Milano, 23 novembre 2012

«L'importanza
della risposta
dose-dipendente»

SIMPOSIO SIGG-SINeG-AIP
COME MIGLIORARE L'APPROCCIO TERAPEUTICO AL PAZIENTE CON MALATTIA DI ALZHEIMER?

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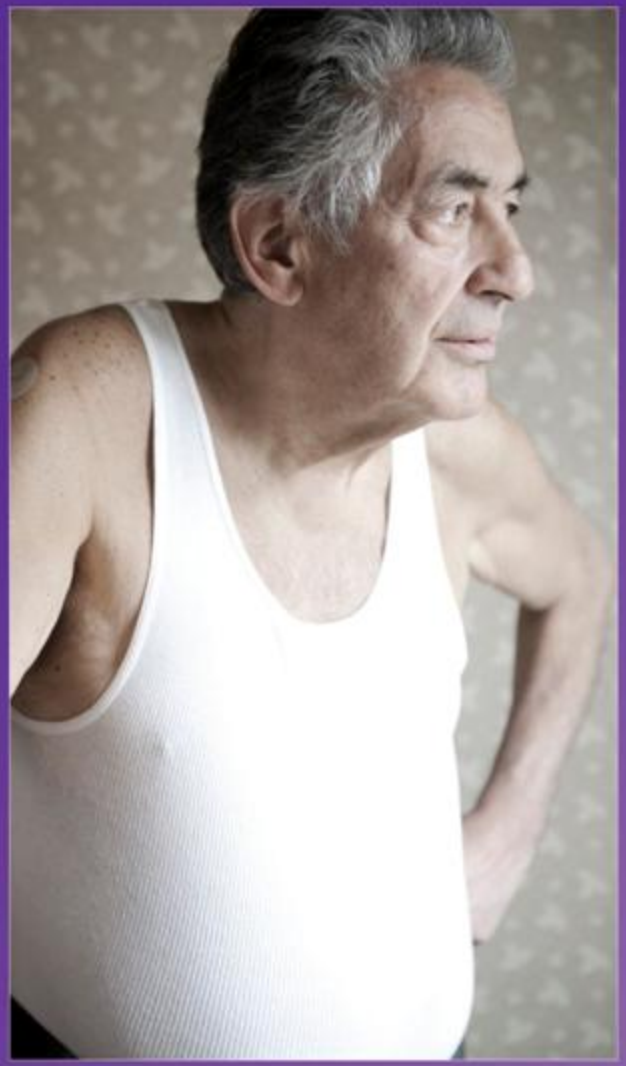
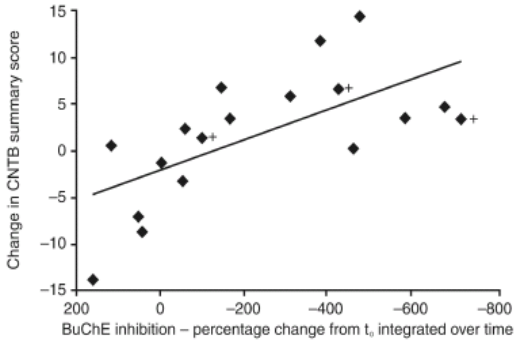
ASSOCIAZIONE ITALIANA PSICOGERIATRIA



Efficacy and safety of the 13.3 mg/24 h rivastigmine patch: The OPtimizing Transdermal Exelon In Mild-to-moderate Alzheimer's disease (OPTIMA) study

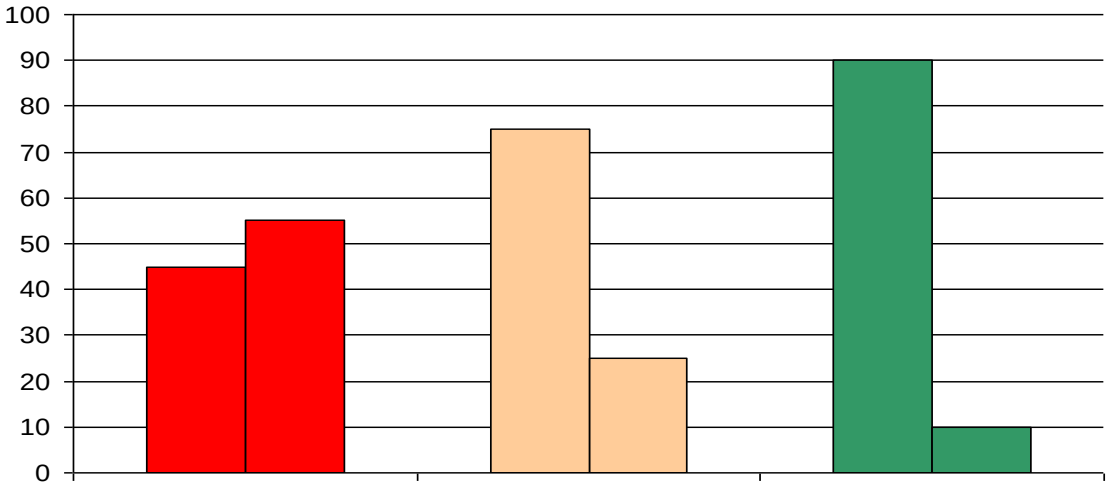
A Santoro et al.
CNS Drugs 2010

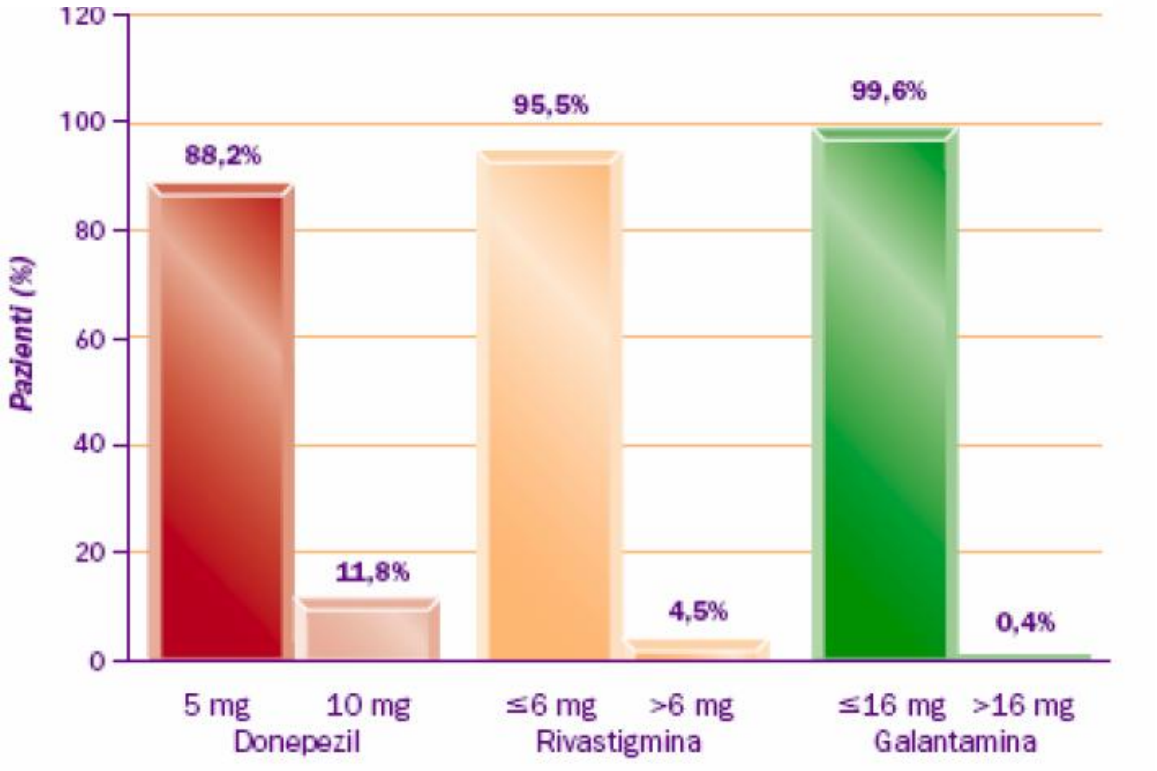


*Subjects 1,006, 1,009, 1,017: time –0.4 (hours) used as pre-dose (0) reading

2. Correlation between BuChE inhibition in CSF and change in CNTB s score following rivastigmine treatment ($r = -0.65$, n = 18, $p < 0.01$)

Darreh-Shori et al. 2002,
Giacobini et al. 2002



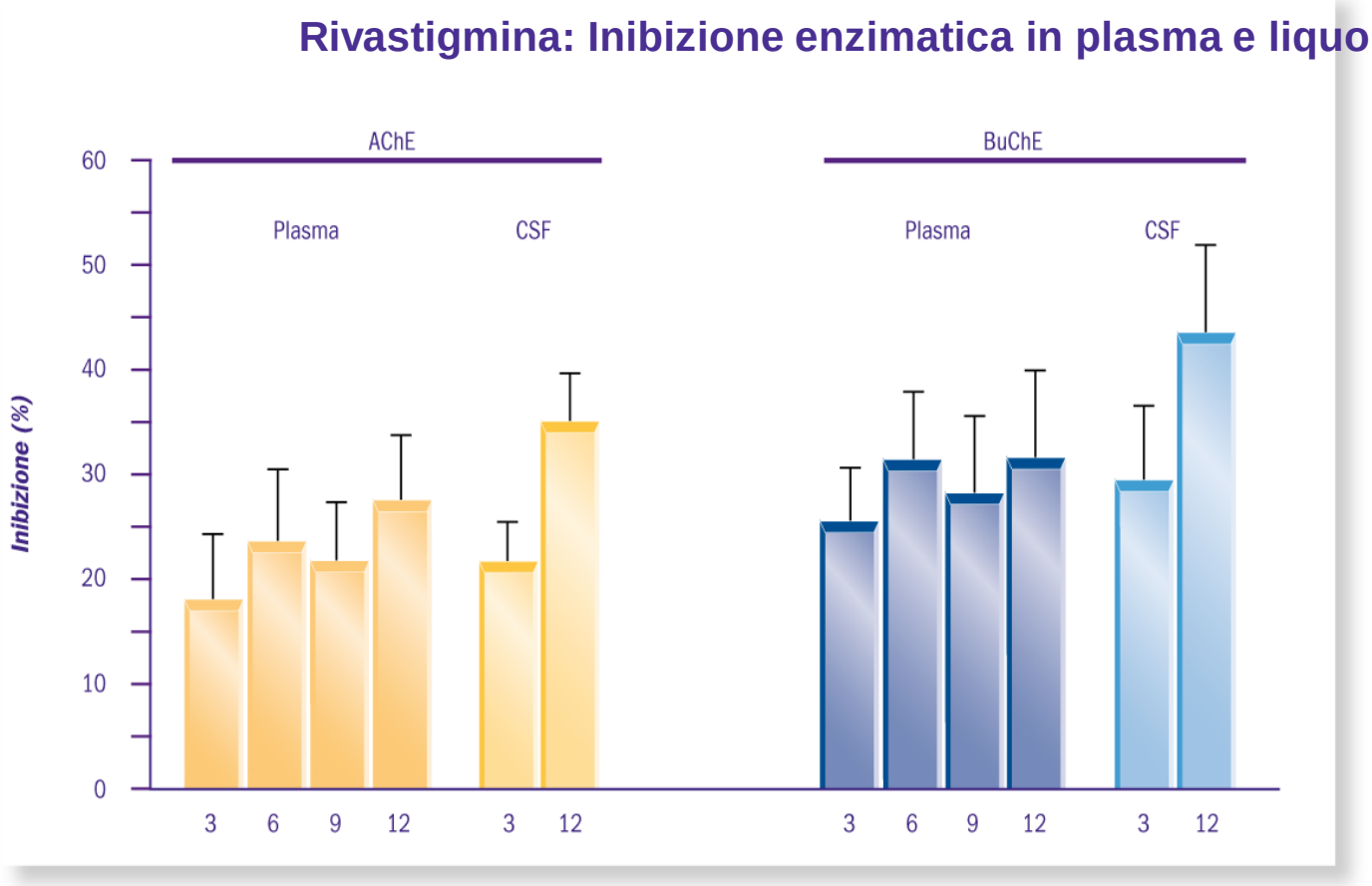


Raschetti et al., 2005

Rivastigmina e l'inibizione delle colinesterasi in pazienti AD

Effetto dose-dipendente

Rivastigmina: Inibizione enzimatica in plasma e liquor



AChE: acetilcolinesterasi; BuChE: butirrilcolinesterasi.
Inibizione media delle colinesterasi in campioni di plasma e CSF, ottenuti da pazienti con AD trattati con rivastigmina per 12 mesi.

Studio a 12 mesi, in aperto, condotto su 11 pazienti AD con punteggio MMSE 24,9±0,8, trattati con rivastigmina due volte al giorno a dosaggi crescenti da 1,5 mg/bid ogni 2 settimane, fino ad una dose massima di 12 mg/die.

Darreh-Shori T et al. Neurology. 2002;59(4):563-572.

Defining optimal treatment with cholinesterase inhibitors in Alzheimer's disease

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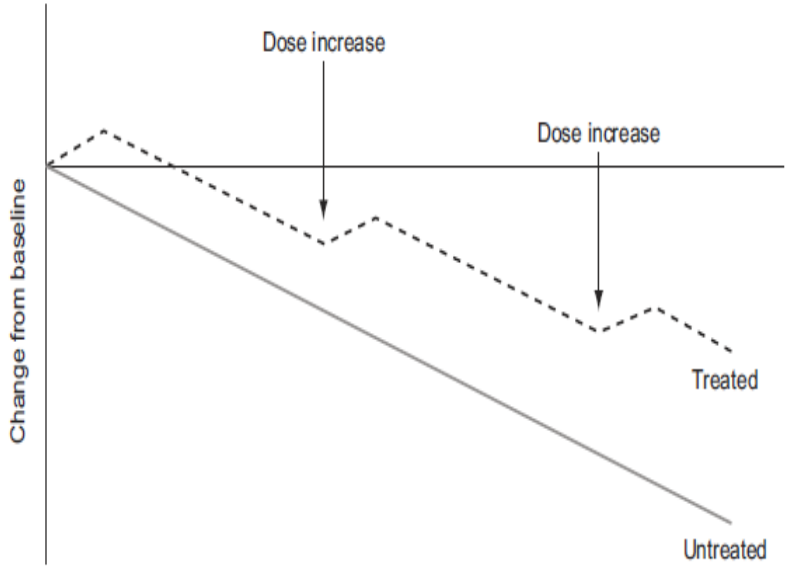
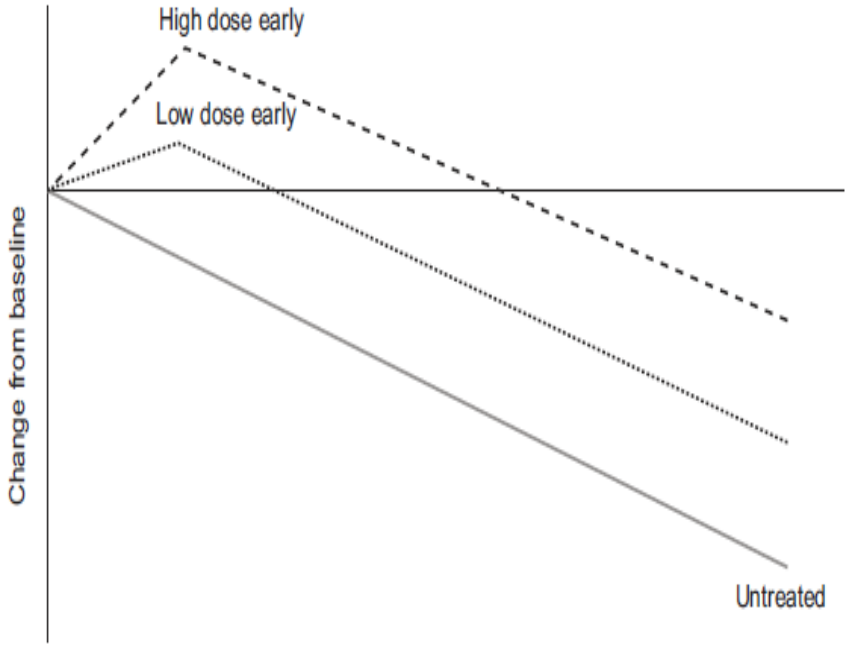
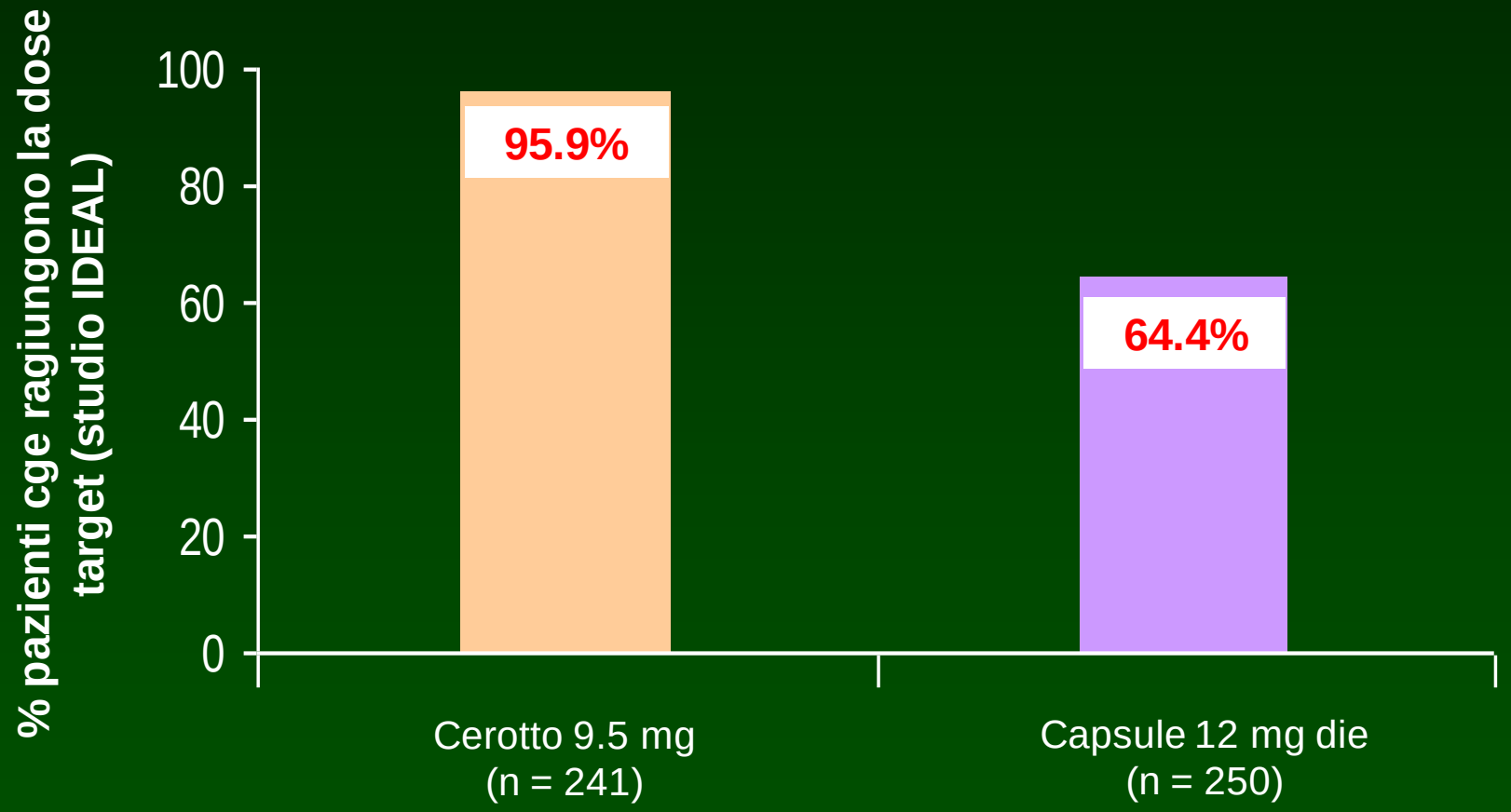
Alzheimer's & Dementia





Beneficio del dosaggio massimo da subito

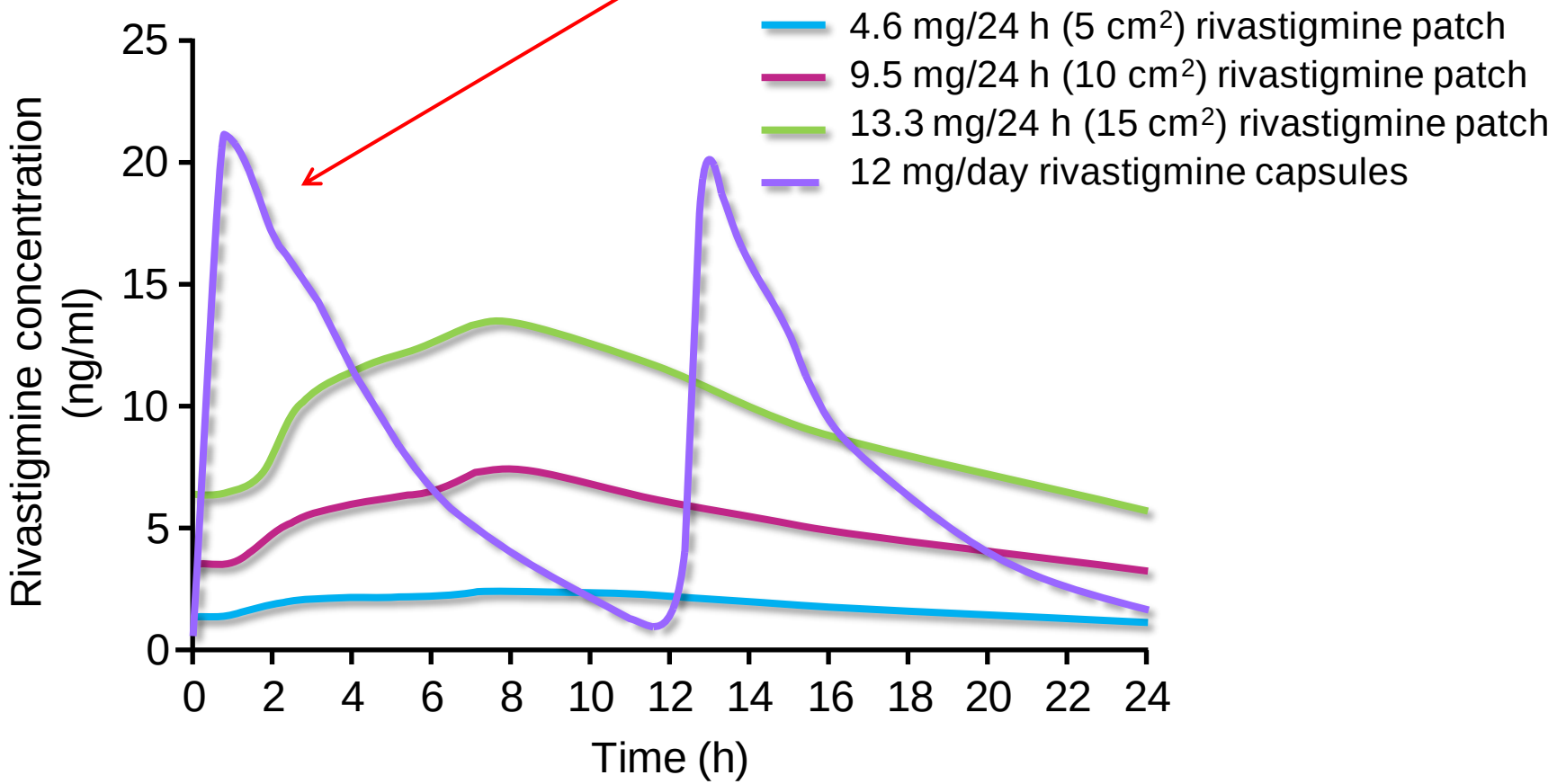
Raggiungimento del dosaggio ottimale: via transdermica vs. orale (IDEAL study)



Winblad B et al., Int J Geriatr Psychiatry, 2007

Pharmacokinetic profiles: rivastigmine capsules and patch[1,2]

Massima concentrazione in tempi rapidi



Plasma concentrations obtained with 13.3 mg/24 h patch suggest the higher dose patch may provide greater exposure than the currently approved maintenance dose of 9.5 mg/24 h but with a lower incidence of GI AE than would be expected with a comparable oral dose

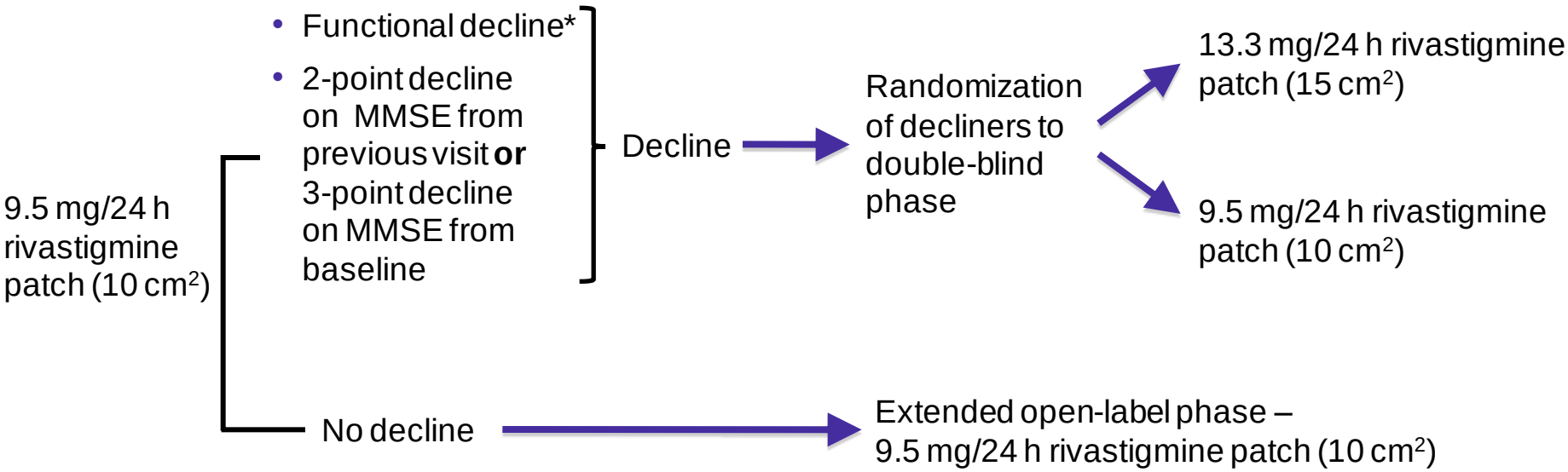
[1]Mercier F *et al. Curr Med Res Opin* 2007;23(12):3199–204. [2]Novartis, data on file.

Background and objectives

- Rivastigmine 9.5 mg/24 h patch is approved for the symptomatic treatment of mild-to-moderate Alzheimer's disease (AD) (2007)
- Approved based on the IDEAL (Investigation of transDermal of Exelon for ALzheimer's disease) study which demonstrated the 9.5 mg/24 h patch to have comparable efficacy to 12 mg/day capsules, but with improved gastrointestinal (GI) tolerability due to its smooth and continuous mode of drug delivery[1]
- The efficacy of rivastigmine capsules is dose-dependent[2]
- The 13.3 mg/24 h rivastigmine patch may provide access to high-dose efficacy, but with a lower incidence of GI adverse events (AE) than would be expected with a comparable oral dose
- The OPTIMA (OPtimizing Transdermal Exelon In Mild-to-moderate Alzheimer's disease) study compared the efficacy, safety and tolerability of the 13.3 mg/24 h patch in patients with AD who demonstrated functional and cognitive decline on the 9.5 mg/24 h patch during an initial open-label phase

[1]Winblad B *et al*. *Int J Geriatr Psychiatry* 2007;22:456–67; [2]Anand R *et al. Int J Geriatr Psychopharmacol* 2000;2:68–72.

OPTIMA Study design



- 24–48 week open-label phase
- Patients titrated up to study dose over a four-week period
- Patients maintained on target study dose for a maximum of 44 weeks
- Evaluation of decline at Weeks 24, 36, and 48

- Decliners: 48-week double-blind phase
- Non-decliners: 48-week open-label phase

*Functional decline was assessed by the investigator.

Participants

- Main inclusion criteria:
  - Males and females (not of child-bearing potential)
  - Clinical diagnosis of dementia of the Alzheimer's type (DSM-IV criteria) and probable AD (NINCDS/ADRDA criteria; MRI/CT scan within 2 years prior to baseline visit)
  - MMSE score of 10–24, inclusive
- Main exclusion criteria:
  - Any medical or neurological condition other than AD that may cause dementia
  - Current diagnosis of uncontrolled seizure disorder; severe/unstable cardiovascular disease; bradycardia; sick-sinus syndrome, or conduction defects; acute, severe or unstable asthmatic conditions; uncontrolled peptic ulceration/GI bleeding within last 3 months; clinically significant urinary obstruction
  - Allergy to vitamin E containing products; sensitivity to cholinergic compounds; skin lesion/disorder that would prevent transdermal patch use
  - History (past 5 years) of malignancy of any organ system, unless stable; history or current diagnosis of cerebrovascular disease
  - Use of ChEIs (or other approved treatments for AD) 2 weeks prior to enrolment, with the exception of stable memantine (at least 3 months)

ChEIs, cholinesterase inhibitors; CT, computed tomography; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.

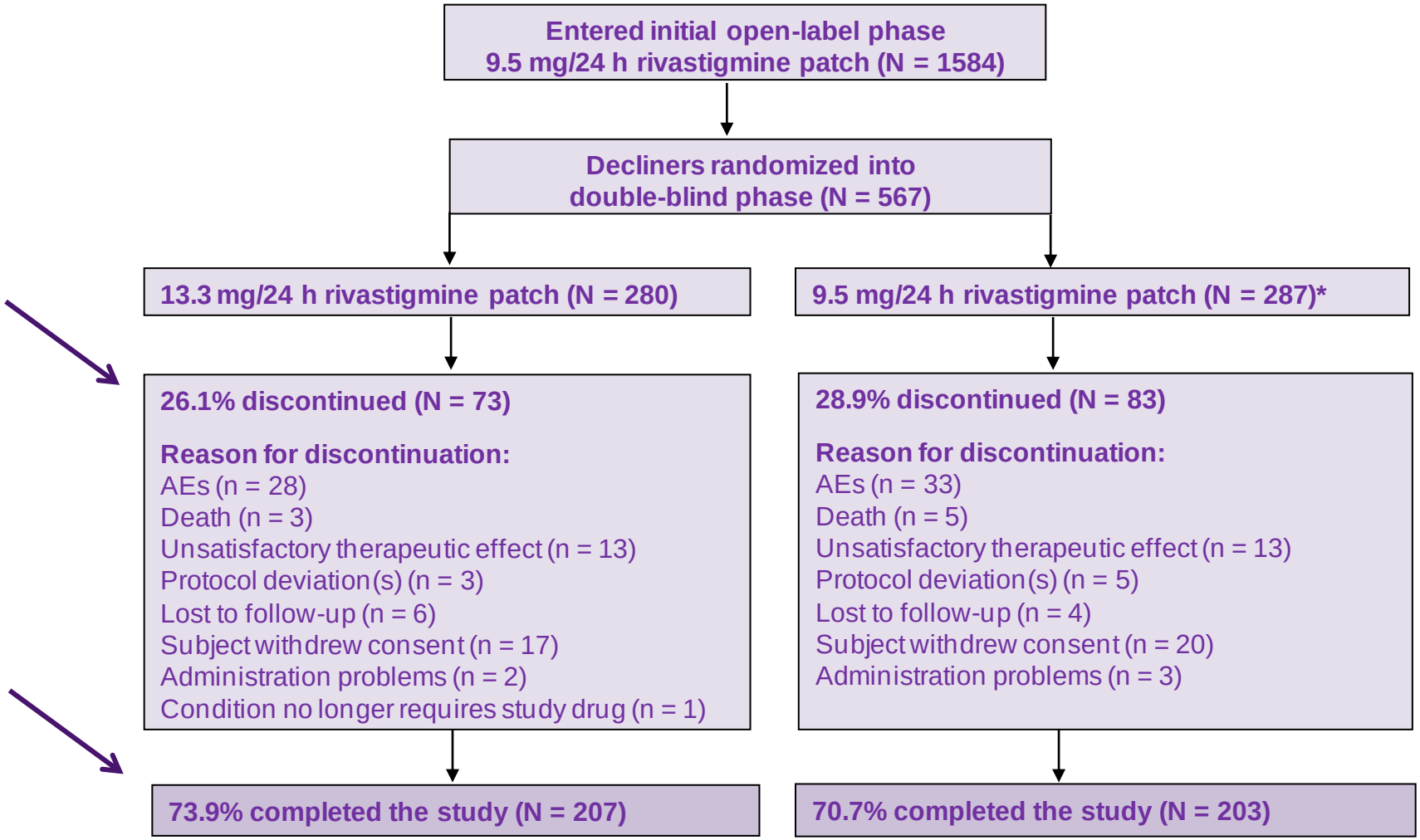
Primary outcomes

- Change from double-blind randomization to Week 48 of the double-blind phase on the:
  - Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living (ADCS-IADL) scale
  - Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-cog)

Secondary outcomes

- Change from double-blind randomization to Week 48 of the double-blind phase on the:
  - Trail Making Test Parts A and B (TMT-A; TMT-B)
  - 10-item Neuropsychiatric Inventory (NPI-10) and NPI-D (distress)
- Incidence of AE, serious AE (SAE) and discontinuations due to AE
- Incidence of GI AE, the degree of burden of GI AE, and discontinuation due to GI AE
- Monitoring vital signs
- Incidence of treatment emerging cardiac abnormalities detected on 12-lead electrocardiogram (**ECG**)

Patient disposition



Percentage (%) calculated using the randomized population; *one patient was randomized in error and continued in the extended open-label phase after randomization

Patient demographics and background characteristics (enrolled population)

	Randomized N= 567	Extended Open Label N= 459	Discontinued N= 558
Gender n (%)			
Male	200 (35.3)	194 (42.3)	198 (35.5)
Female	367 (64.7)	265 (57.7)	360 (64.5)
Age group			
< 65	58 (10.1)	44 (9.6)	53 (9.5)
≥ 65	509 (89.9)	415 (90.4)	505 (90.5)
Time since first symptom of AD noticed by patient/ caregiver (years)			
Mean (SD)	4.09 (2.779)	3.40 (2.553)	3.93 (2.877)
Range	0.2–17.7	0.1–19.2	0.4–19.4
Time since first symptom of AD was diagnosed by physician (years)			
Mean (SD)	1.92 (1.988)	1.40 (1.692)	1.74 (2.012)
Range	0.0-12.6	0.0-10.3	0.0-11.9
MMSE total score			
Mean (SD) baseline	16.9 (3.60)	18.8 (3.25)	17.8 (3.40)
Range	10.0–25.0	10.0–24.0	10.0–24.0

N = Number of patients in the randomized population. n = Number of patients meeting the criterion (for categorical variables) or the number of patients with a measurement (for continuous variables). AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; SD, standard deviation.

Patient demographics and background characteristics (I; randomized population)

Characteristic	13.3 mg/24 h rivastigmine patch* N = 280	9.5 mg/24 h rivastigmine patch* N = 287	Overall N = 567
Gender (%)			
Female	66.1	63.4	64.7
Race (%)			
Caucasian	95.0	98.3	96.6
Black	2.9	0.7	1.8
Oriental	0.7	0.3	0.5
Other	1.4	0.7	1.1
Age (years)			
n	280	287	567
Mean (SD)	75.6 (7.4)	75.9 (6.8)	75.7 (7.1)
Age group (%)			
< 65 years	12.1	6.3	9.2
≥ 65 years	87.9	93.7	90.8
Weight category (%)			
< 50 kg	9.6	8.4	9.0
50–80 kg	68.9	72.8	70.9
> 80 kg	21.4	18.8	20.1

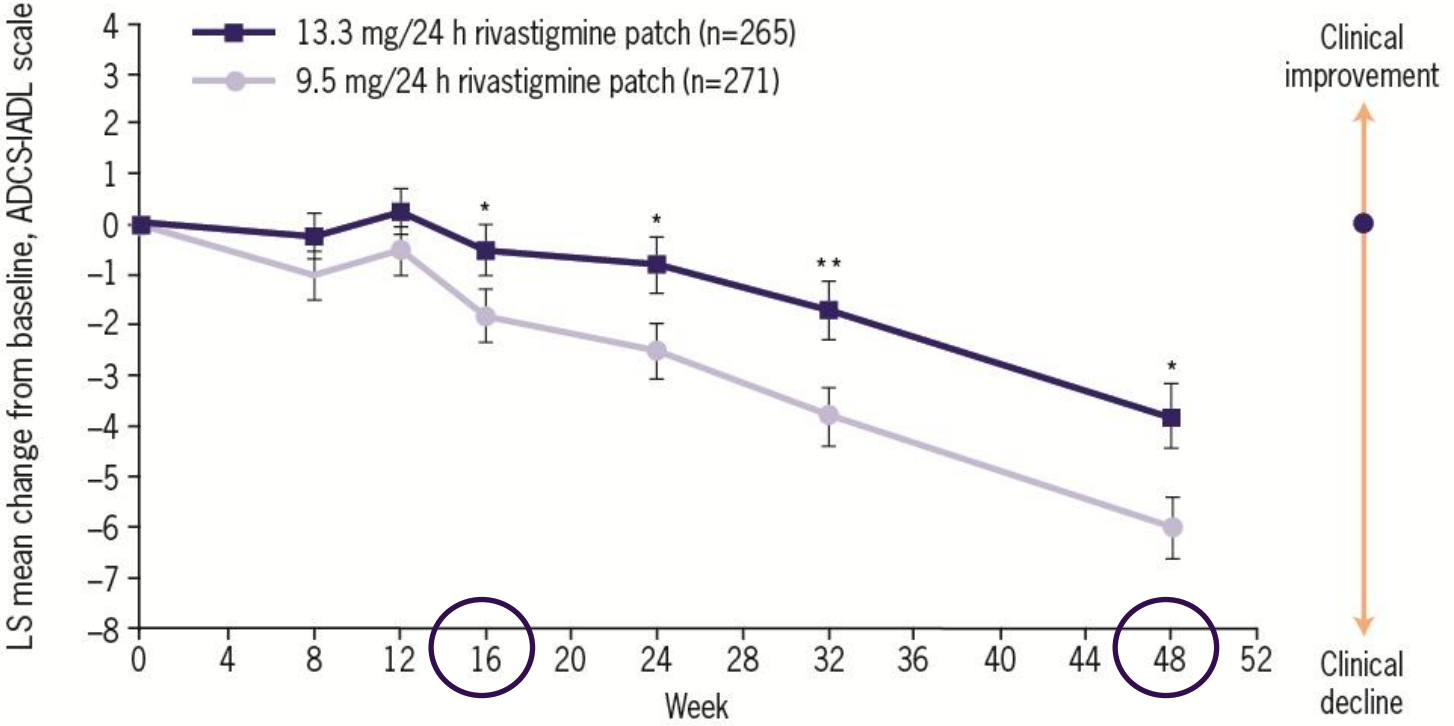
*Randomized population. N = Number of patients in the randomized population; n = Number of patients meeting the criterion (for categorical variables) or the number of patients with a measurement (for continuous variables); n = 287, 280 and 567 for the 9.5 mg/24 h rivastigmine patch, 13.3 mg/24 h rivastigmine patch and total groups unless indicated. SD, Standard deviation.

Patient demographics and background characteristics (II; randomized population)

Characteristic	13.3 mg/24 h rivastigmine patch* N = 280	9.5 mg/24 h rivastigmine patch* N = 287	Overall N = 567
Time since first symptom of AD was noticed by patient/caregiver (years)			
Mean (SD)	3.9 (2.8)	4.3 (2.8)	4.1 (2.8)
Time since first symptom of AD was first diagnosed by a physician (years)			
Mean (SD)	1.8 (1.8)	2.0 (2.1)	1.9 (2.0)
MMSE score			
Mean (SD)	14.1 (4.8)	14.2 (4.6)	14.2 (4.7)
Time to meet decline criteria in initial OL phase (%)			
≤ 36 weeks	50.0	51.2	50.6
> 36 weeks	50.0	48.8	49.4
Prior AChEI use (%)	59.3	64.5	61.9
Prior use of other approved AD treatments (%)	37.5	35.9	36.7

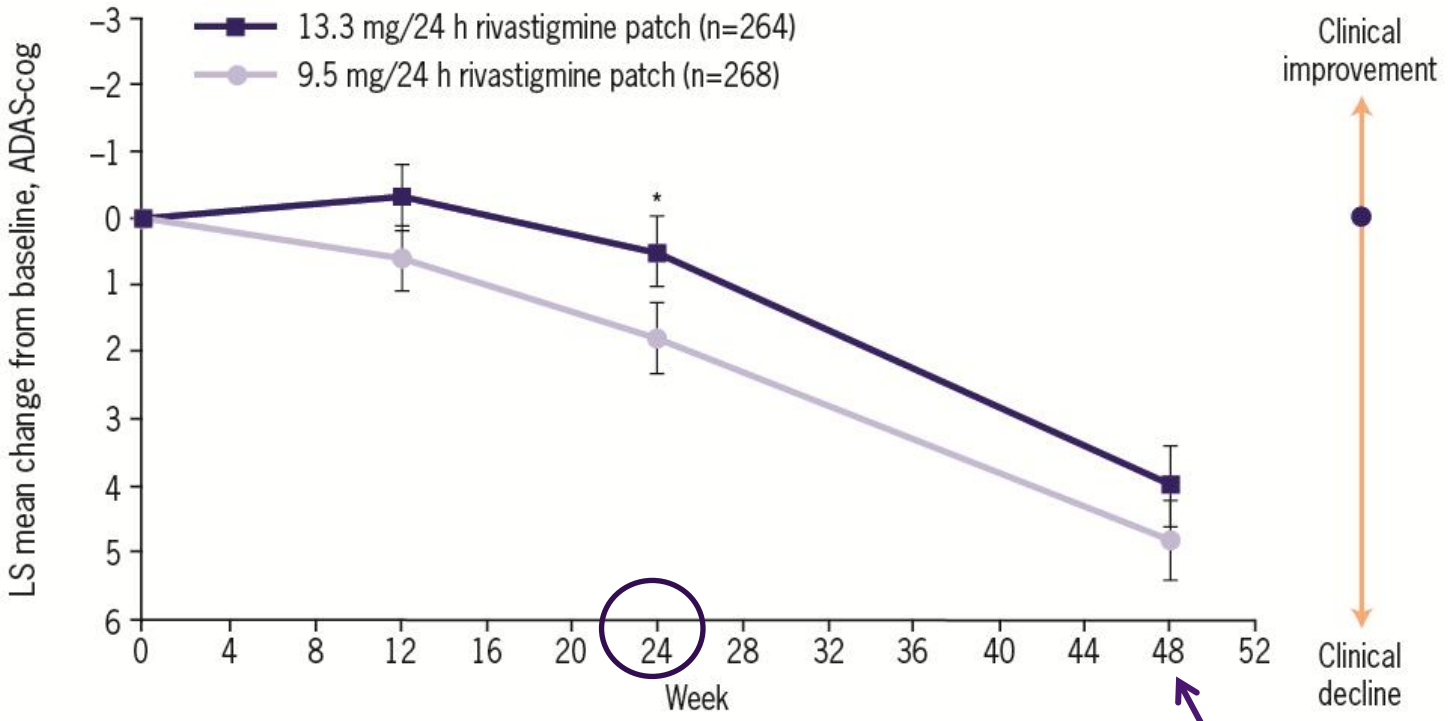
*Randomized population. N = Number of patients in the randomized population. n = Number of patients meeting the criterion (for categorical variables) or the number of patients with a measurement (for continuous variables). n = 287, 280 and 567 for the 9.5 mg/24 h, 13.3 mg/24 h and total groups unless indicated. AChEI, acetylcholinesterase inhibitor; OL, open-label.

Efficacy: superiority of 13.3 mg/24 h patch at Weeks 16–48 on the ADCS-IADL (ITT[DB]-LOCF population)



ITT-DB, Intention-To-Treat double-blind; LOCF, Last Observation Carried Forward; ADCS-IADL, Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living; LS, least-squares; error bars represent the standard error of the mean; *p < 0.05, ** p < 0.001 for 13.3 mg/24 h *versus* 9.5 mg/24 h patch. P-value based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADCS-IADL score.

Efficacy: superiority of 13.3 mg/24 h patch at Week 24 on the ADAS-cog (ITT[DB]-LOCF population)



ITT-DB, Intention-To-Treat double-blind; LOCF, Last Observation Carried Forward; ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale; LS, least-squares; error bars represent the standard error of the mean; *p = 0.027 13.3 mg/24 h *versus* 9.5 mg/24 h patch. P-value based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADAS-cog score.

MMSE ≤14

ADCS-IADL subanalyses: similar decline within treatment groups, irrespective of disease severity

Moderate disease* **MMSE at DB baseline ≥ 10 ≤ 18**	13.3 mg/24 h patch n = 172	9.5 mg/24 h patch n = 176
Baseline	26.7	24.5
Change at Week 24	-1.4	-2.8
Change at Week 48	-4.8	-6.2

Moderate-severe disease† MMSE at DB baseline ≥ 3 ≤ 18	13.3 mg/24 h patch n = 213	9.5 mg/24 h patch n = 217
Baseline	25.3	22.8
Change at Week 24	-1.4	-3.0
Change at Week 48	-4.7	-6.1

*Moderate disease = MMSE at DB baseline ≥ 10 ≤ 18; †Moderate-severe disease = MMSE at DB baseline ≥ 3 ≤ 18; ADCS-IADL, Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living scale; ITT[DB]-LOCF (Intent-to-Treat population in the DB treatment phase using a last-observation carried forward imputation) population.

ADAS-cog subanalyses: similar decline within treatment groups, irrespective of disease severity

Moderate disease* **MMSE at DB baseline ≥ 10 ≤ 18**	13.3 mg/24 h patch n = 172	9.5 mg/24 h patch n = 175
Baseline	34.6	35.0
Change at Week 24	1.6	2.5
Change at Week 48	4.7	5.6

Moderate-severe disease† MMSE at DB baseline ≥ 3 ≤ 18	13.3 mg/24 h patch n = 213	9.5 mg/24 h patch n = 214
Baseline	37.3	38.0
Change at Week 24	1.7	2.6
Change at Week 48	4.6	5.5

Moderate disease = MMSE at DB baseline ≥ 10 ≤ 18; †Moderate-severe disease = MMSE at DB baseline ≥ 3 ≤ 18;
ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale; ITT[DB]-LOCF (Intent-to-Treat population in the DB treatment phase using a last-observation carried forward imputation) population.

Efficacy: no significant between-group differences on other secondary efficacy outcomes (ITT[DB]-LOCF population)

	13.3 mg/24 h rivastigmine patch	9.5 mg/24 h rivastigmine patch	Treatment difference		
			DLSM	95% CI	p-value
TMT-A					
n	254	258			
Mean change from baseline (Week 24)	4.2	10.2	-7.8	(-17.3, 1.7)	0.105
Mean change from baseline (Week 48)	16.3	18.2	-3.8	(-14.3, 6.6)	0.473
TMT-B					
n	235	236			
Mean change from baseline (Week 24)	5.5	0.9	1.6	(-9.9, 13.1)	0.784
Mean change from baseline (Week 48)	9.3	5.8	0.8	(-10.1, 11.8)	0.881
NPI-10					
n	265	271			
Mean change from baseline (Week 48)	1.4	0.9	-0.1	(-1.9, 1.7)	0.927
NPI-D					
n	265	271			
Mean change from baseline (Week 48)	0.6	-0.0	0.2	(-0.7, 1.2)	0.647

DLSM, difference of least-squares means; CI, confidence interval. P-values based on an analysis of covariance adjusted for country and corresponding baseline score.; TMT, Trail Making Test Parts A and B; NPI, Neuropsychiatric Inventory; NPI-D (distress)

Summary: efficacy data

- The 13.3 mg/24 h patch demonstrated superior efficacy compared with the 9.5 mg/24 h patch, with statistical significance reached at the co-primary endpoint at Week 48 ($p = 0.002$) on the ADCS-IADL scale
  - Significant differences in favour of 13.3 mg/24 h patch also observed on the ADCS-IADL at Weeks 16, 24 and 32 ($p = 0.025$, 0.005 and < 0.001, respectively *versus* 9.5 mg/24 h patch)

- Less cognitive decline on the ADAS-cog was observed with the 13.3 mg/24 h patch compared with the 9.5 mg/24 h patch, but this did not reach significance at Week 48 (co-primary endpoint; $p = 0.227$)
  - Statistically significant at Week 24 compared with 9.5 mg/24 h patch ($p = 0.027$)

ADCS-IADL, Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living scale; ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale.

Patient study drug exposure during the 48-week, double-blind phase (safety-DB population)

Duration of exposure (weeks)	13.3 mg/24 h rivastigmine patch* N = 280	9.5 mg/24 h rivastigmine patch* N = 283
Mean (SD)	41.4 (14.3)	41.3 (13.6)
Median	48.0	48.0
Range	1.3–57.1	1.3–56.1

During the double-blind treatment phase, the mean and median duration of exposure to the study drug was similar in both treatment groups

*Safety population.

Deaths, SAE or discontinuation due to AE (safety-DB population)

	13.3 mg/24 h rivastigmine patch* N = 280 n (%)	9.5 mg/24 h rivastigmine patch* N = 283 n (%)
Deaths	3 (1.1)	5 (1.8)
SAE†	44 (15.7)	44 (15.5)
Discontinued due to AE†	27 (9.6)	36 (12.7)
Discontinued due to SAE†	12 (4.3)	18 (6.4)

The safety profile due to deaths and SAE was comparable between the 13.3 mg/24 h and the 9.5 mg/24 h. The incidence of AE and SAE leading to discontinuation was lower in the 13.3 mg/24 h patch group compared with the 9.5 mg/24 h patch group

*Safety population; †Deaths were included. AE, adverse event, SAE, serious adverse event.

AE leading to discontinuation (DB phase)

	13.3 mg/24 h patch* N = 280 n (%)	9.5 mg/24 h patch* N = 283 n (%)	Overall* N = 563 n (%)
Any primary system organ class	**27 (9.6)**	**36 (12.7)**	**63 (11.2)**
Preferred term			
Cardiac disorders	0 (0.0)	4 (1.4)	4 (0.7)
Atrial fibrillation	0 (0.0)	2 (0.7)	2 (0.4)
Gastrointestinal disorders	5 (1.8)	4 (1.4)	9 (1.6)
Vomiting	4 (1.4)	1 (0.4)	5 (0.9)
General disorders and administration site conditions	6 (2.1)	11 (3.9)	17 (3.0)
Application site pruritus	3 (1.1)	3 (1.1)	6 (1.1)
Application site rash	2 (0.7)	2 (0.7)	4 (0.7)
Application site erythema	0 (0.0)	2 (0.7)	2 (0.4)
Application site hypersensitivity	0 (0.0)	2 (0.7)	2 (0.4)
Infections and infestations	2 (0.7)	2 (0.7)	4 (0.7)
Pneumonia	2 (0.7)	1 (0.4)	3 (0.5)
Metabolism and nutrition disorders	3 (1.1)	0 (0.0)	3 (0.5)
Decreased appetite	2 (0.7)	0 (0.0)	2 (0.4)
Dehydration	2 (0.7)	0 (0.0)	2 (0.4)
Nervous system disorders	9 (3.2)	7 (2.5)	16 (2.8)
Cerebrovascular accident	2 (0.7)	1 (0.4)	3 (0.5)
Dizziness	2 (0.7)	0 (0.0)	2 (0.4)
Psychiatric disorders	4 (1.4)	4 (1.4)	8 (1.4)
Aggression	1 (0.4)	3 (1.1)	4 (0.7)
Delirium	0 (0.0)	2 (0.7)	2 (0.4)

Safety population. A patient with multiple occurrences of an AE within a preferred term was counted once only. Only AE leading to discontinuation of study drug and starting on or after the first dose in DB phase are included.

Most common AE, by primary system organ class (I)

- By primary system organ class, AE that were most commonly reported and were experienced by more patients in the 13.3 mg/24 h patch group than the 9.5 mg/24 h patch group were:
  - GI (29.3% *vs* 19.1% in 13.3 and 9.5 mg/24 h patch groups, respectively)
  - Psychiatric disorders (25.4% *vs* 21.6%, respectively)
  - Nervous system disorders (21.4% *vs* 18.4%, respectively)

- Metabolism and nutrition disorders; general disorders and administrative site conditions were also more frequent in the higher dose treatment group.
  - Metabolism and nutrition disorders (11.1% *vs* 8.8% in the 13.3 and 9.5 mg/24 h patch groups, respectively)
  - General disorders and administrative site conditions (23.2% and 21.2%, respectively)

Most common AE, by primary system organ class (II)

- The incidence of cardiac disorders were lower in the higher dose group
  - Cardiac disorders (4.3% *vs* 6.7%, respectively)

Most common AEs, by preferred term (I) (DB phase; DB-safety population)

Preferred term	13.3 mg/24 h patch* N = 280 n (%)	9.5 mg/24 h patch* N = 283 n (%)	Overall N = 563 n (%)
Total	**210 (75.0)**	**193 (68.2)**	**403 (71.6)**
Nausea	34 (12.1)	14 (4.9)	48 (8.5)
Vomiting	29 (10.4)	13 (4.6)	42 (7.5)
Fall	21 (7.5)	17 (6.0)	38 (6.7)
Weight decreased	19 (6.8)	8 (2.8)	27 (4.8)
Application site erythema	18 (6.4)	16 (5.7)	34 (6.0)
Decreased appetite	18 (6.4)	7 (2.5)	25 (4.4)
Diarrhoea	18 (6.4)	13 (4.6)	31 (5.5)
Urinary tract infection	15 (5.4)	12 (4.2)	27 (4.8)
Agitation	14 (5.0)	15 (5.3)	29 (5.2)
Depression	14 (5.0)	13 (4.6)	27 (4.8)

*Safety population. AE are sorted by descending frequency in the 13.3 mg/24 h patch group. A patient with multiple occurrences of an AE within a preferred term was counted only once. Only AE shown occurring in > 3% of patients, in any treatment group.

Most common AEs, by preferred term (II) (DB phase; DB-safety population)

Preferred term	13.3 mg/24 h patch* N = 280 n (%)	9.5 mg/24 h patch* N = 283 n (%)	Overall N = 563 n (%)
Total	**210 (75.0)**	**193 (68.2)**	**403 (71.6)**
Dizziness	12 (4.3)	2 (0.7)	14 (2.5)
Application site pruritus	11 (3.9)	11 (3.9)	22 (3.9)
Headache	11 (3.9)	11 (3.9)	22 (3.9)
Insomnia	11 (3.9)	7 (2.5)	18 (3.2)
Abdominal pain upper	10 (3.6)	3 (1.1)	13 (2.3)
Anxiety	10 (3.6)	7 (2.5)	17 (3.0)
Confusional state	9 (3.2)	7 (2.5)	16 (2.8)
Hypertension	9 (3.2)	8 (2.8)	17 (3.0)
Urinary incontinence	9 (3.2)	5 (1.8)	14 (2.5)
Psychomotor hyperactivity	7 (2.5)	9 (3.2)	16 (2.8)
Aggression	6 (2.1)	9 (3.2)	15 (2.7)

*Safety population. AE are sorted by descending frequency in the 13.3 mg/24 h patch group. A patient with multiple occurrences of an AE within a preferred term was counted only once. Only AE shown occurring in > 3% of patients, in any treatment group.

Most common AE, by preferred term and study period (I) (DB phase) effetti collaterali che tendono a ridursi

Preferred term	Week 0–48		Week 0–24		Week > 24	
	13.3 mg/24 h patch* N = 280 n (%)	9.5 mg/24 h patch* N = 283 n (%)	13.3 mg/24 h patch* N = 280 n (%)	9.5 mg/24 h patch* N = 283 n (%)	13.3 mg/24 h patch* N = 241 n (%)	9.5 mg/24 h patch* N = 246 n (%)
Total	**210 (75.0)**	**193 (68.2)**	**181 (64.6)**	**155 (54.8)**	**102 (42.3)**	**99 (40.2)**
Nausea	34 (12.1)	14 (4.9)	27 (9.6)	10 (3.5)	10 (4.1)	4 (1.6)
Vomiting	29 (10.4)	13 (4.6)	25 (8.9)	8 (2.8)	6 (2.5)	6 (2.4)
Fall	21 (7.5)	17 (6.0)	12 (4.3)	10 (3.5)	9 (3.7)	7 (2.8)
Weight decreased	19 (6.8)	8 (2.8)	7 (2.5)	4 (1.4)	13 (5.4)	5 (2.0)
Application site erythema	18 (6.4)	16 (5.7)	16 (5.7)	13 (4.6)	2 (0.8)	4 (1.6)
Decreased appetite	18 (6.4)	7 (2.5)	15 (5.4)	6 (2.1)	4 (1.7)	1 (0.4)
Diarrhoea	18 (6.4)	13 (4.6)	14 (5.0)	12 (4.2)	4 (1.7)	1 (0.4)
Urinary tract infection	15 (5.4)	12 (4.2)	8 (2.9)	7 (2.5)	8 (3.3)	6 (2.4)
Agitation	14 (5.0)	15 (5.3)	11 (3.9)	9 (3.2)	3 (1.2)	6 (2.4)
Depression	14 (5.0)	13 (4.6)	8 (2.9)	8 (2.8)	6 (2.5)	5 (2.0)

*Safety population. AE are sorted by descending frequency in the 13.3 mg/24 h patch group. A patient with multiple occurrences of an AE within a preferred term was counted only once. Only AE shown occurring in > 3% of patients, in any treatment group.

Most common AE, by preferred term and study period (II) (DB phase)

Preferred term	Week 0–48		Week 0–24		Week > 24	
	13.3 mg/24 h patch* N = 280 n (%)	9.5 mg/24 h patch* N = 283 n (%)	13.3 mg/24 h patch* N = 280 n (%)	9.5 mg/24 h patch* N = 283 n (%)	13.3 mg/24 h patch* N = 241 n (%)	9.5 mg/24 h patch* N = 246 n (%)
Total	**210 (75.0)**	**193 (68.2)**	**181 (64.6)**	**155 (54.8)**	**102 (42.3)**	**99 (40.2)**
Dizziness	12 (4.3)	2 (0.7)	8 (2.9)	1 (0.4)	4 (1.7)	1 (0.4)
Application site pruritus	11 (3.9)	11 (3.9)	10 (3.6)	8 (2.8)	1 (0.4)	3 (1.2)
Headache	11 (3.9)	11 (3.9)	10 (3.6)	10 (3.5)	1 (0.4)	1 (0.4)
Insomnia	11 (3.9)	7 (2.5)	5 (1.8)	3 (1.1)	6 (2.5)	4 (1.6)
Abdominal pain upper	10 (3.6)	3 (1.1)	8 (2.9)	2 (0.7)	2 (0.8)	1 (0.4)
Anxiety	10 (3.6)	7 (2.5)	6 (2.1)	5 (1.8)	4 (1.7)	2 (0.8)
Confusional state	9 (3.2)	7 (2.5)	5 (1.8)	6 (2.1)	4 (1.7)	1 (0.4)
Hypertension	9 (3.2)	8 (2.8)	7 (2.5)	5 (1.8)	2 (0.8)	3 (1.2)
Urinary incontinence	9 (3.2)	5 (1.8)	6 (2.1)	4 (1.4)	3 (1.2)	1 (0.4)
Psychomotor hyperactivity	7 (2.5)	9 (3.2)	5 (1.8)	7 (2.5)	4 (1.7)	2 (0.8)
Aggression	6 (2.1)	9 (3.2)	3 (1.1)	7 (2.5)	3 (1.2)	2 (0.8)

*Safety population. AE are sorted by descending frequency in the 13.3 mg/24 h patch group. A patient with multiple occurrences of an AE within a preferred term was counted only once. Only AE shown occurring in > 3% of patients, in any treatment group.

Summary: safety data (I)

- Higher incidence of AE in the 13.3 *vs* the 9.5 mg/24 h group (75.0% *vs* 68.2%)
- Between-group differences in the first 24 weeks on common AEs tended to decrease with time
- By primary system organ class, the following disorders were most common with the 13.3 *vs* the 9.5 mg/24 h patch
  - GI: 29.3% *vs* 19.1%
  - Psychiatric disorders: 25.4% *vs* 21.6%
  - Nervous system disorders: 21.4% *vs* 18.4%
- Cholinergic AEs occurred more frequently in the 13.3 *vs* the 9.5 mg/24 h group
  - Nausea: 12.1% *vs* 4.9%
  - Vomiting: 10.4% *vs* 4.6%
  - Weight decreased: 6.8% *vs* 2.8%
  - Upper abdominal pain: 3.6% *vs* 1.1%
- However fewer discontinuations were seen in 13.3 *vs* the 9.5 mg/24 h group
  - Discontinuations due to AE: 9.6% *vs* 12.7%, respectively
  - Discontinuations due to SAE: 4.3% *vs* 6.4%, respectively

Summary: safety data (II)

- The profile for deaths and SAE was similar between treatment groups
- The incidence of application site erythema and pruritus was comparable between groups, suggesting the 13.3 mg/24 h patch is not associated with reduced skin tolerability
- No unexpected effects of long-term treatment with either dose

Implications of study findings and conclusions

- The 13.3 mg/24 h patch demonstrated superior efficacy over the 9.5 mg/24 h patch on the ADCS-IADL scale with statistical significance reached at Weeks 16−48
- At Week 24, statistical significance (in favour of the 13.3 mg/24 h patch) was achieved on both the ADAS-cog and ADCS-IADL scales
- The 13.3 mg/24 h patch also showed a good safety and tolerability profile: treatment persistence was improved (fewer discontinuations)
- Other dementia drugs have been approved for the symptomatic treatment of AD based on efficacy results after 24 weeks of treatment as a primary endpoint
- The results of the OPTIMA study have been submitted to the European Medicines Agency (EMA) and the Food and Drug Administration (FDA)
- It is hoped these data will be sufficient to allow approval of the 13.3 mg/24 h patch for treatment of patients with mild-to-moderate AD in a number of countries worldwide

ADCS-IADL, Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living scale;
ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale.