

The rationale and efficacy of Souvenaid, a medical food targeting synaptic dysfunction in early Alzheimer's disease

John W.C. SIJBEN

Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht, The Netherlands

Synaptic loss has been recognized as the strongest structural correlate with memory impairment in AD and is apparent already early in the disease process. Synapses largely consist of neuronal membranes which are mainly composed of phospholipids. Phospholipid synthesis depends on the availability of the rate limiting nutritional precursors and cofactors. Basic science studies indicate that their increased intake enhances synaptogenesis. Animal studies from various labs showed increased cognitive performance and improved neuroimaging markers following dietary enrichment with these compounds. However, lower plasma levels of these nutrients are widely observed in AD, e.g. lower levels of uridine and docosahexaenoic acid are found in early AD patients compared with controls. Based on these insights, the specific nutrient combination Fortasyn®¹ Connect was designed to enhance synapse formation and function in AD. Fortasyn Connect is present in Souvenaid®¹, a medical food intended for use in early AD.

The efficacy and mode of action of Souvenaid is investigated in the clinical trial program, including: 1) 12-week proof-of-concept Souvenir I RCT in drug-naïve mild AD patients; 2) 24-week S-Connect RCT in mild-to-moderate AD patients using AD medication; 3) 24-week Souvenir II RCT² in drug-naïve mild AD patients; 4) 24-week Souvenir II open-label-extension study; 5) 24-month LipiDiDiet RCT³ in prodromal AD; 6) Mode of action studies: a) electroencephalography (EEG) and magnetoencephalography outcomes in Souvenir II; b) biomarkers in LipiDiDiet (MRI atrophy rates and CSF measures); c) magnetic resonance spectroscopy; d) FDG-PET.

The Souvenir I and II studies showed that Souvenaid improved the primary outcome memory performance. The Souvenir II OLE study showed continued improvement of the exploratory memory outcome throughout 48 weeks. The S-Connect study did not show an effect on cognition in mild to moderate AD patients using AD medication. All completed studies showed that Souvenaid is well-tolerated, with a high compliance ($\geq 93\%$). EEG measures were included in Souvenir II to study neuronal activity and thus indirectly synaptic activity. Significant EEG differences suggest that Souvenaid preserves functional connectivity and brain network organization in mild AD, supporting the hypothesis of changed synaptic activity.

These results suggest that Souvenaid is most efficacious in early AD and warrant long-term trials in the very early AD process, like the ongoing LipiDiDiet study. Main and recent findings will be presented.

¹Souvenaid and Fortasyn are registered trademarks of N.V. Nutricia

²Partly funded by NL FND project N°10003

³Funded by the EU FP7 project LipiDiDiet, Grant Agreement N°211696