Sponsor

Novartis

Generic Drug Name

Rivastigmine

Therapeutic Area of Trial

Mild to moderate dementia of the Alzheimer's type

Approved Indication

Treatment of patients with mild to moderately (severe) dementia of the Alzheimer's type.

Protocol Number

CENA713D2340

Title

A 48-week, multicenter, randomized, double-blind, parallel group evaluation of the comparative efficacy, safety, and tolerability of Exelon® 10 and 15 cm2 patch in patients with Alzheimer's disease showing cognitive decline during an initial open-label phase

Phase of Development

Phase IIIb

Study Start/End Dates

25-Jun-2007 (first patient first visit) to 04-May-2011 (last patient last visit); 21-May-2010 (last patient DB dose administration date).

Study Design/Methodology

This was a prospective, multicenter, randomized, DB, parallel-group study of two doses of Exelon patch in patients with Alzheimer's disease (AD). Eligible patients were initially treated with Exelon 10 cm2 patches (18 mg drug load with a nominal delivery rate of 9.5 mg/24 hours) for up to 48 weeks during the initial open-label (IOL) phase. Patients who demonstrated functional and cognitive decline during the IOL phase were randomized to receive Exelon 10 cm2 or 15 cm2 patch (27 mg drug load with a nominal delivery rate of 13.3 mg/24 hours) during a 48 week DB treatment phase.
Those who did not meet the decline criteria by Week 48 of the IOL phase were offered continued treatment with Exelon 10 cm2 for up to 48 weeks in an extended open-label (EOL) treatment phase. Based on discussions with a regulatory authority, Novartis extended the scope of this study to become a registration trial for the Exelon 15cm2 patch dose. As a result, the study was amended to elevate the assessment of overall function based on the ADCS-Instrumental ADL subscale from a secondary to a co-primary endpoint with the assessment of cognitive abilities based on the ADAS-cog subscale.

Centers

147 centers from 7 countries participated: Canada (11 centers), France (8 centers), Germany (24 centers), Italy (34 centers), Spain (3 centers), Switzerland (3 centers), and the United States (64 centers).

Publication

None

Outcome Measures

Primary Outcome Measures

- Change from Baseline in Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) Subscale at Week 48 of Double Blind Period.
- Change in Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL) Subscale Score from Baseline to Week 48 of Double Blind Period.

Secondary Outcome Measures

- Time to Functional Decline as Measured by Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL) Subscale During the Double Blind Period
- Change in Attention and Executive Function as Assessed by the Trail Making Test (Part A) at Week 48 of the Double Blind Period
- Change in Attention and Executive Function as Assessed by the Trail Making Test (Part B) at Week 48 of Double Blind Period
- Change From Baseline in Neuropsychiatric Inventory (NPI-10) Score at Week 48 of Double Blind Period
- Number of Patients With Adverse Events, Serious Adverse Events and Discontinuations Due to Adverse Events

Test Product, Dose, and Mode of Administration

Rivastigmine 5 cm^2 transdermal patch once a day during the first 4 weeks of open label treatment followed by rivastigmine 10 cm^2 transdermal patch once a day from week 4 to week 24, 36 or 48.

Rivastigmine transdermal patch 10 cm^2 and placebo to rivastigmine 15 cm^2 once daily for 48 weeks during the double blind period.

Rivastigmine transdermal patch 15 cm^2 and placebo to rivastigmine 10 cm^2 once daily for 48 weeks during double blind period.

Rivastigmine 10 cm^2 transdermal patch once a day during 48 weeks open label treatment running in parallel to the double blind period.

Statistical Methods

Data were summarized with respect to demographic and baseline characteristics, and efficacy and safety observations and assessments. For continuous variables, summary statistics included n (number of observations), mean, standard deviation, median, minimum and maximum values, as well as frequencies and percentages for categorical variables were presented.
For both co-primary outcome variables (ADAS-cog and ADCS-Instrumental ADL), the statistical analysis was based on the change from DB-baseline to DB-Week 48 of the total score. The treatment groups were compared using least square means derived by an Analysis of Covariance (ANCOVA) model.
As supportive analyses, the primary ANCOVA analyses and summary statistics were also performed for the observed cases (OC) based on ITT-DB population, and with LOCF and with OC based on PP-DB population. The comparison of treatment groups was also performed using the non-parametric van Elteren test stratified by country to assess the robustness of the results of the primary analysis based on ITT-DB with LOCF. This is also referred to as rank ANCOVA. Sensitivity analyses were performed on the ITT-DB population with OC for both co-primary variables based on a mixed-effects repeated measures model (MMRM) examining the treatment group differences as a function of time. The model included fixed effects for treatment group, country, baseline score, visit and treatment group-by-visit interaction and random effect for subject nested within treatment group. Additional sensitivity analyses were performed to evaluate the possibility that missing primary efficacy measure data may not be missing at random utilizing multiple imputations under MAR and different MNAR scenarios using penalty scores.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Male or female patients between 50 and 85 years of age with a diagnosis of probable Alzheimer’s Disease,
- Baseline Mini-Mental State Examination (MMSE) score 10-24 inclusive,
- A primary caregiver willing to accept responsibility for supervising treatment, assessing the patient's condition throughout the study, and for providing input into efficacy assessments.
- For double blind only: Meet the decline criteria of functional decline (as assessed by the investigator) and cognitive decline (assessed by a 2 point reduction in Mini-Mental State Examination score between visits or a 3 point reduction from baseline) at weeks 24 or 36 or 48 during the IOL.

Exclusion Criteria:

- Presence of an advanced, severe, progressive, or unstable disease of any type that could interfere with efficacy and safety assessments or put the patient at particular risk,
- Any medical or neurological condition other than Alzheimers Disease that could explain the patient's dementia,
- A diagnosis of probable or possible vascular dementia,
- A current diagnosis of unsuccessfully-treated depression, or any other mental disorder

that may interfere with the evaluation of the patient's response to study medication,

- A history or current diagnosis of cerebrovascular disease (e.g. stroke),
- A current diagnosis of severe or unstable cardiovascular disease (e.g. unstable coronary artery disease).

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow

Pre-Assignment Details

1,584 participants were enrolled, 1582 received study drug during the initial open label period; of these, 567 were qualified to enter a double blind randomized period.

Initial Open Label

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Table 14.1-1.1a (Page 2 of 2)
Patient disposition for the initial open label phase
(Enrolled population)

Disposition/Reason	Total N=1584 n (%)
Unsatisfactory therapeutic effect	58 (3.7)
Subject's condition no longer requires study drug	0 (0.0)
Subject withdrew consent	88 (5.6)
Lost to follow-up	22 (1.4)
Administrative problems	7 (0.4)
Death	22 (1.4)
Protocol deviation	28 (1.8)

Double blind

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Table 14.1-1.1b (Page 1 of 1)
Patient disposition for the double blind phase, by treatment group
(Randomized population)

Disposition / Reason	Exelon 15 cm2 N=280 n (%)	Exelon 10 cm2 N=287 n (%)	Total N=567 n (%)
Randomized	280 (100.0)	287 (100.0)	567 (100.0)
Exposed to study drug DB phase	280 (100.0)	286 (99.7)	566 (99.8)
Completed*	207 (73.9)	203 (70.7)	410 (72.3)
Discontinued**	73 (26.1)	83 (28.9)	156 (27.5)
Reason for discontinuation			
Lost to follow-up	6 (2.1)	4 (1.4)	10 (1.8)
Adverse Event(s)	28 (10.0)	33 (11.5)	61 (10.8)
Subject withdrew consent	17 (6.1)	20 (7.0)	37 (6.5)
Subject's condition no longer requires study drug	1 (0.4)	0 (0.0)	1 (0.2)
Protocol deviation	3 (1.1)	5 (1.7)	8 (1.4)
Death	3 (1.1)	5 (1.7)	8 (1.4)
Unsatisfactory therapeutic effect	13 (4.6)	13 (4.5)	26 (4.6)
Administrative problems	2 (0.7)	3 (1.0)	5 (0.9)

Extended Open Label

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Table 14.1-1.1c (Page 1 of 1)
Patient disposition for the extended open label phase
(Safety - EOL Population)

Disposition / Reason	Total N=457 n (%)
Subject entering in extended open label phase	459
Completed*	395 (86.4)
Discontinued**	62 (13.6)
Reason for discontinuation	
Administrative problems	4 (0.9)
Adverse Event(s)	18 (3.9)
Lost to follow-up	8 (1.8)
Subject withdrew consent	14 (3.1)
Protocol deviation	5 (1.1)
Unsatisfactory therapeutic effect	6 (1.3)
Death	7 (1.5)

Baseline Characteristics

		Total		
Age	Mean (SD)	74.93 (± 7.131)		
Gender	Male	592		
	Female	992		

Outcome Measure Results

Primary Outcome Measures

Change From Baseline in Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) Subscale at Week 48 of Double Blind Period

The Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) subscale comprises 11 items summed to a total score ranging from 0 to 70, with lower scores indicating less severe impairment. A negative change indicates an improvement from baseline.

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Table 14.2-1.2 (Page 1 of 2)
Change from baseline in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog)
in the double-blind phase, by treatment group
(ITT - DB Population)

Pop./ Visit		Exelon 15 cm2 N=265 n	Mean	SD	Median (Min, Max)	Exelon 10 cm2 N=271 n	Mean	SD	Median (Min, Max)	Exelon 15 cm2 vs Exelon 10 cm2 DLSM	95% CI	p-value
ITT-DB LOCF	Baseline	264	34.4	11.57	33.5 (10, 63)	268	34.9	12.04	33.0 (11, 64)			
DB-Wk 12	Value	264	34.2	12.63	34.0 (7, 63)	268	35.5	12.94	34.5 (7, 65)			
	Change	264	-0.2	6.45	0.0 (-21, 23)	268	0.6	6.27	1.0 (-24, 21)	-0.9	(-2.0, 0.1)	0.091
DB-Wk 24	Value	264	35.4	13.19	35.0 (6, 64)	268	37.1	13.34	35.0 (5, 67)			
	Change	264	1.0	7.01	1.0 (-21, 23)	268	2.2	6.63	2.0 (-23, 20)	-1.3	(-2.5, -0.2)	0.027*
DB-Wk 48	Value	264	38.5	13.46	39.0 (10, 68)	268	39.7	13.97	39.0 (11, 70)			
	Change	264	4.1	8.00	4.0 (-24, 34)	268	4.9	7.49	5.0 (-22, 26)	-0.8	(-2.1, 0.5)	0.227

- The baseline assessment corresponds to the last assessment in the initial open label phase.
- A negative change indicates an improvement from baseline. A negative difference (DLSM) indicates greater improvement in Exelon 15cm2 as compared to Exelon 10cm2.
- Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADAS-Cog score.
- * p < 0.05
- n is the number of patients with an assessment at baseline and the corresponding visit.

Change in Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL) Subscale Score From Baseline to Week 48 of Double Blind Period

The Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL) is a 16 item subscale of the caregiver-based ADCS-IADL scale, developed for the use in dementia studies. The ADCS-IADL total score ranges from 0 to 56, with higher scores indicating less severe impairment. A positive change indicates an improvement from baseline.

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Table 14.2-2.2 (Page 1 of 3)
Change from baseline in Alzheimer's Disease Cooperative Study -Instrumental Activities of Daily Living (ADCS-IADL) in the double-blind phase, by treatment group
(ITT - DB Population)

Pop./ Visit		Exelon 15 cm2 N=265 n	Mean	SD	Median	(Min, Max)	Exelon 10 cm2 N=271 n	Mean	SD	Median	(Min, Max)	Exelon 15 cm2 vs Exelon 10 cm2 DLSM	95% CI	p-value
ITT-DB LOCF	Baseline	265	27.5	13.31	28.0	(0, 55)	271	25.8	13.33	25.0	(1, 52)			
DB-Wk 8	Value	265	27.3	13.41	27.0	(0, 56)	271	25.0	13.13	24.0	(1, 52)			
	Change	265	-0.2	6.28	0.0	(-25, 18)	271	-0.8	6.27	0.0	(-35, 16)	0.8	(-0.2, 1.9)	0.114
DB-Wk 12	Value	265	27.5	13.79	27.0	(0, 56)	271	25.4	13.25	25.0	(0, 53)			
	Change	265	0.1	6.65	0.0	(-30, 18)	271	-0.4	7.06	0.0	(-32, 21)	0.7	(-0.5, 1.8)	0.252
DB-Wk 16	Value	265	26.7	13.75	26.0	(0, 56)	271	24.0	13.45	22.0	(1, 55)			
	Change	265	-0.7	6.63	0.0	(-30, 15)	271	-1.8	7.28	-1.0	(-35, 25)	1.3	(0.2, 2.5)	0.025*
DB-Wk 24	Value	265	26.0	13.46	26.0	(0, 55)	271	22.9	13.22	22.0	(1, 54)			
	Change	265	-1.5	7.23	-1.0	(-41, 20)	271	-2.8	7.42	-2.0	(-36, 18)	1.7	(0.5, 2.9)	0.005*
DB-Wk 32	Value	265	25.2	13.79	25.0	(0, 56)	271	21.7	13.58	21.0	(0, 53)			
	Change	265	-2.2	7.22	-1.0	(-33, 18)	271	-4.0	8.12	-3.0	(-39, 16)	2.1	(0.9, 3.4)	<0.001*
DB-Wk 48	Value	265	23.1	14.08	22.0	(0, 56)	271	19.6	13.35	17.0	(0, 55)			
	Change	265	-4.4	8.21	-3.0	(-42, 23)	271	-6.2	8.78	-5.0	(-41, 21)	2.2	(0.8, 3.6)	0.002*

- The baseline assessment corresponds to the last assessment in the initial open label phase.
- A positive change indicates an improvement from baseline. A positive difference (DLSM) indicates greater improvement in Exelon 15cm2 as compared to Exelon 10cm2.
- Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADCS-IADL score.
- * p < 0.05
- n is the number of patients with an assessment at baseline and the corresponding visit.

Secondary Outcome Measures

Time to Functional Decline as Measured by Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL) Subscale During the Double Blind Period

Functional decline was defined by either an at least 1 point decrease in the Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL) subscale score in a visit and confirmed by the following visit/assessment or at least 2 points decrease from the double blind randomization baseline.

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Table 16.1.9-1.6 (Page 15 of 33)
Time to functional decline from baseline in double-blind phase for Alzheimer's Disease Cooperative Study - Instrumental Activities of Daily Living (ADCS-IADL) total scores, by treatment group
(ITT - DB OC Population)

The LIFETEST Procedure

Stratum 1: TRTN = Exelon 10 cm2

Summary Statistics for Time Variable TFDECL

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval Transform	[Lower	Upper)
75	218.000	LINEAR	169.000	226.000
50	90.000	LINEAR	85.000	113.000
25	57.000	LINEAR	57.000	61.000

Mean	Standard Error
146.347	6.844

NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

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Table 16.1.9-1.6 (Page 30 of 33)
Time to functional decline from baseline in double-blind phase for Alzheimer's Disease Cooperative Study - Instrumental Activities of Daily Living (ADCS-IADL) total scores, by treatment group
(ITT - DB OC Population)

The LIFETEST Procedure

Stratum 2: TRTN = Exelon 15 cm2

Summary Statistics for Time Variable TFDECL

Quartile Estimates

Percent	Point Estimate	Transform	95% Confidence Interval [Lower	Upper)
75	337.000	LINEAR	186.000	344.000
50	91.000	LINEAR	85.000	113.000
25	57.000	LINEAR	57.000	58.000

Mean	Standard Error
165.281	8.220

NOTE: The mean survival time and its standard error were underestimated because the largest observation was censored and the estimation was restricted to the largest event time.

Change in Attention and Executive Function as Assessed by the Trail Making Test (Part A) at Week 48 of the Double Blind Period

Change from baseline to week 48 in total time to perform Trail Making Test (TMT) part A. This test provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions. The TMT part A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. The score represents the amount of time required to complete the task. Total values for TMT part A range between 0 and 300 seconds. A negative change indicates an improvement from baseline.

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Table 14.2-3.2 (Page 1 of 4)
Change from baseline in Trail Making Test (TMT) Part A and B in the double-blind phase, by treatment group
(ITT - DB Population)

Trail making test : Part A

Pop./ Visit		Exelon 15 cm2 N=265 n	Mean	SD	Median	(Min, Max)	Exelon 10 cm2 N=271 n	Mean	SD	Median	(Min, Max)	Exelon 15 cm2 vs Exelon 10 cm2 DLSM	95% CI	p-value
ITT-DB LOCF	Baseline	254	191.3	95.65	181.5	(30, 300)	258	199.4	95.86	209.0	(28, 300)			
DB-Wk 24	Value	254	195.6	96.92	199.5	(34, 300)	258	209.6	94.13	237.5	(34, 300)			
	Change	254	4.2	57.80	0.0	(-250, 246)	258	10.2	57.51	0.0	(-140, 264)	-7.8	(-17.3, 1.7)	0.105
DB-Wk 48	Value	254	207.6	96.12	229.5	(30, 300)	258	217.6	93.49	278.5	(28, 300)			
	Change	254	16.3	66.09	0.0	(-220, 246)	258	18.2	62.57	0.0	(-180, 264)	-3.8	(-14.3, 6.6)	0.473

Change in Attention and Executive Function as Assessed by the Trail Making Test (Part B) at Week 48 of Double Blind Period

Change from baseline to week 48 in total time to perform Trail Making Test (TMT) part B. This test provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions. TMT has two parts: Part A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. Task requirements are similar for TMT-Part B except the person must alternate between numbers and letters. Total values for TMT part B range between 0 and 420 seconds. A negative change from baseline indicates an improvement in condition.

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Table 14.2-3.2 (Page 3 of 4)
Change from baseline in Trail Making Test (TMT) Part A and B in the double-blind phase, by treatment group
(ITT - DB Population)

Trail making test : Part B

Pop./ Visit		Exelon 15 cm2 N=265 n	Mean	SD	Median	(Min, Max)	Exelon 10 cm2 N=271 n	Mean	SD	Median	(Min, Max)	Exelon 15 cm2 vs Exelon 10 cm2 DLSM	95% CI	p-value
ITT-DB LOCF	Baseline	235	372.2	84.83	420.0	(66, 420)	236	380.8	86.44	420.0	(56, 420)			
DB-Wk 24	Value	235	377.7	85.82	420.0	(78, 420)	236	381.6	84.10	420.0	(68, 420)			
	Change	235	5.5	66.58	0.0	(-235, 269)	236	0.9	71.71	0.0	(-240, 364)	1.6	(-9.9, 13.1)	0.784
DB-Wk 48	Value	235	381.4	83.08	420.0	(73, 420)	236	386.6	81.16	420.0	(56, 420)			
	Change	235	9.3	68.80	0.0	(-240, 325)	236	5.8	65.38	0.0	(-255, 364)	0.8	(-10.1, 11.8)	0.881

Change From Baseline in Neuropsychiatric Inventory (NPI) Score at Week 48 of Double Blind Period

Change from baseline to week 48 as assessed by the Neuropsychiatric Inventory (NPI) total score. A negative change indicates an improvement from baseline.

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Table 14.2-4.2 (Page 1 of 4)
Change from baseline in Neuropsychiatric Inventory (NPI) score in the double-blind phase, by treatment group
(ITT - DB Population)

NPI-10: Total score (frequency x severity)

Pop./ Visit		Exelon 15 cm2 N=265 n	Mean	SD	Median	(Min, Max)	Exelon 10 cm2 N=271 n	Mean	SD	Median	(Min, Max)	Exelon 15 cm2 vs Exelon 10 cm2 DLSM	95% CI	p-value
ITT-DB LOCF	Baseline	265	12.4	12.50	9.0	(0, 69)	271	14.4	13.69	11.0	(0, 69)			
DB-ENDPT	Value	265	13.8	14.00	10.0	(0, 63)	271	15.4	14.55	11.0	(0, 73)			
	Change	265	1.4	11.51	0.0	(-47, 60)	271	0.9	10.98	0.0	(-38, 41)	-0.1	(-1.9, 1.7)	0.927

Safety Results

Number of Patients With Adverse Events, Serious Adverse Events and Discontinuations Due to Adverse Events

Table 12-7 Adverse events during the IOL phase, by primary system organ class and decline status (Safety-IOL population)

Primary system organ class	Decliners N = 567 n (%)	Non-decliners N = 459 n (%)	Discontinued N = 556 n (%)	Total N = 1582 n (%)
Any system organ class	366 (64.6)	314 (68.4)	455 (81.8)	1135
Blood and lymphatic system disorders	2 (0.4)	5 (1.1)	10 (1.8)	17 (1.1)
Cardiac disorders	13 (2.3)	21 (4.6)	39 (7.0)	73 (4.6)
Ear and labyrinth disorders	10 (1.8)	17 (3.7)	13 (2.3)	40 (2.5)
Endocrine disorders	1 (0.2)	0 (0.0)	2 (0.4)	3 (0.2)
Eye disorders	13 (2.3)	7 (1.5)	4 (0.7)	24 (1.5)
Gastrointestinal disorders	77 (13.6)	79 (17.2)	137 (24.6)	293 (18.5)
General disorders and administration site conditions	116 (20.5)	104 (22.7)	221 (39.7)	441 (27.9)
Hepatobiliary disorders	0 (0.0)	4 (0.9)	4 (0.7)	8 (0.5)
Immune system disorders	1 (0.2)	1 (0.2)	1 (0.2)	3 (0.2)
Infections and infestations	77 (13.6)	76 (16.6)	70 (12.6)	223 (14.1)
Injury, poisoning and procedural complications	42 (7.4)	38 (8.3)	54 (9.7)	134 (8.5)
Investigations	36 (6.3)	35 (7.6)	27 (4.9)	98 (6.2)
Metabolism and nutrition disorders	33 (5.8)	28 (6.1)	40 (7.2)	101 (6.4)
Musculoskeletal and connective tissue disorders	43 (7.6)	39 (8.5)	37 (6.7)	119 (7.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.9)	15 (3.3)	20 (3.6)	40 (2.5)
Nervous system disorders	82 (14.5)	65 (14.2)	106 (19.1)	253 (16.0)
Psychiatric disorders	103 (18.2)	81 (17.6)	125 (22.5)	309 (19.5)
Renal and urinary disorders	21 (3.7)	18 (3.9)	23 (4.1)	62 (3.9)
Reproductive system and breast disorders	8 (1.4)	5 (1.1)	7 (1.3)	20 (1.3)
Respiratory, thoracic and mediastinal disorders	23 (4.1)	24 (5.2)	32 (5.8)	79 (5.0)
Skin and subcutaneous tissue disorders	31 (5.5)	20 (4.4)	25 (4.5)	76 (4.8)
Vascular disorders	36 (6.3)	31 (6.8)	37 (6.7)	104 (6.6)

System Organ Classes are sorted alphabetically.
A patient with multiple AEs within a primary SOC is counted only once.

Table 12-9 Adverse events in the double-blind phase, by primary system organ class and treatment group (Safety-DB population)

Primary system organ class	Exelon 15 cm² N = 280 n (%)	Exelon 10 cm² N = 283 n (%)	Total N = 563 n (%)
Any primary system organ class	210 (75.0)	193 (68.2)	403 (71.6)
Blood and lymphatic system disorders	4 (1.4)	7 (2.5)	11 (2.0)
Cardiac disorders	12 (4.3)	19 (6.7)	31 (5.5)
Ear and labyrinth disorders	7 (2.5)	3 (1.1)	10 (1.8)
Endocrine disorders	3 (1.1)	1 (0.4)	4 (0.7)
Eye disorders	3 (1.1)	4 (1.4)	7 (1.2)
Gastrointestinal disorders	82 (29.3)	54 (19.1)	136 (24.2)
General disorders and administration site conditions	65 (23.2)	60 (21.2)	125 (22.2)
Hepatobiliary disorders	1 (0.4)	0 (0.0)	1 (0.2)
Immune system disorders	0 (0.0)	4 (1.4)	4 (0.7)
Infections and infestations	49 (17.5)	52 (18.4)	101 (17.9)
Injury, poisoning and procedural complications	34 (12.1)	30 (10.6)	64 (11.4)
Investigations	24 (8.6)	14 (4.9)	38 (6.7)
Metabolism and nutrition disorders	31 (11.1)	25 (8.8)	56 (9.9)
Musculoskeletal and connective tissue disorders	20 (7.1)	38 (13.4)	58 (10.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (1.8)	8 (2.8)	13 (2.3)
Nervous system disorders	60 (21.4)	52 (18.4)	112 (19.9)
Psychiatric disorders	71 (25.4)	61 (21.6)	132 (23.4)
Renal and urinary disorders	14 (5.0)	17 (6.0)	31 (5.5)
Reproductive system and breast disorders	0 (0.0)	1 (0.4)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	13 (4.6)	12 (4.2)	25 (4.4)
Skin and subcutaneous tissue disorders	6 (2.1)	17 (6.0)	23 (4.1)
Social circumstances	0 (0.0)	1 (0.4)	1 (0.2)
Vascular disorders	15 (5.4)	20 (7.1)	35 (6.2)

Table 12-12 Number of patients who died, had serious AEs or discontinued due to AEs in the double-blind phase, by treatment group (Safety-DB population)

Event	Exelon 15 cm² N = 280 n (%)	Exelon 10 cm² N = 283 n (%)	Total N = 563 n (%)
Death	3 (1.1)	5 (1.8)	8 (1.4)
Serious adverse events (SAEs) [a]	44 (15.7)	44 (15.5)	88 (15.6)
Discontinued due to adverse events (AEs) [a]	27 (9.6)	36 (12.7)	63 (11.2)
Discontinued due to SAE (s) [a]	12 (4.3)	18 (6.4)	30 (5.3)

Extended open-label phase

During the EOL phase, Gastrointestinal disorders were reported in 52 patients (11.4%), and the most common was nausea (12 patients: 2.6%). General disorders and administration site conditions were reported in approximately 10.5% of patients. With the exception of application site erythema (2.2%), all specific preferred terms related to application site reactions were reported in less than 1% of patients (PT-Table 14.3.1-1.1c).

Other Relevant Findings

No other important or notable findings were reported in this study.

Date of Clinical Trial Report

23-Sep-2011

Date Posted to the Novartis Clinical Trial Results Database
04-May-2012 NOTE: This field will be completed by the person posting the template.
Date of Latest Update
Definition: Date of most recent update (ie, template was modified to include publication information). June13, 2012