


Effect Size Analyses of Souvenaid in Patients with Alzheimer's Disease

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Abstract.

Background: Souvenaid[®] (uridine monophosphate, docosahexaenoic acid, eicosapentaenoic acid, choline, phospholipids, folic acid, vitamins B12, B6, C, and E, and selenium), was developed to support the formation and function of neuronal membranes.

Objective: To determine effect sizes observed in clinical trials of Souvenaid and to calculate the number needed to treat to show benefit or harm.

Methods: Data from all three reported randomized controlled trials of Souvenaid in Alzheimer's disease (AD) dementia (Souvenir I, Souvenir II, and S-Connect) and an open-label extension study were included in analyses of effect size for cognitive, functional, and behavioral outcomes. Effect size was determined by calculating Cohen's *d* statistic (or Cramér's V method for nominal data), number needed to treat and number needed to harm. Statistical calculations were performed for the intent-to-treat populations.

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Results: In patients with mild AD, effect sizes were 0.21 (95% confidence intervals: -0.06, 0.49) for the primary outcome in Souvenir II (neuropsychological test battery memory z-score) and 0.20 (0.10, 0.34) for the co-primary outcome of Souvenir I (Wechsler memory scale delayed recall). No effect was shown on cognition in patients with mild-to-moderate AD (S-Connect). The number needed to treat (6 and 21 for Souvenir I and II, respectively) and high number needed to harm values indicate a favorable harm:benefit ratio for Souvenaid versus control in patients with mild AD.

Conclusions: The favorable safety profile and impact on outcome measures converge to corroborate the putative mode of action and demonstrate that Souvenaid can achieve clinically detectable effects in patients with early AD.

Keywords: Alzheimer's disease, effect size, number-needed-to-treat, Souvenaid

INTRODUCTION

Cognitive decline, particularly episodic memory loss, is one of the first symptoms of Alzheimer's disease (AD). As AD progresses, cognitive decline leads to impairments in functional abilities. Memory impairment is associated with increasing synaptic abnormalities [1], and synaptic dysfunction is now recognized as one of the pathological hallmarks of AD [2]. Slowing or even reversing synaptic dysfunction offers a potential approach to modify the inexorable progression of AD. Data showing that the availability of specific nutrients influences the structure and functionality of neuronal membranes provided a scientific rationale for investigating nutritional interventions to support synaptic function [3]. Furthermore, studies have shown that patients with early AD have a poorer nutrient status despite a putative increase in their nutritional need to support the formation of neuronal membrane components [4]. Accumulating evidence from clinical and epidemiological studies showing that nutritional factors can influence AD risk and progression has encouraged the implementation of dietary and lifestyle guidelines to help adults reduce their risk [5]. AD progression involves multiple factors interacting over a long period of time, suggesting the need for multimodal lifestyle approaches with the potential to influence many biological processes that contribute to neurological decline. The concept of using dietary modification and nutritional support to provide neuroprotection is compelling [5].

Souvenaid is a food for special medical purposes that contains the nutrient combination Fortasyn Connect (docosahexaenoic acid 1200 mg, eicosapentaenoic acid 300 mg, uridine monophosphate 625 mg, choline 400 mg, folic acid 400 mcg, vitamin B6 1 mg, vitamin B12 3 mcg, vitamin C 80 mg, vitamin E 40 mg, selenium 60 mcg, and phospholipids 106 mg). These precursors and cofactors are necessary to form neuronal membranes and hypothesized to support

the synthesis of new synapses and maintenance of existing synapses [6]. Preclinical studies demonstrated that Fortasyn Connect increases markers of synaptogenesis [3, 7, 8], enhances neurotransmitter synthesis and release [8], preserves white and grey matter integrity [9], improves cerebral blood flow and volume [9], reduces amyloid- β production and toxicity [10, 11], and restores neurogenesis [12], all of which may contribute to an overall neuroprotective effect.

Three double-blind, multi-center, randomized, controlled clinical trials (RCTs) evaluated the effects of Souvenaid on cognition and memory performance in patients with AD [13–16]. The trials used clinically relevant, validated tests of cognitive and memory performance. Since memory performance directly correlates with quantitative and qualitative measures of synapse function [1, 2], such standard tests might also serve as a proxy measure of synaptogenesis and neuroprotection. Results from Souvenir I (12-week duration) [13] and Souvenir II (24-week duration) [14] showed that Souvenaid improved memory performance in patients with mild AD not taking AD medication (Mini-Mental State Examination [MMSE] 20–26 and MMSE \geq 20, respectively). In Souvenir I, the co-primary outcome measures were the 12-week change from baseline on the delayed verbal recall test of the Wechsler Memory Scale revised edition (WMS-r) and the 13-item modified Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). Souvenaid significantly improved the co-primary endpoint of WMS-r delayed verbal recall after 12 weeks of intervention versus control. However, no effect was observed on the other co-primary outcome (ADAS-cog) [13]. In Souvenir II, the primary outcome parameter was the memory domain composite z-score based on a Neuropsychological Test Battery (NTB). This memory composite score was derived from the Rey Auditory Verbal Learning Test (RAVLT: immediate recall, delayed recall, and recognition performance) and the

WMS-r verbal paired associates (VPA) immediate and delayed recall. Significant improvements were observed on the NTB memory domain z-score for the active versus control group during the 24-week study period ($p=0.023$). In addition, an exploratory analysis of results from a 24-week open-label extension (OLE) of Souvenir II suggested that memory function improved throughout 48 weeks in patients with mild AD taking Souvenaid [16]. The third RCT in patients with more advanced dementia (mild-to-moderate AD; MMSE 14–24) and receiving AD medication did not show an effect of Souvenaid on cognition [15].

While Souvenaid achieved statistically significant improvements in the primary outcome measures of memory performance in patients with mild AD, assessing the magnitude of these effects in the context of progressively deteriorating cognitive performance is challenging. Effect size analysis, which indicates the size or magnitude of the difference between the groups, is regarded as a useful tool in the assessment of clinical interventions [17]. Accepted measures of effect size include the mean difference between groups (Cohen's d), where effect sizes are conventionally defined as small ($d=0.20$, medium ($d=0.50$) and large $d=0.80$) [18], and Cramér's V , which is usually interpreted in the same way as Cohen's d [19]. In evidence-based medicine, analyses of number needed to treat (NNT) and number needed to harm (NNH) are the preferred indices for the effect of an intervention [20]. NNT data estimate the number of individuals that need to be treated with the intervention of interest for one person to benefit compared with a control subject in a clinical study. NNH data estimate the number of individuals that are treated for one person to experience an adverse outcome compared with a control subject in a clinical study. Effect size analyses have been reported previously for drug therapies in patients with AD [17], but, to our knowledge, not for nutritional approaches. Effect size quantification and NNT/NNH analysis may be informative in the assessment of nutritional interventions for AD in the context of the overall management of these patients and relevance for clinical practice.

To determine the magnitude of the effect of Souvenaid observed in clinical trials of patients with AD, effect size indices and NNT and NNH values were calculated for the three completed RCTs and the OLE study. Here we present results from effect size and NNT/NNH analyses for cognitive, functional and behavioral outcomes, as well as safety parameters.

MATERIALS AND METHODS

Study populations

The study population comprised all patients for whom Souvenaid data are available including data from Souvenir I, Souvenir II, or S-Connect studies performed between 2006 and 2011. The study population and methodology of the studies have been described in detail previously [13–16]. Briefly, all studies included men and women ≥ 50 years of age who were diagnosed with probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria [21]. Eligible patients had mild AD, defined by an MMSE score of 20–26 inclusive (Souvenir I) or ≥ 20 (Souvenir II), or mild-to-moderate AD, defined by an MMSE score of 14–24 inclusive (S-Connect). Subjects in Souvenir I and II had to be drug-free for AD medication, whereas subjects in S-Connect had to be on a stable dose of approved AD medication. In addition, a 24-week OLE study to the Souvenir II study was performed between 2010 and 2012 to evaluate longer-term safety and compliance with Souvenaid (i.e., total intervention period of 48 weeks). Eligibility criteria for the OLE study allowed patients to use AD medication. All subjects received Souvenaid or a control product (similar across studies) once-daily for the duration of the study. All trials were registered in the Dutch Trial Register (Souvenir I: NTR702, Souvenir II: NTR1975, S-Connect: NTR1683 and OLE: NTR2571). The institutional review boards of each participating centers approved the studies. Written informed consent was obtained from all study participants and study partners prior to conducting study procedures.

Outcome measures

Effect sizes and NNT were calculated for all cognitive, functional, and behavioral outcome parameters. In Souvenir I, changes from baseline were measured at week 12 for the following endpoints: WMS-r immediate and delayed verbal recall, modified 13-item cognitive subscale of the ADAS-Cog-13, MMSE, Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL), Neuropsychiatry Inventory (NPI), Clinician's Interview Based Impression of Change plus Caregiver Input (CIBIC-plus) (at week 12), and Quality of Life in Alzheimer's Disease (QOL-AD) composite score.

Table 1
Number needed to treat for Souvenaid compared with control in three randomized controlled clinical trials and an open-label extension (OLE) study

| Study | Outcome Parameter | Event Rate (%) | | NNT* |
|-----------------------------|------------------------------------|----------------|---------|------|
| | | Active | Control | |
| Souvenir I (12 weeks) | ADAS-cog-13: < -4 | 17.8 | 11.1 | 15 |
| | WMS-r delayed memory: >0 | 40.0 | 24.5 | 6 |
| | WMS-r immediate memory: >0 | 50.0 | 39.8 | 10 |
| | MMSE: >0 | 45.9 | 41.1 | 21 |
| Souvenir II (24 weeks) | NTB memory: ≥ 0.0 | 68.9 | 64.1 | 21 |
| | NTB memory: ≥ 0.3 | 37.9 | 26.2 | 9 |
| | NTB executive function: ≥ 0.3 | 24.7 | 16.2 | 12 |
| | NTB total score: ≥ 0.0 | 63.9 | 53.9 | 10 |
| | NTB total score: ≥ 0.3 | 25.3 | 14.6 | 9 |
| OLE [†] (48 weeks) | NTB memory: ≥ 0.0 | 73.6 | 57.8 | 6 |
| | NTB memory: ≥ 0.3 | 51.3 | 34.3 | 6 |
| S-Connect (24 weeks) | ADCS-ADL: >0 | 31.1 | 23.8 | 14 |

*The number needed to treat (NNT) data give an estimation of the number of individuals that need to be treated with the active product (Souvenaid) for one to benefit compared with the control product. Positive values are indicative of a better response to active versus control and vice versa. The lower the NNT, the more effective the treatment (ideal NNT = 1). High values are indicative of small differences between groups (i.e., no effective treatment). Cut-off values for the occurrence of an 'event' (yes/no) were calculated as the change from baseline at study endpoint, except for CIBIC-plus (values at week 12 were used). [†]Calculations based on data method (see paragraph Statistical Analyses).

In Souvenir II, changes from baseline were measured at week 24 for the following endpoints: NTB memory domain z-score, NTB executive function domain z-score, NTB total composite z-score, and Disability Assessment in Dementia (DAD) scale. In the OLE of Souvenir II, changes from baseline were measured at week 48 for the NTB memory domain z-score. In S-Connect, changes from baseline were measured at week 24 for the following endpoints: ADAS-Cog-11, a cognitive composite z-score based on four neuropsychological tests (Digit Span from the WMS – Third Edition], the Concept Shifting Test, the Letter Digit Substitution Test, and Category Fluency), ADCS-ADL, and Clinical Dementia Rating – Sum of Boxes (CDR-SB). Standardized effect sizes for the primary endpoints assumed in the study protocols were 0.45 (ADAS-cog-13) and 0.47 (WMS-r delayed) for Souvenir I, 0.40 (Memory domain z-score) for Souvenir II, and 0.19 (ADAS-cog-11) for S-Connect.

NNH was calculated for reported adverse events (AEs), i.e., any AE, related AEs and AEs in specific body systems (body as a whole, gastrointestinal system disorders, central and peripheral nervous system disorders, psychiatric disorders, and respiratory system) and the drop-out rate.

Statistical analyses

Effect sizes for continuous parameters with a normal distribution were calculated using the mean change from baseline in both the active (Souvenaid)

and control groups and the pooled standard deviation of the change from baseline in both groups using the Cohen's *d* statistic [18]. The Cramér's *V* method was used to calculate effect sizes for nominal data [19]. Cohen's *d* values range from $-\infty$ to $+\infty$, and are presented so that a positive effect size indicates improvement in the active (Souvenaid) group versus control and vice versa. Cramér's *V* values range from 0 (no association) to 1 (perfect association).

NNT and NNH were calculated as '100/(event rate in active group [%] – event rate in control group [%])' and rounded up to the nearest number. Literature and current trial results were used to define cut-off values for the occurrence of an 'event' (yes/no) (Table 1). Unless the effect size was significantly different from zero, a negative NNT or NNH was not reported. For a significant effect size, a negative NNT was reported as a NNH for the given outcome, and a negative NNH was reported as a NNT.

For the OLE study, effect size and NNT for the NTB memory domain z-score could not be calculated directly because there was no control group. Therefore, the change in NTB memory domain z-score during the OLE study was estimated for a control group using two different extrapolation methods converted to a 24-week period: (1) the change from week 12 measured at week 24 in the control group of Souvenir II (data method), and (2) the change from baseline in a memory composite from the AN-1792 active vaccination trial [22] measured at month 12 (literature method). NNH for the OLE study was

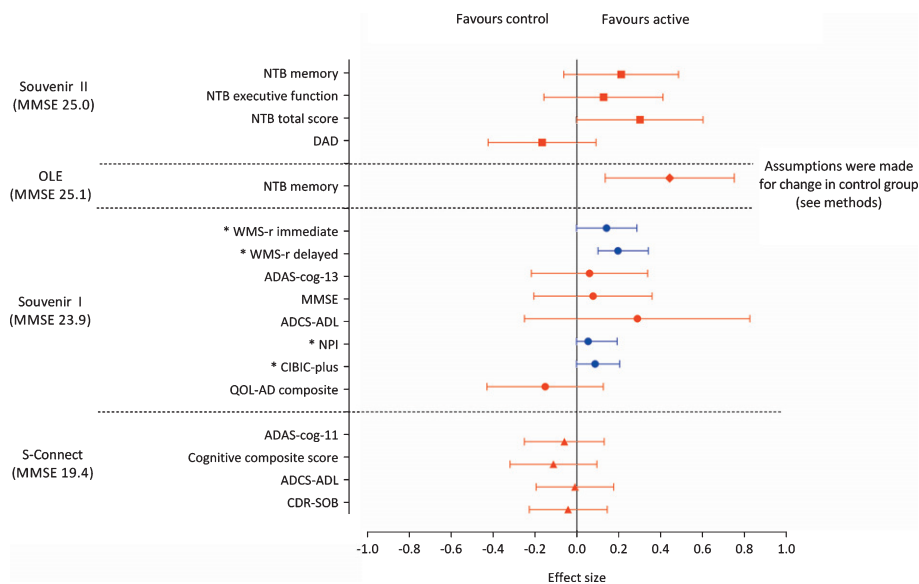


Fig. 1. Effect sizes (point estimate and 95% CI) for the main primary and secondary outcome measures in the Souvenir I (●), Souvenir II (■), open-label extension (OLE) (◆), and S-Connect (▲) studies in patients with mild and mild to moderate Alzheimer’s disease. Mean baseline values of the Mini-Mental State Examination (MMSE) score of the total study populations are shown in the figure. Effect sizes were calculated using Cohen’s *d* [18] (red) for change from baseline values, except for CIBIC-plus (values at week 12 were used), and Cramér’s V [19] (blue) for nominal data. Cohen’s *d* values range from $-\infty$ to $+\infty$, with a positive effect size indicating improvement in the active (Souvenaid) group versus control and vice versa. Cramér’s V values range from 0 (no association) to 1 (perfect association).

calculated based on the occurrence of AEs in the control group of the Souvenir II study period and the occurrence of new AEs in all subjects during the OLE period.

Calculations were performed for the ITT populations of the studies. Data are presented as point estimates and 95% confidence intervals (CI) unless stated otherwise. Statistical analyses were performed using SAS® software (SAS Enterprise Guide 4.3 for Windows, SAS Institute Inc., Cary, NC, USA). The statistical analyses were performed and validated by an independent statistician not involved with the original clinical trial data analyses.

RESULTS

The effect sizes and NNT values for the three RCTs and the OLE study are shown in Fig. 1 and Table 1, respectively. Table 1 does not show data for outcome parameters where the NNT values were negative or greater than 25 because these data are not considered to be statistically meaningful. Specifically, NNT data for the following endpoints were not considered to be meaningful in the context of this analysis: ADCS-ADL: >0 and QOL-AD: >0 for Souvenir I; DAD: ≥ 0 for Souvenir II; ADAS-cog-11: < -4 , Cognitive

composite: ≥ 0.0 and CDR-SB: <0 for S-Connect) or greater than 25 (ADAS-cog-13: < -7 , NPI: <0 , and CIBIC-plus: ≤ 3 for Souvenir I; NTB executive function: ≥ 0.0 for Souvenir II; ADAS-cog-11: < -7 and Cognitive composite: ≥ 0.3 for S-Connect).

In Souvenir I, the co-primary outcome measures were the 12-week change from baseline on the delayed verbal recall test of the WMS-r and the 13-item modified ADAS-cog. The Cohen’s *d* effect size for WMS-r delayed recall was 0.20 (95% confidence intervals [CI] 0.10, 0.34). The 95% CIs for the Cramér’s V effect size of the co-primary outcome WMS-r delayed recall in Souvenir I were 0.10 to 0.34. No detectable effect was seen on the 13-item modified ADAS-cog. Calculated NNT values were 6 for WMS-r delayed recall and 15–26 for ADAS-cog (Table 1). NNH values in the Souvenir I study ranged from 13 (any AE) to 138 (AEs related to gastrointestinal disorders). The NNH value for study drop-out in Souvenir I was 58.

In Souvenir II, the Cohen’s *d* effect size for the primary outcome (NTB memory z-score) was 0.21 (–0.06, 0.49). The 95% CIs for the Cohen’s *d* effect size of NTB total z-score (Souvenir II) were greater than zero (0.002, 0.604). NNT values for the NTB memory score ranged from 9 to 21. For the Souvenir

II and OLE studies, event rates for all type of AEs were lower in the Souvenaid group than the control group, therefore NNH were not applicable. The NNH values for study drop-out were 65 and 206 in Souvenir II and the OLE, respectively.

For the two RCTs in mild AD (Souvenir I and Souvenir II), the effect sizes for 11 of the 13 cognition/memory, function and behavior measures were positive, ranging from a point estimate of 0.06 (95% CI 0.00, 0.19) to 0.30 (0.00, 0.60). In two of the 13 measures, (QOL-AD -0.15 [-0.43 , 0.13] and the DAD score -0.16 [-0.42 , 0.09]) the 95% confidence intervals crossed zero (Fig. 1). Analyses of the exploratory efficacy parameter in the OLE study, the NTB memory z-score, showed effect sizes of 0.45 (0.14, 0.75) and 0.53 (0.22, 0.84), and NNT values of 6 and 5 using the data method (Fig. 1, Table 1) and the literature method, respectively.

In S-Connect, in patients with mild-to-moderate AD, the primary outcome of cognition was assessed by the 11-item ADAS-cog. The effect sizes for cognition and function were negative and close to zero, ranging from -0.11 (-0.32 , 0.10) to -0.01 (-0.19 , 0.18). Corresponding NNT values were high or could not be calculated (Table 1), except for ADCS-ADL (NNT = 14). Together, these data suggest no significant benefit on the assessed cognitive and functional outcomes for Souvenaid versus control during 24 weeks in patients with mild-to-moderate AD taking AD medication. NNH values in the S-Connect study ranged from 36 to 109 for AEs related to respiratory disorders and gastrointestinal disorders, respectively, or were not calculable.

DISCUSSION

This analysis assessed the effect sizes of Souvenaid in patients with mild AD or mild-moderate AD. Analysis of the Souvenir II trial in patients with mild AD showed that the effect size for the primary endpoint (NTB memory) was ≥ 0.20 . Similarly, in the Souvenir I study, the effect size for the co-primary endpoint (WMSr delayed recall) is considered large enough to be detectable. NNT values for the NTB total score, ADAS-cog and memory outcomes in Souvenir I and Souvenir II ranged from 6 to 26 on one overall cognitive outcome (NTB total score) and the specific memory outcomes at 12 to 24 weeks. For the two memory outcome measures the effect sizes were smaller than the protocol assumptions, but reached statistical significance. The difference between actual

effect sizes and protocol assumptions is attributable to a conservative estimation in the variance and more powerful tests used in the analysis of results compared with the power calculation used in the trial protocols.

Memory performance represents a clinically relevant outcome measure because impairment in this domain is typically the earliest and most pervasive symptom in AD. Furthermore, memory preservation may be considered as a proxy for neuroprotective effects of an intervention in early AD that achieves beneficial effects on disease-relevant pathological processes. A significant association has been demonstrated between memory impairment and loss of synapses [1]. In S-Connect, conducted in patients with mild-moderate AD taking AD medication, effects were not detectable. The ADAS-cog used as the primary outcome of the S-Connect study was less sensitive to cognitive effects than the WMSr in the Souvenir I study and this may have contributed to the absence of a detectable benefit in S-Connect. Biologically, the production of synapses is compromised by reduced neuronal number and the potential to benefit from neuroprotection and synaptogenesis may be limited in later stages of AD-related dementia (i.e., mild-moderate) compared with (very) mild AD-related dementia because of the more marked neurodegeneration.

The primary efficacy endpoint in Souvenir II was the NTB memory domain score, a composite measure of individual memory test scores [23]. Compared with a single memory item, the NTB memory domain score has the advantage of clustering raw memory test scores, which decreases variation associated with individual tests and helps to improve the strength of the underlying cognitive constructs [14]. The NTB total score comprises all NTB components including tests of memory and executive functioning. In the primary analysis of Souvenir II, Souvenaid demonstrated a significant effect on NTB memory score (the primary endpoint) and there was a trend for an effect on NTB total score (a secondary endpoint) over the 24-week study period [14]. The present analysis suggests a more pronounced effect size for NTB total than for NTB memory. However, these effect size analyses are based on change from baseline at week 24, whereas *p*-values for NTB scores in the primary analysis of Souvenir II are based on the trajectory of the scores over the 24-week time period [14]. Analysis of the OLE showed that in patients treated for 48 weeks, the effect size for NTB memory was more pronounced than observed at 24 weeks

in Souvenir II. Effect size and NNT values in the OLE are based on assumptions because there was no control group in this open-label study setting. This is an important limitation for the interpretation of these results and should be taken into consideration when assessing this study in the context of the wider literature.

Effect size, NNT and NNH analyses help to inform discussion about whether interventional effects may be considered clinically meaningful by identifying where the benefit is likely to occur, by indicating how likely the benefit is to be observable and by providing an overall assessment of the risk:benefit ratio [17]. Effect sizes previously reported for cholinesterase inhibitors were 0.15, 0.23, and 0.28 for low, medium, and high doses, respectively, based on the primary endpoint of ADAS-Cog [17]. NNT values reported for anti-dementia drugs ranged from 4–14, using cognition as a clinical endpoint, whereas NNH values ranged from 6–20 [24–26]. The magnitude of these effect sizes was considered sufficient for regulatory approval and clinical use [27].

Evidence shows that levels of specific nutrients needed to support the formation of phospholipids and to maintain neuronal membrane integrity may be reduced in patients with AD [4]. Clinical trials in patients with early AD showed that Souvenaid increases the availability of these nutrients [28] and improves memory performance [13, 14, 16]. NNT values of 6–10/21 (for memory) suggest that for every six patients taking Souvenaid one will achieve a clinically detectable benefit in memory performance. However, NNT calculations are valid only when the outcome measure in question, for example WMS-r delayed memory in Souvenir I, is statistically different between interventions. NNH values for Souvenaid are very high or not calculable, in accordance with its good safety and tolerability profile. In the three RCTs, there were no significant differences in the incidence of adverse events between Souvenaid and control groups [13–15]. Overall, the NNT and NNH values indicate a favorable harm:benefit ratio for Souvenaid versus control in patients with mild AD, and inconclusive findings in patients with moderate AD. The favorable harm:benefit ratio and impact on disease-relevant outcome measures (effect size) converge to corroborate the benefit of the intervention.

The limitations of these analyses are the relatively small sample sizes and a limited duration of follow up in the controlled studies included. Placebo or practice effect observed after 12 weeks (the first assessments

after baseline) for the overall NTB memory domain and various other NTB parameters in Souvenir II make it impossible to compare data from Souvenir I and II studies at similar time points. Although the OLE study period provides follow up through 48 weeks, this part of study does not have a control arm and projections are used to calculate effect sizes. Measurements of changes in cognitive tests are subject to potential methodological variation, which may impact the interpretation of NNT values determined from multiple endpoints. The primary and secondary endpoints were not identical between different studies and, therefore, we have reported NNT values for all main outcome measures. In line with the primary analyses, benefits were not shown in other domains, such as behavior and function, which may be attributable to the early stage of disease of the participants and lack of sensitivity of the outcome measures used. In addition, the trial populations included in the analyses are not identical. In the S-Connect trial, all patients were being treated with an acetylcholinesterase inhibitor, memantine, or both, and the mean MMSE in the active group was 19.5, whereas in both Souvenir I and Souvenir II trials, concurrent drug therapy for AD was not permitted and mean MMSE scores were higher (23.8 and 24.9, respectively), reflecting a less severe disease stage at study entry. All RCTs conducted with Souvenaid in AD dementia have been published and there is no publication bias for the available data.

The effect of Souvenaid on memory performance in patients with early AD should be evaluated in the context of the worsening AD trajectory. Additionally, the possibility of idiosyncratic effects should be considered. For example, individuals with cognitively demanding roles who perform well on standard measures and indicate high levels of cognitive performance, may also report difficulties successfully carrying out their jobs. These patients may have experienced relatively small, but crucial, levels of cognitive decline. A nutritional approach that can reverse even modest levels of memory impairment without safety risks may be a useful option for such individuals as part of an overall clinical management approach for patients with early AD. Combining nutritional management specifically designed for neuroprotection with other lifestyle interventions such as cognitive stimulation and physical exercise may contribute to an enhanced effect size. Indeed, in this complex multifactorial disease, several small steps may be critical to meaningful progress.

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TRIAL REGISTRATION

Souvenir I: Dutch Trial Registration: NTR702, registered 20-Jun-2006 (additional registration in ISRCTN registry: ISRCTN72254645, registered 19-Jul-2006); Souvenir II: Dutch Trial Registration: NTR1975 registered 16-Sep-2009; Souvenir II OLE: Dutch Trial Registration: NTR2571 registered 15-Oct-2010; S-Connect: Dutch Trial Registration: NTR1683 registered 23-Feb-2009

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