Sponsor

Novartis

Generic Drug Name

Rivastigmine (Transdermal Patch)

Trial Indication(s)

Alzheimer's disease (AD)

Protocol Number

CENA713D2320

Protocol Title

A 24-week, multicenter, randomized, double-blind, placebo and active-controlled, parallel-group evaluation of the efficacy, safety and tolerability of the once-daily Exelon® patch formulation in patients with probable Alzheimer's disease (MMSE 10-20)

Clinical Trial Phase

Phase III

Study Start/End Dates

27-Nov-2003 to 11-Jan-2006

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a 24-week, multicenter, randomized, double-blind, placebo and active controlled, parallel-group evaluation of the efficacy, safety, and tolerability of the once-daily Exelon® patch formulation in patients with probable AD. An approximately equal number of patients were randomly assigned to each of four treatment groups. Two different rivastigmine target patch sizes (10 and 20 cm^2) were evaluated. The active control was rivastigmine capsule (Exelon®) at a target dose of 12mg/Day. The placebo control comprised both matching placebo capsule and matching placebo patch sizes.

Centers

100 centers in 21 countries : Chile (2 centers), Czech Republic (6), Denmark (3), Finland (1), Germany (5), Guatemala (2), Israel (5), Italy (4), Korea (6), Mexico (4), Norway (5), Peru (3), Poland (5), Portugal (3), Russia (8), Slovakia (4), Sweden (4), Taiwan (4), USA (23), Uruguay (1), and Venezuela (2)

Objectives:

Primary Objective:

- To confirm the efficacy of the Exelon® patch in patients with probable AD (Mini-Mental State Examination (MMSE 10-20)) by testing the following hypotheses:
    i. Exelon® 20 cm^2 per day target patch size was superior to placebo with respect to change from baseline at Week 24 simultaneously in AD Assessment Scale - Cognitive Subscale (ADAS-Cog) and AD Cooperative Study - Clinical Global Impression of Change (ADCS-CGIC) scores.
    ii. Exelon® 20 cm^2 per day target patch size was non-inferior to Exelon® 12 mg per day target capsule with respect to change from baseline at Week 24 in ADAS-Cog score.
    iii. Exelon® 10 cm^2 per day target patch size was superior to placebo with respect to change from baseline at Week 24 simultaneously in ADAS-Cog and ADCS-CGIC scores.
    iv. Exelon® 20 cm^2 per day target patch size was superior to placebo with respect to change from baseline at Week 24 in ADCS- Activities of Daily Living (ADL) score.

Secondary Objective:

- To explore the efficacy, safety, and tolerability of Exelon® patch and capsules in patients with probable AD (MMSE 10-20) by testing the following hypotheses:
    1. Exelon® patches (target sizes of 10 and 20 cm^2) and Exelon® capsules (target 12 mg/day) were superior to placebo with respect to change from baseline at Week 24 in:
        i. caregiver-based activities of daily living (ADCS-ADL) (for comparison of 20 cm^2 target patch size and placebo, see primary objective no. 4)
        ii. neuropsychiatric symptoms (Neuropsychiatric Inventory (NPI))
        iii. brief, global cognitive testing (MMSE)
        iv. executive function (Ten point clock test)
        v. attention (Trail Making Test (TMT Part A))
        vi. caregiver satisfaction/preferences (Alzheimer's Disease Caregiver Preference Questionnaire (ADCPQ))

    2. Exelon® patch and Exelon® capsule have comparable safety over 24 weeks of planned exposure, as measured by incidence of adverse events, serious adverse events, and in vital signs
    3. Exelon® patch and Exelon® capsule had comparable safety over 24 weeks of planned exposure, as assessed by the incidence of adverse events (AEs), serious AEs (SAEs), and changes in vital signs. Exelon® 10 cm^2 target patch size had superior tolerability to Exelon® 12 mg target capsule over 24 weeks of planned exposure, as measured by the incidence of gastrointestinal (GI) adverse events (particularly nausea and vomiting), the degree of burden (severity x incidence) of GI adverse events (nausea and vomiting) and discontinuations due to GI adverse events.
    4. All four sizes of Exelon® patches (5, 10, 15, 20 cm^2) had acceptable adhesion and skin irritation over 24 weeks of planned exposure.
    5. To evaluate the safety and tolerability of Exelon®patch for up to 28 weeks of open-label treatment in patients with probable AD (MMSE 10-20) who successfully completed the double-blind treatment phase.

Test Product (s), Dose(s), and Mode(s) of Administration

Exelon patch sizes of 10 and 20 cm^2 (once daily) for transdermal application and Exelon® 12 mg target capsule (6 mg twice a day) : All patches were round in shape, beige in color, and sealed in a white pouch.

Statistical Methods

The primary analysis population for the confirmative testing of all four hypotheses was the Intent-to-treat (ITT) Last Observation Carried forward (LOCF) population; which included all patients with at least one primary efficacy post-baseline assessment on treatment. For ADAS-Cog and ADCS-ADL, treatment groups were compared using an analysis of covariance (Analysis of covariance (ANCOVA) on change from baseline) model which included country and the baseline total score as factor and covariate variables, respectively. For the non-inferiority hypothesis based on ADAS-Cog, the upper boundary of the two-sided 95% confidence interval (CI) for the difference between treatment groups was compared to the pre-defined non-inferiority margin of 1.25. The treatment comparison of the ADCS-CGIC was based on a Cochran-Mantel-Haenszel test (van Elteren) with country as stratification variable. The statistical hypotheses were tested sequentially according to the prospectively specified order at the alpha level of 5%. The primary analyses were repeated for the ITT population with retrieved dropouts (ITT+RDO) and all randomized population (RND), in order to support the conclusions drawn from the primary analysis population. In addition, a proportional odds regression model was performed on ADCS-CGIC. All safety analyses were performed using the safety population; which included all patients who received at least one dose of study medication and had at least one post-baseline safety assessment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Males, and females who are surgically sterile or one year postmenopausal, all aged 50-85 years.
- Had a diagnosis of dementia of the Alzheimer's type according to the DSM-IV criteria.
- Had a primary caregiver willing to accept responsibility for supervising the treatment, (e.g., application and removal of the patch daily at approximately the same time of day) assessing the condition of the patient throughout the study, and for providing input to efficacy assessments in accordance with all protocol requirements.

Exclusion Criteria:

- The presence of an advanced, severe, progressive, or unstable disease of any type that could have interfered with efficacy and safety assessments or put the patient at particular risk.
- Any medical or neurological condition other than AD that could explain the patient's dementia.
- Current diagnosis of active, uncontrolled seizure disorder or unstable cardiovascular disease.

Participant Flow Table

Patient disposition for each treatment group - all patients

Disposition/Reason	Exelon 20 cm^2 n (%)	Exelon 10 cm^2 n (%)	Exelon capsule n (%)	Placebo n (%)	Total n (%)
Total number of patients					
Screened					1464
Randomized	303 (100.0)	293 (100.0)	297 (100.0)	302 (100.0)	1195 (100.0)
Exposed to study drug	303 (100.0)	291 (99.3)	294 (99.0)	302 (100.0)	1190 (99.6)
Completed	241 (79.5)	229 (78.2)	234 (78.8)	266 (88.1)	970 (81.2)
Discontinued	62 (20.5)	64 (21.8)	63 (21.2)	36 (11.9)	225 (18.8)
Adverse event(s)	26 (8.6)	28 (9.6)	24 (8.1)	15 (5.0)	93 (7.8)
Subject withdrew consent	19 (6.3)	21 (7.2)	17 (5.7)	6 (2.0)	63 (5.3)
Unsatisfactory therapeutic effect	4 (1.3)	3 (1.0)	8 (2.7)	6 (2.0)	21 (1.8)
Lost to follow-up	4 (1.3)	3 (1.0)	5 (1.7)	3 (1.0)	15 (1.3)
Death	5 (1.7)	4 (1.4)	2 (0.7)	3 (1.0)	14 (1.2)
Administrative problems	2 (0.7)	1 (0.3)	4 (1.3)	2 (0.7)	9 (0.8)
Protocol violation	2 (0.7)	3 (1.0)	2 (0.7)	1 (0.3)	8 (0.7)
Abnormal laboratory value(s)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Subject's condition no longer required study drug	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

Baseline Characteristics

Demographic summary statistics – safety population

Demographic variable	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)	Total N = 1190 n (%)
Age (years)					
Mean (SD)	74.2 (7.7)	73.6 (7.9)	72.8 (8.2)	73.9 (7.3)	73.6 (7.8)
Range	50-88	50-90	50-87	50-89	50-90
Age group – n (%)					
< 65 years	38 (12.5)	36 (12.4)	48 (16.3)	31 (10.3)	153 (12.9)
≥ 65 – ≤ 75 years	109 (36.0)	121 (41.6)	124 (42.2)	133 (44.0)	487 (40.9)
> 75 years	156 (51.5)	134 (46.0)	122 (41.5)	138 (45.7)	550 (46.2)
Sex – n (%)					
Male	103 (34.0)	93 (32.0)	101 (34.4)	101 (33.4)	398 (33.4)
Female	200 (66.0)	198 (68.0)	193 (65.6)	201 (66.6)	792 (66.6)
Race – n (%)					
Caucasian	227 (74.9)	220 (75.6)	219 (74.5)	227 (75.2)	893 (75.0)
Black	3 (1.0)	1 (0.3)	5 (1.7)	2 (0.7)	11 (0.9)
Oriental	27 (8.9)	25 (8.6)	29 (9.9)	27 (8.9)	108 (9.1)
Other	46 (15.2)	45 (15.5)	41 (13.9)	46 (15.2)	178 (15.0)

Background characteristics summary statistics – safety population

Background characteristic	Exelon 20 cm^2 N = 303	Exelon 10 cm^2 N = 291	Exelon capsule N = 294	Placebo N = 302	Total N = 1190
Patient's relatives with AD disease – n (%)					
None	220 (72.6)	225 (77.3)	230 (78.2)	221 (73.2)	896 (75.3)
Mother	46 (15.2)	32 (11.0)	27 (9.2)	36 (11.9)	141 (11.8)
Father	9 (3.0)	11 (3.8)	11 (3.7)	16 (5.3)	47 (3.9)
Sibling	32 (10.6)	21 (7.2)	29 (9.9)	29 (9.6)	111 (9.3)
Other	14 (4.6)	15 (5.2)	12 (4.1)	19 (6.3)	60 (5.0)
Time since first symptom of AD was noticed by patient/caregiver (years)					
Mean (SD)	3.3 (2.5)	3.3 (2.2)	3.4 (2.3)	3.5 (2.4)	3.4 (2.3)
Range	0.0 - 16.6	0.3 - 15.7	0.1 - 16.0	0.2 - 15.0	0.0 - 16.6
Time since first symptom of AD was diagnosed by physician (years)					
Mean (SD)	1.1 (1.4)	1.1 (1.4)	1.1 (1.4)	1.1 (1.4)	1.1 (1.4)
Range	0.0 - 8.0	0.0 - 7.4	0.0 - 8.4	0.0 - 9.2	0.0 - 9.2
Patient who met criteria of probable dementia with Lewy bodies – n (%)					
No	289 (95.4)	276 (94.8)	282 (95.9)	291 (96.4)	1138 (95.6)
Yes	14 (4.6)	15 (5.2)	12 (4.1)	11 (3.6)	52 (4.4)
Patient's living situation – n (%)					
Living alone	30 (9.9)	43 (14.8)	35 (11.9)	27 (8.9)	135 (11.3)
Living with caregiver or other(s)	265 (87.5)	240 (82.5)	255 (86.7)	264 (87.4)	1024 (86.1)
Assisted living/group home	8 (2.6)	8 (2.7)	4 (1.4)	11 (3.6)	31 (2.6)
Years of formal education					
Mean (SD)	9.9 (4.4)	9.9 (4.3)	9.9 (4.4)	9.9 (4.3)	9.9 (4.3)
Range	0 - 20	0 - 19	0 - 18	0 - 20	0 - 20
MMSE at baseline					
Mean (SD) – n (%)	16.6 (2.9)	16.6 (3.1)	16.4 (3.1)	16.4 (3.0)	16.5 (3.0)
Range	10 - 24	6 - 24	9 - 26	10 - 20	6 - 26
< 15 – n (%)	75 (24.8)	68 (23.4)	89 (30.3)	88 (29.1)	320 (26.9)
≥ 15 – n (%)	228 (75.2)	222 (76.3)	205 (69.7)	213 (70.5)	868 (72.9)

Summary of Efficacy

Primary Outcome Result(s)

Summary of primary efficacy results, ITT (LOCF) population

Objective	Variable		
	ADAS-Cog	ADCS-CGIC	ADCS-ADL
1 Superiority of Exelon 20 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	p < 0.001	p = 0.054	-
2 Non-inferiority of Exelon 20 cm^2 target patch size compared to Exelon 12 mg/day target capsules at Week 24, based on ADAS-Cog	(-2.06, 0.17)*	-	-
3 Superiority of Exelon 10 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	p = 0.005	p = 0.010	-
4 Superiority of Exelon 20 cm^2 target patch size over placebo at Week 24, based on ADCS-ADL	-	-	p = 0.017

* Non-inferiority established, as the 95%-confidence interval for the difference between treatment groups (a negative difference indicates greater efficacy of Exelon 20 cm^2 versus capsule) was entirely below the corresponding predefined non-inferiority margin of 1.25.

Summary of primary efficacy results, ITT (LOCF) population (FDA)

Objective		Variable	
		ADAS-Cog	ADCS-CGIC
1	Superiority of Exelon 20 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	p < 0.001	p = 0.054
2	Superiority of Exelon 10 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	p = 0.005	p = 0.010

ADAS-Cog change from baseline – ITT (LOCF) population

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon Capsule N = 256	Placebo N = 282
Week 16		n	257	248	253	280
	Baseline	Mean	27.5	27.0	27.9	28.5
	Post-baseline	Mean	26.1	26.1	27.4	28.5
	Change	Mean	-1.4	-0.8	-0.5	-0.0
		p-value	0.007*	0.090	0.274	
Week 24		n	262	248	253	281
	Baseline	Mean	27.4	27.0	27.9	28.6
	Post-baseline	Mean	25.8	26.4	27.3	29.5
	Change	Mean	-1.6	-0.6	-0.6	1.0
		p-value	<0.001*	0.005*	0.003*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included. Negative change score indicates improvement. p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* p < 0.05

ADAS-Cog change from baseline – ITT+RDO (LOCF) population

Visit			Exelon 20 cm^2 N = 279	Exelon 10 cm^2 N = 267	Exelon Capsule N = 275	Placebo N = 289
Week 16		n	278	263	272	288
	Baseline	Mean	27.3	27.1	28.0	28.5
	Post-baseline	Mean	26.0	26.3	27.4	28.7
	Change	Mean	-1.3	-0.8	-0.6	0.2
		p-value	0.002*	0.033*	0.107	
Week 24		n	278	263	272	288
	Baseline	Mean	27.3	27.1	28.0	28.5
	Post-baseline	Mean	25.8	26.5	27.4	29.7
	Change	Mean	-1.6	-0.6	-0.6	1.2
		p-value	<0.001*	0.001*	0.001*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included. Negative change score indicates improvement. p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

ADAS-Cog change from baseline – ITT (OC) population

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon Capsule N = 256	Placebo N = 282
Week 16		n	256	248	251	280
	Baseline	Mean	27.5	27.0	27.9	28.5
	Post-baseline	Mean	26.1	26.1	27.4	28.5
	Change	Mean	-1.4	-0.8	-0.5	-0.0
		p-value	0.007*	0.091	0.272	
Week 24		n	218	209	214	243
	Baseline	Mean	27.4	26.6	27.7	28.6
	Post-baseline	Mean	25.6	26.0	27.0	29.6
	Change	Mean	-1.8	-0.6	-0.7	1.0
		p-value	< 0.001*	0.003*	0.003*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included. Negative change score indicates improvement. p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

ADAS-Cog mean treatment difference in change from baseline

Population / visit		Exelon 20 cm^2 versus Capsule		
		ITT (LOCF)	ITT+RDO (LOCF)	ITT (OC)
Week 16	LS-Mean	-0.83	-0.78	-0.83
	LB 95%-CI	-1.88	-1.80	-1.89
	UB 95%-CI	0.22*	0.23*	0.22*
Week 24	LS-Mean	-0.95	-0.95	-1.14
	LB 95% CI	-2.06	-2.05	-2.35
	UB 95% CI	0.17*	0.14*	0.08*

A negative LS-mean treatment difference indicates superiority of Exelon 20 cm^2 versus capsule. Mean and 95%-Confidence Interval of LS mean between treatments are derived from two-way analyses of covariance

* upper boundary of 95%-Confidence Interval (UB 95%-CI) for the difference between treatment groups is below the corresponding pre-defined non-inferiority margin 1.25

ADAS-Cog categorical analysis – Patients with improvement

Population / Visit		Exelon 20 cm^2	Exelon 10 cm^2	Exelon capsule	Placebo
ITT (LOCF)	N	257	248	253	280
Week 16	n (%)	74 (28.8)	65 (26.2)	70 (27.7)	69 (24.6)
	p-value	0.248	0.685	0.369	
	N	262	248	253	281
Week 24	n (%)	86 (32.8)	68 (27.4)	72 (28.5)	56 (19.9)
	p-value	< 0.001*	0.048*	0.013*	
ITT+RDO (LOCF)	N	278	263	272	288
Week 16	n (%)	77 (27.7)	68 (25.9)	73 (26.8)	69 (24.0)
	p-value	0.245	0.590	0.375	
	N	278	263	272	288
Week 24	n (%)	92 (33.1)	70 (26.6)	79 (29.0)	57 (19.8)
	p-value	< 0.001*	0.061	0.006*	
ITT (OC)	N	256	248	251	280
Week 16	n (%)	74 (28.9)	65 (26.2)	70 (27.9)	69 (24.6)
	p-value	0.235	0.685	0.338	
	N	218	209	214	243
Week 24	n (%)	79 (36.2)	58 (27.8)	64 (29.9)	48 (19.8)
	p-value	< 0.001*	0.034*	0.008*	

Improvement: at least 4 points improvement over baseline
p-values are derived from CMH test blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

ADCS-CGIC categorical analysis – ITT (LOCF) population

Visit	Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16 – n (%)				
Markedly improved (1)	3 (1.2)	4 (1.6)	1 (0.4)	1 (0.4)
Moderately improved (2)	21 (8.2)	24 (9.7)	20 (8.0)	22 (8.1)
Minimally improved (3)	58 (22.7)	48 (19.4)	48 (19.3)	53 (19.4)
Unchanged (4)	109 (42.7)	104 (42.1)	111 (44.6)	116 (42.5)
Minimally worse (5)	40 (15.7)	53 (21.5)	43 (17.3)	53 (19.4)
Moderately worse (6)	20 (7.8)	14 (5.7)	23 (9.2)	25 (9.2)
Markedly worse (7)	4 (1.6)	0 (0.0)	3 (1.2)	3 (1.1)
n	255	247	249	273
mean	3.9	3.9	4.0	4.0
SD	1.13	1.08	1.10	1.10
p-value	0.177	0.195	0.804	
Week 24 – n (%)				
Markedly improved (1)	5 (1.9)	5 (2.0)	3 (1.2)	2 (0.7)
Moderately improved (2)	32 (12.3)	29 (11.7)	29 (11.5)	26 (9.4)
Minimally improved (3)	48 (18.5)	43 (17.3)	60 (23.7)	50 (18.0)
Unchanged (4)	94 (36.2)	105 (42.3)	96 (37.9)	91 (32.7)
Minimally worse (5)	50 (19.2)	41 (16.5)	30 (11.9)	65 (23.4)
Moderately worse (6)	27 (10.4)	22 (8.9)	30 (11.9)	36 (12.9)
Markedly worse (7)	4 (1.5)	3 (1.2)	5 (2.0)	8 (2.9)
n	260	248	253	278
mean	4.0	3.9	3.9	4.2
SD	1.27	1.20	1.25	1.26
p-value	0.054	0.010*	0.009*	

p-values are derived from CMH test (van Elteren test) blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

ADCS-CGIC categorical analysis – patients with improvement

Population/Visit		Exelon 20 cm^2	Exelon 10 cm^2	Exelon capsule	Placebo
ITT (LOCF)					
Week 16	N	255	247	249	273
	n (%)	82 (32.2)	76 (30.8)	69 (27.7)	76 (27.8)
	p-value	0.266	0.422	0.917	
Week 24	N	260	248	253	278
	n (%)	85 (32.7)	77 (31.0)	92 (36.4)	78 (28.1)
	p-value	0.216	0.473	0.047*	
ITT+RDO (LOCF)					
	N	268	262	266	279
Week 16	n (%)	87 (32.5)	79 (30.2)	73 (27.4)	76 (27.2)
	p-value	0.157	0.359	0.969	
		273	264	271	285
Week 24	n (%)	90 (33.0)	79 (29.9)	94 (34.7)	79 (27.7)
	p-value	0.123	0.521	0.073	
ITT (OC)					
Week 16	N	255	247	249	273
	n (%)	82 (32.2)	76 (30.8)	69 (27.7)	76 (27.8)
	p-value	0.266	0.422	0.917	
Week 24	N	214	206	213	238
	n (%)	77 (36.0)	68 (33.0)	82 (38.5)	70 (29.4)
	p-value	0.069	0.384	0.042*	

Improvement: markedly, moderately, or minimally improved.
p-values are derived from CMH test blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

ADCS-ADL change from baseline – ITT (LOCF) population

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	261	247	253	280
	Baseline	Mean	47.5	50.1	49.3	49.2
	Post-baseline	Mean	47.8	49.5	48.9	47.7
	Change	Mean	0.4	-0.6	-0.4	-1.6
		p-value	0.035*	0.226	0.143	
Week 24			263	247	254	281
	Baseline	Mean	47.6	50.1	49.3	49.2
	Post-baseline	Mean	47.6	49.9	48.8	46.9
	Change	Mean	-0.0	-0.1	-0.5	-2.3
		p-value	0.017*	0.013*	0.039*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included.
Positive change score indicates improvement p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

ADCS-ADL change from baseline – ITT+RDO (LOCF) population

Visit			Exelon 20 cm^2 N = 279	Exelon 10 cm^2 N = 267	Exelon capsule N = 275	Placebo N = 289
Week 16		n	278	264	274	288
	Baseline	Mean	47.9	50.1	49.8	49.3
	Post-baseline	Mean	48.0	49.2	49.3	47.3
	Change	Mean	0.1	-0.9	-0.5	-1.9
		p-value	0.017*	0.185	0.051	
Week 24			278	264	274	288
	Baseline	Mean	47.9	50.1	49.8	49.3
	Post-baseline	Mean	47.6	49.7	49.2	46.5
	Change	Mean	-0.4	-0.4	-0.5	-2.8
		p-value	0.008*	0.005*	0.008*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Positive change score indicates improvement
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo. * $p < 0.05$

ADCS-ADL change from baseline – ITT (OC) population

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	261	247	252	280
	Baseline	Mean	47.5	50.1	49.3	49.2
	Post-baseline	Mean	47.8	49.5	48.9	47.7
	Change	Mean	0.4	-0.6	-0.4	-1.6
		p-value	0.035*	0.227	0.142	
Week 24			217	209	219	245
	Baseline	Mean	47.7	50.3	49.6	49.4
	Post-baseline	Mean	47.9	50.2	49.4	47.2
	Change	Mean	0.2	-0.1	-0.3	-2.2
		p-value	0.016*	0.021*	0.034*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Positive change score indicates improvement
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

ADCS-ADL categorical analysis – Patients with improvement

Population / Visit		Exelon 20 cm^2	Exelon 10 cm^2	Exelon capsule	Placebo
ITT (LOCF)					
Week 16	N	261	247	253	280
	n (%)	136 (52.1)	115 (46.6)	118 (46.6)	112 (40.0)
	p-value	0.005*	0.138	0.120	
Week 24	N	263	247	254	281
	n (%)	125 (47.5)	111 (44.9)	114 (44.9)	107 (38.1)
	p-value	0.031*	0.121	0.099	
ITT+RDO (LOCF)					
Week 16	N	278	264	274	288
	n (%)	141 (50.7)	119 (45.1)	123 (44.9)	112 (38.9)
	p-value	0.006*	0.182	0.167	
Week 24	N	278	264	274	288
	n (%)	126 (45.3)	114 (43.2)	121 (44.2)	107 (37.2)
	p-value	0.059	0.173	0.087	
ITT (OC)					
	N	261	247	252	280
Week 16	n (%)	136 (52.1)	115 (46.6)	118 (46.8)	112 (40.0)
	p-value	0.005*	0.138	0.106	
Week 24	N	217	209	219	245
	n (%)	105 (48.4)	93 (44.5)	100 (45.7)	91 (37.1)
	p-value	0.017*	0.127	0.054	

Improvement: at least 1 point improvement over baseline
p-values are derived from CMH test blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

Secondary Outcome Result(s)

NPI-12 change from baseline – ITT (LOCF) population

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	260	248	253	280
	Baseline	Mean	15.0	13.9	15.1	14.8
	Post-baseline	Mean	12.9	12.1	13.6	12.4
	Change	Mean	-2.1	-1.8	-1.5	-2.4
		p-value	0.547	0.684	0.319	
Week 24		n	263	248	253	281
	Baseline	Mean	15.1	13.9	15.1	14.9
	Post-baseline	Mean	12.8	12.2	12.8	13.2
	Change	Mean	-2.3	-1.7	-2.2	-1.7
		p-value	0.686	0.744	0.512	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Negative change scores indicate improvement.
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.

MMSE change from baseline – ITT (LOCF) population

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	259	250	256	281
	Baseline	Mean	16.6	16.7	16.4	16.4
	Post-baseline	Mean	17.8	17.7	17.0	16.6
	Change	Mean	1.1	1.0	0.6	0.2
		p-value	< 0.001*	0.007*	0.108	
Week 24		n	262	250	256	281
	Baseline	Mean	16.6	16.7	16.4	16.4
	Post-baseline	Mean	17.6	17.8	17.2	16.4
	Change	Mean	0.9	1.1	0.8	0.0
		p-value	0.002*	< 0.001*	0.002*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included.
Positive change score indicates improvement.
p-values are derived from CMH test (van Elteren test) blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

Ten point clock test change from baseline – ITT (LOCF) population

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	247	243	245	266
	Baseline	Mean	4.7	4.5	4.5	4.3
	Post-baseline	Mean	4.7	4.6	4.6	4.4
	Change	Mean	0.1	0.1	0.1	0.0
		p-value	0.211	0.194	0.223	
Week 24		n	251	245	246	269
	Baseline	Mean	4.7	4.5	4.4	4.3
	Post-baseline	Mean	4.9	4.6	4.6	4.2
	Change	Mean	0.3	0.1	0.2	-0.1
		p-value	0.077	0.079	0.152	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included.
Positive change score indicates improvement.
p-values are derived from CMH test (van Elteren test) blocking for country and are based on comparison of each Exelon treatment group with placebo.

Trail Making Test A change from baseline – ITT (LOCF) population

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	233	238	237	257
	Baseline	Mean	174.8	182.6	176.0	177.9
	Post-baseline	Mean	167.9	169.3	167.5	183.0
	Change	Mean	-6.9	-13.2	-8.4	5.2
		p-value	0.010*	< 0.001*	0.004*	
Week 24		n	238	241	240	258
	Baseline	Mean	176.5	183.3	177.2	178.3
	Post-baseline	Mean	170.0	171.0	167.4	186.0
	Change	Mean	-6.5	-12.3	-9.8	7.7
		p-value	0.005*	< 0.001*	< 0.001*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included.
Negative change score indicates improvement.
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

Summary of Safety

Safety Results

Number (%) of evaluations with caregiver's rating of adhesion by Exelon patch size - safety population

	Exelon patch size			
Adhesion	**5 cm^2**	**10 cm^2**	**15 cm^2**	**20 cm^2**
Total number of evaluations - N	695	1336	301	334
Patch remained completely on – n (%)	588 (84.6)	1131 (84.7)	236 (78.4)	245 (73.4)
Edges of the patch were lifting off – n (%)	85 (12.2)	151 (11.3)	49 (16.3)	69 (20.7)
Patch was mostly half off – n (%)	12 (1.7)	21 (1.6)	8 (2.7)	13 (3.9)
Patch was just hanging on – n (%)	4 (0.6)	16 (1.2)	4 (1.3)	4 (1.2)
Patch was completely detached – n (%)	6 (0.9)	17 (1.3)	4 (1.3)	3 (0.9)

N = total number of evaluations for that patch size.

Number (%) of patients with SAEs according to target treatment group and system organ class - safety population

Primary system organ class	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Total patients with SAEs	36 (11.9)	23 (7.9)	21 (7.1)	26 (8.6)
Nervous system disorders	10 (3.3)	6 (2.1)	6 (2.0)	5 (1.7)
Cardiac disorders	8 (2.6)	3 (1.0)	2 (0.7)	4 (1.3)
Gastrointestinal disorders	7 (2.3)	2 (0.7)	2 (0.7)	2 (0.7)
Infections & infestations	4 (1.3)	3 (1.0)	4 (1.4)	4 (1.3)
General disorders & administration site conditions	3 (1.0)	1 (0.3)	0 (0.0)	1 (0.3)
Metabolism & nutrition disorders	3 (1.0)	1 (0.3)	1 (0.3)	2 (0.7)
Psychiatric disorders	3 (1.0)	5 (1.7)	3 (1.0)	3 (1.0)
Injury, poisoning & procedural complications	2 (0.7)	3 (1.0)	0 (0.0)	8 (2.6)
Investigations	2 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)
Respiratory, thoracic & mediastinal disorders	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)
Hepatobiliary disorders	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)
Renal & urinary disorders	1 (0.3)	2 (0.7)	0 (0.0)	1 (0.3)
Surgical & medical procedures	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Musculoskeletal & connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Neoplasms benign, malignant & unspecified	0 (0.0)	3 (1.0)	1 (0.3)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

System Organ Class ordered by descending frequency in the Exelon 20 cm^2 treatment group

Number (%) of patients with cardiac disorder SAEs according to target treatment group – safety population

Preferred term	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Patients with cardiac disorder SAEs	8 (2.6)	3 (1.0)	2 (0.7)	4 (1.3)
Cardiac failure	3 (1.0)	0 (0.0)	0 (0.0)	2 (0.7)
Angina pectoris	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.7)
Atrial fibrillation	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus bradycardia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Sinus tachycardia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Acute myocardial infarction	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Arrhythmia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Tachyarrhythmia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

System Organ Class ordered by descending frequency in the Exelon 20 cm^2 treatment group

Number (%) of patients with nervous system disorder SAEs according to target treatment group – safety population

Preferred term	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Patients with nervous system disorder SAEs	10 (3.3)	6 (2.1)	6 (2.0)	5 (1.7)
Cerebrovascular accident	3 (1.0)	2 (0.7)	1 (0.3)	1 (0.3)
Dizziness	2 (0.7)	1 (0.3)	0 (0.0)	1 (0.3)
Transient ischaemic attack	2 (0.7)	1 (0.3)	1 (0.3)	0 (0.0)
Cerebellar haemorrhage	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Loss of consciousness	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Somnolence	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)
Cerebral haemorrhage	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Cerebral infarction	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Cerebrovascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Extrapyramidal disorder	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Normal pressure hydrocephalus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Senile dementia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

System Organ Class ordered by descending frequency in the Exelon 20 cm^2 treatment group

Number (%) of patients with gastrointestinal disorder SAEs according to target treatment group – safety population

Preferred term	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Patients with gastrointestinal disorder SAEs	7 (2.3)	2 (0.7)	2 (0.7)	2 (0.7)
Vomiting	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)
Abdominal discomfort	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Inguinal hernia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Intestinal infarction	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Rectal polyp	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)

System Organ Class ordered by descending frequency in the Exelon 20 cm^2 treatment group

Other Adverse Events by System Organ Class

Number (%) of patients with most frequent AEs by preferred term (at least 3% for any group) - safety population

	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Total no. of patients with AEs	200 (66.0)	147 (50.5)	186 (63.3)	139 (46.0)
Preferred Term				
Nausea	64 (21.1)	21 (7.2)	68 (23.1)	15 (5.0)
Vomiting	57 (18.8)	18 (6.2)	50 (17.0)	10 (3.3)
Diarrhea	31 (10.2)	18 (6.2)	16 (5.4)	10 (3.3)
Weight decreased	23 (7.6)	8 (2.7)	16 (5.4)	4 (1.3)
Dizziness	21 (6.9)	7 (2.4)	22 (7.5)	7 (2.3)
Decreased appetite	15 (5.0)	2 (0.7)	12 (4.1)	3 (1.0)
Headache	13 (4.3)	10 (3.4)	18 (6.1)	5 (1.7)
Anorexia	12 (4.0)	7 (2.4)	14 (4.8)	3 (1.0)
Depression	12 (4.0)	11 (3.8)	13 (4.4)	4 (1.3)
Insomnia	12 (4.0)	4 (1.4)	6 (2.0)	6 (2.0)
Abdominal pain	11 (3.6)	7 (2.4)	4 (1.4)	2 (0.7)
Asthenia	9 (3.0)	5 (1.7)	17 (5.8)	3 (1.0)
Anxiety	8 (2.6)	9 (3.1)	5 (1.7)	4 (1.3)
Agitation	7 (2.3)	3 (1.0)	11 (3.7)	5 (1.7)
Fall	7 (2.3)	6 (2.1)	7 (2.4)	10 (3.3)
Hypertension	4 (1.3)	2 (0.7)	12 (4.1)	11 (3.6)

AEs are listed by descending frequency in the Exelon 20 cm^2 treatment group

Number (%) of patients with AEs - most frequently affected system organ class - safety population

	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
At least one adverse event	200 (66.0)	147 (50.5)	186 (63.3)	139 (46.0)
System organ class				
Gastrointestinal disorders	116 (38.3)	58 (19.9)	108 (36.7)	43 (14.2)
Nervous system disorders	56 (18.5)	31 (10.7)	54 (18.4)	29 (9.6)
Psychiatric disorders	47 (15.5)	38 (13.1)	50 (17.0)	37 (12.3)
Metabolism & nutrition disorders	38 (12.5)	13 (4.5)	31 (10.5)	12 (4.0)
Investigations	35 (11.6)	10 (3.4)	22 (7.5)	9 (3.0)
Infections & infestations	34 (11.2)	33 (11.3)	29 (9.9)	30 (9.9)
General disorders & administration site conditions	31 (10.2)	24 (8.2)	31 (10.5)	12 (4.0)
Musculoskeletal & connective tissue disorders	16 (5.3)	12 (4.1)	11 (3.7)	15 (5.0)
Cardiac disorders	15 (5.0)	7 (2.4)	9 (3.1)	9 (3.0)
Injury, poisoning & procedural complications	15 (5.0)	12 (4.1)	14 (4.8)	25 (8.3)
Skin & subcutaneous tissue disorders	11 (3.6)	20 (6.9)	14 (4.8)	16 (5.3)
Vascular disorders	11 (3.6)	7 (2.4)	18 (6.1)	15 (5.0)
Renal & urinary disorders	9 (3.0)	7 (2.4)	4 (1.4)	6 (2.0)
Respiratory, thoracic & mediastinal disorders	8 (2.6)	5 (1.7)	13 (4.4)	13 (4.3)

System Organ Class ordered by descending frequency in the Exelon 20 cm^2 treatment group

Number (%) of patients with AEs leading to discontinuation of study drug - safety population

	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Any primary system organ class	31 (10.2)	31 (10.7)	25 (8.5)	18 (6.0)
Gastrointestinal disorders	10 (3.3)	3 (1.0)	13 (4.4)	4 (1.3)
Nervous system disorders	9 (3.0)	9 (3.1)	8 (2.7)	4 (1.3)
Skin & subcutaneous tissue disorders	5 (1.7)	2 (0.7)	3 (1.0)	1 (0.3)
General disorders & administration site conditions	4 (1.3)	8 (2.7)	1 (0.3)	1 (0.3)
Psychiatric disorders	3 (1.0)	6 (2.1)	1 (0.3)	2 (0.7)
Cardiac disorders	2 (0.7)	1 (0.3)	3 (1.0)	4 (1.3)
Investigations	2 (0.7)	4 (1.4)	2 (0.7)	1 (0.3)
Metabolism & nutrition disorders	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)
Blood & lymphatic system disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Ear & labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Infections & infestations	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
Injury, poisoning & procedural complications	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Renal & urinary disorders	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Respiratory, thoracic & mediastinal disorders	0 (0.0)	1 (0.3)	2 (0.7)	0 (0.0)

System Organ Class ordered by descending frequency in the Exelon 20 cm^2 treatment group
Some patients experienced events in more than one system organ class

Serious Adverse Events and Deaths

Number (%) of patients who died, had SAEs or discontinued because of SAEs or non-serious AEs during double-blind treatment – safety population

Patients with serious or significant AEs	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Deaths	5 (1.7)**	4 (1.4)*	2 (0.7)	3 (1.0)#
SAEs	36 (11.9)	23 (7.9)	21 (7.1)	26 (8.6)
Discontinued due to AEs	31 (10.2)	31 (10.7)	25 (8.5)	18 (6.0)
Discontinued due to SAEs	12 (4.0)	12 (4.1)	7 (2.4)	9 (3.0)
Discontinued due to non-serious AEs	20 (6.6)	19 (6.5)	19 (6.5)	9 (3.0)

* An additional patient died from cardiac arrest 7 days after discontinuation due to an SAE of delirium
** One patient died whilst receiving 5 cm^2 patch treatment (no up-titration had occurred)
# An additional patient died from cardiac arrest 17 days after discontinuation of study treatment

Number (%) of patients who died according to target treatment group, system organ class and preferred term – safety population

Primary system organ class Preferred term	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Total patients who died	5 (1.7)**	4 (1.4)*	2 (0.7)	3 (1.0)#
Cardiac disorders	2 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)
Cardiac failure	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
General disorders & administration site conditions	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden death	1 (0.3)[a]	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Injury, poisoning & procedural complications	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Head injury	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Subdural hematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Nervous system disorders	0 (0.0)	2 (0.7)	1 (0.3)	1 (0.3)
Cerebrovascular accident	0 (0.0)	2 (0.7)	1 (0.3)	1 (0.3)
Respiratory, thoracic & mediastinal disorders	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory failure	2 (0.7)[b]	0 (0.0)	0 (0.0)	0 (0.0)

* An additional patient died from cardiac arrest 7 days after discontinuation of study treatment due to an SAE of delirium
** One of these patients died whilst receiving 5 cm^2 patch treatment (no up-titration had occurred)
# An additional patient died from cardiac arrest 17 days after discontinuation
[a] Attributed by the investigator to progression of chronic ischemic heart disease
[b] respiratory failure was secondary to pneumonia

Other Relevant Findings

Notable abnormal vital signs by treatment (Safety population)

Variable	Result	Exelon 20 Cm2 N=303 n (%)	Exelon 10 Cm2 N=291 n (%)	Exelon capsule N=294 n (%)	Placebo N=302 n (%)
Sitting after 5 minutes					
Pulse	High	2(0.7)	0(0.0)	0(0.0)	0(0.0)
	Low	2(0.7)	4(1.4)	4(1.4)	1(0.3)
Diastolic blood pressure	High	3(1.0)	1(0.3)	0(0.0)	2(0.7)
	Low	3(1.0)	1(0.3)	1(0.3)	2(0.7)
Systolic blood pressure	High	4(1.3)	5(1.7)	9(3.1)	5(1.7)
	Low	5(1.7)	2(0.7)	6(2.0)	4(1.3)
Standing after 3 minutes					
Pulse	High	1(0.3)	1(0.3)	1(0.3)	0(0.0)
	Low	3(1.0)	3(1.0)	2(0.7)	0(0.0)
Diastolic blood pressure	High	1(0.3)	4(1.4)	0(0.0)	2(0.7)
	Low	1(0.3)	3(1.0)	3(1.0)	3(1.0)
Systolic blood pressure	High	5(1.7)	3(1.0)	7(2.4)	4(1.3)
	Low	4(1.3)	3(1.0)	7(2.4)	6(2.0)
Weight	High	14(4.6)	10(3.4)	20(6.8)	26(8.6)
	Low	37(12.2)	24(8.2)	30(10.2)	17(5.6)
	High and Low	0(0.0)	0(0.0)	2(0.7)	1(0.3)

Clinically Notable Criteria:
Pulse (bpm) > 120 bpm / < 50 bpm with increase/decrease from baseline of >= 15 bpm
Systolic Blood Pressure (mmHg) > 180 mmHg / < 90 mmHg with increase/decrease from baseline of >= 20 mmHg
Diastolic Blood Pressure (mmHg) > 105 mmHg / < 50 mmHg with increase/decrease from baseline of>= 15 mmHg
Weight (kg) -Change from baseline of >=7%
- Note: The categories Low, High and High/Low are mutually exclusive

ECG evaluations (safety population)

		Exelon 20 cm^2	Exelon 10 cm^2	Exelon capsule	Placebo
Mean baseline and change from baseline		N = 303	N = 291	N = 294	N = 302
ECG feature					
QT interval (msec)	n	130	123	125	141
	Baseline	393.7	394.8	390.8	395.3
	Change	5.0	1.4	2.2	1.1
QTcF interval (msec)	n	130	123	125	141
	Baseline	408.8	408.3	403.4	410.3
	Change	-2.6	-0.1	0.2	2.6
QTcB interval (msec)	n	130	123	125	141
	Baseline	417.1	415.7	410.3	418.5
	Change	-6.5	-0.8	-0.9	3.3
PR interval (msec)	n	127	119	120	133
	Baseline	162.3	161.0	162.8	166.9
	Change	1.7	0.1	-2.0	-0.3
RR interval (msec)	n	130	123	125	141
	Baseline	900.9	914.5	914.5	901.5
	Change	53.2	12.1	15.5	-9.5
QRS duration (msec)	n	130	123	125	141
	Baseline	91.5	90.4	90.5	93.1
	Change	-0.5	0.6	1.0	-0.4
Ventricular rate (bpm)	n	130	123	125	141
	Baseline	68.4	68.0	67.5	68.5
	Change	-3.7	-0.7	-1.2	0.4

QTcF – corrected QT interval (Fridericia correction)
QTcB – corrected QT interval (Bazett correction)

Number (%) of patients with investigator's most severe rating of skin irritation study by Exelon and Placebo patch size - safety population

	Exelon patch size				Placebo patch size			
Skin irritation	**20 cm^2**	**15 cm^2**	**10 cm^2**	**5 cm^2**	**20 cm^2**	**15 cm^2**	**10 cm^2**	**5 cm^2**
Patients with any rating - N	177	234	537	556	203	243	547	560
Patients with no skin irritation	105 (59.3)	145 (62.0)	276 (51.4)	427 (76.8)	136 (67.0)	196 (80.7)	408 (74.6)	492 (87.9)
Patients with no, slight or mild skin irritation	164 (92.7)	215 (91.9)	481 (89.6)	546 (98.2)	192 (94.6)	238 (97.9)	530 (96.9)	558 (99.6)
- Any severe rating – n (%)	2 (1.1)	4 (1.7)	12 (2.2)	2 (0.4)	2 (1.0)	1 (0.4)	1 (0.2)	0 (0.0)
Erythema - N	177	234	537	556	203	243	547	559
- No, slight or mild – n (%)	166 (93.8)	221 (94.4)	496 (92.4)	549 (98.7)	195 (96.1)	241 (99.2)	538 (98.4)	557 (99.6)
- Moderate or severe – n (%)	11 (6.2)	13 (5.6)	41 (7.6)	7 (1.3)	8 (3.9)	2 (0.8)	9 (1.6)	2 (0.4)
Edema- N	177	234	537	556	203	243	547	559
- No, slight or mild – n (%)	175 (98.9)	232 (99.1)	527 (98.1)	553 (99.5)	202 (99.5)	243 (100.0)	546 (99.8)	559 (100.0)
- Moderate or severe– n(%)	2 (1.1)	2 (0.9)	10 (1.9)	3 (0.5)	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Scaling - N	177	234	537	556	203	243	547	560
- No, dryness, glossy effect, or mild – n (%)	176 (99.4)	234 (100.0)	530 (98.7)	554 (99.6)	203 (100.0)	243 (100.0)	545 (99.6)	560 (100.0)
- Moderate or severe– n (%)	1 (0.6)	0 (0.0)	7 (1.3)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Fissures - N	177	234	537	556	203	243	547	560
- No or superficial – n (%)	177 (100.0)	233 (99.6)	535 (99.6)	556 (100.0)	203 (100.0)	243 (100.0)	547 (100.0)	560 (100.0)
- Single or deep – n (%)	0 (0.0)	1 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus - N	177	234	537	556	203	243	547	560
- Negative, slight or mild – n (%)	171 (96.6)	223 (95.3)	501 (93.3)	550 (98.9)	197 (97.0)	239 (98.4)	537 (98.2)	560 (100.0)
- Moderate or severe – n (%)	6 (3.4)	11 (4.7)	36 (6.7)	6 (1.1)	6 (3.0)	4 (1.8)	10 (2.1)	0 (0.0)
Pain, stinging and/or burning- N	177	234	537	556	203	243	547	560
- No, slight or mild – n (%)	177 (100.0)	232 (99.1)	531 (98.9)	555 (99.8)	199 (98.0)	243 (100.0)	547 (100.0)	560 (100.0)
- Moderate or severe– n (%)	0 (0.0)	2 (0.9)	6 (1.1)	1 (0.2)	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)

N= total number of patients with evaluations for that patch size
The most severe rating was used for patients with multiple occurrences of an irritation sub-category

Publication

Bengt Winbald, Jeffery Cummings, Niels Andreasen, George Grossberg, Marco Onofrj, Carl Sadowsky, Stefanie Zechner, Jennifer Nagel, Roger Lane. A 6-month double-blind, Randomized, Placebo-controlled study of a Transdermal patch in Alzheimer's Disease-Rivastigmine Patch versus Capsule. International journal of Geriatric Psychiatry. 2007 May; 22 (5):456-67.

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