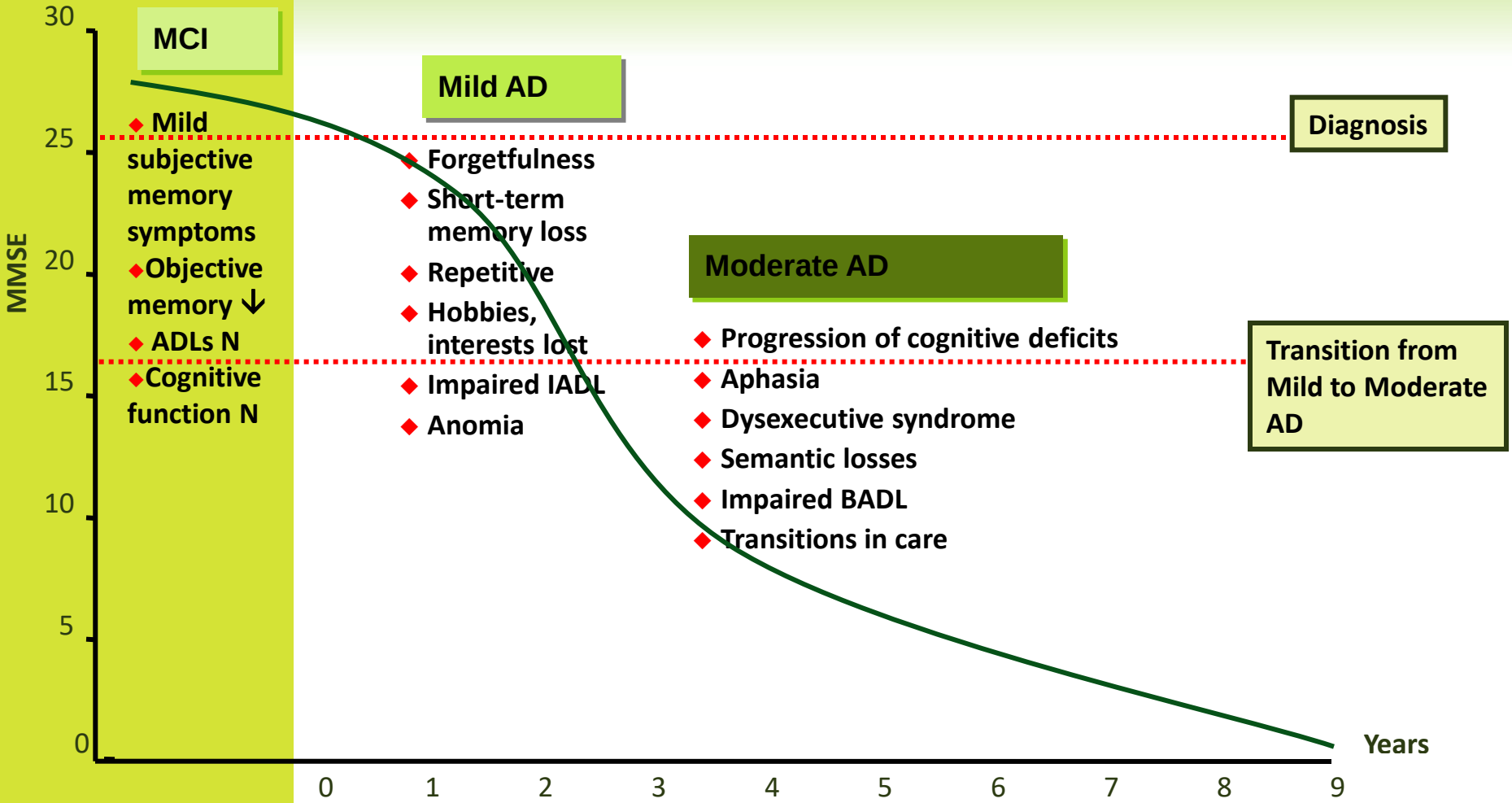
'Reasons to Treat: Benefits of Early and Continuous Therapy in Alzheimer's disease'

충남대학교병원 정신과 김정란

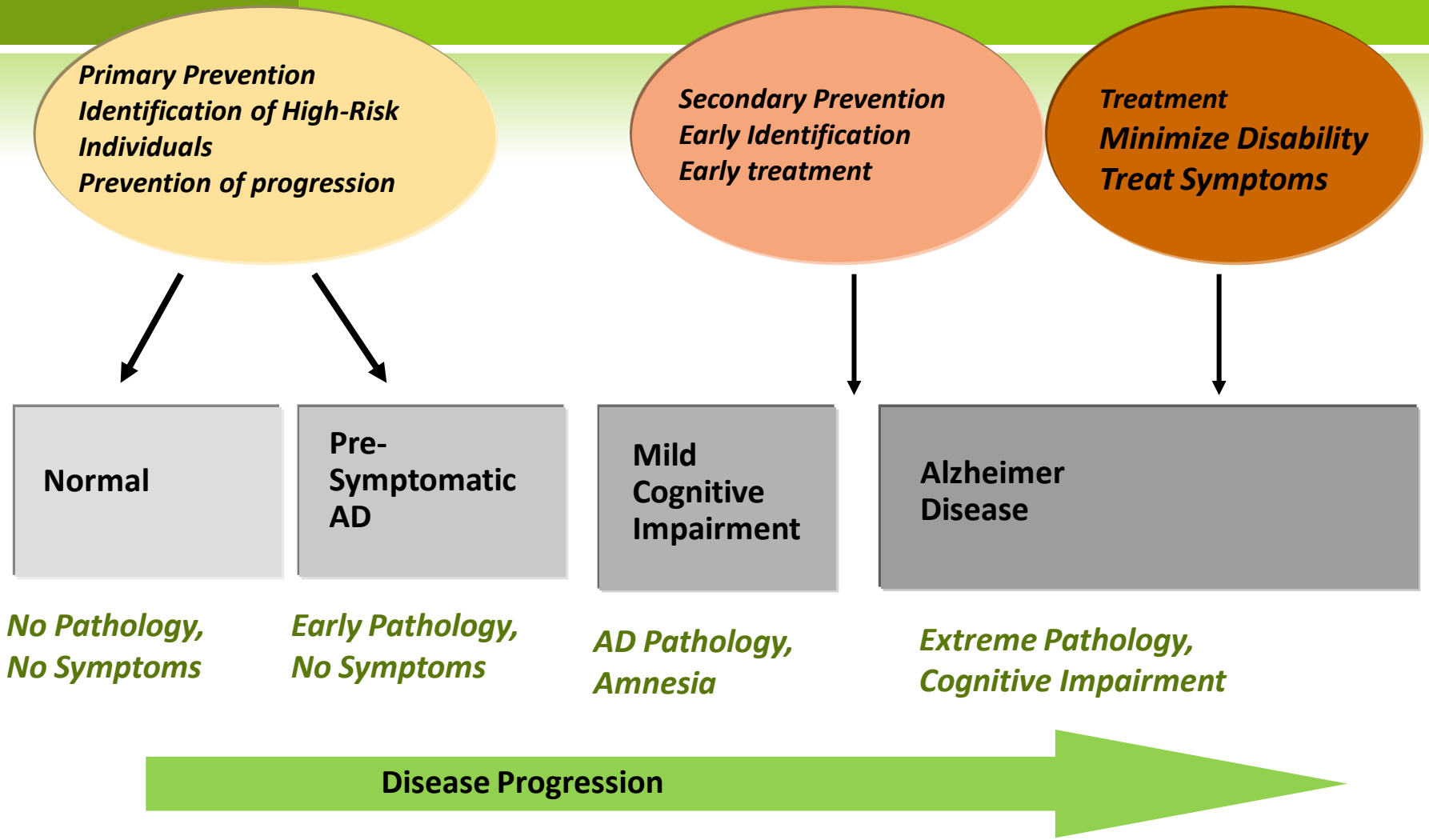
What is Alzheimer's disease?

- **A progressive, degenerative disease**
- **Its core symptoms are:**
  - Cognitive decline
  - Functional decline
  - Behavioral disturbances
- **Neurofibrillary tangles and plaques may lead to loss of cholinergic neuronal function**
- **Cholinergic hypothesis**
  - cholinergic deficit in cerebral cortex triggered Alzheimer's disease

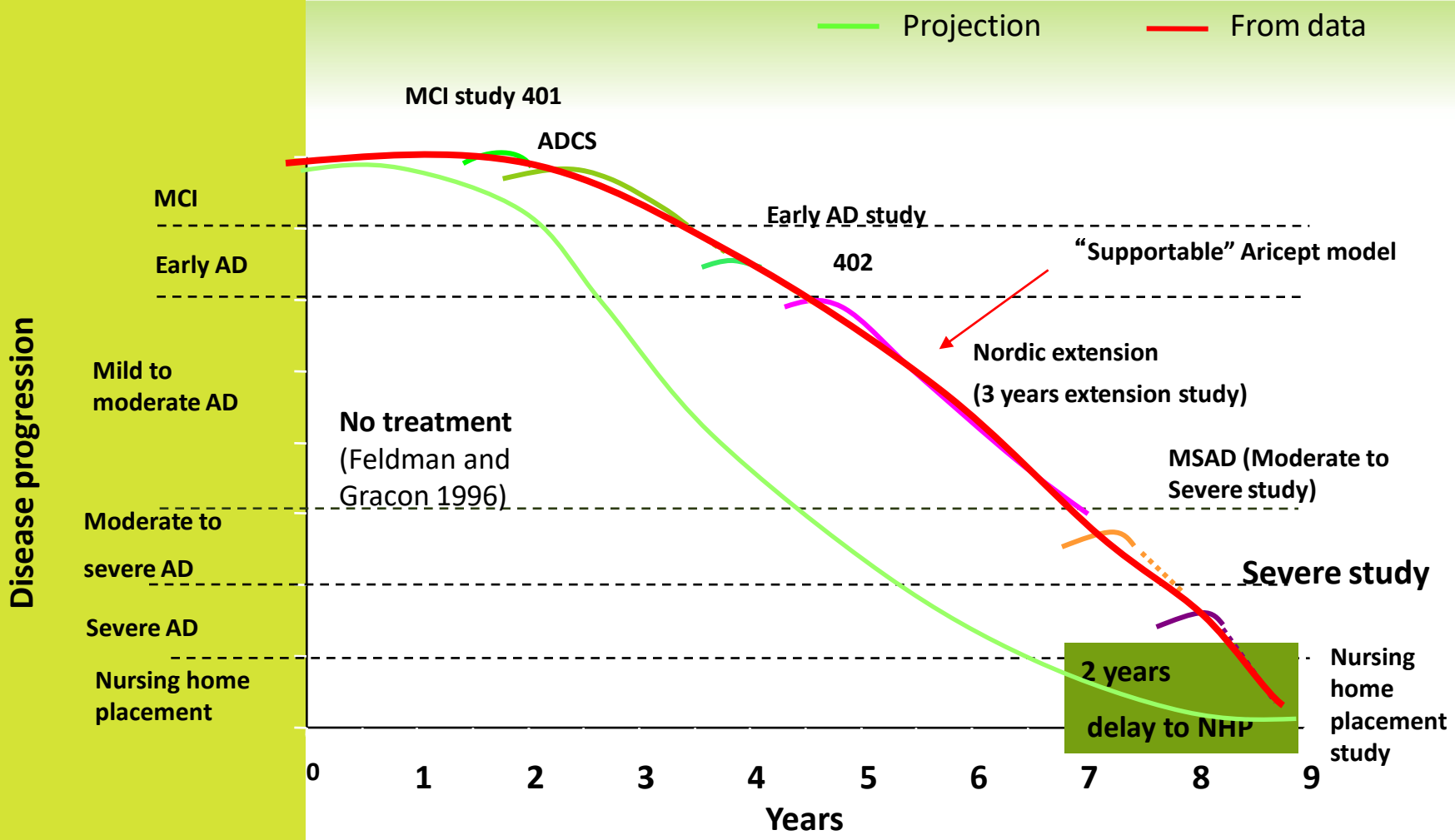
Symptom Progression in AD



Modified from Feldman HH & Woodward M. *Neurology*. 2005;65:S10-17


Primary Prevention
Identification of High-Risk Individuals
Prevention of progression
Secondary Prevention
Early Identification
Early treatment
Treatment
Minimize Disability
Treat Symptoms
Normal
Pre-Symptomatic AD
Mild Cognitive Impairment
Alzheimer Disease
No Pathology, No Symptoms
Early Pathology, No Symptoms
AD Pathology, Amnesia
Extreme Pathology, Cognitive Impairment
Disease Progression

Proven efficacy of Aricept through all dementia course



MCI STUDY (NEUROLOGY 2004;63:651-657)

CME

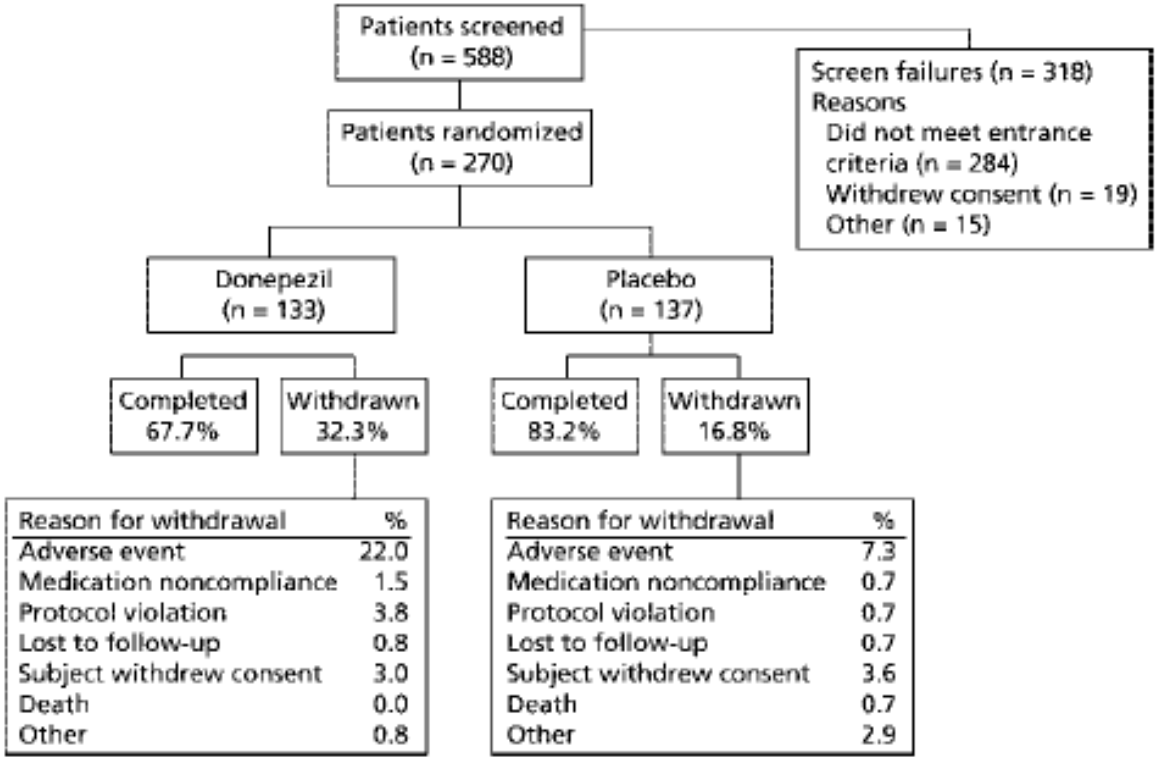
Efficacy of donepezil in mild cognitive impairment

A randomized placebo-controlled trial

S. Salloway, MD, MS; S. Ferris, PhD; A. Kluger, PhD; R. Goldman, PhD; T. Griesing, PhD; D. Kumar, MS; and S. Richardson, PhD, for the Donepezil "401" Study Group*

- *Design*: 24-week, multicenter, randomized, double-blind, placebo-controlled study
- *Patients*: A total of 270 patients with MCI (24≤MMSE score) were enrolled and randomized to receive either donepezil or placebo

Design and patient disposition



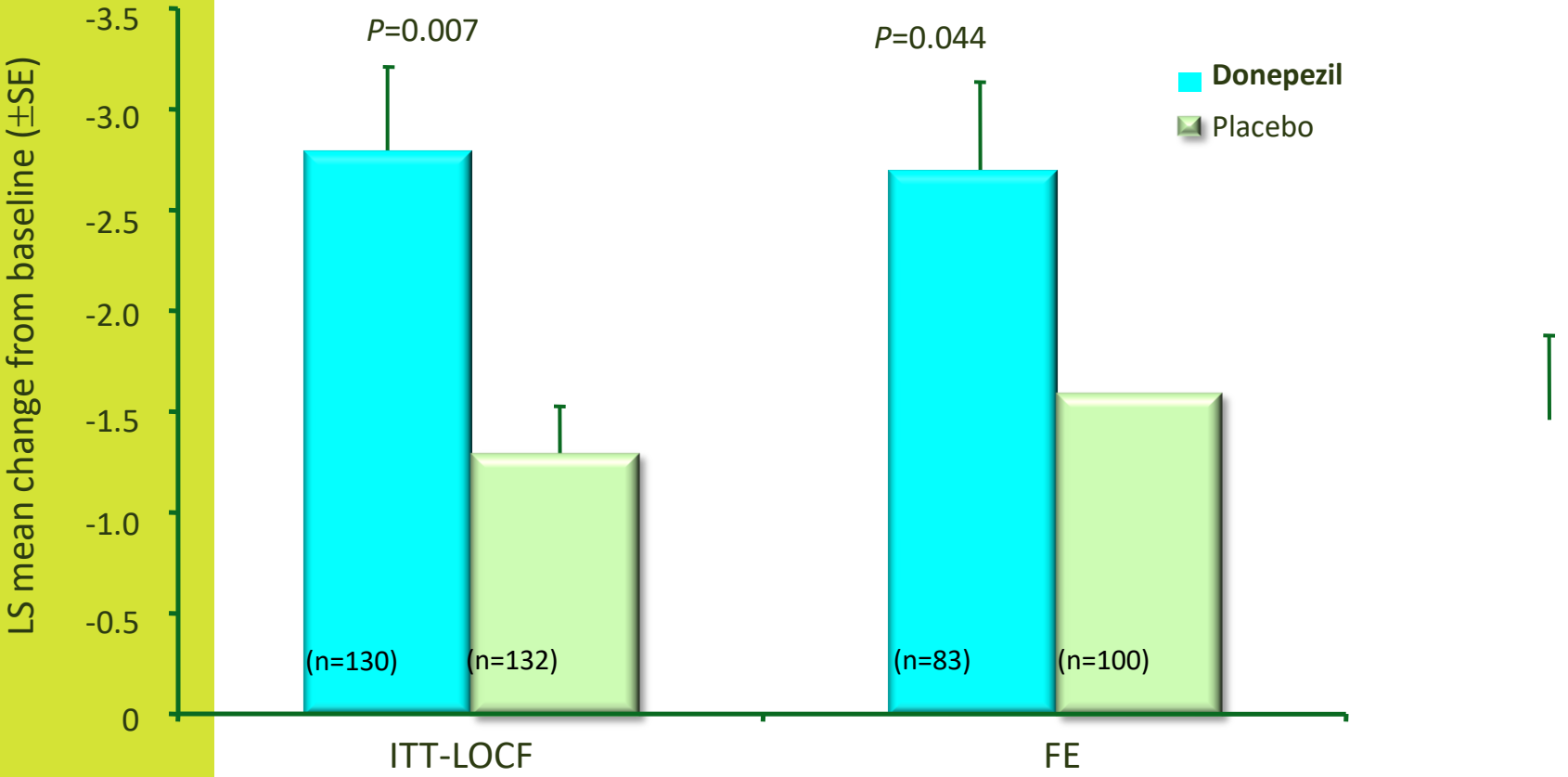
Reason for withdrawal	%
Adverse event	22.0
Medication noncompliance	1.5
Protocol violation	3.8
Lost to follow-up	0.8
Subject withdrew consent	3.0
Death	0.0
Other	0.8

Reason for withdrawal	%
Adverse event	7.3
Medication noncompliance	0.7
Protocol violation	0.7
Lost to follow-up	0.7
Subject withdrew consent	3.6
Death	0.7
Other	2.9

Figure 1. Patient enrollment and completion through the study.

Result of MCI study (1)

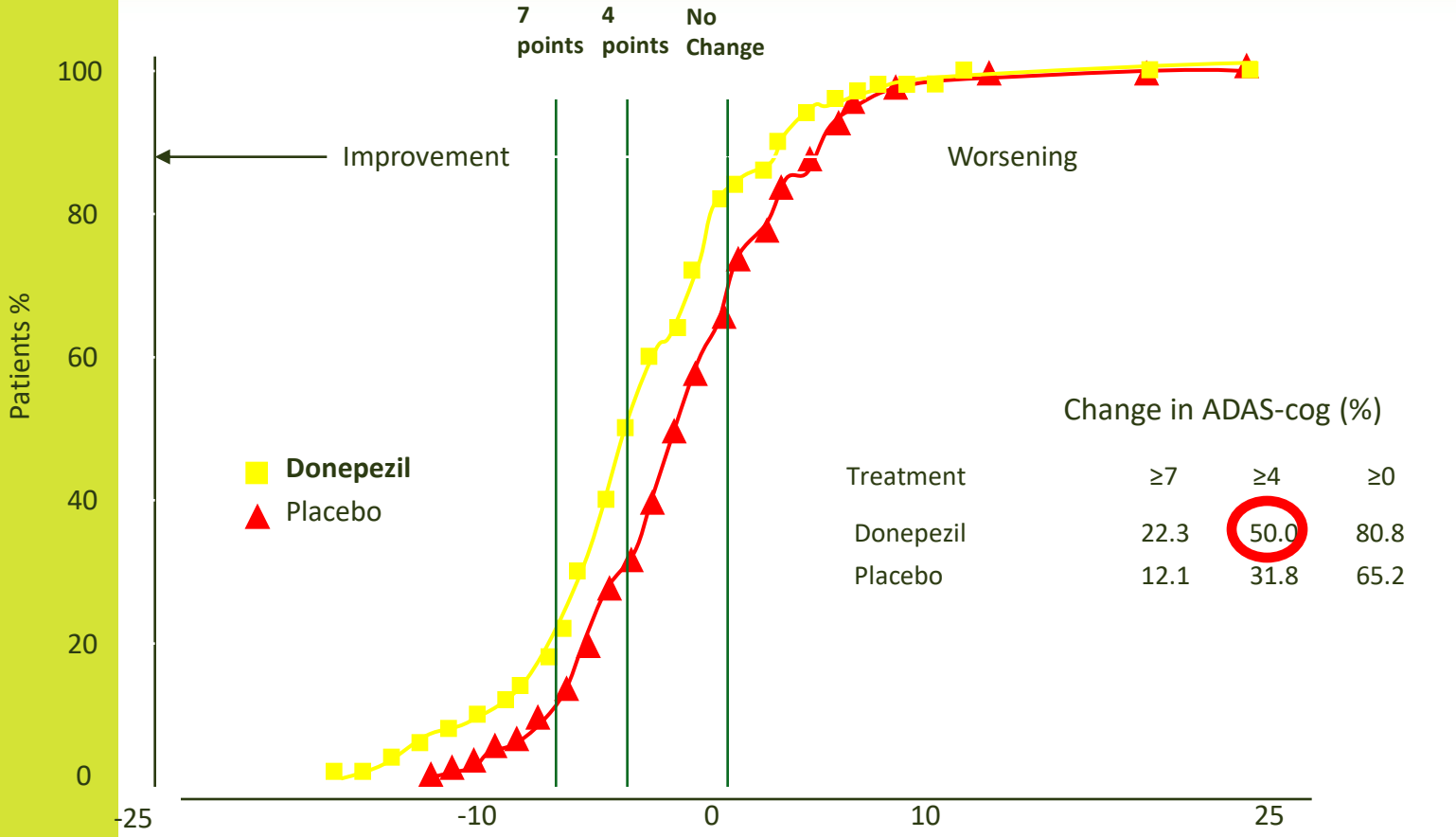
Modified ADAS-cog Score at Week 24



Neurology 2004;63;651-657

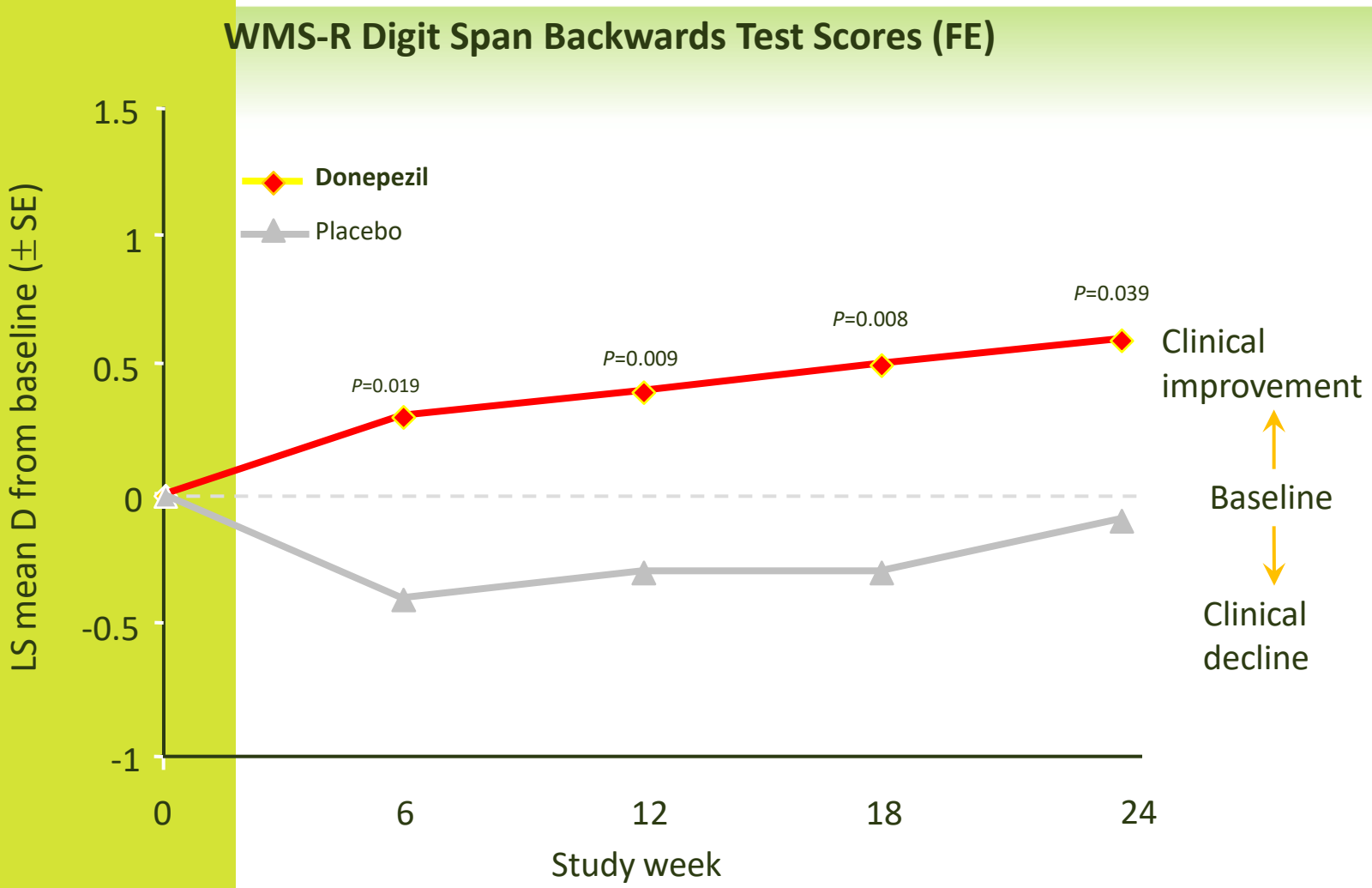
Result of MCI study (2)

Cumulative percentage of patients with specified changes from baseline in ADAS-cog



Neurology 2004;63;651-657

Result of MCI study (3)



Neurology 2004;63;651-657

Result of MCI study (4)

Table 2 *Changes in primary and secondary outcomes after 24 weeks*

	Donepezil			Placebo		
Psychometric test: change from baseline ± SE	ITT-LOCF, n = 130	ITT-OC, n = 89	FE, n = 83	ITT-LOCF, n = 132	ITT-OC, n = 110	FE, n = 100
Primary efficacy measure						
NYU Paragraph Test Delayed Recall	0.8 ± 0.3	1.1 ± 0.4	0.9 ± 0.4*	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.3
Secondary efficacy measures						
ADAS-cog/13 item (total)	−3.1 ± 0.5†	−3.3 ± 0.5*	−3.2 ± 0.5†	−1.2 ± 0.5	−1.9 ± 0.4	−1.6 ± 0.5
NYU Paragraph Test Immediate Recall	0.8 ± 0.3	1.2 ± 0.3*	1.1 ± 0.3*	0.2 ± 0.2	0.2 ± 0.2	0.3 ± 0.3
WMS-R Digit Span Backwards	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2*	0.1 ± 0.2	0.0 ± 0.2	−0.1 ± 0.2
Symbol Digit Modalities (no. correct)	4.4 ± 0.7	4.8 ± 0.9	4.9 ± 0.9*	2.7 ± 0.6	2.4 ± 0.6	2.2 ± 0.7

* $p \leq 0.05$ and † $p \leq 0.01$ vs placebo.

ITT = intent-to-treat population; LOCF = last observation carried forward; OC = observed cases analysis; FE = fully evaluable population; NYU = New York University; ADAS-cog = Alzheimer Disease Assessment Scale 13-item cognitive subscale; WMS-R = Wechsler Memory Scale–Revised.

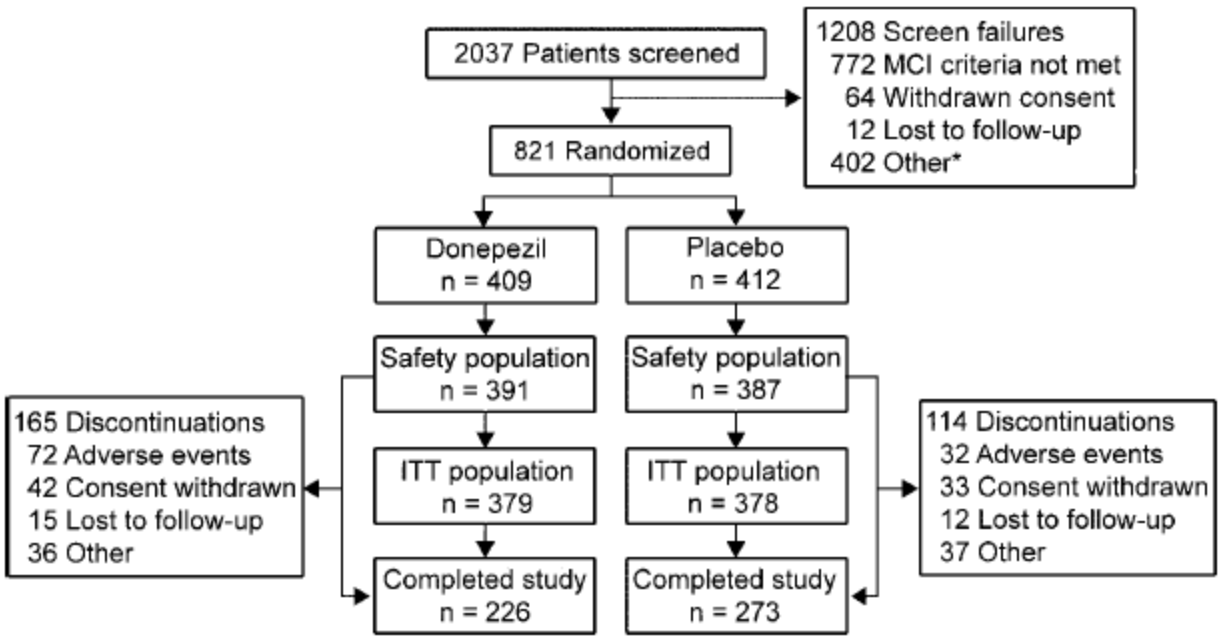
MCI Study (Neurology, 2009)

Donepezil treatment of patients with MCI

A 48-week randomized, placebo-controlled trial

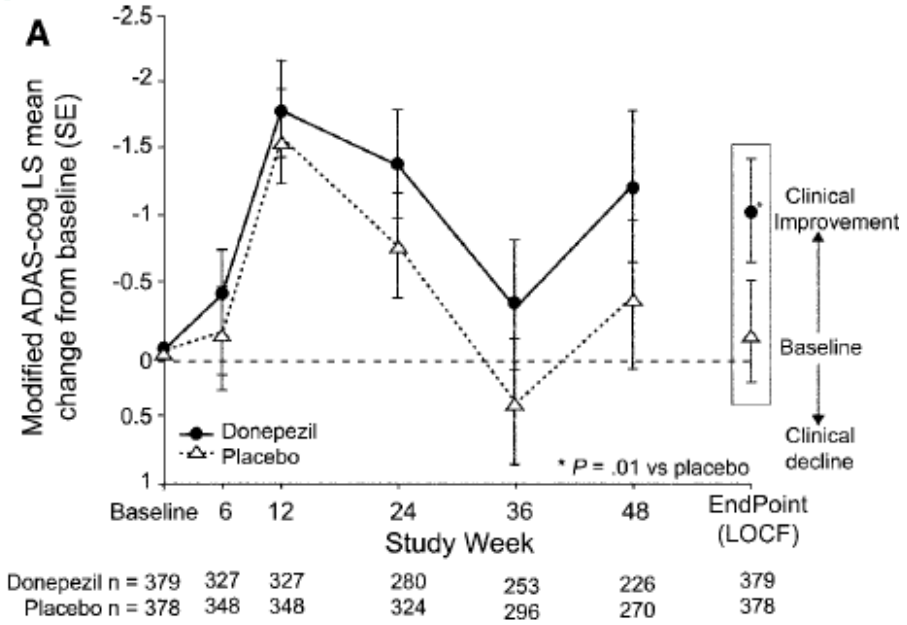
R.S. Doody, MD, PhD
S.H. Ferris, PhD
S. Salloway, MD, MS
Y. Sun, PhD
R. Goldman, PhD
W.E. Watkins, MS
Y. Xu, PhD
A.K. Murthy, PharmD

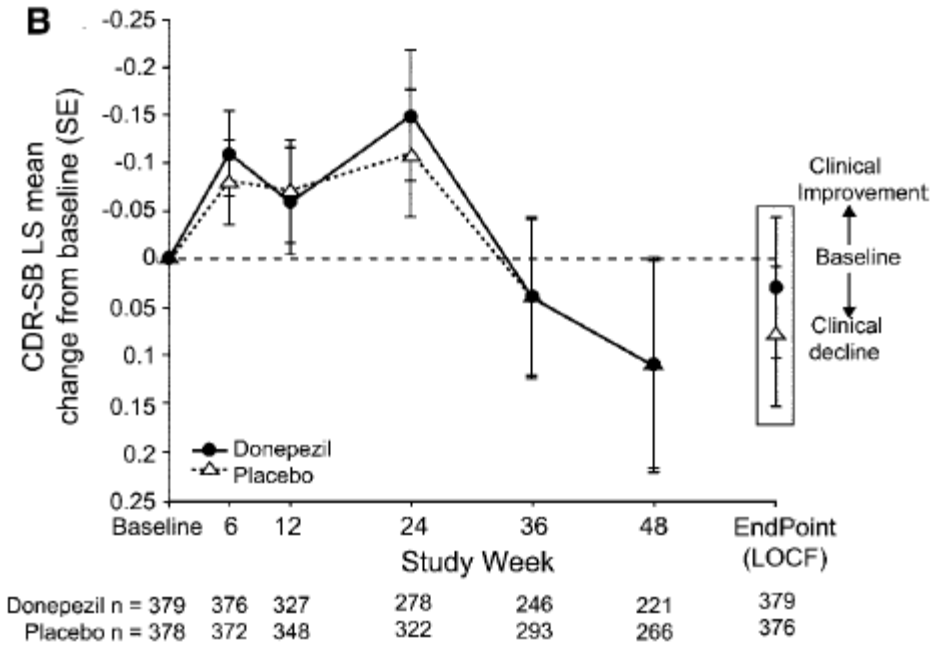
Figure 1 **Subject disposition**



Results (neurology, 2009)

Figure 2 **Efficacy of treatment with donepezil 10 mg in patients with mild cognitive impairment**





ARICEPT for Mild Cognitive Impairment (ADCS group)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2005 VOL. 352 NO. 23

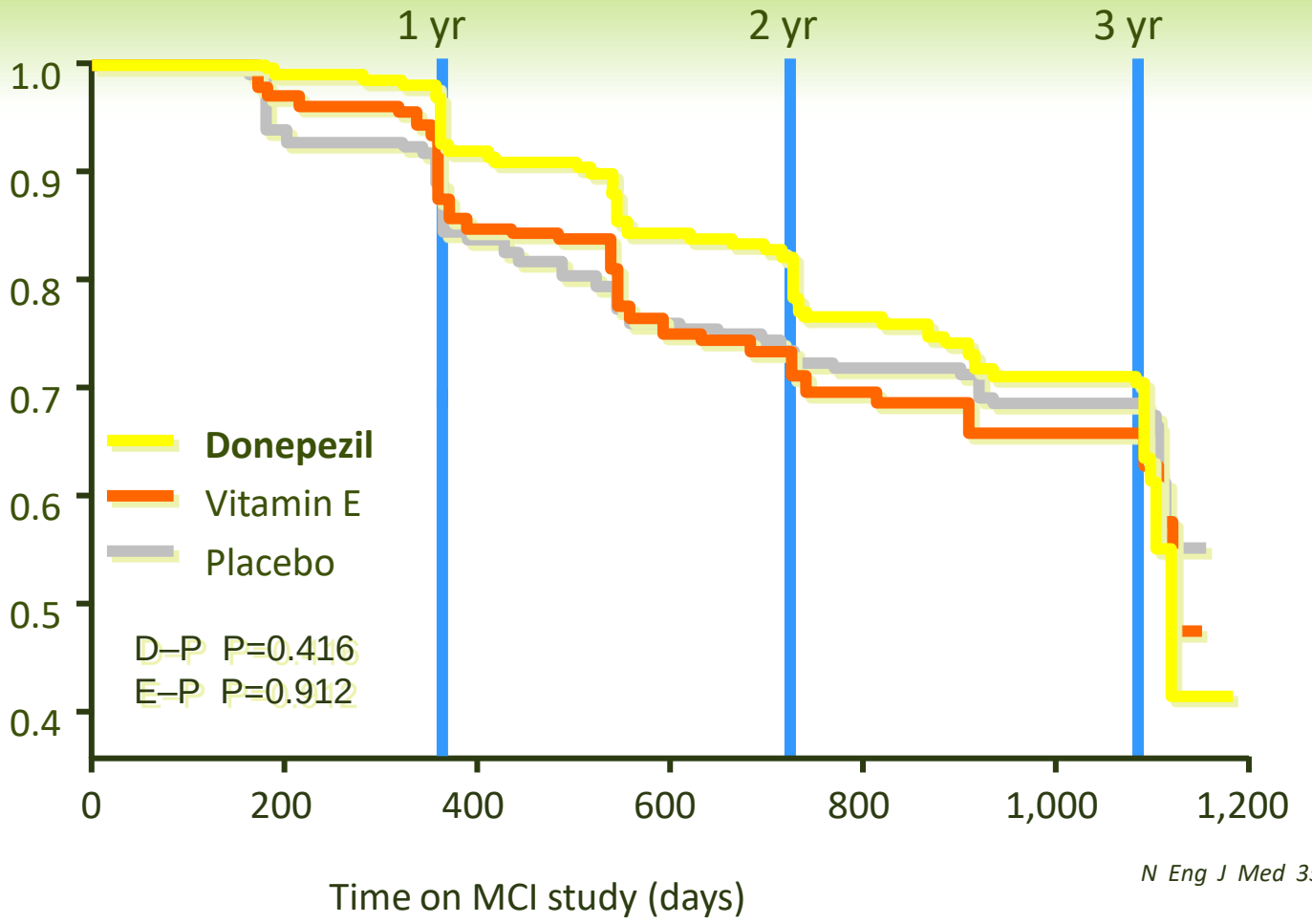
Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

- *Design*: 3 years, randomized, multicenter, randomized, double-blind, placebo-controlled, parallel study

  (→ Open-label donepezil after conversion to AD)

ARICEPT DELAYS CONVERSION TO DEMENTIA (OVERALL PROGRESSION RATE TO AD : 16% PER YEAR)



N Eng J Med 352;23

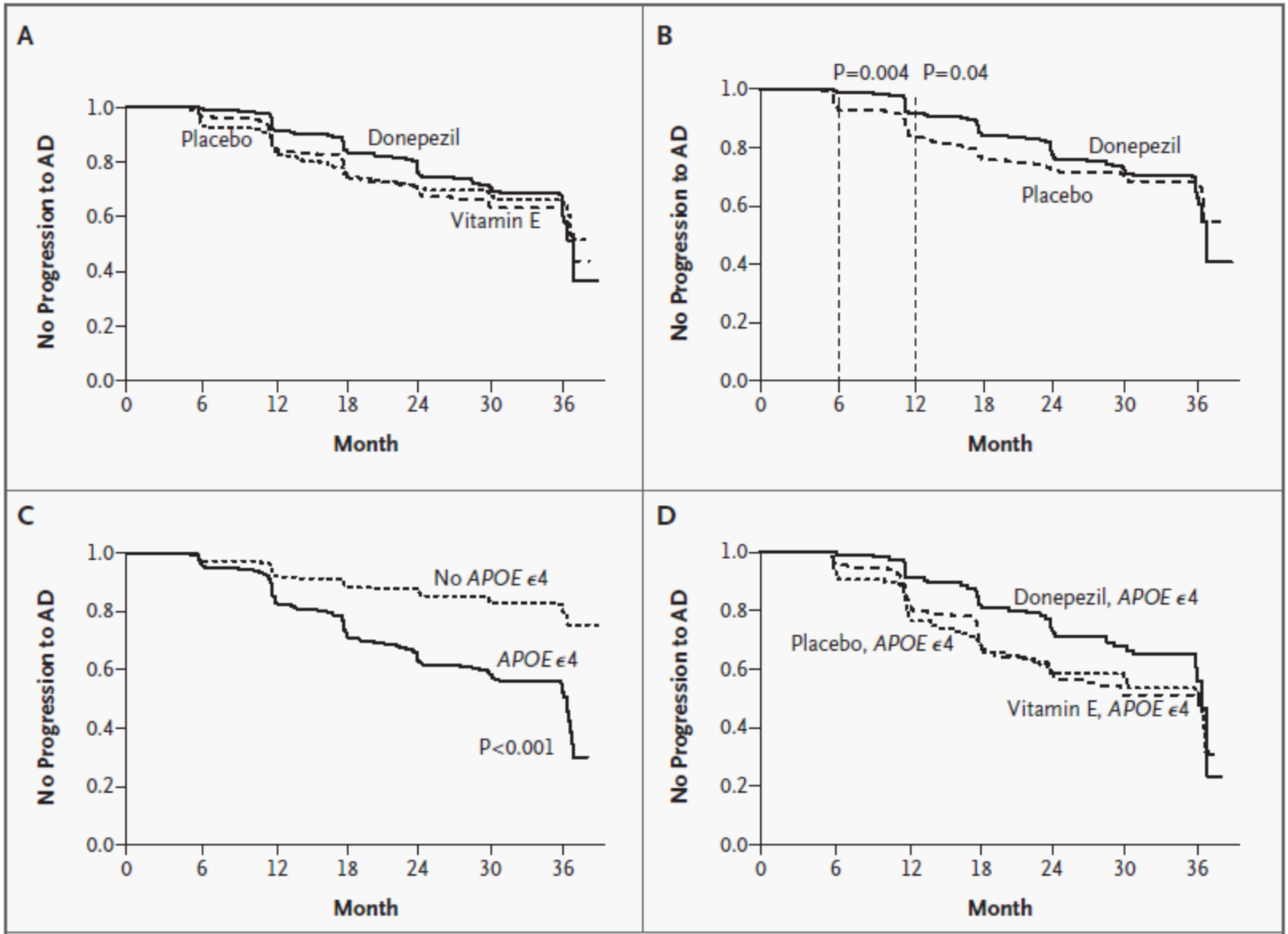


Figure 1. Kaplan–Meier Estimates of the Rate of Progression from Mild Cognitive Impairment to Alzheimer's Disease (AD).

Benefit for early stage AD patients

Efficacy of Donepezil in Early-Stage Alzheimer Disease

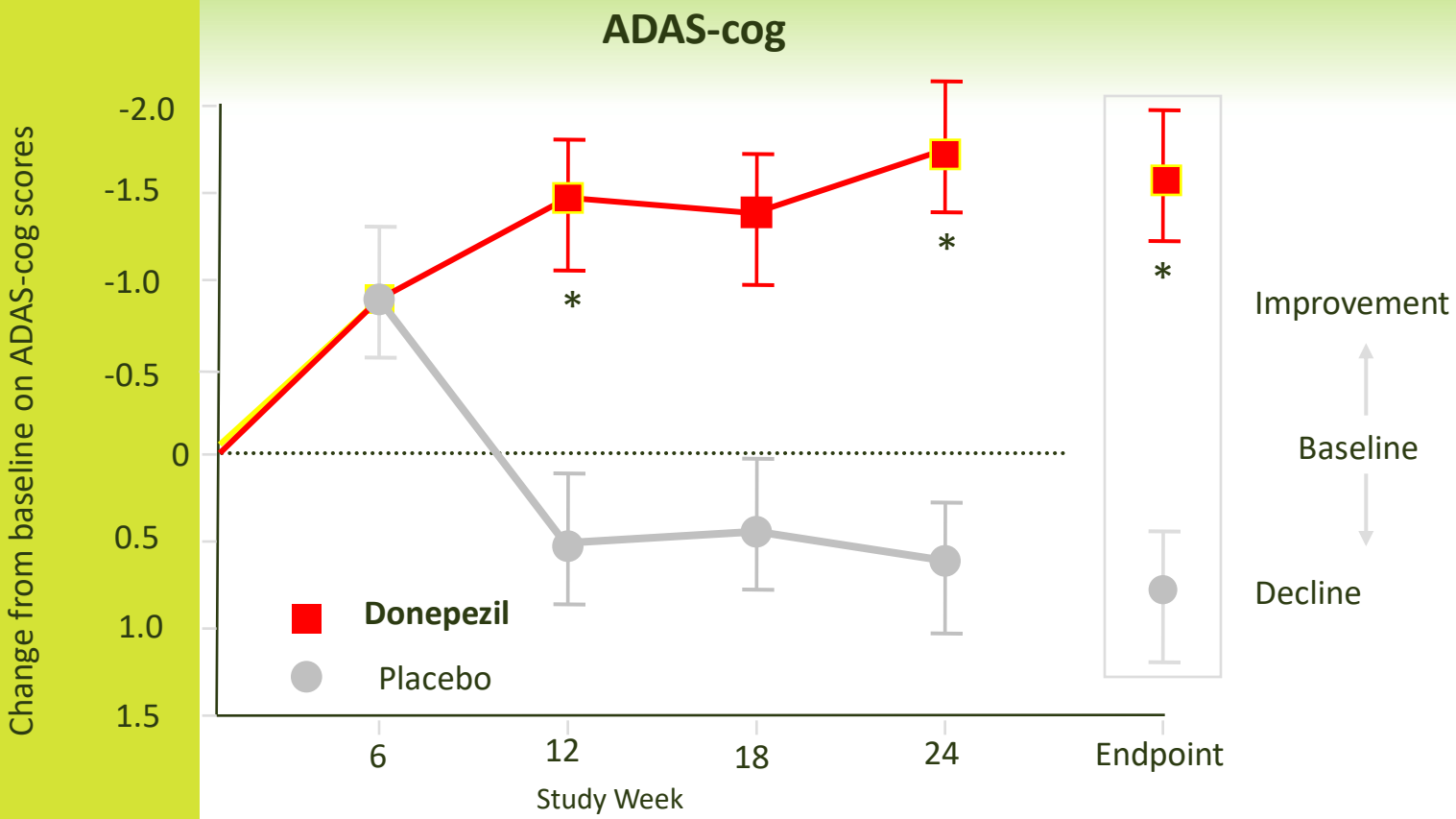
A Randomized Placebo-Controlled Trial

Ben Seltzer, MD; Parvaneh Zolnouni, MD; Margarita Nunez, MD; Robert Goldman, PhD; Dinesh Kumar, MA; John Ieni, PhD; Sharon Richardson, PhD; for the Donepezil "402" Study Group

Arch Neurol. 2004;61:1852-1856

- *Design*: 24-week, multicenter, randomized, double-blind, placebo-controlled study
- *Patients*: A total of 153 patients with early AD (21≤ MMSE score ≤26) were enrolled and randomized to receive either donepezil or placebo

Result of Early AD study (1)

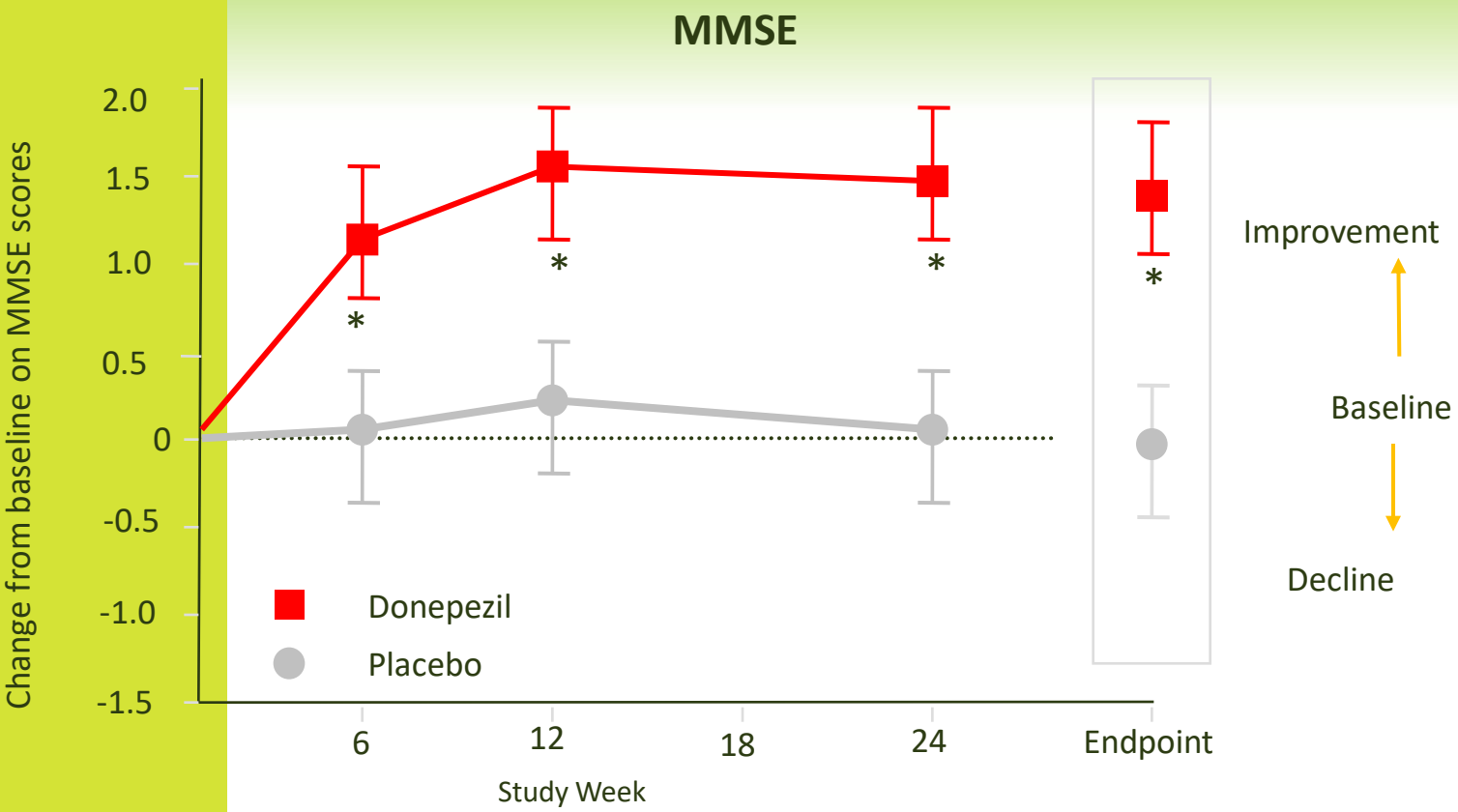


***Improvement ≥4 points : 16% placebo, 37% donepezil**

***Improvement ≥7 points : 7% placebo, 10% donepezil**

Arch Neurol. 2004;61:1852-1856

Result of Early AD study (2)



*** Improvements from week 6 (P=.02) through week 24 (P=.03)**

*** Difference 1.8 points (P = .002) at the end point**

Arch Neurol. 2004;61:1852-1856

Mild to Moderate AD (Nordic study 2001), 2006

3-Year Study of Donepezil Therapy in Alzheimer's Disease: Effects of Early and Continuous Therapy

B. Winblad[a] A. Wimo[b] K. Engedal[c] H. Soininen[d] F. Verhey[e]
G. Waldemar[f] A.-L. Wetterholm[g] A. Haglund[g] R. Zhang[h] R. Schindler[h]
for the Donepezil Nordic Study Group

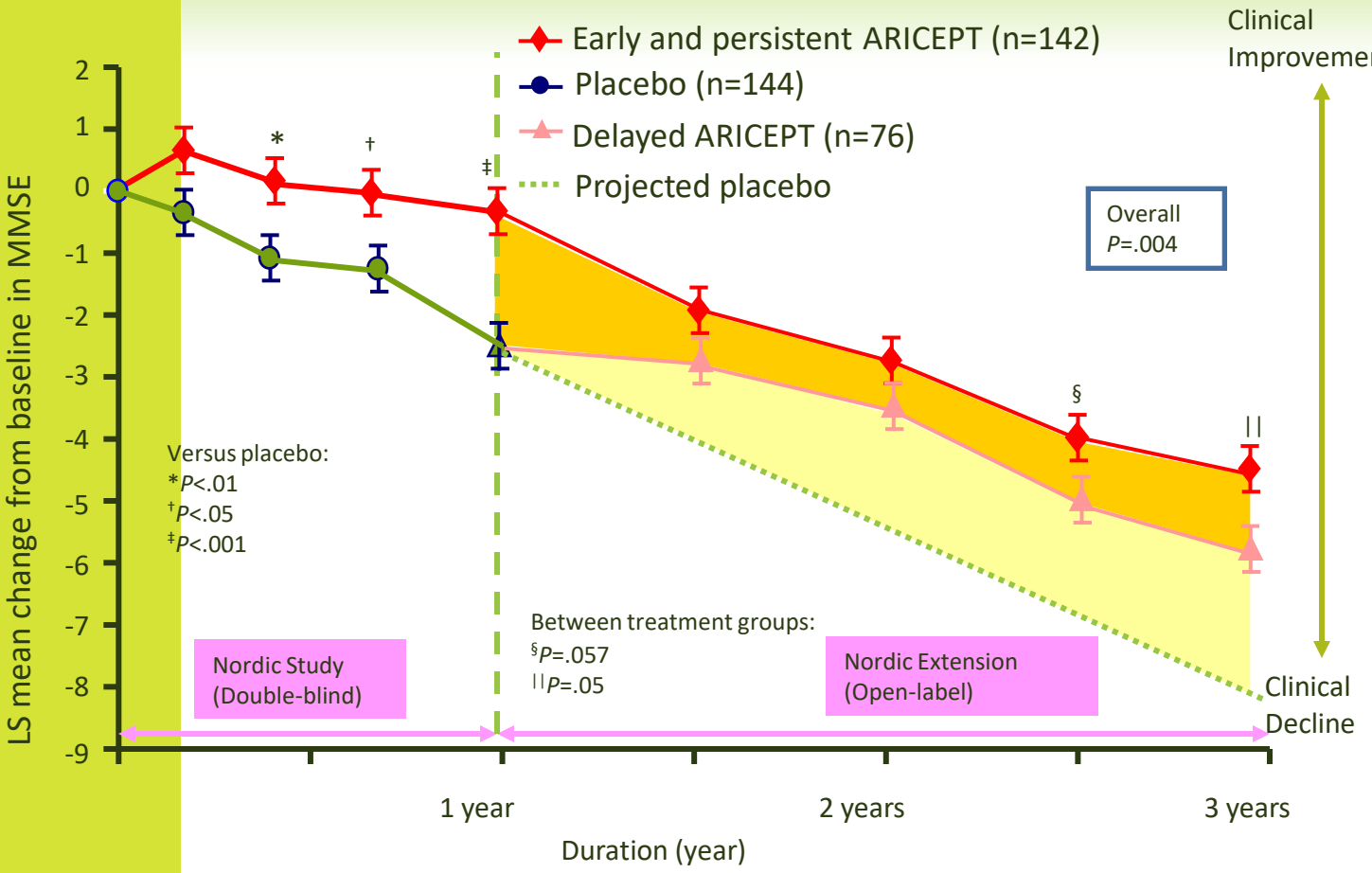
- *Design*: 52-week, double-blind phase (1 year)→ open-label extension (2 year)

☞ total 3 year nordic extension study

- *Patients*: N=286 with possible or probable AD (MMSE 10~26)

  - donepezil 5mg/day for 4 weeks, followed by 10mg/day

Benefit of early and persistent treatment



Efficacy of ARICEPT for Moderate to Severe AD

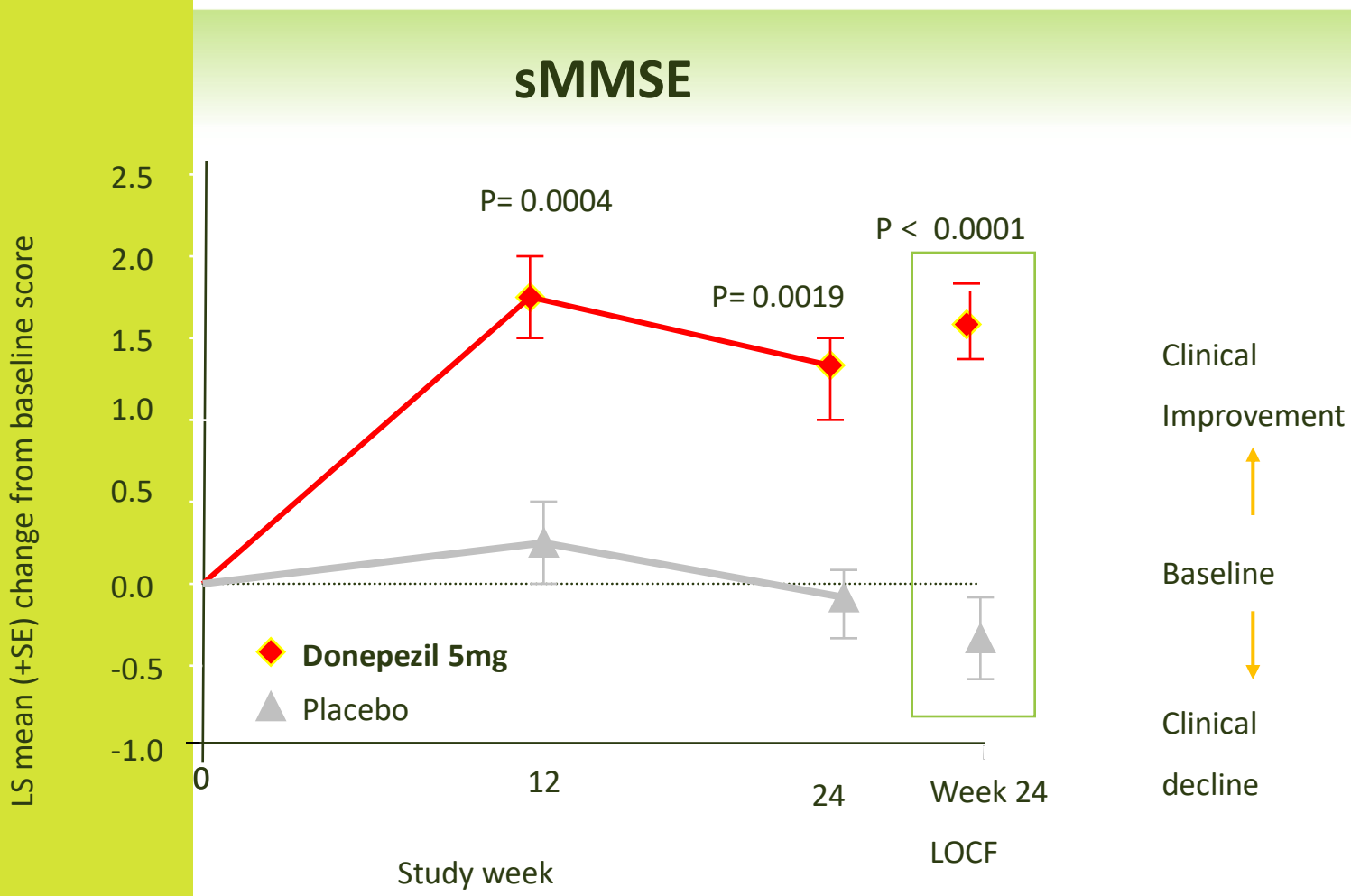
A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease

H. Feldman, MD; S. Gauthier, MD; J. Hecker, MD, B. Vellas, MD, PhD; P. Subbiah, MD; E. Whalen, PhD, and the Donepezil MSAD Study Investigators Group*

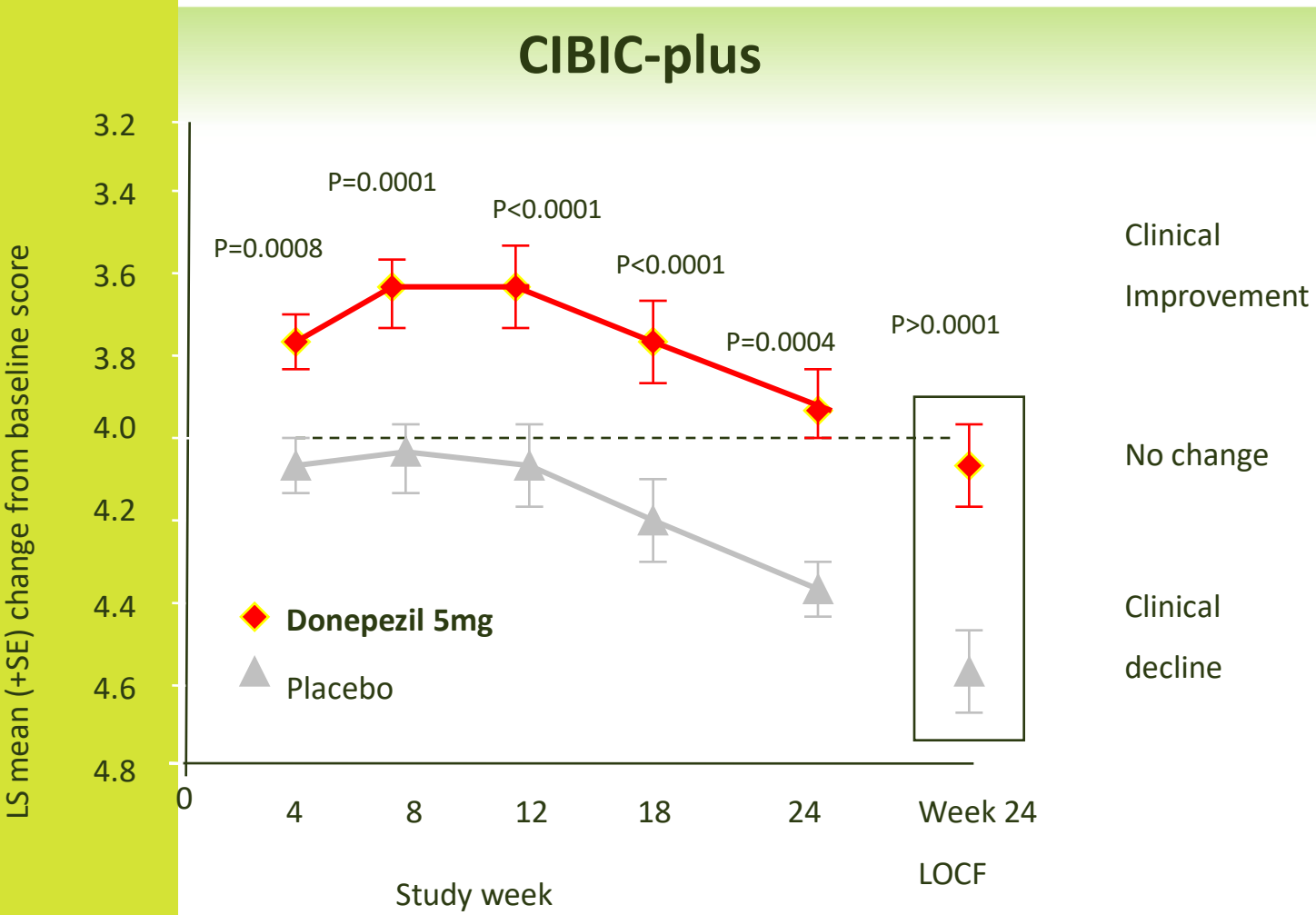
NEUROLOGY 2001;57:613–620

- *Design*: 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study
- *Patients*: 290 patients (sMMSE 5 to 17) were randomized to receive either donepezil or placebo

Result of Moderate to Severe AD (1)



Result of Moderate to Severe AD (2)



Efficacy of ARICEPT for Severe AD

INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2005; **20**: 559–569.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1325

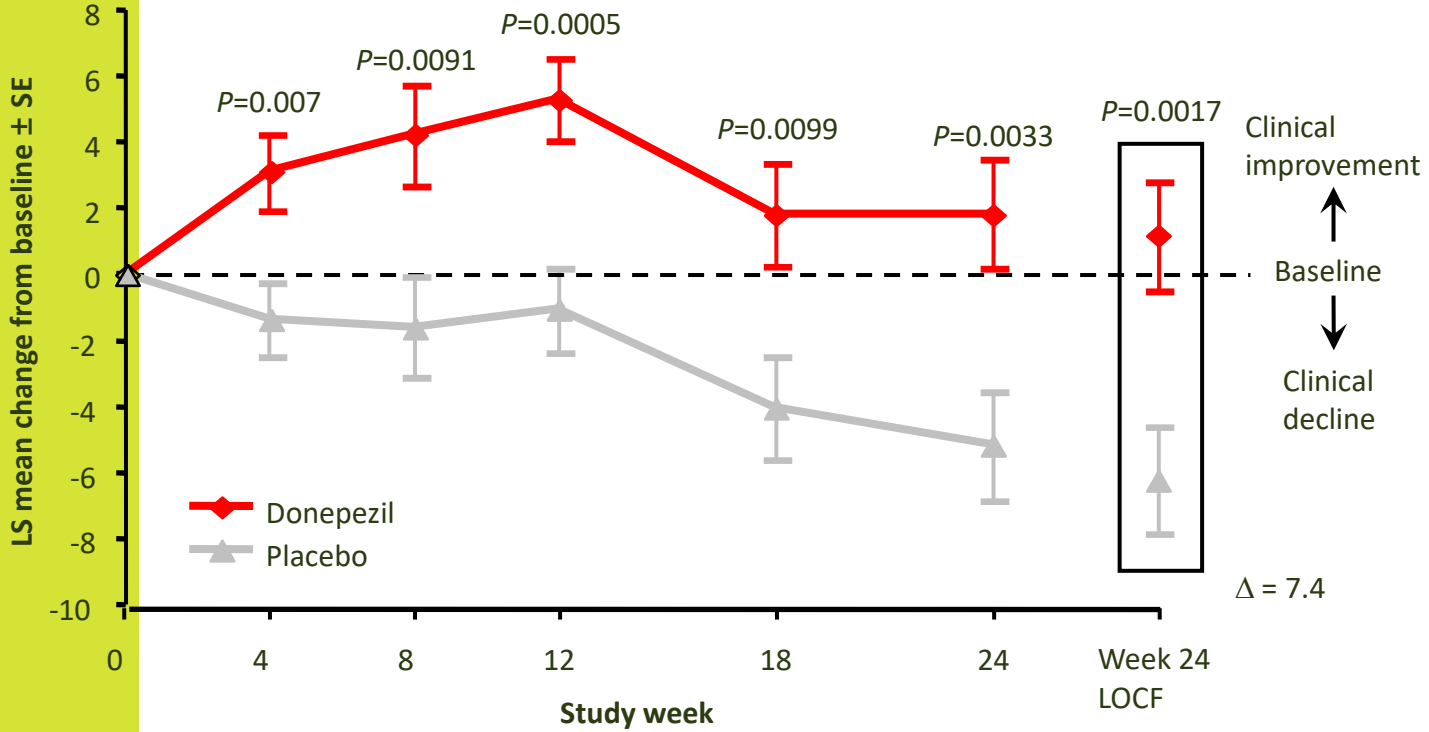
Efficacy and safety of donepezil in patients with more severe Alzheimer's disease: a subgroup analysis from a randomized, placebo-controlled trial

Howard Feldman[1]*, Serge Gauthier[2], Jane Hecker[3], Bruno Vellas[4], Yikang Xu[5], John R. Ieni[6], Elias M. Schwam[7] and the Donepezil MSAD Study Investigators Group

- ***Design***: 24-week, multicenter, randomized, double-blind, placebo-controlled study
- ***Patients***: A total of 145 patients with more severe AD (sMMSE 5 to 12) were enrolled and randomized to receive either donepezil or placebo

Result: SIB

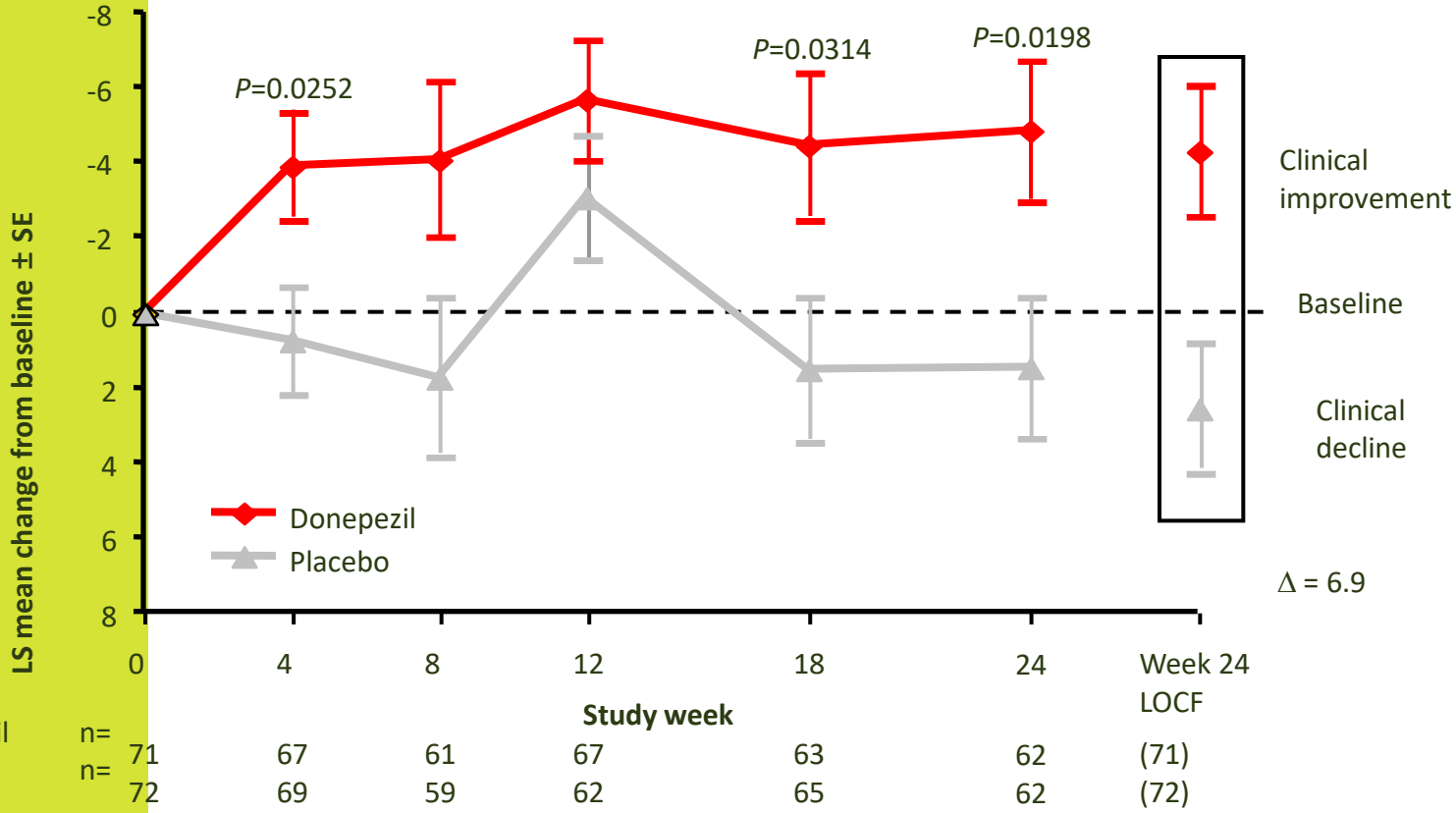
SIB



Donepezil	n= 71	67	61	66	63	62	(71)
Placebo	n= 73	70	61	62	65	63	(73)

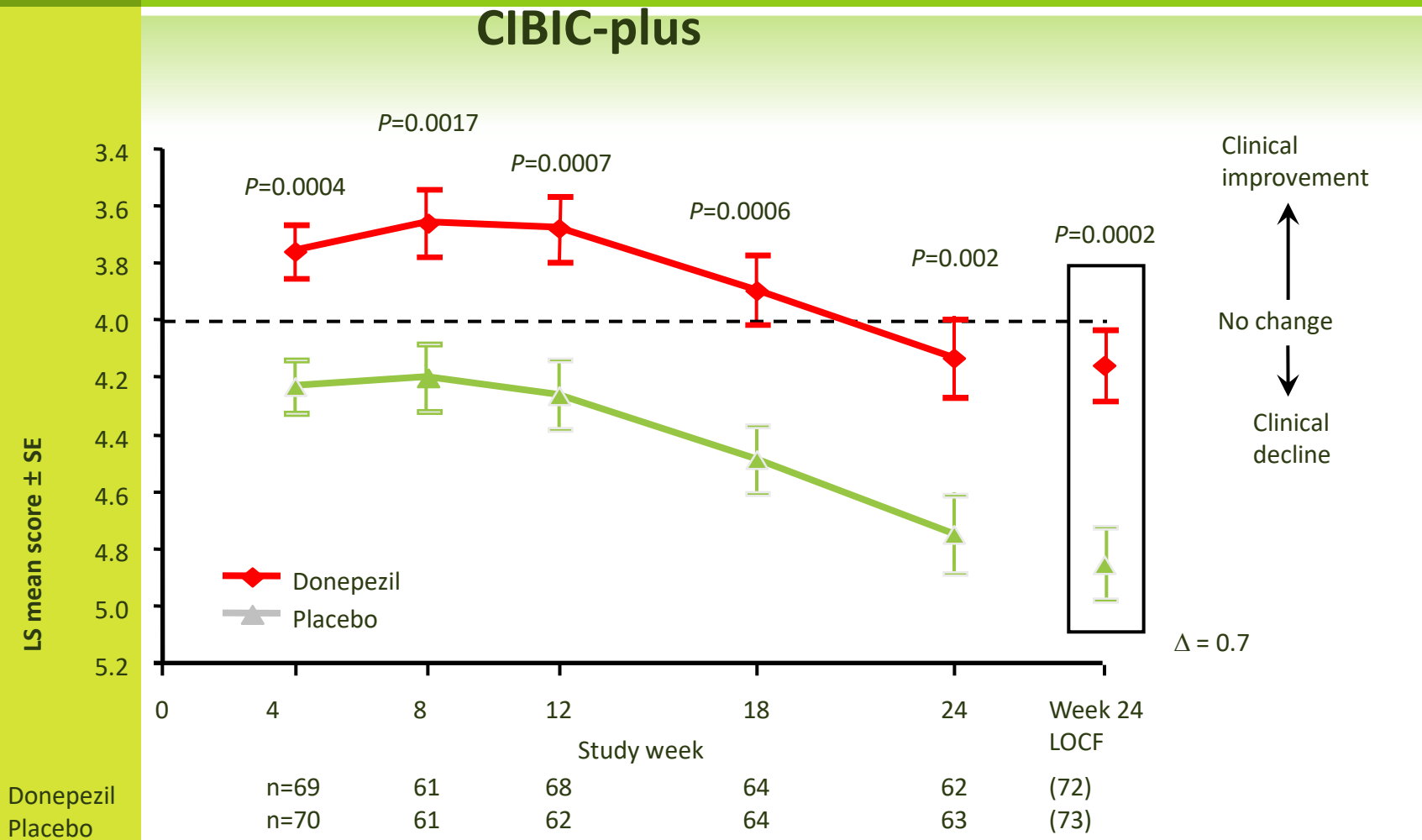
Result: NPI

12-Item NPI Total



Donepezil	n=	71	67	61	67	63	62	(71)
Placebo	n=	72	69	59	62	65	62	(72)

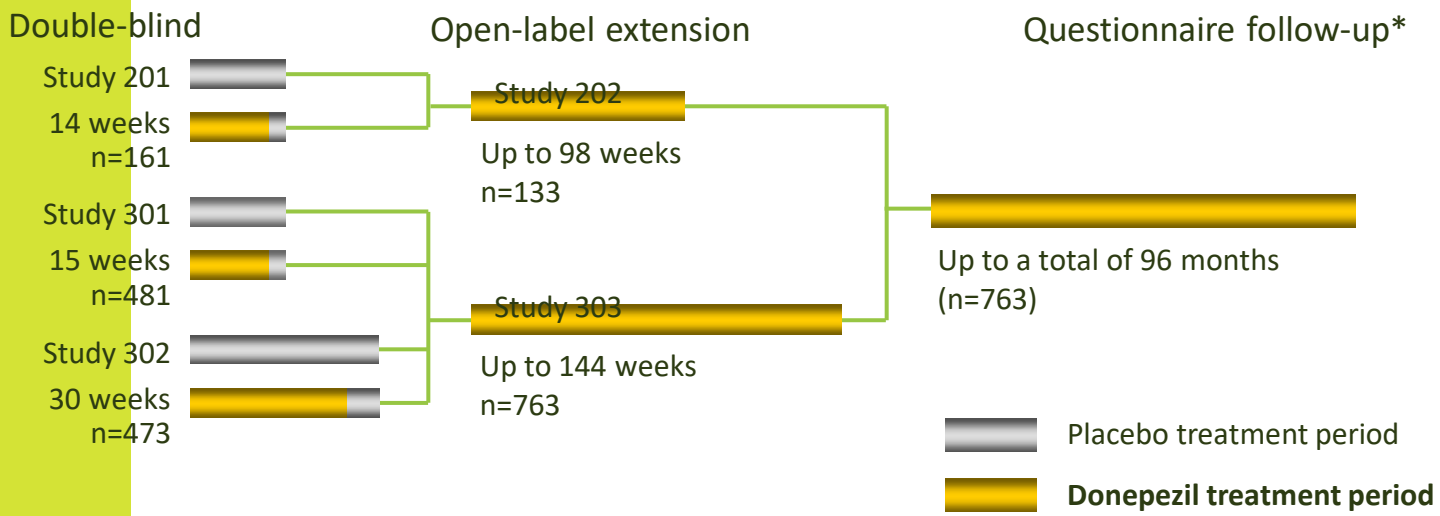
Result: CIBIC-plus



Efficacy of ARICEPT for DNHP (J Am Geriatr Soc, 2003)

Donepezil Is Associated with Delayed Nursing Home Placement in Patients with Alzheimer's Disease

David S. Geldmacher, MD,† George Provenzano, PhD,‡ Thomas McRae, MD,§ Vera Mastey, MS,‖ and John R. Ieni, PhD¶*

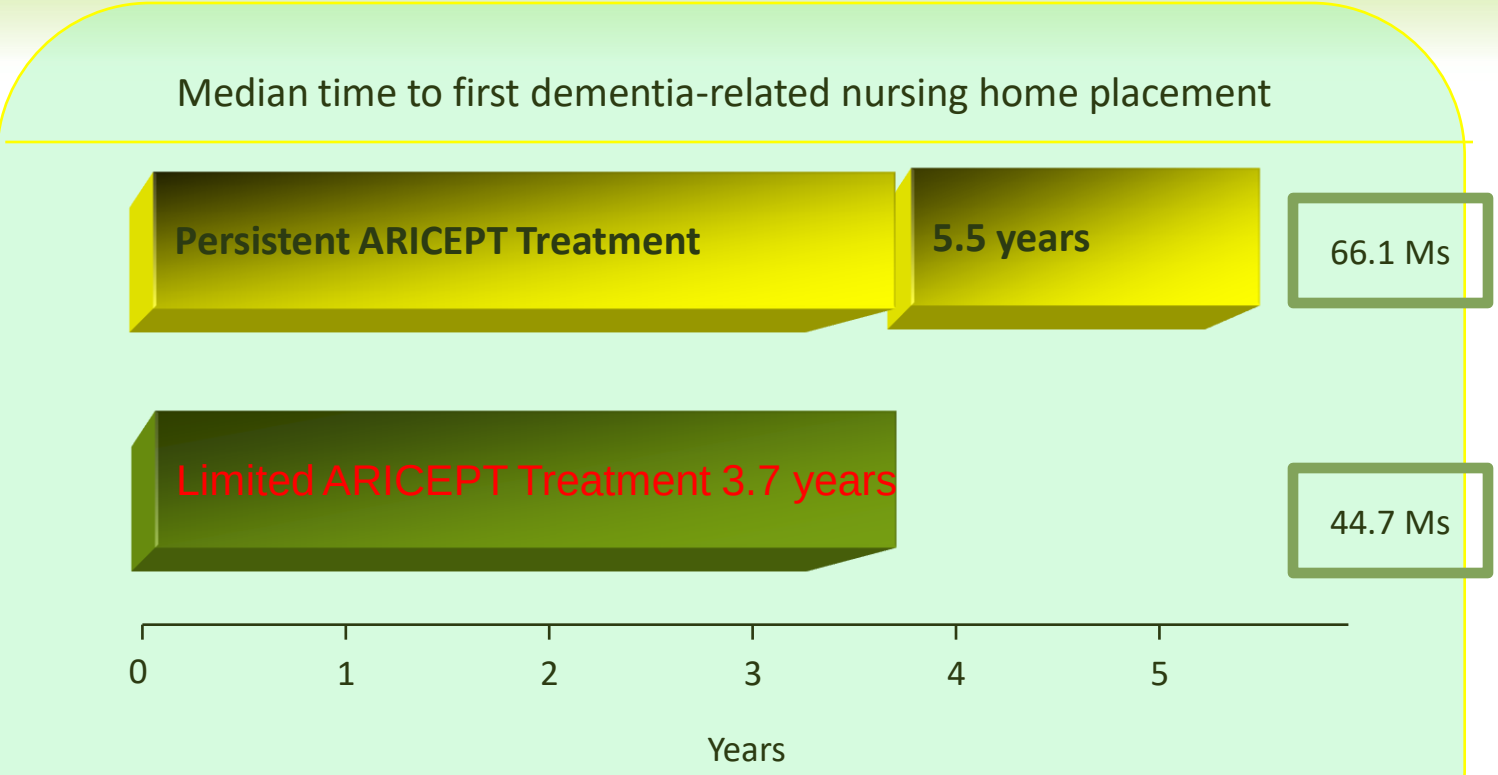


2 year delay to NHP

Permanent NHP

Minimal use Group : 45.5 Ms

Maximal use group : 63.0 Ms



Keep patients in the community for more than 5 years

Geldmacher DS et al. J Am Geriatr Soc. 2003;51:937-944

Long-term efficacy of ARICEPT

ELSEVIER

European Neuropsychopharmacology 10 (2000) 195–203

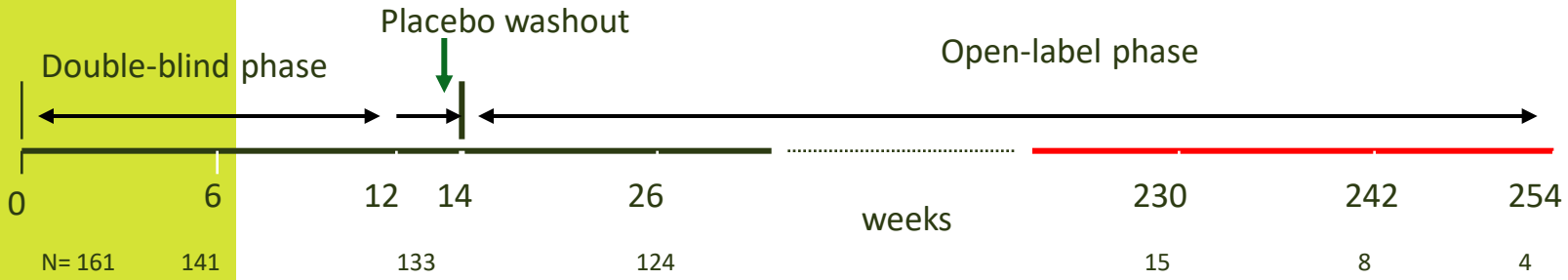
EUROPEAN NEURO-PSYCHOPHARMACOLOGY

www.elsevier.com/locate/euroneuro

Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of a US multicentre open-label study

S.L. Rogers[a,*], R.S. Doody[b], R.D. Pratt[c], J.R. Ieni[c]

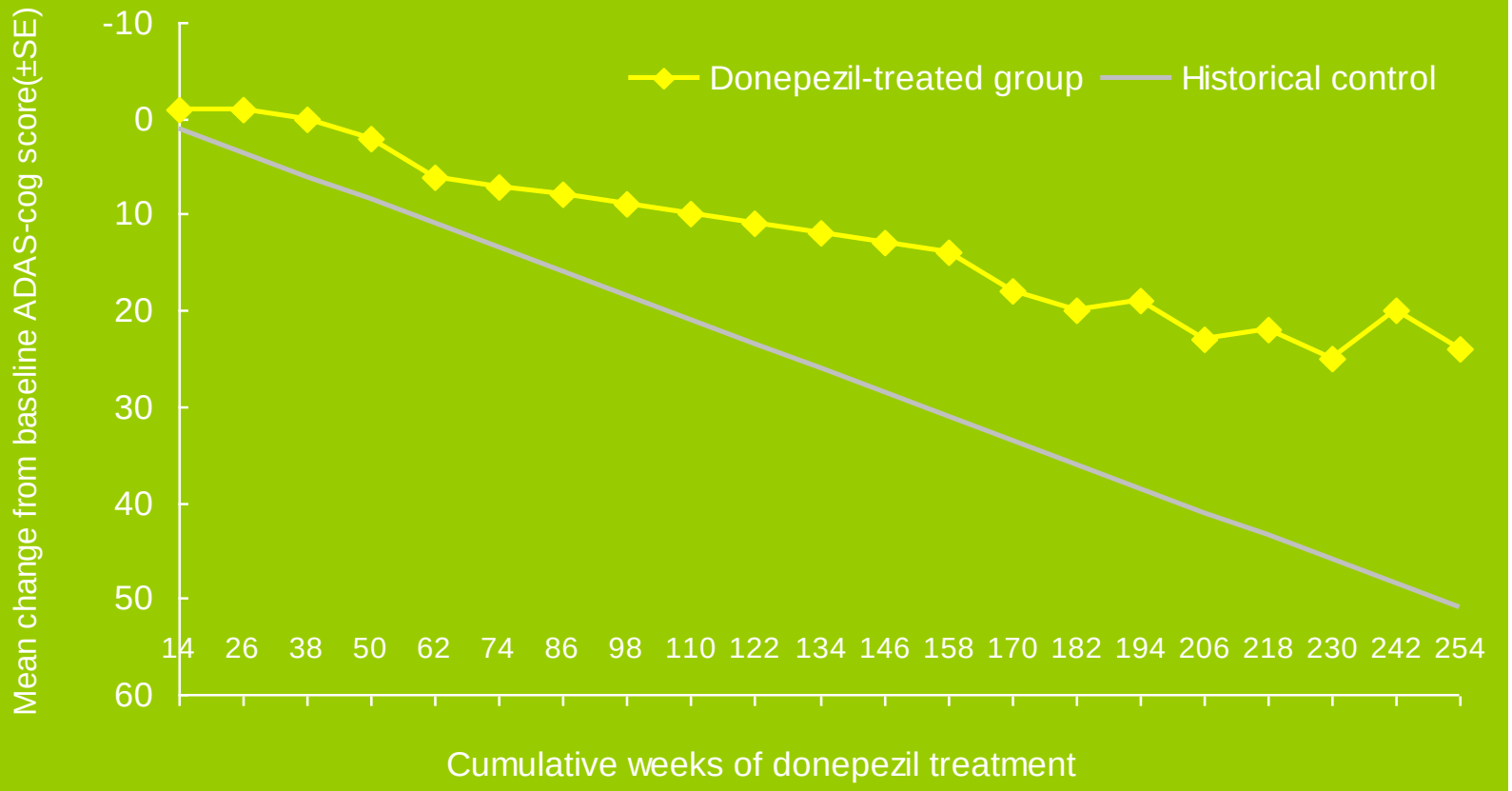
- *Design*: for up to cumulative 254 weeks *(4.9 years)*



Result of long-term efficacy of ARICEPT

→ *over 254 cumulative weeks*

ADAS-cog



Summary

- ARICEPT® significantly improved cognition, global function and behavioral symptoms in patients with mild to severe AD.
- ARICEPT® shows the benefit in all course of AD patients
- ARICEPT® is safe and well tolerate in severe AD patients
- ARICEPT® is a only approved AChE-Inhibitors in severe AD and VaD

Aricept is the first choice of dementia treatment

ARICEPT IS THE ONLY AChE-I FOR ALL STAGE OF AD