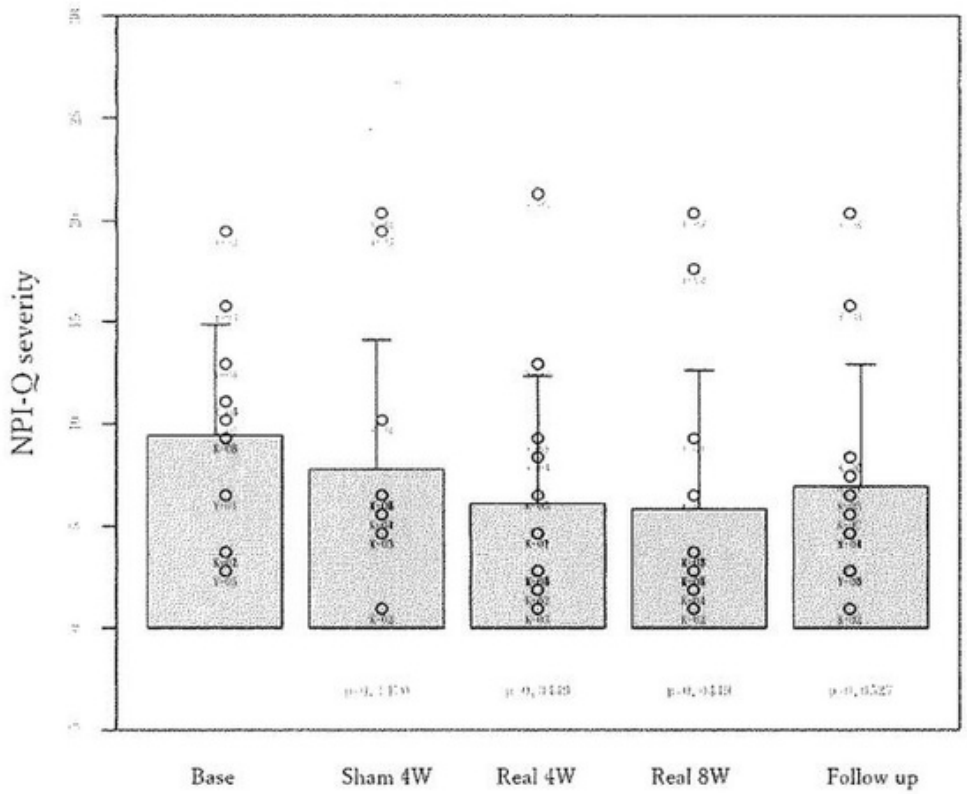
(1): Marked improvement (2): improvement (3): slight improvement (4): Unchanging
(5): slight worsening (6): worsening (7): Marked worsening

②Change rate of NPI-Q severity

The Change rate of NPI-Q severity was 9.95±61.85% during the sham stimulation period (4 weeks later), 32.03±50.691% during the real stimulation period (8 weeks later), and 35.04±56.850% during the real stimulation period (12 weeks later).

Compared to the sham stimulation period (4 weeks later), the real stimulation period (8 weeks later) (Wilcoxon signed rank test p=0.0420) and the real stimulation period (12 weeks later) (Wilcoxon signed rank test p=0.0039) showed significant improvement.

Change rate of NPI-Q severity (Total score)



NPI-Q is an evaluation method that can quantify the frequency, severity, and caregiver burden of BPSD (Behavioral and Psychological Symptoms of Dementia) in dementia patients.
It consists of a total of 12 items: delusions, hallucinations, excitement, depression, anxiety, euphoria, indifference, disinhibition, irritability, abnormal behavior, nighttime behavior, and eating behavior.

2) Degree of NPI-Q burden (total score of 10 items)

① Improvement of NPI-Q burden

表. Improvement of NPI-Q burden

Analysis target population : FAS

Treatment period	(1)	(2)	(3)	(4)	(5)	(6)	(7)	Total
Sham device	3 (25.0%)	0 (0.0%)	3 (25.0%)	5 (41.7%)	0 (0.0%)	0 (0.0%)	1 (8.3%)	12 (100.0%)
Actual device	3 (25.0%)	1 (8.3%)	3 (25.0%)	3 (25.0%)	2 (16.7%)	0 (0.0%)	0 (0.0%)	12 (100.0%)

Wilcoxon Signed Rank Test p=0.4375

(1): Marked improvement (2): improvement (3): slight improvement (4): Unchanging
(5): slight worsening (6): worsening (7): Marked worsening

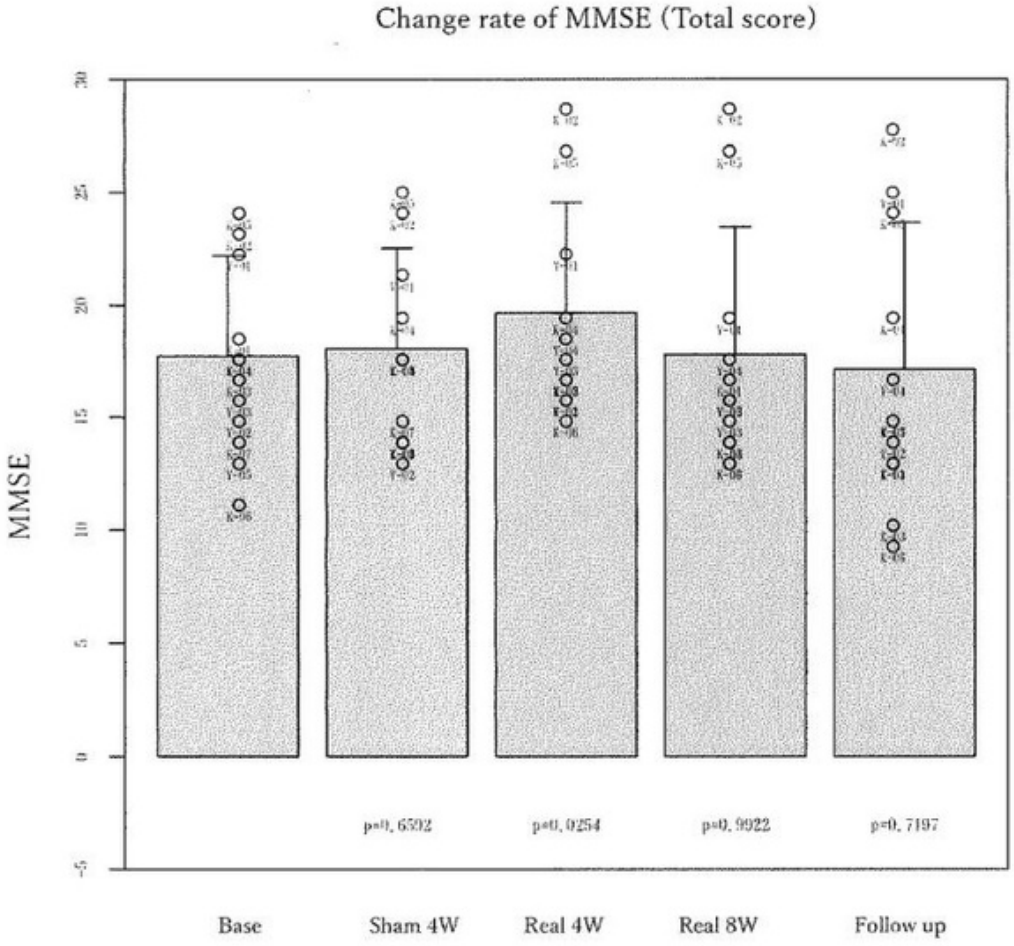
②Change rate of NPI-Q burden

The Change rate of NPI-Q burden was 6.10±136.54% during the sham stimulation period (4 weeks later), 48.64±81.79% during the real stimulation period (8 weeks later), and 51.09±54.59% during the real stimulation period (12 weeks later).
Compared to the sham stimulation period (4 weeks later), the real stimulation period (8 weeks later) (Wilcoxon signed rank test p=0.0645) and the real stimulation period (12 weeks later) (Wilcoxon signed rank test p=0.1484) did not show a significant improvement.

3) MMSE

The Change rate of MMSE was -3.5±17.50% during the sham stimulation period (4 weeks later), 12.1±14.57% during the real stimulation period (8 weeks later), and -0.7±16.09% during the real stimulation period (12 weeks later).

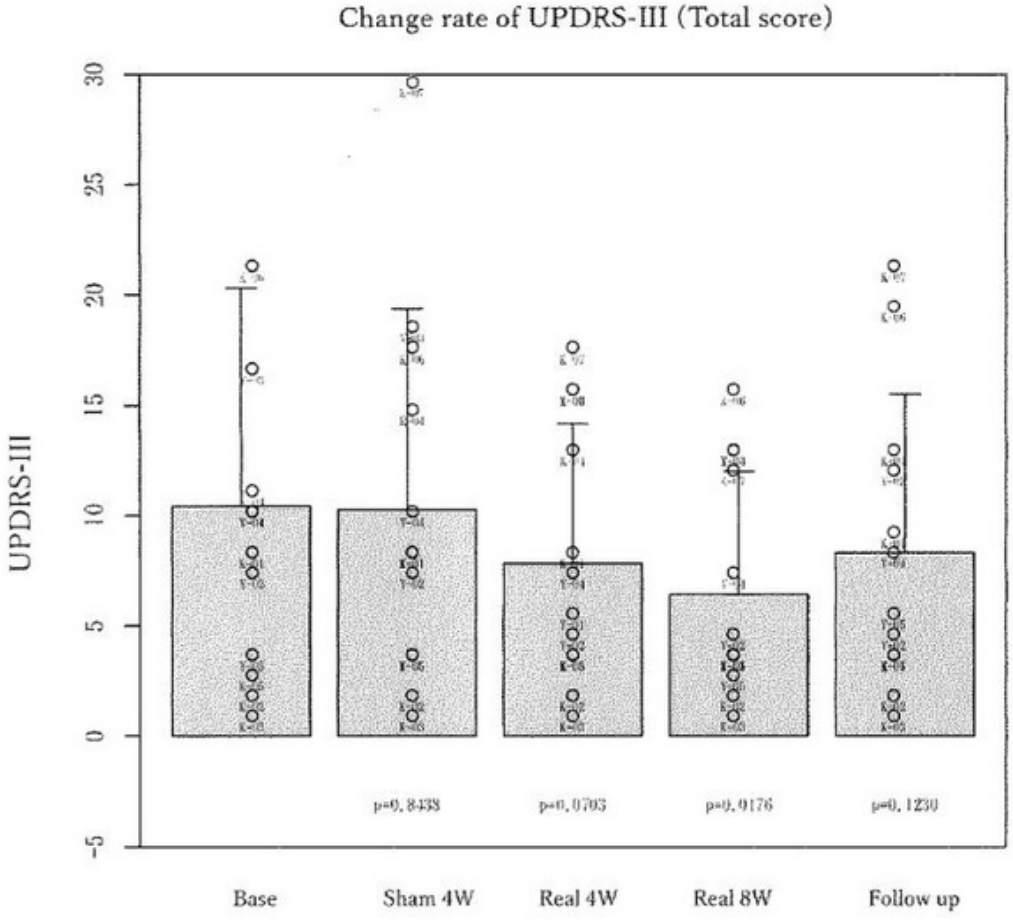
Compared to the sham stimulation period (4 weeks later) and the real stimulation period (8 weeks later) (Wilcoxon signed rank test p=0.0186) showed significant improvement.



The MMSE (Mini-Mental State Examination) is often used to assess cognitive decline. It takes about 10 minutes to give verbal instructions, and evaluate from the answers and reactions to each question, such as the date and place, repeating words and calculations, and copying figures. The maximum score is 30, and a score of 23 or less is considered probable dementia.

15.3. Secondary endpoint

1) MDS UPDRSIII Motion function test (patients with symptoms of parkinsonism)
The Change rate of UPDRS III motion function test was -4.6±21.29% during the sham stimulation period (4 weeks later), 12.3±30.67% during the real stimulation period (8 weeks later), and 26.0±36.79% during the real stimulation period (12 weeks later).
Compared to the sham stimulation period (4 weeks later), the real stimulation period (8 weeks later) (Wilcoxon signed rank test p=0.0156) and the real stimulation period (12 weeks later) (Wilcoxon signed rank test p=0.0039) showed significant improvement.



Evaluate the motor function in Parkinson's disease (parkinsonism). Speech, facial expression, upper limb movement, lower limb movement, standing, walking, postural stability, limb tremor, etc. are evaluated.

2) MoCA-J

The Change rate of MoCA-J was -9.2±26.20% during the sham stimulation period (4 weeks later), 6.7±19.75% during the real stimulation period (8 weeks later), and 2.2±22.58% during the real stimulation period (12 weeks later).

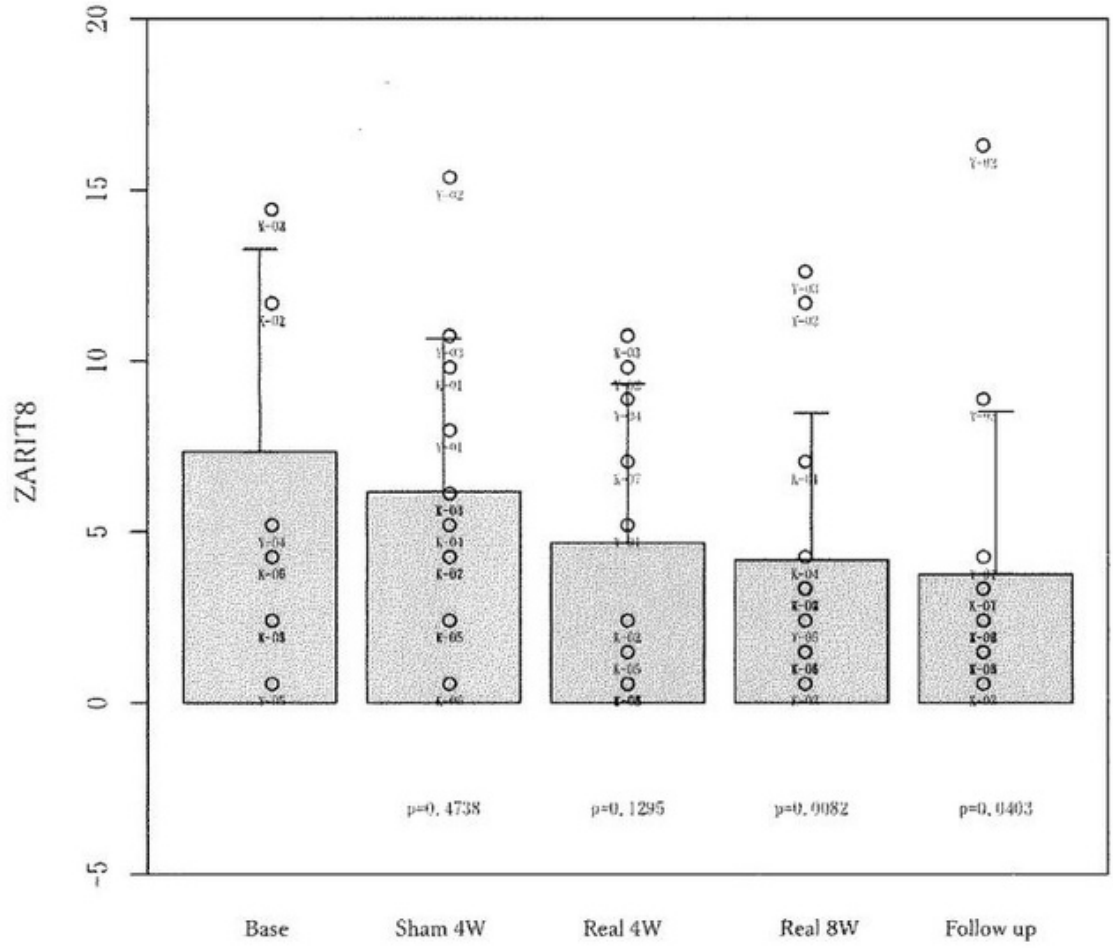
Compared to the sham stimulation period (4 weeks later), the real stimulation period (8 weeks later) (Wilcoxon signed rank test p=0.6558) and the real stimulation period (12 weeks later) (Wilcoxon signed rank test p=0.3077) did not show a significant improvement.

3) Zarit-8

The Change rate of Zarit-8 was -22.7±120.27% during the sham stimulation period (4 weeks later), 17.9±85.06% during the real stimulation period (8 weeks later), and 51.2±27.05% during the real stimulation period (12 weeks later).

Compared to the sham stimulation period (4 weeks later), the real stimulation period (12 weeks later) (Wilcoxon signed rank test p=0.0233) showed significant improvement.

Change rate of ZARIT8 (Total score)



A way to assess caregiver burden is the degree of distress suffered regarding the caregiver's emotional, physical health, social life and economic status. This is a caregiver burden scale consisting of 22 items.

4) CFI

The Change rate of CFI was 47.0±48.63% during the sham stimulation period (4 weeks later), 35.6±89.43% during the real stimulation period (8 weeks later), and 62.5±38.23% during the real stimulation period (12 weeks later).

Compared to the sham stimulation period (4 weeks later), the real stimulation period (8 weeks later) (Wilcoxon signed rank test p=0.7813) and the real stimulation period (12 weeks later) (Wilcoxon signed rank test p=0.3125) did not show significant improvement.

5) BI

The Change rate of BI was -2.9±16.17% during the sham stimulation period (4 weeks later), 7.2±17.95% during the real stimulation period (8 weeks later), and -5.4±16.14% during the real stimulation period (12 weeks later).

Compared to the sham stimulation period (4 weeks later), the real stimulation period (8 weeks later) (Wilcoxon signed rank test p=0.4631) and the real stimulation period (12 weeks later) (Wilcoxon signed rank test p=1.000) did not show significant improvement.

6) Safety evaluation

No adverse events were observed during both the sham stimulation period and the real stimulation period.

16. Discussion

In the primary endpoint, significant improvement was observed in "improvement in NPI-Q severity" and " change rate in NPI-Q severity (after 8 and 12 weeks)" during the real stimulation period compared to the sham stimulation period. The improvement effect on BPSD was observed.
As for the change rate of NPI-Q burden, a tendency toward improvement was observed, but no statistically significant difference was observed.
A statistically significant improvement was observed in Zarit-8, which is a secondary endpoint, and it is thought that there is the effect in reducing the burden on caregivers.
In addition, a significant improvement was shown in "change rate of MMSE (8 weeks later)", and the improvement effect in cognitive function was observed.

In the secondary endpoint, "change rate in UPDRS III motion function test (8 and 12 weeks later)" showed significant improvement during the real stimulation period compared to the sham stimulation period.
Improvement effect was also observed for Parkinson's symptoms associated with dementia with Lewy body.
On the other hand, regarding safety, no adverse events for patients and the devices were observed during both the sham stimulation period and the real stimulation period.
From the above, the usefulness of Ultra-Ma was suggested in this clinical study targeting dementia with Lewy body. Based on this result, we will plan to conduct a verification test to confirm the usefulness of Ultra-Ma.