News Release

Evaluation of the efficacy of zonisamide in individuals at high risk of developing Lewy body disease: Insights for the design of future clinical trials toward preventive and preemptive therapy

Key Points

- **By the time motor or cognitive symptoms appear, neurodegeneration is already advanced: however, no effective disease-modifying therapy –preventive or progression-slowing treatment– has yet been established.**
- **This study investigated the potential disease-modifying effect of zonisamide, an antiparkinsonian drug, in 29 high-risk individuals (prodromal Lewy body disease) presenting with prodromal symptoms such as constipation, REM sleep behavior disorder, and hyposmia, together with abnormal findings on DaT-SPECT and/or cardiac MIBG scintigraphy.**
- **Participants were randomly assigned to the zonisamide group (n=14) or placebo group (n=15) in a 96-week, double-blind, placebo-controlled, multicenter phase II clinical trial (NaT-PROBEi trial).**
- **In the primary outcome, the change in DaT-SPECT specific binding ratio over 96 weeks showed no significant difference between groups.**
- **In the secondary outcomes, the zonisamide group showed worsening of non-motor symptoms (depression, quality of life), whereas two participants in the placebo group developed Parkinson's disease.**
- **Although zonisamide did not demonstrate disease-modifying effects, the study provided important insights for future trial design, including the need for better participant stratification, longer follow-up periods, and the development of alternative biomarkers for preventive and preemptive trials.**
- **This work represents a Japan-oriented contribution to the global research effort exploring the feasibility of intervention before disease onset in neurodegenerative disorders.**

Summary

A research group led by Professor Masahisa Katsuno and Dr. Keita Hiraga (first author) from the Department of Neurology, Nagoya University Graduate School of Medicine, in collaboration with the

National Center for Geriatrics and Gerontology and Nagoya City University Graduate School of Medical Sciences, conducted the first pharmacological intervention trial targeting the prodromal stage of Lewy body disease, which is a neurodegenerative disorder that includes Parkinson's disease and dementia with Lewy bodies. Lewy body disease affects about one million people in Japan. Because neurodegeneration is already advanced when motor and cognitive symptoms appear, early intervention during the prodromal stage, when symptoms such as constipation, REM sleep behavior disorder, and hyposmia emerge, is considered essential.

Using a screening method developed by the Katsuno group (Hattori et al. *J Neurol.* 2020; Hattori et al. *NPJ Parkinson Dis*. 2023) to identify individuals at high risk of developing Lewy body disease, the team enrolled 29 participants with prodromal symptoms and abnormal findings on DaT-SPECT and/or cardiac MIBG scintigraphy. Participants were randomly assigned to receive zonisamide (n=14) or placebo (n=15) in a 96-week, double-blind, placebo-controlled, multicenter phase II trial (NaT-PROBEi trial).

Changes in the DaT-SPECT specific binding ratio (primary outcome) did not differ significantly between groups. While non-motor symptoms worsened in the zonisamide group, two participants in the placebo group developed Parkinson's disease.

Although zonisamide did not demonstrate disease-modifying effects, this study clarified key challenges for future preventive trials, including participant stratification, longer follow-up, and improved biomarker selection.

These findings were published in the U.S. scientific journal "*npj Parkinson's Disease*" on December 1, 2025.

Research Background

In neurodegenerative diseases, including dementia, the accumulation of abnormal proteins is now known to occur more than 20 years before the onset of clinical symptoms. Therefore, suppressing disease progression before symptom onset has become a key goal (Figure 1). Lewy body disease is a group of

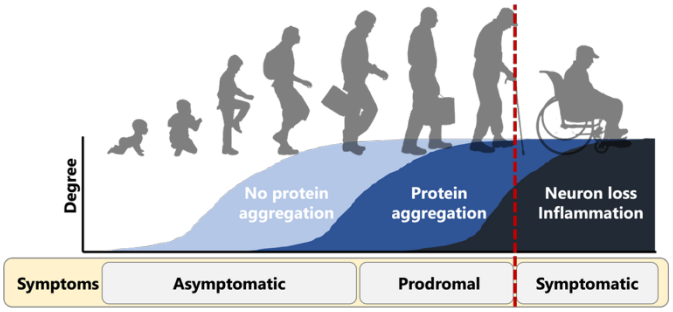

Figure 1. Time-course of neurodegeneration

neurodegenerative disorder characterized pathologically by the accumulation of α-synuclein and encompasses both Parkinson's disease and dementia with Lewy bodies. Parkinson's disease causes motor symptoms such as bradykinesia, rigidity, and tremor, as well as cognitive impairment, and the number of patients in Japan is estimated at approximately 200,000. Dementia with Lewy bodies, affecting an estimated 600,000–900,000 individuals nationwide, is the second most common form of dementia after Alzheimer's disease and is characterized by hallucinations, fluctuations in attention, and parkinsonian motor features. Recent studies have highlighted prodromal symptoms of Lewy body disease, such as autonomic dysfunction (constipation), REM sleep behavior disorder, and hyposmia, which may appear 10–20 years before motor or cognitive symptoms. Detecting individuals at risk during this prodromal stage is critical for future preventive interventions.

Our group previously established the NaT-PROBE cohort, a prospective study that identifies individuals at high risk of developing Lewy body disease through questionnaires assessing prodromal symptoms (Figure 2). We found that about 6% of health-check examinees aged ≥50 years exhibited multiple prodromal symptoms (Hattori et al. *J Neurol.* 2020). Among these, approximately one-third showed abnormal uptake on DaT-SPECT or cardiac MIBG scintigraphy (Hattori et al. *NPJ Parkinson Dis.* 2023). Furthermore, we demonstrated elevated plasma neurofilament light chain levels, a marker of neurodegeneration, in these high-risk individuals (Hiraga et al., *NPJ Parkinson Dis.* 2024).

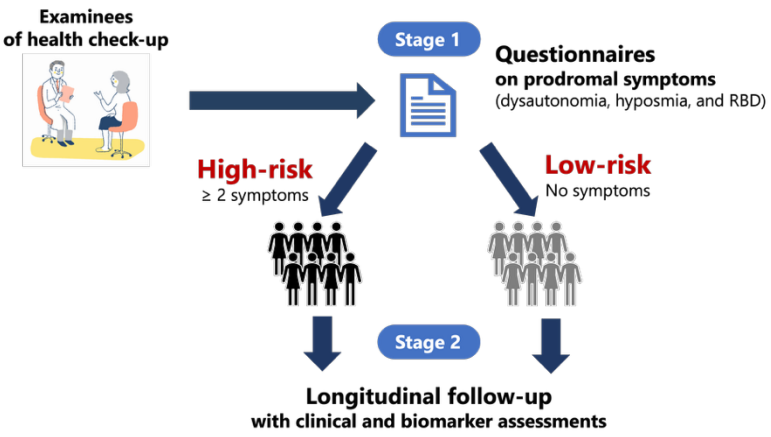

Figure 2. High-risk cohort study of Lewy body disease

Zonisamide is an antiparkinsonian drug approved in Japan for both Parkinson's disease and dementia with Lewy bodies. In addition to improving motor symptoms, preclinical studies have suggested its potential neuroprotective effects. An observational study in early Parkinson's disease also reported that zonisamide slowed the decline of the DaT SPECT specific binding ratio, indicating possible disease-modifying properties.

In the present study, we conducted the NaT-PROBEi trial, a multicenter,

double-blind, placebo-controlled phase II clinical trial evaluating the disease-modifying effects of zonisamide in 29 individuals at high risk of developing Lewy body disease, defined by multiple prodromal symptoms and abnormal DaT-SPECT and/or MIBG findings.

Research Results

Participants were randomly assigned to receive zonisamide (n=14) or placebo (n=15) in a 96-week, double-blind, placebo-controlled, multicenter phase II clinical trial (Figure 3).

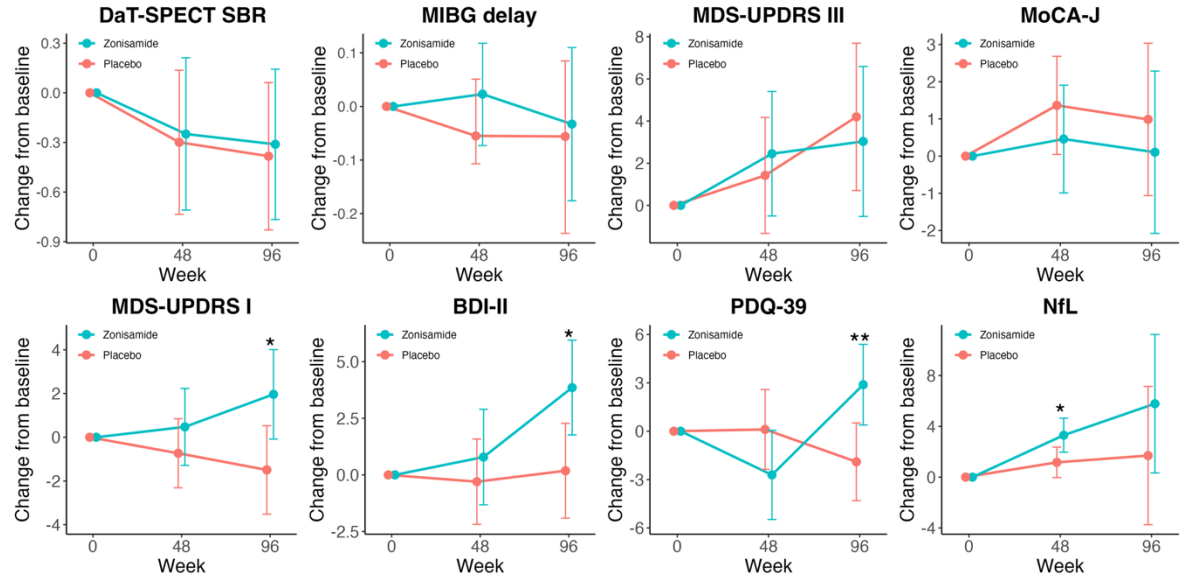

Figure 3. 96-week changes in the primary outcome and key secondary outcomes

No significant between-group differences were observed in the primary outcome, the 96-week change in DaT-SPECT specific binding ratio from baseline. Similarly, there were no significant differences in the 96-week changes in motor function (MDS-UPDRS III), cognitive function (MoCA-J), or neurodegeneration marker (plasma neurofilament light chain). In contrast, the zonisamide group showed worsening of non-motor symptoms (MDS-UPDRS I), depression (BDI-II), and quality of life (PDQ-39), while two participants in the placebo group developed Parkinson's disease during the study period. The main adverse events included somnolence, fatigue, decreased appetite, and constipation.

The observed changes in DaT-SPECT SBR were milder than expected, suggesting that the study design had limited statistical power. Although zonisamide did not demonstrate a disease-modifying effect, this trial highlighted the importance of participant satisfaction, extended observation periods, and the selection of alternative biomarkers for future preventive clinical studies.

Research Summary and Future Perspective

Although findings are inconclusive due to limited power, this study provides valuable methodological insights for preventive Lewy body disease trials. Following the 96-week trial, participants are being observed up to 144 weeks to determine whether the incidence of Lewy body disease differs between the zonisamide and placebo groups during the drug-free extension period. In parallel, the NaT-PROBE cohort study continues with annual follow-ups to develop prognostic stratification models that will facilitate recruitment for future clinical trials aimed at early intervention and disease prevention.

Publication

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