MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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GAMMASENSE FOR ALZHEIMER'S DISEASE

EXECUTIVE SUMMARY

GammaSense is a gamma sensory simulation device developed by Cognito Therapeutics (United States) to improve outcomes in a range of neurodegenerative diseases, including Alzheimer's disease. GammaSense used sensory stimulation to evoke gamma oscillations in the brain, and thus improving synaptic connections between neurons, activating microglia, and enhancing the removal of pathological proteins from the brain. The device delivers non-invasive 40 Hz visual and auditory stimulation to induce steady-state gamma brainwave activity.

The clinical efficacy and safety of GammaSense have been reported in two phase II clinical trials with mild to moderate Alzheimer's disease. The study found that one-hour therapy with GammaSense was well-tolerated and has the potential to improve functional abilities, cognitive function, sleep quality, and reduce brain atrophy in mild to moderate Alzheimer's disease patients. However, more evidence of the safety and effectiveness of the device in larger groups of patients is warranted.

Keywords: Alzheimer's disease, dementia, cognitive impairment, neurodegenerative disease, gamma simulation, gamma oscillations

INTRODUCTION

Alzheimer's disease is caused by the presence of beta-amyloid and tau proteins that build up in the brain to the point that they obstruct normal cognitive functions. This usually manifests with changes in memory, abstract thinking, judgment, behaviour, mood, and emotions, and ultimately interferes with physical control over the body. As the disease progress, the person's ability to remember, understand, reason, and communicate will gradually decline.[1,2]

Alzheimer's disease is the most common cause of dementia (60 to 70%) in people over the age of 65. There are over 55 million people living with dementia worldwide.[3] This number is estimated to rise to 78 million by 2030 and to 139 million by 2050.[2] Alzheimer's disease and other forms of dementia are the top ten causes of death globally, ranking third in America and Europe in 2019.[4]

In the Asia Pacific region, the number of people with dementia is estimated to increase from 23 million people in 2015 to 71 million people in 2050. In Malaysia, the estimated number of people with dementia was 123,000 in 2015, and was projected to further increased to 261,000 by 2030 and 590,000 by 2050.[2]

Currently, there is no treatment to cure Alzheimer's disease. Lecanemab, a humanized IgG1 monoclonal antibody developed by Eisai and Biogen Inc. has recently received FDA accelerated approval for moderately slow mild cognitive decline and reduced amyloid-β plaques in patients with early Alzheimer's disease. Although the phase III trials confirmed the drug's benefit, the treatment is associated with adverse events such as amyloid-related imaging abnormalities, infusion-related reactions, and headache.[5]

Care required for people with dementia includes primary health care, specialist care, community-based services, rehabilitation, long-term care, and palliative care. The disability associated with dementia is a key driver of costs related to the condition. In 2019, the global cost of dementia was estimated to be USD 1.3 trillion. The cost is projected to increase to USD 1.7 trillion by 2030, or USD 2.8 trillion if corrected for increases in care costs.[6] In Malaysia, the mean cost of hospitalisation for dementia per episode of care is RM 10,034.[7]

THE TECHNOLOGY

GammaSense is a gamma sensory simulation device (Figure 1) developed by Cognito Therapeutics Inc. (United States) to improve outcomes in a range of neurodegenerative diseases, including Alzheimer's disease, and is personalized based on the brain's responses. The device uses sensory stimulation to evoke gamma oscillations in the brain that have been shown to improve synaptic connections between neurons, activate microglia, and enhance the removal of pathological proteins from the brain in animal studies. This may lead to reduced neurodegeneration and brain atrophy, as well as improved sleep, cognitive, and functional abilities.[8]

GammaSense includes a handheld controller, an eye-set for visual stimulation, and headphones for auditory stimulation, that work together to deliver precisely timed, non-invasive 40 Hz stimulation to induce steady-state gamma brainwave activity. Stimulation output parameters are determined and verified by a physician based on both patient-reported comfort information and in-clinic electroencephalography (EEG) evaluation. The device is then configured to the determined settings, and all subsequent use is within this predefined operating range.[9]

Once prescribed, the patient uses GammaSense at home for daily sessions lasting one hour. The on-off periods of the visual stimulation are perceivable by the patient but not disruptive; The patient remains aware of their surroundings and can converse with a care partner during the use of the system. The patient can adjust the brightness of the visual stimulation and the volume of the auditory stimulation within this predefined operating range via push buttons on the controller, with assistance from a care partner as needed. The system logs device usage and stimulation output settings for adherence monitoring; this information is uploaded to a secure cloud server for remote monitoring.[9]

Figure 1. GammaSense

PATIENT GROUP AND INDICATION

GammaSense is indicated for patients with neurodegenerative diseases, including Alzheimer's disease.

CURRENT PRACTICE

There are a few treatments available to treat the symptoms of Alzheimer's disease.[10]

a) Pharmacological treatment

To manage symptoms (cognitive, non-cognitive, behavioural), improve independence, and preserve function.

- Acetylcholinesterase inhibitors: Donepezil, Galantamine, Rivastigmine
- N-methyl-D-aspartate (NMDA) receptor antagonist: Memantine

b) Non-pharmacological treatment

To promote positive effects on cognition, quality of life, mood, and other behavioral and psychological symptoms of dementia.

- Cognitive and Quality of life (QoL):
  - Cognitive stimulation therapy
  - Physical therapy
- Behaviour & Psychological Symptoms of Dementia (BPSD):
  - Address causes & triggering factors
  - Psychological intervention
  - Personalised & tailored activity

SAFETY AND EFFICACY

A systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines such as Google Scholar and US FDA. Based on retrievable evidence, two phase II clinical trials were included in this review.

A. Efficacy

Two phase II clinical trials reported the efficacy of GammaSense based on the changes in functional abilities, sleep quality, cognitive functions, and brain atrophy.

i) Functional Abilities

A randomised, controlled, single-blind, multicentre clinical trial (OVERTURE study) was conducted by Megerian et al. to evaluate the safety, adherence rates, and effectiveness of GammaSense stimulation device in subjects with mild to moderate cognitive impairment who are aged 55 and older. A total of 135 participants on the Alzheimer's disease spectrum were screened. Patients with mild to moderate Alzheimer's disease were randomised (n=74) to active treatment group (GammaSense) or to sham group. Patients in the active treatment group received precisely timed, non-invasive visual and auditory stimulations during eye-closed conditions to induce cortical 40 Hz steady-state oscillations in one-hour daily sessions over a six-month period. Patients in the sham group were exposed to similar sensory stimulation designed to not evoke cortical 40 Hz steady-state oscillations that are observed in the active treatment patients. The safety was assessed by MRI, physical and neurological exams, while efficacy was assessed using Alzheimer's disease cognitive and functional instruments and volumetric MRI. Over the six-month treatment period, changes in Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) scores were significantly better in the treatment group compared to sham group, indicating a 78% slowing in functional decline ($p<0.0003$).[11]

A single-blinded, randomised, placebo-controlled phase IIA clinical trial was conducted by Chan et al. to assess safety, compliance, entrainment, and exploratory clinical outcomes following treatment with GammaSense for four months. Fifteen participants with mild Alzheimer's disease were randomised to active treatment group (40 Hz light and sound, n=8) or a sham group (constant light and white noise, n=7). The impact of GammaSense on daily rhythm was measured from the actigraphy recording, inter-daily stability (IS) and inter-daily variability (IV). Inter-daily stability is defined as the ratio between the variance of the average 24-hour pattern and the overall variance and measures day-to-day consistency of activity rhythms (eg: bedtime schedule or ability to become active at a regular time), while IV is defined as the ratio between the mean square first derivative and the overall variance and measure the robustness of the daily rhythm. After four months of treatment, there was a significant improvement in IS in active treatment group compared to sham group ($p=0.036$). There was no significant change for IV in the treatment group.[12]

ii) Sleep Quality

In the sub-analysis of OVERTURE study, nighttime activities of 22 patients who were randomised to treatment group (n=14) or sham group (n=8) were monitored with continuous actigraphy recording over a 24-week treatment period. The average nighttime period was 7.23 hours for the treatment group, and 7.64 hours for the sham group. Compared to the first 12-week period, nighttime active durations were significantly ($p<0.03$) reduced in the treatment group, whereas active durations were significantly ($p<0.03$) increased in patients of the sham group.[9]

iii) Cognitive Function

From the OVERTURE study, the treatment group demonstrated a statistically significant 83% ($p<0.013$) reduction in cognitive decline, shown by changes in Mini-mental State Examination (MMSE) scores after six months of treatment. The two treatment groups showed no statistically significant differences in other outcome measures such as modified Alzheimer's disease Composite Score (MADCOMS), Alzheimer's Disease Assessment Scale-14 (ADAS-cog14), and Clinical Dementia Rating-Sum of Boxes (CDR-SB).[11]

In the phase IIA trial by Chan et al, the active group showed significant improvement from baseline in accuracy on the Face-Name Association Delayed Recall Test (FNA-DRT) ($p=0.0040$), while no significant change was observed in the sham group. The differences in accuracy in the FDA-DRT between groups were statistically significant. There were no significant differences between groups in other cognitive functions as assessed by MMSE, Montreal Cognitive Assessment (MoCA), ADAS-cog14, and CDR-SB.[12]

iv) Brain Atrophy

Quantitative MRI analysis from OVERTURE study revealed that whole brain volume loss in the treatment group demonstrated a significant, 72% reduction in brain atrophy ($p<0.01$) compared to sham group after six months of treatment. Reduced lateral ventricle enlargement and diminished loss in cortical thickness in the occipital cortex have been also observed. MRI data demonstrated the absence of amyloid-related imaging abnormalities (ARIA) in all patients.[11]

In another analysis, 75 patients from OVERTURE study who received treatment with GammaSense stimulation device were compared with Alzheimer's Disease Neuroimaging Initiative (ADNI) database. The ADNI study collected regular brain scans from 200 Alzheimer's patients and 400 people diagnosed with mild cognitive impairment. Analysis between the groups suggested a difference in white matter atrophy favoring the treatment group. The treatment group participants exhibited 0.38±0.82 percentage increase and ADNI study participants exhibited -2.45±0.40 percentage decrease in white matter volume after a six-month period ($p<0.004$).[13]

In a phase IIA trial by Chan et al, a significant difference in ventricular enlargement between the active (n=7) and control group (n=6) was observed ($p=0.0024$) after three months of treatment. The control group exhibited ventricular enlargement (4.34±1.72%, $p=0.0016$), while the active group had no significant change in ventricular volume (1.33±2.33%) from baseline to month three ($p=0.18$). Hippocampal (HPC) volume declined in the control group (-1.75±1.48%, $p=0.0034$), but not in the active group (-0.69±2.35%, $p=0.438$). No significant changes were seen in either group in total brain volume or cortical thickness.[12]

Phase III OVERTURE study was to be conducted in 2022 to evaluate the safety, effectiveness, and cost-effectiveness of GammaSense stimulation device in

patients with mild cognitive impairment. Cognito Therapeutics also plans to focus on other neurodegenerative diseases as shown in Figure 2.[8]

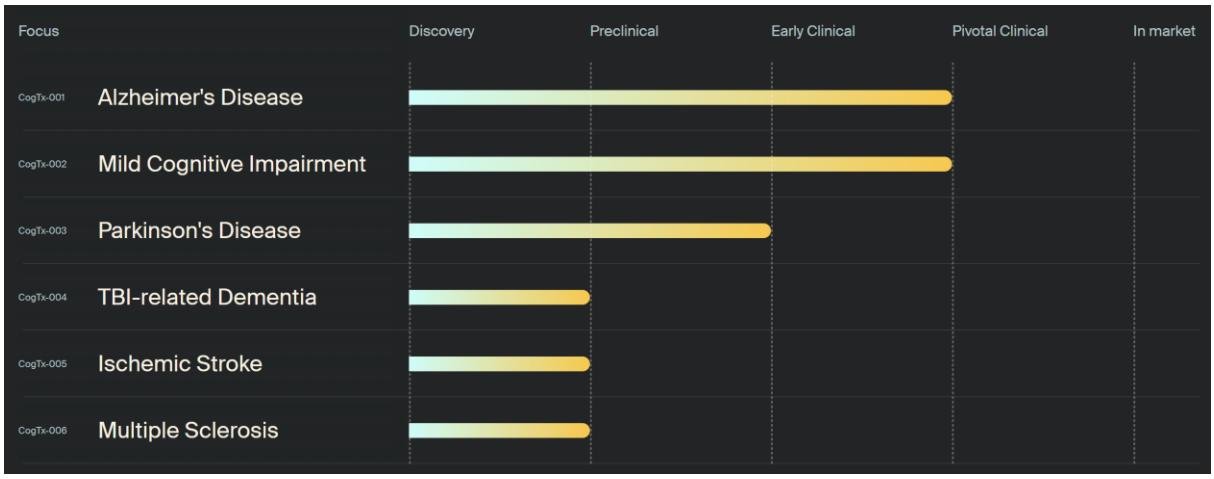

Figure 2. Focus on other neurodegenerative diseases

B. Safety

From the sub-analysis of OVERTURE study, one-hour therapy with GammaSense (n=14) was well-tolerated throughout the six-month period. Several adverse events were reported in the treatment group such as headache (26%), eye irritation (11%), dizziness (5%), ear irritation (5%), and anxiety (5%). One patient from each treatment group and sham group discontinued the treatment due to an adverse event.[9]

Chan et al. also reported that GammaSense was well-tolerated with non-significant adverse events such as drowsy, dry eye, numb, nervousness or anxiety, and light sensitivity.[12]

GammaSense has received FDA Breakthrough Device Designation in 2021 for treatment of the cognitive and functional symptoms associated with Alzheimer's disease in individuals diagnosed with mild to moderate Alzheimer's.[13]

ESTIMATED COST

There was no retrievable data on the cost of the device. The cost of a similar device, Neuro Gamma 3 is USD1,799. The Neuro Gamma 3 is a transcranial-intranasal photobiomodulation device that also has a neuromodulating effect on gamma oscillations.[14]

OTHER ISSUES

A. Organisational

In the OVERTURE study, patients and caregivers participated in multiple in-depth interviews to assess the feasibility and adherence to a daily, in-home gamma stimulation therapy for six-month. Patients were given options to enter 12-month extension. In total, 20,562 treatment sessions have been completed by 74 patients

in the main and extension period. Adherence data showed that the sham group had a final mean adherence of 95.9%±9.0%, while the treatment group had a final mean adherence of 90.2%±13.3%, and the difference was not significant (p=0.14). Patients easily adopted and adhered to daily self-administered therapy, with 60% of enrolled participants choosing to continue with the extension period.[15]

In the phase IIA trial, compliance was measured using timestamp recording built into the device to indicate when the device was on and with photogenic records of participants as they were using the device. After four months of daily stimulation, there was no significant difference in compliance between groups, mean usage was 91%±7% and 87%±9% for the control and active groups, respectively (p=0.355). Both the active and control groups used their devices with equal compliance at home for an hour daily.[12]

B. Societal/ethical

There was no societal or ethical issue identified. This device may require assistance from a care partner as needed.

POTENTIAL IMPACT

The early study showed that one-hour therapy with GammaSense, a gamma sensory simulation device was well-tolerated and has the potential to improve functional abilities, cognitive function, sleep quality, and reduce brain atrophy in mild to moderate Alzheimer's disease patients. However, more evidence of the safety and effectiveness of the device in larger groups of patients is warranted.

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