Souvenaid

Alzheimer's Disease

Key clinical evidence

International experts agree that there is an urgent need to address the burden of cognitive decline in an aging population, for those with MCI/AD and the wider society. The efficacy and safety of Souvenaid has been assessed in a research programme spanning > 20 years, including high quality international clinical trials of > 2000 participants at varying stages of cognitive decline and impairment (i.e., at risk elderly, those with age related cognitive decline, mild cognitive impairment (MCI) and patients with mild-moderate Alzheimer's disease (AD)).

Disclaimer

Souvenaid is a food for special medical purposes for the dietary management of early Alzheimer's disease, including Mild Cognitive Impairment (MCI), and must be used under medical supervision.

www.souvenaid.com

Key messages on clinical research

The Souvenaid research programme builds on the findings from pre-clinical studies that demonstrated an effect of administering the specific nutrients in Souvenaid (Fortasyn Connect) on synapse function/formation. Figure 1 provides an overview of the key proof of concept, intervention and observational studies undertaken or ongoing.

The main findings of this research are:

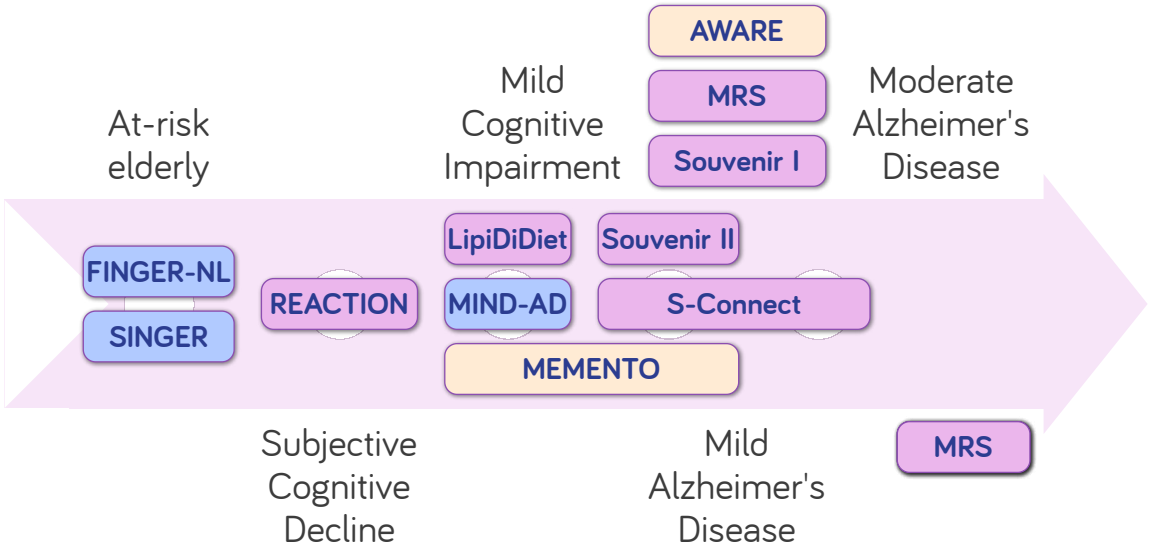
The majority of key nutrients contained in Fortasyn Connect have been found in a meta-analysis of studies to be significantly lower in the blood of patients with AD[1] Rijpma et al, 2017[2] reported evidence from brain scans which showed that Souvenaid improved formation of neuronal phospholipid, supporting the proposed mode of action of the product in synapse formation, which may impact on cognitive function.

Souvenaid has been shown in randomised controlled trials (RCTs) to slow the decline in cognitive abilities and positively impact memory[3,4] in MCI and mild AD, ***respectively***. A similar effect on cognition has not been observed in moderate AD[5], however Souvenaid was well tolerated in combination with AD medication.

- All studies[2-9] have found excellent compliance and acceptance of Souvenaid and that it is safe and well tolerated. 'Real-life' observational studies[6,10] also reported positive benefits (slower decline) on use of Souvenaid on behavioural, daily living activities/function and on memory.

- Many of the researchers and expert guidance[2,6,11] conclude that use of Souvenaid is more beneficial when started early in the disease process and that its continuous long-term use is required for ongoing synapse formation to potentially impact on cognitive ability[2].
- International studies to determine the impact of multimodal lifestyle interventions including the use of Souvenaid (FINGER-NL and MIND-AD) on cognitive decline and memory are ongoing.

Patient focused, cognitive decline outcome measures e.g., memory tests, function brain scans, compliance and safety

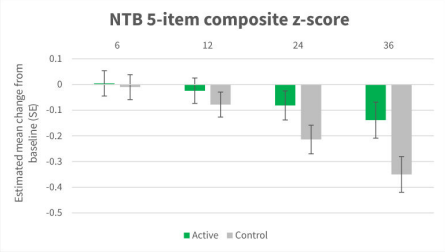


Observational studies | FINGER-like randomized controlled trials | Randomized controlled trials

Trial and type	Population	# of Subjects / Duration	Key outcomes investigated	Links to key publications
LipiDiDiet (RCT)	Prodromal AD (Mild Cognitive Impairment stage)	N=311 / 6 years	Cognition, function, memory, brain volumes	Soininen et al. 2021 Alzheimer's and Dementia Soininen et al. 2017 Lancet Neurology
Souvenir I (RCT)	Mild AD	N=225 / 3 months	Memory, cognition	Scheltens et al. 2010 Alzheimer's and Dementia
Souvenir II (RCT)	Mild AD	N=259 / 6 months	Memory	Scheltens et al. 2012 Journal of Alzheimer's Disease
MRS (RCT)	Mild AD	N=33 / 1 month	Phospholipid metabolism	Rijpma et al. 2017 Alzheimer's Research and Therapy
S-Connect (RCT)	Mild & Moderate AD	N=527 / 6 months	Cognition	Shah et al. 2013 Alzheimer's Research and Therapy
REACTION (RCT)	Subjective Cognitive Decline	N=60 / 6 months	Feasibility, memory, cognition	***Coming soon***
AWARE (RWE)	Mild AD	N=73 / 6-12 months	Activities of daily life	***Coming soon***
MEMENTO (RWE)	MCI and Mild AD	N=500 / 3-6 months	Cognition, bahavior, function	Bianchetti et al. 2018 Journal of Gerontology and Geriatrics
MIND-AD (FINGER)	MCI due to AD	N=103 / 6 months	Feasibility	***Coming soon***
FINGER-NL (FINGER)	At-risk elderly	N=1200* / 2 years	Cognition, function, memory	***Study ongoing***

* Planned, still recruiting

LipiDiDiet multinutrient clinical trial in Mild Cognitive Impairment (MCI) [3, 9]



The LipiDiDiet[1] study is a randomized double blind, placebo-controlled trial of 311 people with prodromal AD (MCI with underlying AD pathology) assigned to active (Souvenaid once per day) or control (isocaloric placebo drink) groups. The study assessed the effects of Souvenaid on cognition, and brain atrophy at baseline, 6 months, 12 months, and yearly thereafter up to 6 years using a range of established and validated clinical outcomes in this population. The primary outcome was cognition measured by a Neuropsychological Test Battery (NTB) and secondary measures included the NTB memory domain, NTB executive function domain, and NTB total; Clinical Dementia Rating-Sum of Boxes (CDR-SB) – a measure of cognition and function; and hippocampal, ventricular, and whole brain atrophy based on magnetic resonance imaging (MRI) brain scans. The subjects were recruited from four European countries, aged 55-85 at enrolment and did not use AD drugs. Results from 24 months and 36 months of the intervention have now been reported.

Analysis from the first 24-months[9] showed favourable effects on some secondary outcomes (e.g., CDR-SB and hippocampal atrophy) but not on the primary NTB endpoint. As some effects were observed at 24 months but cognitive decline was less than anticipated in the control group, it was proposed that the longer intervention may lead to more pronounced effects.

Results from 36 months of the intervention were published in 2021 showing significant positive benefits on cognition, function, and rates of brain atrophy (brain shrinkage) in the active group (Souvenaid) specifically.

- Significant reductions in decline on the primary outcome of NTB measuring cognition (60% reduction in decline) as illustrated in figure 1.
- Statistically significant differences between groups in favour of the active group were observed for the CDR-SB (45% less worsening;), memory (76% less worsening;). Such a sustained benefit over 3 years has not been reported before in early AD. The CDR-SB benefits occurred in conjunction with several NTB items supporting the positive impact of the active intervention on cognition and function.
- The rates of deterioration for hippocampal, whole brain and ventricular volume (brain atrophy) were significantly less in the active than the control group, showing potential effect on disease pathology. The effect on hippocampal atrophy may be the basis for the memory benefit reported for the active group. The decline rates in hippocampal atrophy in the control group were typical of those for MCI/mild AD reported.
- A small to medium Cohen's d effect size (0.25–0.31) similar to that of established clinically relevant AD treatment was found.

The active product was found to be safe, very well tolerated, and compliance with the supplement at 36 months was very high (means of 91.4% in the active group and 90.8% in the control group).

Given the observed positive impact on cognition, brain function and atrophy, the study demonstrated that long-term nutritional intervention with Souvenaid has the potential to alter disease trajectories over 3

years. The authors suggest that the duration of the nutritional intervention and early initiation in the disease may be factors that contribute to the observed benefits.

Souvenir I study: Efficacy of Souvenaid in mild Alzheimer's Disease (AD)

This RCT[8], was a proof-of-concept study designed to investigate the impact of Souvenaid on cognitive function in subjects with mild AD who were not taking any AD medication. The trial consisted of a 12-week core study followed by a 12-week exploratory and optional extension, in 5 European countries. Subjects were randomized to one of two nutritional treatment groups: Souvenaid (n = 99) or an iso-caloric control product (n = 100). These study products were taken once-daily over the study period.

Co-primary outcome measures were the delayed verbal recall task of the Wechsler Memory Scale–revised (WMS-r), a sensitive measure of episodic memory, and the 13-item modified Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog) subscale at week 12. Secondary outcome measures included 12-item Neuropsychiatric Inventory, Alzheimer's disease Co-operative Study–Activities of Daily Living, Quality of Life in Alzheimer's Disease.

This study demonstrated that:

- Patients with mild AD who consumed Souvenaid experienced a significant improvement in WMS-r–delayed verbal recall score (one of the co-primary outcomes measures in this study) at 12 weeks compared to controls.
- There was no difference between the groups for the other co-primary outcome measure (ADAS-cog), which was unchanged in both groups at 12 weeks.
- Although no significant between group differences in either of the co-primary outcome measures (WMS-r and ADAS-cog) were observed at 24 weeks, a post hoc analysis revealed a significant improvement in WMS-r immediate verbal recall score in the Souvenaid group compared to controls at 24 weeks.
- Compliance was excellent (95%) and the product was well tolerated.

The Souvenir I study provided proof-of-concept support for the hypothesis that combinations of defined nutrients have the potential to fulfill a nutritional need and raise the nutritional levels. Subsequently, this may promote the synthesis of synaptic membranes and provide relevant clinical benefits for patients with mild AD.

Souvenir II study: Efficacy of Souvenaid in mild Alzheimer's Disease (AD)

In the second study in this series (Souvenir II), this RCT aimed to confirm and extend the findings from the Souvenir I study[4]. Individuals with the same clinical diagnosis as those who took part in the Souvenir I study (mild AD) were recruited in 6 European countries, and a different and potentially more sensitive tool to assess cognitive function (memory function domain Z-score of the Neuropsychological Test Battery [NTB]) was used as the primary outcome. This study also included biomarkers of synaptic activity and connectivity (Electroencephalography [EEG]) to gain an understanding of the potential mechanism of action of Souvenaid. The nutritional treatment (24 weeks) was longer than in the Souvenir I study. Subjects were randomized to one of two treatment groups: Souvenaid (n = 130) or an iso-caloric control product (n = 129), once daily.

This study demonstrated that:

- Souvenaid has a beneficial effect on cognitive function in mild AD, as evidenced by the NTB memory domain Z-score which was significantly increased in the Souvenaid versus the control group over the 24-week intervention period. The results from this follow-up study confirm the earlier finding that Souvenaid improved memory performance in individuals with mild AD.
- EEG measures of functional connectivity were significantly different in trajectory over 24 weeks between study groups in favour of the Souvenaid group. These findings suggest that Souvenaid has an effect on brain functional connectivity, supporting the hypothesis that the intervention enhances synapse formation and function.
- Compliance was very high (96.6% [control] and 97.1% [Souvenaid]).

MRS/PL study - The medical food Souvenaid affects brain phospholipid metabolism in mild AD [2]

Souvenaid contains nutritional precursors and co-factors for phospholipid synthesis aiming to improve neuronal phospholipid metabolism at synapses and so cognitive function. This randomised controlled trial (RCT) explored whether Souvenaid affects brain phospholipid metabolism in 34 patients with mild AD. Patients were randomized to active (Souvenaid n=16) or control (isocaloric placebo n=17) product for 4 weeks and advised to minimize intake of high-choline foods and maintain stable intakes of nutritional supplements and (where possible) medication.

Magnetic resonance spectroscopy (MRS) was performed to assess markers of phospholipid synthesis (phosphomonoesters (PME) and breakdown phosphodiesters (PDE)); neural integrity (N-acetyl aspartate); gliosis (myo-inositol); and choline metabolism (choline-containing compounds). The primary outcome parameters were phospholipid synthesis (PME) and breakdown (PDE) levels and the PME/PDE ratio. In addition, blood samples were taken to assess plasma levels of some of the key nutritional precursors and co- factors in the active product.

Thirty-three patients (aged 60-86 years) completed the study, and it was reported that PME/PDE ratio and choline-containing compounds levels were significantly higher in the Souvenaid than the control group at the end of the intervention. Plasma levels of uridine, choline, and vitamin E, as well as percentages of DHA, EPA, and total long-chain polyunsaturated fatty acids were higher in the active than the control group. The active product was found to be safe and generally well tolerated.

This was the first study in patients with mild AD to show that daily intake of the blend of nutrients in the Souvenaid improved neuronal phospholipid synthesis/formation compared to breakdown. These findings support the proposed mode of action of the nutritional precursors and co-factors in Souvenaid on synapse formation and cognitive function. The authors propose that continuous, prolonged intake of the Souvenaid is required to support long term synapse formation and potentially cognitive function.

S-Connect study: Efficacy of Souvenaid in mild – moderate Alzheimer's Disease (AD)

Early studies[8,4] demonstrated a beneficial effect of Souvenaid on memory performance in patients with mild AD who were not taking any AD medication. The S-connect study[5] followed those 2 studies but in a slightly different population: individuals with mild – moderate AD who were also taking medication to manage their AD (cholinesterase inhibitors and/or memantine). In this study, 527 patients from European

centres were randomized to Souvenaid (n = 265) or an iso-caloric control product (n = 262), taken once daily over the course of the 24-week trial.

The primary outcome measure was the effect on cognition as measured by the 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), which assesses memory, language, praxis, attention, and other cognitive abilities. The secondary outcomes assessed the effect on cognition, functional abilities, global clinical impression, safety, and nutritional blood parameters of Souvenaid as compared with the control product.

This study demonstrated that:

- Souvenaid did not slow cognitive decline in individuals treated for mild – moderate AD. Both the treatment and control groups showed a moderate increase of ADAS-cog scores, with no significant difference between study groups. These findings suggest that there was cognitive deterioration over the 24-week study period, which is consistent with expectations for patients with mild – moderate AD.
- Souvenaid may be more beneficial for patients if started at an earlier stage of the disease process, when the neurodegenerative damage is still limited and thus there are greater possibilities to delay cognitive decline with a nutritional intervention.
- Compliance was high (94.1% [Souvenaid] and 94.5% [control]). Souvenaid resulted in the predicted change in peripheral nutritional blood biomarkers and was well tolerated in combination with standard care AD medication.

REACTION Study (Reducing the Effects of Aging on Cognition with Therapeutic Intervention of an oral multi-Nutrient combination)

Age-related cognitive decline (ARCD) are the cognitive changes that can occur in individuals because of aging. This may progress to MCI when an older adult has more learning or memory problems than other adults of the same age. Some adults with MCI may go on to develop AD or other dementias What Is Mild Cognitive Impairment? | National Institute on Aging (nih.gov).

The structure (morphology) of the spines of neuronal dendrites and their ability to change shape (plasticity) is involved in learning and memory. It is thought that altered dendritic spine morphology and loss of synaptic plasticity, as well as loss of entire synapses, can lead to cognitive changes seen in ARCD and MCI.

This pilot study being undertaken at the University of Miami, Florida (USA) aims to examine the feasibility of recruiting people with Subjective Cognitive Decline and the impact of nutritional intervention with Souvenaid on memory, cognition and quality of life in the early stages of cognitive changes in healthy older adults.

This study is ongoing with results due in 2024..

AWARE study: Efficacy of Souvenaid in mild Alzheimer's Disease (AD)

The AWARE observational study[10] evaluated the impact of Souvenaid on daily living in individuals with mild AD. This study was an open-label, prospective, observational, 12-month study that recruited 116 patients with mild AD who were already taking Souvenaid before their recruitment to the study. The primary outcome was 6-month change from baseline in activities of daily living measured by the validated Amsterdam instrumental activities of daily living (A-IADL) questionnaire. Some of the subjects also provided valid A-IADL scores at 12 months.

A historical dataset of individuals attending memory clinics in the Netherlands who had been diagnosed with mild AD was used for comparison (reference population)[7].

The subjects in this study had less decline in A-IADL scores over 6 and 12 months than a broadly similar reference population who were not taking Souvenaid. These findings suggest that Souvenaid may slow clinical deterioration in individuals with mild AD. There was a high rate of self-reported adherence with study product (96%). Souvenaid was well accepted and tolerated.

MEMENTO study: Effectiveness of a specific nutritional supplement on cognitive, behavioural, and functional symptoms in MCI and AD dementia: caregivers' judgements[6].

Caregivers input and judgement on patient's symptoms and the effectiveness of pharmacological interventions play a key role in the clinical management of patients with MCI and dementia. Observational studies report that dietary patterns influence the risk of developing MCI and AD[12]. Randomized clinical trials have shown that the multi-nutrient intervention, Souvenaid, positively impacts on cognition and memory in MCI and mild AD[3,4].

To determine patient and caregiver judgements about changes in cognitive, behavioural, and functional areas after intervention with Souvenaid, the MEMENTO study was undertaken in 500 patients attending Alzheimer's Evaluation Units in 30 Italian centres. This observational study recorded responses to standardised questions on cognitive (e.g., memory of appointments/dates, orientation in new places), behavioural (e.g., apathy/loss of interest, sleep disturbances), and functional (e.g., household activities, reading) areas of 'real life'.

Patients took Souvenaid for an average of 4 months and depending on the cognitive/functional or behavioural domain area being assessed, 28.6-49.6% of caregivers provided a positive judgement on the product's effectiveness particularly for 'memory of appointments, apathy and domestic activities'. Depending on the domain area, 36.2-46.2% of patients provided a positive judgement of supplement use particularly for 'memory and mood'. Overall, caregivers of patients with MCI and higher Mini Mental State Examination (MMSE) scores reported statistically significant positive judgements of effectiveness compared to caregivers of AD patients in several areas questioned (see table 3 in publication). Furthermore, patients with higher duration of use of the supplement reported a higher benefit for its use.

This study confirms the findings of randomized clinical trials on use of Souvenaid but by caregivers and patients in 'real life' behavioural and functional areas as well as cognition. It also supports the idea that use of the supplement should be early in the disease progression, and it should be taken for a prolonged period of time.

'FINGERS-like' clinical trials using Souvenaid

A suboptimal diet is associated with worsening cognition and a poorer nutritional status may increase an individual's risk of cognitive decline. Based on a Finnish intervention trial[13], WW-FINGERS is a worldwide research network that aims to share outcomes and experience of lifestyle intervention trials for dementia

prevention and risk reduction. Studies carried out by the network aim to target multimodal lifestyle interventions (e.g., diet, cognitive training, physical exercise, vascular and metabolic monitoring, and social activity) to prevent cognitive impairment and disability.

There are many studies underway around the world studying the effects of lifestyle interventions, 2 of which (FINGER-NL and MIND-AD) use Souvenaid as part of the dietary modification for the active group.

1 **FINGER-NL** is a 2-year randomized controlled multi-domain lifestyle intervention study which includes Souvenaid, aiming to investigate the effects of a FINGER-like intervention battery in 1206 older Dutch adults at risk of cognitive decline. This study will investigate whether these lifestyle changes have an impact on cognitive outcomes, such as memory. The study is ongoing and is due to be completed in 2024.
Souvenaid® is not available in the Dutch market and is used in a clinical trial setting.
2 **MIND-AD (Mini)** tested a multimodal lifestyle intervention alone or combined with Souvenaid in people with MCI in 4 EU countries[14]. 93 participants with MCI were recruited and randomly allocated to one of the following groups 1. Multimodal lifestyle intervention 2. Multimodal lifestyle intervention + Souvenaid 3. Regular health advice. The study is complete with data analysis underway.

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