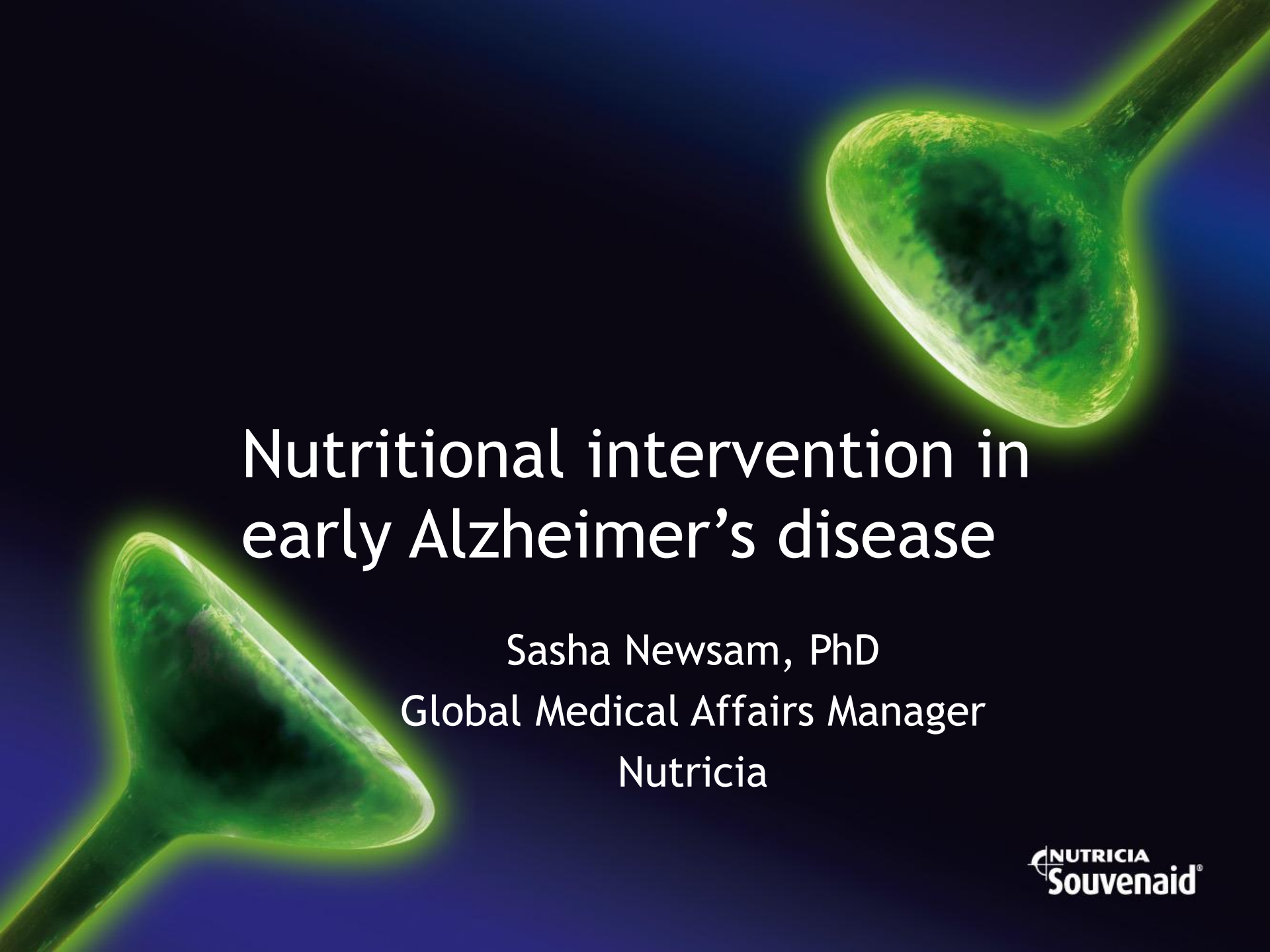

Nutritional intervention in early Alzheimer's disease

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NUTRICIA Souvenaid®

Agenda

- Nutrition and brain function
- Single nutrient intervention
- Diet and risk of Alzheimer’s disease
- What is an FSMP?
- Souvenaid as a viable management option for AD

Nutritional need to maintain brain function

- The brain needs specific nutrients to build and maintain its structure[1]
- Nutritional deficiencies are associated with impaired brain function, for example:
  - Omega 3 fatty acid levels affect mood, behaviour, stress, depression and dementia[1-3]
  - Vitamin B deficiency is linked to neurologic disorders and psychologic disturbances[1]
- The need to supply specific nutrients to the brain may be increased in neurological disease, such as AD[4]

1. Bourre. J Nutr Health Aging 2006a,b; 2. Bourre. J Nutr Health Aging 2005; 3. Phillips et al. Nutr Neurosci 2012; 4. van Wijk et al. J Alzheimers Dis. 2012

Single nutrient interventions in AD/MCI: in general no beneficial effects on cognition

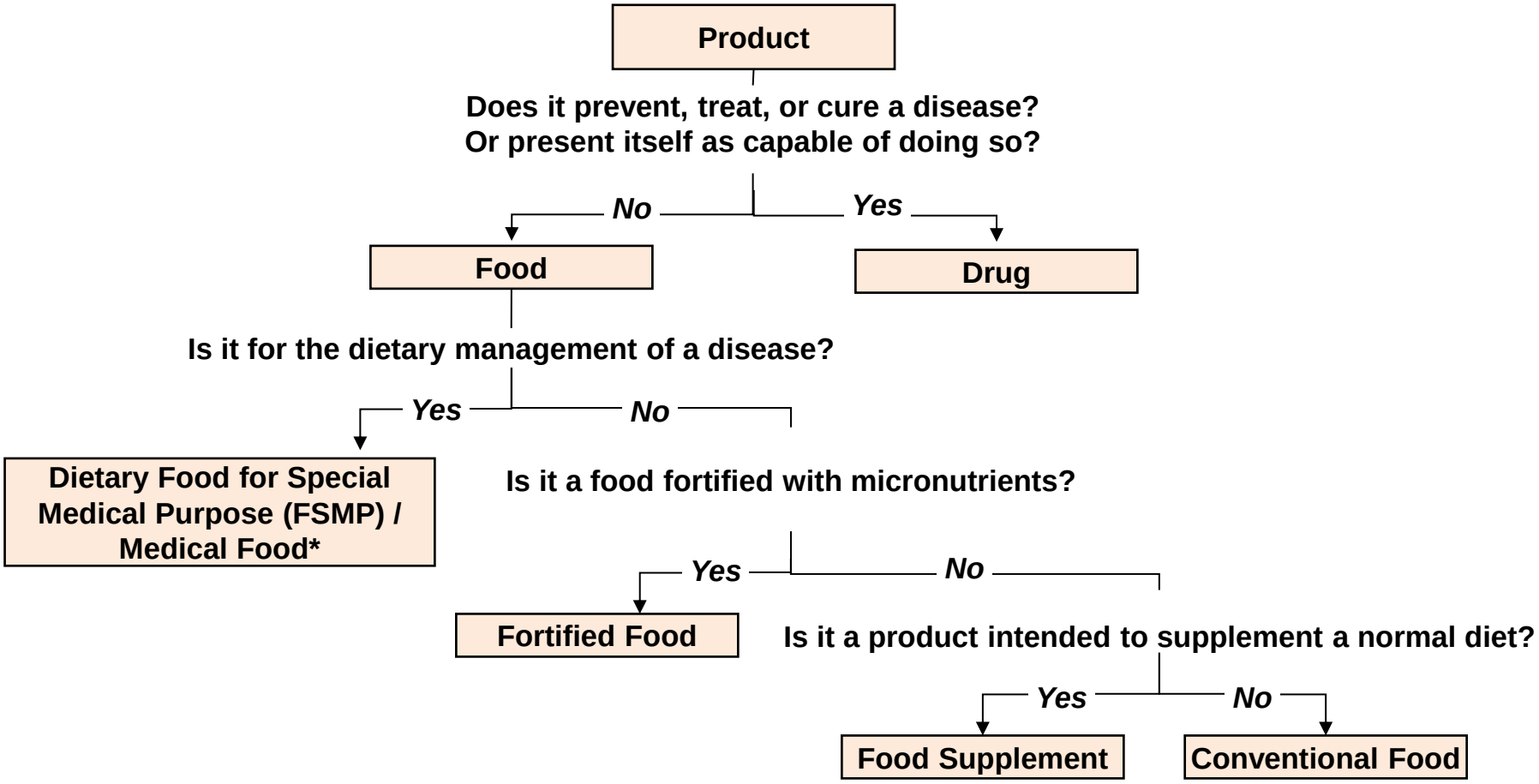
Nutrient	Author	Journal		#Subjects/ Duration	Outcome
n3 PUFAs	Quinn 2010	JAMA		402 18 months	DHA compared with placebo **did not slow the rate of cognitive and functional decline** in mild-moderate AD patients.
	Freund-Levi 2006	Arch Neurol		174 6 months	Administration of n3PUFA in mild -moderate AD patients did **not delay the rate of cognitive decline** according to the MMSE or the cognitive portion of the ADAS. However, positive effects were observed in a small group of patients with very mild AD (MMSE>27)
B-vitamins	Aisen 2008	JAMA		409 18 months	This regimen of high-dose B vitamin supplements does **not slow cognitive decline** in individuals with mild to moderate AD.
	McMahon 2006	N Eng J Med		276 24 months	The results of this trial do **not support the hypothesis that homocysteine lowering with B vitamins improves cognitive performance**.
Vitamin E / Antioxidants	Dysken 2014	JAMA		304 Mean f-up 27 months	Among patients with mild to moderate AD, 2000 IU/d of **alpha-tocopherol compared with placebo resulted in slower functional decline**.
	Petersen 2005	N Eng J Med		769 36 months	Vitamin E had **no benefit in patients with mild cognitive impairment**.
	Galasko 2012	Arch Neurol		52 16 weeks	However, this treatment (vitamin E + vitamin C plus α-lipoic acid) raised the caution of **faster cognitive decline**
Vitamin D2	Stein 2011	J Alz Disease		32 8 weeks	We conclude that high-dose vitamin D provides **no benefit for cognition** or disability over low-dose vitamin D in mild-moderate AD
Ginkgo biloba	DeKosky 2008	JAMA		3069 median f-up 6.1 Y	Ginkgo biloba at 120 mg twice a day was **not effective in reducing either the overall incidence rate of dementia or AD incidence** in elderly individuals with normal cognition or those with MCI.

Diet and AD risk

- Epidemiological data has shown an association between certain dietary patterns and a lower risk of AD, e.g.[4]
  - Regular intake of fish (providing PUFAs)[5,6]
  - Mediterranean diet
  - Adherence to nutritional recommendations in middle-age adults is associated with future memory performance[7]
- These data suggest that supplementation with specific combinations of nutrients is more effective in improving cognitive performance than single nutrient supplementation
- AD is multifaceted and heterogenous disease so it is unlikely that a single intervention will be the answer

1. Malouf et al., *Cochrane Database Syst Rev*. 2008;(4):CD004514 2. Farina et al., *Cochrane Database Syst Rev*. 2012;11:CD002854. 3.Malouf et al., *Cochrane Database Syst Rev*. 2003;(3):CD00432; 4.Salerno-Kennedy et al. Int J Vitam Nutr Res. 2005 ; 5. Kalmijn . J Nutr Health Aging 2000; 6. Barberger-Gateau et al. BMJ 2002; 7. Kesse-Guyot et al. Am J Clin Nutr 2011

Regulatory overview



** For individuals with distinctive/special dietary needs which cannot be met by modification of normal diet.*

Definition of FSMP

European Union

".. a category of foods for particular nutritional uses specially processed or formulated and intended for the **dietary management of patients and to be used under medical supervision**. They are intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to **take, digest, absorb, metabolize or excrete** ordinary foodstuffs or certain nutrients contained therein or metabolites, or with other medically-determined nutrient requirements, whose dietary management **cannot be achieved only by modification of the normal diet**, by other foods for particular nutritional uses, or by a combination of the two" (Directive 1999/21/EC).

FSMPs must be based on sound medical and nutritional principles and that its use in accordance with the manufacture's instructions is **safe, beneficial and effective in meeting the particular nutritional requirements of the patients** for which it is intended, as **demonstrated by generally accepted scientific data** (Directive 2009/39/EC, repealed/replaced by Regulation 609/2013).

Souvenaid: an FSMP

Fortasyn™ Connect

- UMP
- Omega-3 fatty acids
- Choline
- Phospholipids
- B vitamins
- Antioxidants

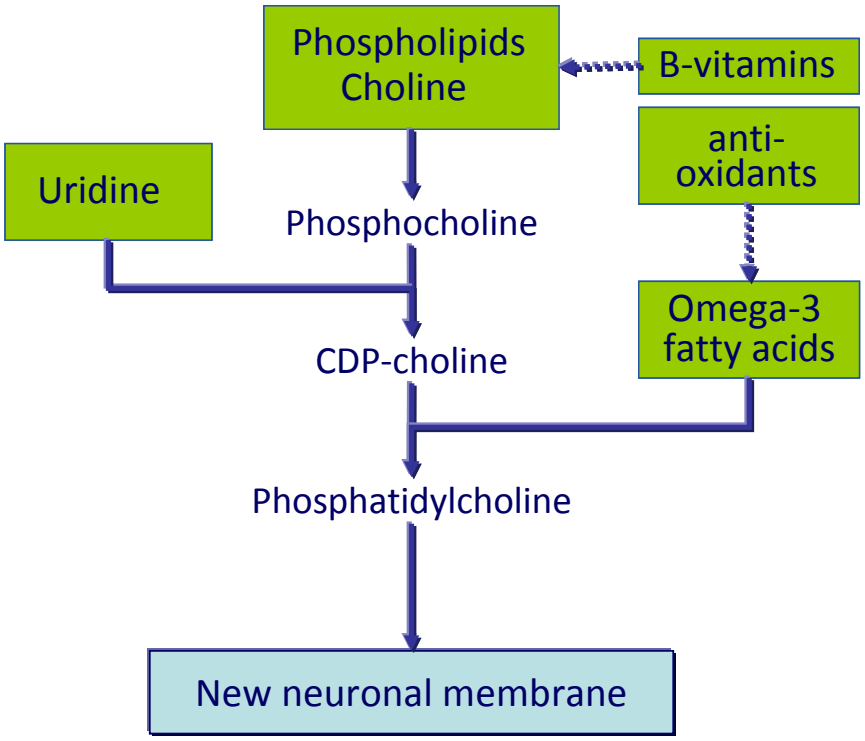
Designed to:

Support the formation of synapses

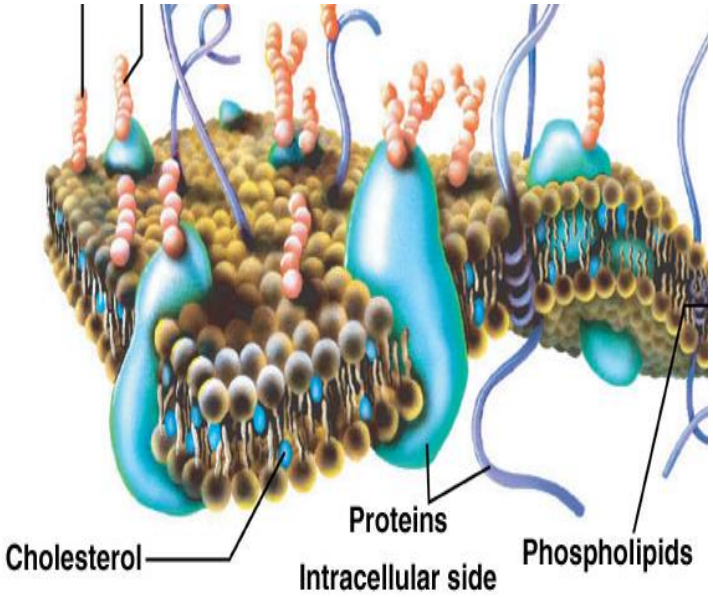
- DHA 1200 mg
- EPA 300 mg
- UMP 625 mg
- Choline 400 mg
- Folic acid 400 µg
- B6 1 mg
- B12 3 µg
- Vit C 80 mg
- Vit E 40 mg
- Se 60 µg
- Phospholipids 106mg

Dietary precursor control of neural membrane synthesis

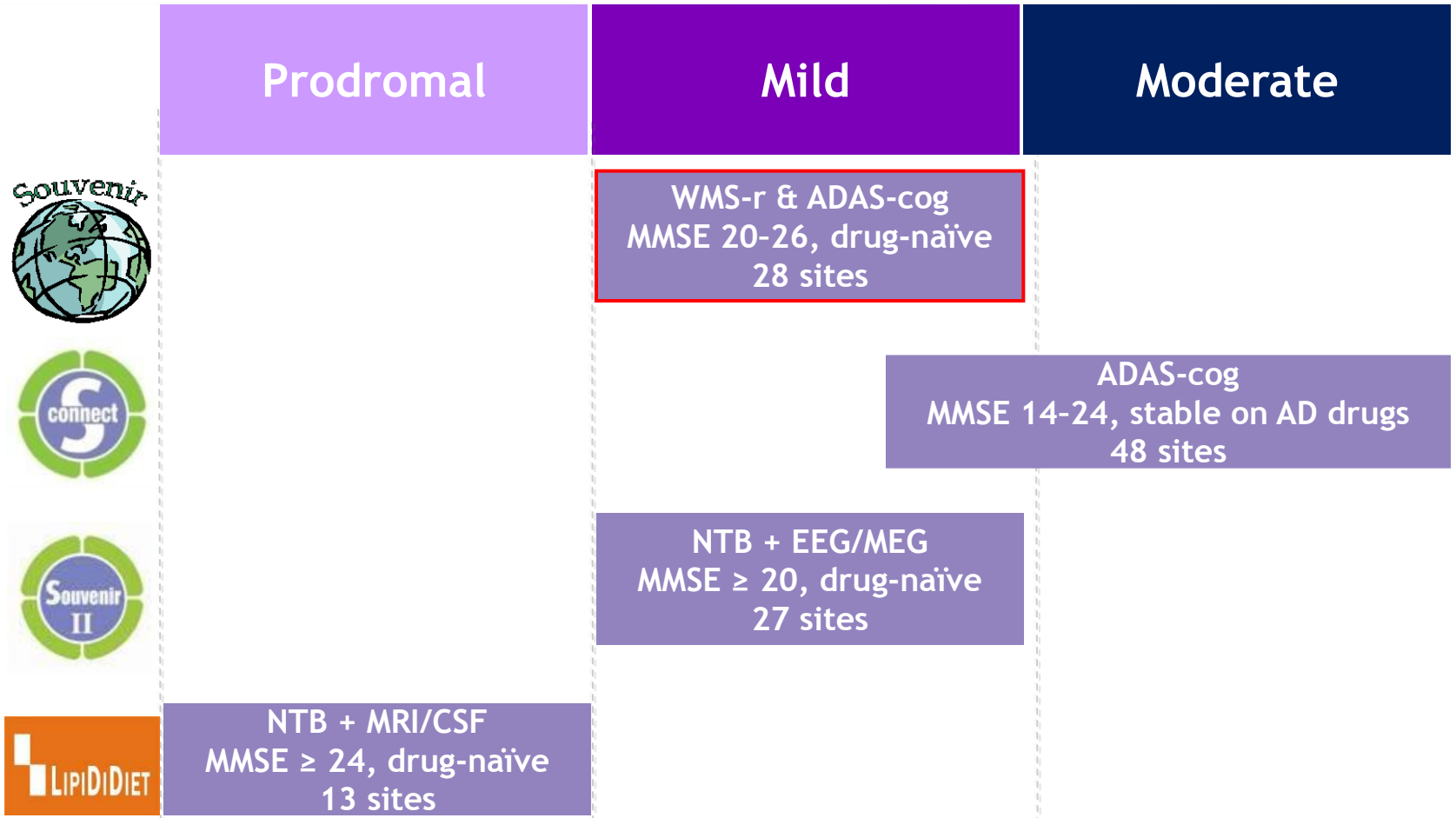
The Kennedy pathway for biosynthesis neuronal membrane



Phospholipids are main constituents of synapses



Full clinical trial programme



Souvenir I: this project receives funding from NL STW.
Souvenir II: This project receives funding from the NL Food & Nutrition Delta project, FND N° 10003.
LipiDiDiet: Funded by the EU FP7 project LipiDiDiet, Grant Agreement N° 211696.

Souvenir I: Primary endpoint
MMSE 20–26, drug-naïve 12 weeks

Delayed verbal memory (Wechsler Memory Scale – recall task)

Significantly more responders in mild AD after 12 weeks (p=0.021)*

Significantly more responders in very mild (MMSE 24-26) AD after 12 weeks (p=0.019)*

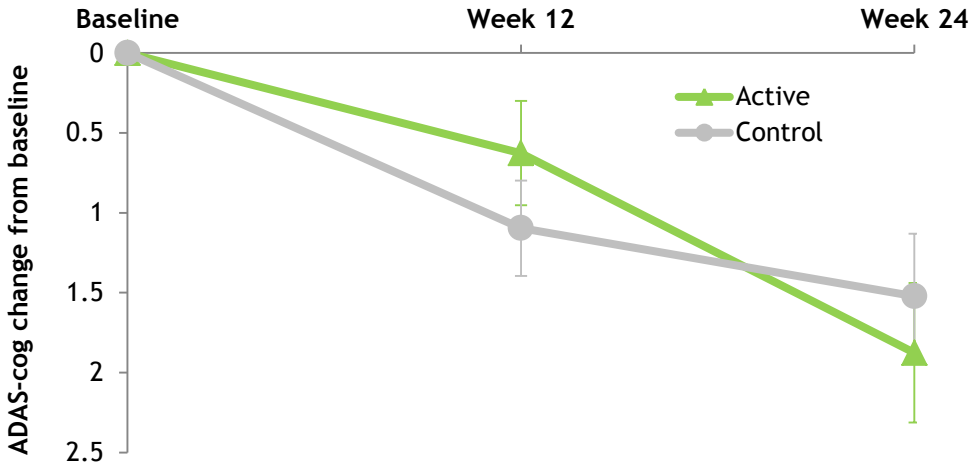
*** Chi-square – skewed distribution: 40% scored 0 on WMS-r @**

Scheltens et al. *Alzheimers Dement*. 2010;6:1-10.

S-Connect: Primary endpoint

ADAS-cog 24 weeks, MMSE 14–24, stable on AD drugs

No significant effect* (p=0.513) during 24 weeks

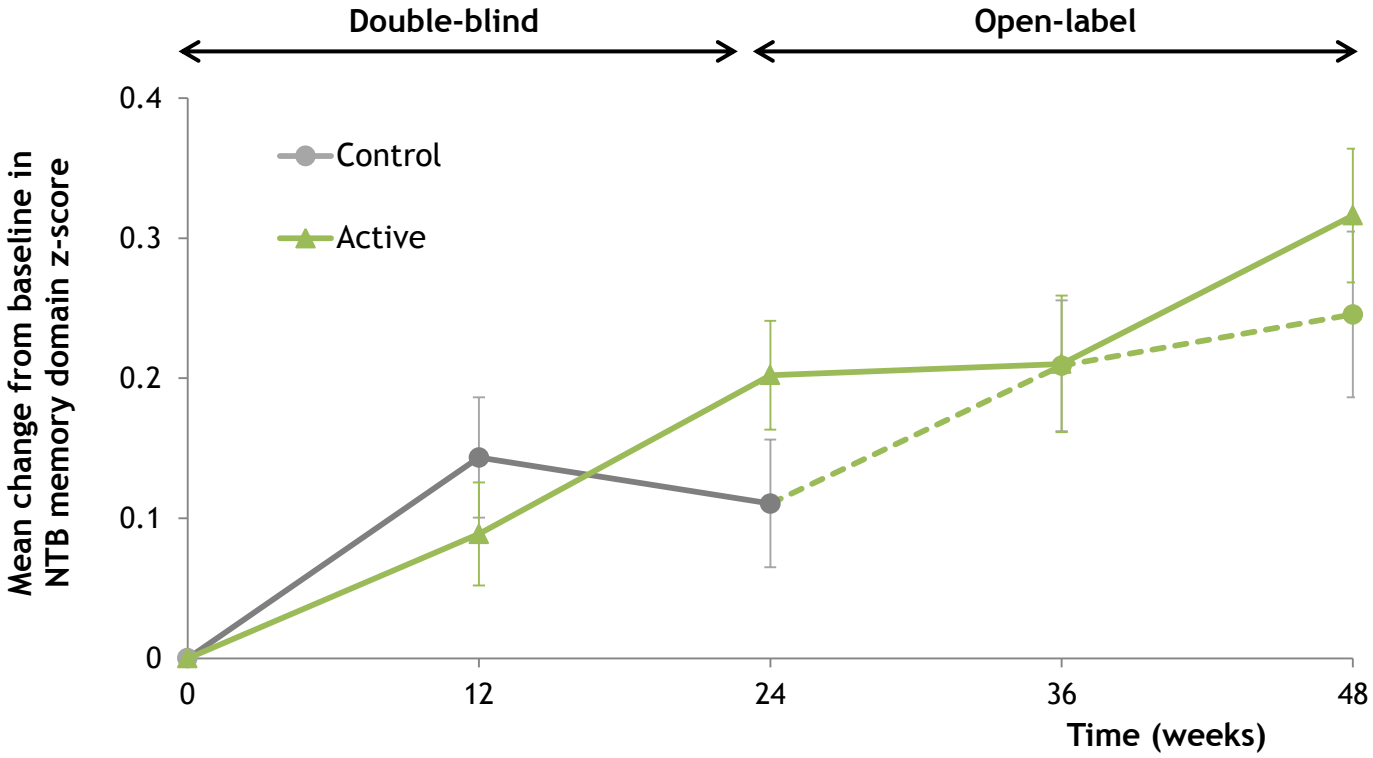


ITT, MMRM, data are mean ±SE.

*Statistical analysis run by Rush Alzheimer's Disease Center, Rush University Medical Center.

Shah et al. Alzheimer's Research & Therapy(2013), 5:59.

Exploratory Outcome: Sustainable NTB memory domain improvement



	0	12	24	36	48
Control (*N*)	-	*100*	*103*	*85*	*83*
Active (*N*)	-	*107*	*103*	*83*	*83*

Significant increase from week 24 to week 48 in both groups.
Active - Active: p=0.038
Control - Active: p=0.029

Thank you for your attention

Any questions?