NOVARTIS

Exelon® (rivastigmine tartrate)

Briefing Document for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting

May 17, 2006

Document status: Final

Release date: 13 Apr 2006

Number of pages: 66

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Table of contents

List of abbreviations

AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study (ADCS) - Activities of Daily Living
ADCS-CGIC	ADCS - Clinician's Global Impression of Change
ADL	Activities of daily living
AE	Adverse event
ANCOVA	Analysis of covariance
b.i.d.	bis in die (twice a day)
CDR	Cognitive Drug Research
CGIC	Clinician's Global Impression of Change
CMH	Cochran Mantel-Haenszel
CRF	Case report form
FDA	Food and Drug Administration
D-KEFS	Delis-Kaplan Executive Function System
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ITT	Intent-to-Treat
ITT+RDO	Intent-to-Treat and Retrieved drop out
LB	Lewy body (bodies)
LOCF	Last Observation Carried Forward
MMSE	Mini-Mental State Examination
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases- and Stroke/Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
NPI-D	Neuropsychiatric Inventory – Depression
OC	Observed Cases
PD	Parkinson's disease
PDD	Dementia associated with Parkinson's disease
PPT	Pedunculopontine
RDO	Retrieved drop out
sNDA	Supplemental New Drug Application
TPCT	Ten-Point Clock Test
UPDRS	Unified Parkinson's Disease Rating Scale

1 Purpose of Meeting

Data from the EXPRESS trial ("Rivastigmine for Dementia Associated with Parkinson's Disease" / ENA713B 2311) supported the supplemental New Drug Application (NDA 20823; SE1-016) for Exelon that was submitted to the Food and Drug Administration (FDA) on August 31, 2005. This application was submitted after a follow-up to an End-of-Phase 2 meeting with the Division on May 18, 2005 where Novartis was subsequently informed on May 24, 2005 that the Division would accept filing of a sNDA for Exelon for the proposed indication of the treatment of dementia associated with Parkinson's disease based on the results of the EXPRESS study alone. The purpose of this Advisory Committee Meeting is to discuss the sNDA and to determine whether this application justifies the proposed indication for Exelon.

2 Current indication

Exelon is currently approved for the treatment of mild to moderate dementia of the Alzheimer's type. In three pivotal placebo-controlled clinical trials involving more than 3,300 patients with mild to moderately severe AD, Exelon, at doses of 6-12 mg/day, was shown to provide significant improvement in cognition, (based on ADAS-cog), activities of daily living, and global assessment of efficacy.

AEs were generally mild to moderate and were primarily gastrointestinal. Exelon treatment was not associated bradycardia or cardiac arrhythmia. To date, clinically significant drug interactions have not been reported with Exelon. Post-marketing exposure to Exelon is estimated at 2.1 million patient years. Therefore, the safety profile of Exelon in AD has been well established.

3 Parkinson's disease dementia (PDD)

It is estimated that approximately 1.5 million Americans currently have PD with 60,000 additional cases diagnosed each year (National Parkinson's Foundation). The risk for the development of dementia in these patients is approximately 4-6 times higher than compared to non-PD age matched controls (Aarsland, et al. 2001a, Hughes, et al. 2000). A review of 27 studies representing 4,336 patients reported a mean prevalence of PDD of 40% (Cummings 1988). In a longtitudinal study by Aarsland (2003), the 8-year cumulative prevalence of dementia in a population-based and representative cohort of patients with PD was 78%. The risk of mortality in PD compared to the healthy elderly increases approximately two-fold when patients develop dementia (Levy, et al. 2002, Hughes, et al. 2004).

Dementia in PD is characterized by cognitive impairment, including executive dysfunction, amnestic or retrieval-type memory deficit and attentional impairment that is accompanied with declining activities of daily living and behavioral dysfunction, particularly psychosis.

It has been shown that dementia and associated behavioral complications (e.g., hallucinations) predict and decrease time to nursing home placement (Goetz 1993), and that cognitive and behavioral impairment are the greatest contributors to caregiver distress (Aarsland, et al. 1999). Behavioral impairment, such as hallucinations, and the additional potential for

dopaminergic induced psychosis may indicate the need for antipsychotic treatment. However, the increased risks of neuroleptic malignant syndrome, worsening of cognitive function and mortality associated with the use of atypical antipsychotics in this population mean that the management of these patients is particularly challenging to the clinician.

Dementia in PD is therefore, a significant factor that increases the burden on caregivers and health professionals, often leads to institutionalization and confers an increased risk of mortality, regardless of whether the patient is living in the community (Louis, et al. 1997) or in a nursing home (Fernandez and Lapane 2002).

Currently there is no approved treatment for the dementia in PD.

4 PDD, a distinct disease entity

4.1 Clinical features of PDD and differentiation from AD

PDD is a disorder characterized by motor, autonomic, cognitive, and neuropsychiatric symptoms in which dementia follows the diagnosis of PD by at least one year.

There are unique clinical features, particularly associated with PD, that distinguish PDD from AD. The presence of extrapyramidal motor symptoms, autonomic dysfunction, REM sleep disorder differentiates patients with PDD from AD in clinical settings.

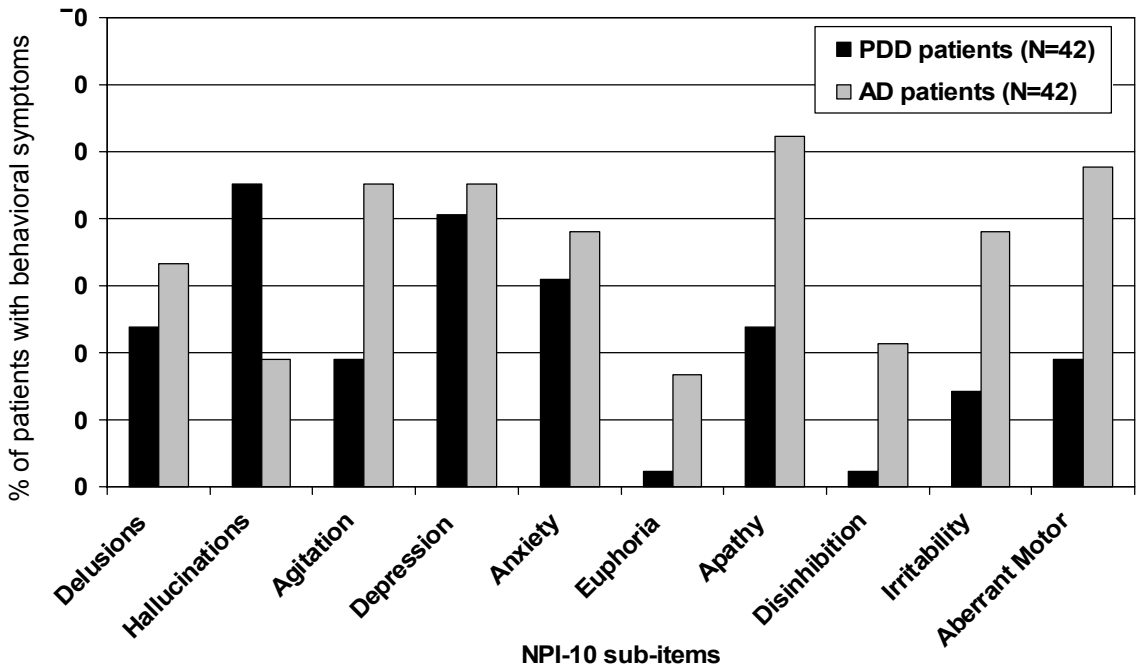
The core components of dementia in PDD, like AD, include cognitive decline, gradual loss in activities of daily living and behavioral dysfunction. The cognitive decline in PDD is primarily composed of memory deficits (amnestic or retrieval type), executive dysfunction, visuospatial deficits, mental slowness and fluctuating attention. Although executive dysfunction, visuospatial deficits and amnestic type memory loss are also seen in AD, there is usually more prominent language dysfunction at early phases of the disease and attentional deficit and mental slowness may not be prominent until later stages of the dementia. (Table 4-1).

Table 4-1 Core Components of Cognitive Deficits in PDD and AD

Cognitive Domain	PDD	AD
Memory	+++	+++
	Present (Retrieval or amnestic type)	Present (Amnestic type)
Executive dysfunction	+++	++
Bradyphrenia	+++	+
Fluctuating attention	++	+
Early visuospatial deficits	+++	+++
Language changes	+	++

Likewise, the components of behavioral dysfunction in the two dementias are similar; however, the prominence of these behavioral symptoms in PDD and AD facilitates distinct clinical diagnosis (Figure 4-1). In particular, visual hallucinations are frequent in patients with PD and are associated with higher risk of developing dementia, whereas in AD hallucination are not usually observed until late stages of dementia.

Figure 4-1 Behavioral distinctions between PDD and AD



Mean MMSE scores : PDD : 18.8 (SD 5.7) AD : 18.8 (SD 5.7)
Source: Aarsland, et al. 2001b.

DSM-IV criteria for the diagnosis of dementia PD exclude AD and NINCDS-ADRDA criteria for the probable diagnosis of AD exclude PD, allowing differential diagnosis in all clinical care settings.

In 2005, an expert report by Cummings, Emre and Olanow was commissioned by Novartis [Appendix 3] to address the question of whether PDD is a different disease entity from AD and whether practitioners can differentiate these conditions. The report was based on evidence from the published literature. The experts concluded that:

- there is a distinction between PDD and AD, based on epidemiological, genetic, clinical, pathological and neuroimaging scientific evidence in the literature.
- operational criteria based on DSM-IV and clinical pre-diagnosis of idiopathic PD permit the two conditions to be distinguished.
- the operational criteria can be applied by community practitioners so that they can readily differentiate between these conditions.

4.2 Neuropathology of PDD compared to AD

PDD is classified as in the spectrum of alpha-synucleinopathies (Leech, et al. 2001; Apaydin et al. 2002; Braak, et al. 2003). Several types of pathological changes are associated with dementia in PD and differentiate it from AD (Table 4-2). A unique pathological feature of PD and PDD is the marked nigro-striatal dopaminergic neuronal degeneration. Cell loss in the

medial substantia nigra is associated with the presence of dementia in PD (Rinne, et al. 1989). Extra-nigral pathology in the locus ceruleus may also contribute to cognitive deterioration in PDD (Zweig, et al. 1993).

The presence of cortical Lewy bodies (LB) in the basal forebrain cholinergic nuclei and in the pedunculopontine nucleus (PPT) also correlates strongly with the occurrence of dementia in patients with PD. This differs from AD, in which the clinical symptoms of dementia correlate best with the density of plaques and neurofibrillary tangles in the cortex (Jellinger 1988, Hurtig, et al. 2000, Apaydin, et al. 2002). The significance of LB pathology in patients with PDD has been clearly demonstrated in recent studies that used unique immunohistochemical staining techniques for identification of the alpha-synuclein constituent of LBs in the brain tissue (Braak, et al. 2005, Apaydin, et al. 2002). Recently, Braak, et al (2005), reported that in a pathology series of 88 patients with PDD, the burden of Alzheimer type pathology was mild and was insufficient to result in the dementia in these patients. The authors, therefore, concluded that dementia in patients with PD is mainly attributable to the progress of the underlying PD pathology. All patients in this series with cortical LB had co-existing LB pathology in their brain stem. This indicates that the evolution of LB pathology in the brain in PDD is different than the evolution of Alzheimer pathology in AD, which usually begins in the cortical areas of the brain.

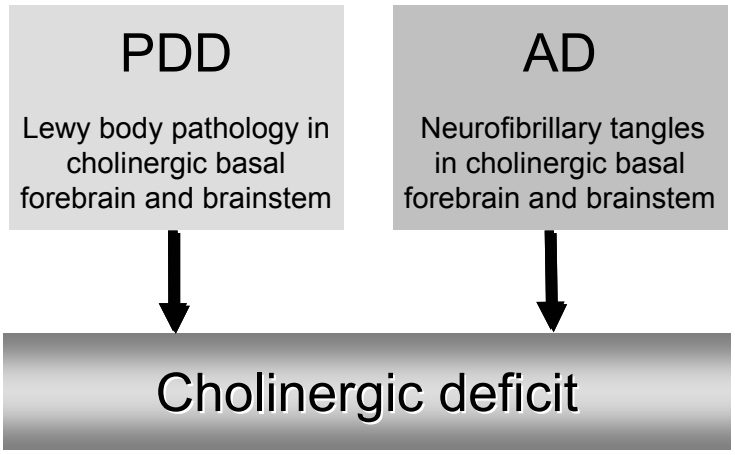
Table 4-2 Summary of pathophysiology of PDD and AD

	PDD	AD
Pathological hallmark	Lewy bodies	Plaques/neurofibrillary tangles
Cholinergic deficit	+++	++
Striatal Cell loss and Dopaminergic deficit	+++	+/-
Predominant brain region affected	Cortical/fronto-subcortical circuits	Cortical/ Hippocampus

Cholinergic deficit has been demonstrated in patients with PD, in the form of cholinergic neuronal loss in the nucleus basalis of Meynert (Zarow, et al. 2003), and these changes are most pronounced when patients are demented (Arendt, et al. 1983; Gaspar and Gray 1984; Whitehouse, et al. 1983).

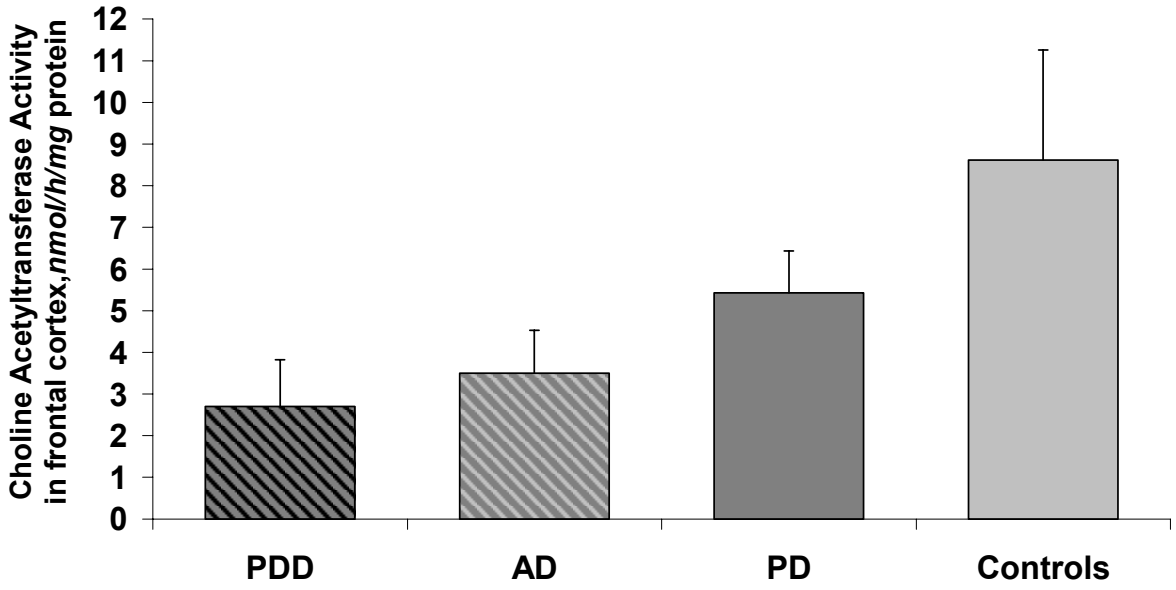
Although the characteristic neuropathology and its evolution in patients with PDD and AD are distinct, they share a common cholinergic deficit (Figure 4-2).

Figure 4-2 PDD and AD have a common cholinergic deficit



It has been demonstrated that the severity of the cholinergic deficiency in PDD is greater and more widespread than that occurring in AD (Figure 4-3), and this deficit may occur earlier in the course of PDD (Bohnen, et al. 2003; Kuhl, et al. 1996; Perry, et al. 1985). There is also substantial evidence to indicate that cholinergic deficits, in addition to contributing to cognitive symptoms, play an etiological role in the neuropsychiatric symptoms seen in patients with PDD (Perry, et al. 1985).

Figure 4-3 Cholinergic deficit in PDD compared to AD



Source: Perry E, et al. 1985.

Summary

Dementia in PD is a significant factor that increases the burden on caregivers and health professionals, often leads to institutionalization and confers an increased risk of mortality.

The presence of pre-exisiting PD with associated extrapyramidal motor symptoms, autonomic dysfunction and REM sleep disorder, together with more prominent deficits in retrieval memory executive dysfunction, bradyphrenia and attention, allows for clinical differentiation of patients with PDD from those with AD in routine clinical practice.

The neuropathology of PDD and AD differs. The dementia of PDD correlates most highly with the presence of cortical LBs and is associated with degeneration of the nigrostriatal dopamine system. The dementia of AD correlates best with the presence of cortical senile plaques and neurofibrillary tangles. Similarly, neuroimaging evidence supports a distinction between PDD and AD based on differences in the distribution of atrophy on structural imaging and degree of involvement of nigrostriatal dopaminergic function demonstrated on functional imaging.

Although PDD and AD have quite different neuropathological characteristics and evolution, they share a common cholinergic deficit. The severity of the cholinergic deficiency in PDD is generally greater than that occurring in AD. This deficit seems to occur earlier in the course of PDD and may result in a more rapid rate of cognitive decline in early stage disease as patients develop dementia.

Practitioners who are not dementia specialists are able to make a diagnosis of PDD based on:

- the presence of motor symptoms and history of PD that precede the onset of dementia
- the profile of cognitive and behavioral features described above that distinguish dementia in PD from AD
- the application of DSM-IV criteria for presence of dementia, which requires exclusion of patients with a diagnosis of AD

Conclusions

PDD compared to AD is characterized by:

- pre-exisiting PD with motor signs apparent years prior to the onset of dementia
- distinctive patterns of cognitive impairment
- prominent neuropsychiatric symptoms
- distinct neuropathology
- a common cholinergic deficit

A diagnosis of PDD can be made based on currently available clinical methods in all settings of care.

5 Rationale for Exelon treatment in PDD

Exelon® (rivastigmine tartrate) is a slowly reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase. Exelon capsules were approved by the US Food and Drug Administration (FDA) on April 21, 2000 for the treatment of mild to moderate dementia of the Alzheimer's type (NDA No.20-823).

PDD and AD share a common cholinergic deficit resulting in cognitive, behavioral and functional impairment. Inhibition of the cholinesterase enzymes involved in the breakdown of acetylcholine with Exelon, provides significant improvement in symptoms of dementia in patients with AD and in previous open label studies in PDD.

5.1 Prior studies of Exelon in PDD

To date, there are 3 published accounts (Reading, et al. 2001; Bullock & Cameron 2002; Giladi, et al. 2003) of small, uncontrolled of Exelon in PDD patients.

Table 5-1 Summary of published open-label studies with Exelon in PDD

Reference	N	Patient population, characteristics	Duration/dose	Outcome
Reading, et al. 2001	15	Open study, PD (for a mean of 12 years) with hallucinations in past 3 months, mean age 71 years, baseline MMSE 20	14 weeks, 3 weeks wash-out / 1.5-6 mg b.i.d	cognitive and behavioral improvement with treatment
Bullock & Cameron 2002	5	Open study, PD for a mean of 10 years, mean age 75 years, baseline MMSE 20.6	ranged 20 - 52 weeks/ Exelon 1.5-6 mg b.i.d	cognitive and functional improvement and improved visual hallucinations with treatment
Giladi, et al. 2003	28	Open study, PD for a mean of 7 years, mean age 75 years, baseline MMSE 19.5	26 weeks, 8 weeks wash-out / Exelon 1.5-6 mg b.i.d	global and cognitive improvement with treatment

In these small open-label studies, patients with a similar duration of PD to that of patients included in the EXPRESS study, treated for periods ranging from 14-52 weeks, experienced meaningful improvements in cognition, attention, behavior (visual hallucinations, sleep), global performance, activities of daily living, and caregiver distress. Gastrointestinal side effects appeared to be lower than in AD and, other than tremor that may emerge at higher doses, motor symptoms of the underlying PD were unaffected or improved.

These pilot studies provided a signal that supported the clinical and pharmacologic rationale for Exelon treatment in PDD.

6 Study ENA713B 2311 (EXPRESS)

6.1 Study Objective

The primary objective was to evaluate the efficacy and safety of Exelon (3 to 12 mg/day) compared with placebo for a treatment period of 24 weeks in patients with PDD.

6.2 Study Design

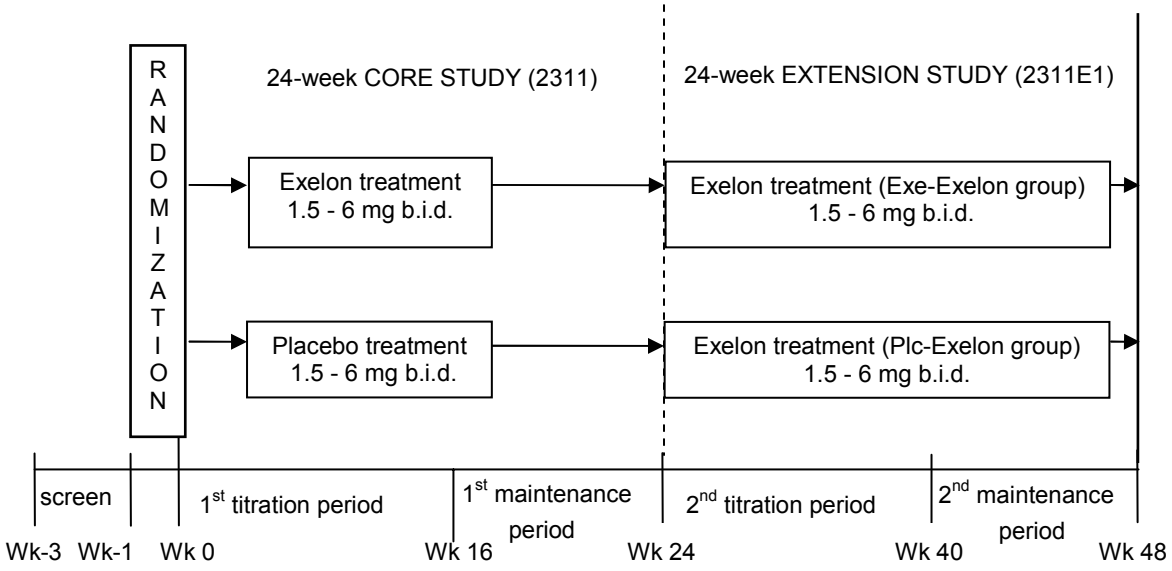
The design of the double-blind core study and open-label extension study are shown in Figure 6-1.

The core study consisted of a 2:1 randomized, parallel group, placebo-controlled design, to allow more patients to receive active therapy and maximize the amount of safety data. The 24-week core study was placebo-controlled to enable comparison of symptom progression. The study consisted of a 16-week dose-titration period followed by an 8-week maintenance period. Dose selection was based on the established dose regimen for Exelon in the treatment of AD. Under this regimen patients have their dose titrated upwards in 1.5 mg b.i.d. increments, and are maintained at the highest tolerated dose.

Following the completion of the core study, all patients who elected to continue in the extension study, regardless of whether they had been receiving placebo or Exelon, received a starting dose of 1.5 mg b.i.d. and were titrated or retitrated to their maximum tolerated dose of Exelon over a period of 16-weeks. The retitration of patients who had received Exelon during the core study was necessary to preserve the established randomization blinding. In a similar fashion to the core study, the dose titration period was followed by an 8-week maintenance period.

Exelon-treated PDD patients in the core study supply the main evidence for the efficacy and safety of the studied dose range. Exelon-treated patients, who continued to take Exelon in the extension study (Exe-Exelon), supply and confirm the evidence of efficacy and safety of the dose range for long-term treatment with Exelon.

Figure 6-1 Study design



6.3 Patient Selection

Patients were to have a diagnosis of PD, based on UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria and dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), with onset of symptoms of dementia at least 2 years after the first diagnosis of idiopathic PD and having no other possible causes. They were to have a Mini-Mental State Examination (MMSE) score of 10-24 (i.e. mild to moderate severity). Patients with a diagnosis of Alzheimer's disease and vascular dementia were excluded.

6.4 Efficacy Assessment Scales

Primary

1. **Cognition:** Alzheimer's Disease Assessment Scale-cognitive subscale (**ADAS-cog**). The ADAS-cog is a psychometric instrument designed to evaluate the severity of cognitive behavioral dysfunctions characteristic of people with dementia. Orientation, memory, language, and praxis are the domains directly assessed by this scale. The 11-item ADAS-cog scale was used in study 2311.
2. **Global clinical rating of change:** The Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change (**ADCS-CGIC**) provides a single global rating of change from baseline in cognition, behavior and functioning, measured on a 7–point scale. Scores of 1, 2, and 3 indicate improvement (marked, moderate, and minimal), a score of 4 indicates no change and scores of 5, 6, and 7 indicate worsening (minimal, moderate and marked).

ADAS-cog is a well established scale which has been used widely in clinical trials to evaluate cognitive symptoms of various dementias. The domains assessed by ADAS-cog are also important features of dementia in PD.

ADAS-CGIC, a global assessment scale, was used to confirm the that efficacy demonstrated on ADAS-cog was meaningful in terms of patients' overall improvement.

Secondary

1. Cognitive Drug Research (**CDR**) Computerized Assessment System tests for the assessment of attention. Power of Attention, which is the composite score for combination of the speed scores of the three tasks (simple reaction time, digit vigilance, and choice reaction time), was the outcome measure for this scale.
2. Delis-Kaplan Executive Function System (**D-KEFS**). A battery of four tests for executive functioning: Verbal Fluency Test, Color-Word Interference Test, Card Sorting Test and Symbol Digit Modalities Test were performed in selected French and English speaking centers. At all other sites only the Verbal Fluency Test was performed.
3. Alzheimer's Disease Cooperative Study – Activities of Daily Living (**ADCS-ADL**) for the assessment of ability to perform activities of daily living.
4. Neuropsychiatric Inventory (**NPI**) for the assessment of behavior including delusions, hallucinations, apathy, depression, irritability, agitation, disinhibition, euphoria, aberrant

motor behavior, anxiety sleep and appetite. NPI Caregiver Distress Scale (**NPI-D**) for the assessment of caregiver distress due to behavioral disturbances.

5. Ten Point Clock Test (**TPCT**). Patient is asked to draw a clock from memory with a specified time. Assesses visuospatial impairment, planning, memory and executive function.
6. Mini-Mental State Examination (**MMSE**). A 30 item test which evaluates severity of cognitive impairment by assessing orientation, memory comprehension, naming, and praxis.

The ADAS-cog, MMSE, CDR-attention battery, D-KEFS verbal fluency and TPCT are direct patient performance scales. The ADCS-ADL, and NPI are assessed through interview with the caregiver. The ADCS-CGIC was assessed through patient and caregiver interviews by an independent clinician who was blinded to the other assessment scales employed in this study.

6.4.1 Validation of assessment scales

Although used in small published studies, some of the efficacy scales employed in the core and extension studies had not previously been fully validated for use in PDD. These scales were examined in a separate supplementary study (Study Report 2314), which tested the sensitivity to detect disease severity and test-retest reliability of various assessment scales of dementia (including ADAS-cog) in patient of PDD and AD.

The study results demonstrated in that the ADAS-cog scale was able to differentiate between mild and moderate severity (based on MMSE scores of 10-17 and 18-24, respectively), PDD and AD (t-test supported by an ANOVA model). Thus, in PDD and AD patients, mean ADAS-cog at baseline showed a distinct and statistically significant separation between mild and moderate dementia severity.

The test-retest reliability of the ADAS-cog was explored by obtaining a correlation coefficient between baseline and Week 4 results. For ADAS-cog, mean values were similar between baseline and Week 4, and correlation coefficients were strongly positive for all dementia type/severity combinations. Overall, the scale achieved a strongly reproducible result across the two time points, suggesting that ADAS-cog is a consistent and reliable scale to use in these patient populations.

In addition, an independent expert report by Harvey, et al. in 2004 [Summary of Clinical Efficacy – Appendix 1] provided advice to Novartis regarding the validity and reliability of the ADAS-cog and ADCS-ADL and a summary of the available literature for validity of scales used in the validation study (2314) protocol. The report concluded that the ADAS-cog has demonstrated sensitivity to clinical change in treatment trials in patients with AD and PDD and the level of benefit shown on the ADAS-cog scale by cholinesterase therapy in PDD is at least consistent with the improvements seen in AD.

6.5 Dose selection rationale

The dose range selected for use is the same as that currently approved for use in AD (6 - 12 mg/day, given as 3 - 6 mg b.i.d). Additional dose-ranging studies were not performed in PDD. The dose regimen design in the PDD studies consisted of stepwise upward titration, with dose reduction for intolerability, and efficacy evaluation at the start and end of the maintenance

period. This design was to evaluate the proposed dose range and not explore the dose/response relationship.

6.6 Definition of Endpoints and Statistical Methods

6.6.1 Endpoints for the primary analysis

The primary analyses in the core study examined the change from baseline in:

a) total ADAS-cog score, treatment comparisons were made with an analysis of covariance (ANCOVA).

b) ADCS-CGIC, treatment comparisons of the categorical variable were made with a van Elteren test.

The test hypothesis was superiority of Exelon over placebo in the ITT + RDO population for both primary variables after 24 weeks of treatment.

6.6.2 Secondary endpoints

Secondary (exploratory) variables in the core study, also measured as a change from baseline, were:

- Cognitive Drug Research (CDR) Computerized Assessment System of Power of Attention *for assessment of attention.*
- Delis-Kaplan Executive Function System (D-KEFS), verbal fluency, *for assessment of executive function.*
- Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL).
- Neuropsychiatric Inventory (NPI) *for assessment of neuropsychiatric symptoms*.
- Mini-Mental State Examination (MMSE), *for assessment of severity of cognitive impairment.*
- Ten-point Clock Test (TPCT), *for assessment of visuospatial impairment and executive function.*

Treatment comparisons were made using an analysis of covariance (ANCOVA) (for continuous variables), a van Elteren test (for ordered categorical variables) or a Cochran-Mantel-Haenszel test (CMH) (for dichotomized variables).

Most efficacy measurement variables from the core study were also assessed in the open-label extension study in the same way as in the core study, except that statistical analysis was descriptive and not inferential. Further descriptive (unplanned) analyses in the core study were applied as relevant for examining any topics of interest in the context of routine data review/exploration.

Statistical tests used to compare the treatment groups in the core study are summarized in Table 6-1.

Table 6-1 Statistical tests employed for the primary endpoints (core study 2311)

Scale/test	Efficacy variable	Statistical test (Exelon vs. placebo)
Primary		
ADAS-cog	Change from baseline in the sum score of the 11 items in ADAS-cog	ANCOVA model using treatment, country and baseline ADAS-cog as covariates; 95% confidence interval (CI) calculated for the difference between Least Squares Means (LSMEANS)
ADCS-CGIC	Overall clinical rating of change from baseline on a 7-point scale	CMH test using modified ridit scores with country as stratification (van Elteren test) blocking for country

Source: [Report 2311-Section 6.1.5]

Additional pre-planned analyses for the primary outcome measure included: categorical analysis of improvement ≥4 points on ADAS-cog and categorical analysis of any improvement and of improvement < 4 on CGIC.

Post-hoc sensitivity analyses were performed assuming different methods of imputing missing data in ADAS-cog scores. Results of these analyses are provided in Section 6.10.1.2 and 6.10.1.3.

The results of post-hoc safety and efficacy analyses are provided throughout this document. Post-text tables for these analyses are provide in [Appendix 1].

Unless specified otherwise, all statistical tests were conducted against a 2-sided alternative hypothesis, employing a significance level of 0.05.

6.6.3 Sample size and power calculations

The sample size calculation was based on the two primary efficacy variables ADAS-cog total score and ADCS-CGIC. Patients were randomized to Exelon and placebo in a ratio of 2:1. Variability estimates (standard deviation) for the change from baseline in the ADAS-cog ranged from 6 to 7 points, based on 6-month ADAS-cog data from completed Exelon studies in AD patients (ITT analysis). To ensure adequate power in case of a higher variability in the PDD population as compared to the AD population, a standard deviation of 7.5 points was assumed. Using a two-sided test with a significance level of 0.05 and a pooled standard deviation of 7.5 points, a total sample size of 531 patients (354 on Exelon and 177 on placebo) was required to detect a difference of at least 2.25 points in the total ADAS-Cog score between Exelon and placebo with a power of 90%.

Assumptions regarding variability and treatment differences for the ADCS-CGIC were based on data available for the CIBIC-Plus, a scale very similar to the ADCS-CGIC, observed across four large double-blind Exelon studies in AD patients. However, to ensure adequate power in case of a higher variability in the PDD population as compared to the AD population, a standard deviation of 1.3 was assumed. Using a two-sided test with a significance level of 0.05 and a pooled standard deviation of 1.3 points, a total sample size of 525 patients (350 on Exelon and 175 on placebo) was required to detect a difference of at least 0.40 points (ITT analysis) with a power of 90%.

To ensure that the study has adequate power to detect statistically significant results for both primary variables, 540 evaluable patients were planned to be recruited.

The sample size calculations were performed using PASS 2000. A non-parametric adjustment for the sample size estimation of the ADCS-CGIC was applied.

6.6.4 Analysis populations

Data collected from each center were pooled. There were 3 prospectively planned analysis populations, two based on the Intent-to-treat population (ITT) and one on the Observed case population (OC). All three analysis populations included patients who received at least one dose of study medication and had at least a pre- and post-baseline efficacy assessment (Table 6-2).

Table 6-2 Analysis populations (core study 2311)

Population	Description, Purpose	Definition
All randomized **Exelon:** N=362 **Placebo:**N=179		
ITT + RDO (LOCF) **Exelon:** n=335 (92.5%) **Placebo:** n=166 (92.7%)	***ITT-Last Observation Carried Forward*** (includes Retrieved Drop-Outs) *Planned ITT population.*	all randomized patients taking ≥ 1 dose of study dug, with: ≥ 1 pre- & ≥ 1 post-baseline value for ≥ 1 primary efficacy variable, ***using the following imputation scheme*** (in sequence): 1. if missing, use retrieved drop-out value when patient returns; 2. if missing, use last preceding value
ITT (LOCF) **Exelon:** n=290 (80.1%) **Placebo :** n=159 (88.8%)	***ITT-Last Observation Carried Forward*** *Modified ITT population (adjusts for drop-outs)*	all randomized patients taking ≥ 1 dose of study dug, with: ≥ 1 pre- & ≥ 1 post-baseline value for ≥ 1 primary efficacy variable, ***using the following imputation scheme*** (in sequence): 1. if missing use last value on or ≤ 2 days after last study drug; 2. if assessment > 2 days after last study drug, exclude from analysis
OC **Exelon:** n=290 (80.1%) **Placebo:** n=159 (88.8%) (or as available)	***Observed cases*** *(no imputed values, for test at specific sites)*	all randomized patients taking ≥ 1 dose of study drug, with at least ≥ 1 pre- & ≥ 1 post-baseline value for ≥ 1 primary efficacy variable, ***using no imputation***

RDO (Retrieved drop-out) assessment = assessments made on patients prematurely dropping out but who provide retrieval assessments at or close to the time of their scheduled assessments
Source: [Report 2311-Section 6.1.1] [Report 2311-Table 7-3]

6.7 Patient Disposition and Demographics

There were 68 centers in 12 countries (Austria, Belgium, Canada, France, Germany, Italy, Netherlands, Norway, Spain, Portugal, Turkey and the United Kingdom).

A total of 109 patients failed to qualify for randomization. Of the 541 patients randomized, 76% completed the core study. The main reasons for discontinuation were, in general, what has been reported in dementia trials. Across all groups, adverse events (AEs) were the most common reason for discontinuation. The percentage of patients who discontinued was higher in the Exelon group compared to placebo (Table 6-3). This difference was mainly accounted for by the higher rate of discontinuations due to AEs (17.1% on Exelon vs. 7.8% on placebo) and by consent withdrawals. Discontinuations due to unsatisfactory therapeutic effect and deaths were more frequent in the placebo group (Table 6-3).

Table 6-3 Patient disposition

	Exelon		Placebo		Total	
Number (%) of patients						
Screened					650	
Randomized	362	(100)	179	(100)	541	(100)
Exposed	362	(100)	179	(100)	541	(100)
Completed	263	(72.7)	147	(82.1)	410	(75.8)
Discontinued	99	(27.3)	32	(17.9)	131	(24.2)
Main reason for discontinuation	n	(%)	n	(%)	n	(%)
Adverse event(s)	62	(17.1)	14	(7.8)	76	(14.0)
Consent withdrawal	21	(5.8)	2	(1.1)	23	(4.3)
Death	4	(1.1)	7	(3.9)	11	(2.0)
Protocol violation(s)	5	(1.4)	2	(1.1)	7	(1.3)
Unsatisfactory therapeutic effect	2	(0.6)	4	(2.2)	6	(1.1)
Lost to follow-up	4	(1.1)	1	(0.6)	5	(0.9)
Administrative reasons	0	(0.0)	2	(1.1)	2	(0.4)
Abnormal test procedure result(s)	1	(0.3)	0	(0.0)	1	(0.2)

Source: [Post-text table 7.1-1]

6.7.1 Demographics at Baseline

Baseline demographic characteristics for age, gender and race were comparable in both treatment groups (Table 6-4). The overall demographic characteristics (87% aged 65 years or over, 65% male) were representative of patients with PD and PDD (Tanner, et al. 1997).

Table 6-4 Demographic summary by treatment group – Safety population

		Exelon	Placebo	Total
		N = 362	N = 179	N = 541
Age (years)	Mean ± SD	72.8 ± 6.7	72.4 ± 6.4	72.7 ± 6.6
	Median	73.5	73.0	73.0
	Range	50 - 91	53 - 88	50 - 91
Age group – n (%)	< 65 years	49 (13.5)	19 (10.6)	68 (12.6)
	≥ 65 years	313 (86.5)	160 (89.4)	473 (87.4)
Gender – n (%)	Male	234 (64.6)	117 (65.4)	351 (64.9)
	Female	128 (35.4)	62 (34.6)	190 (35.1)
Race – n (%)	Caucasian	360 (99.4)	179 (100)	539 (99.6)
	Other	2 (0.6)	0	2 (0.4)

Source: [Post-text table 7.4-1]

Duration of PD, duration of PDD, and time interval between diagnosis of PD and initial symptoms of dementia were also well balanced between the treatment groups (Table 6-5). The mean duration between diagnosis of PD and first symptoms of PDD was 6.8 years. The distribution of PD severity as measured by Hoehn and Yahr staging was similar in the two groups and indicated a moderate stage of PD severity for majority of patients. The average MMSE scores in both treatment groups were comparable at study entry and indicated a mild to moderate stage of dementia.

Table 6-5 Baseline characteristics by treatment group – Safety population

		Exelon	Placebo	Total
		N = 362	N = 179	N = 541
Time since first symptom of idiopathic PD was noticed by patient/ caregiver (years)	n	360	179	539
	Mean ± SD	9.8 ± 5.9	10.5 ± 6.3	10.0 ± 6.0
	Median (min-max)	8.8 (2.2 - 33)	9.8 (2.1 - 34.9)	9.0 (2.1 - 34.9)
Time since idiopathic PD was first diagnosed by physician (years)	n	362	179	541
	Mean ± SD	8.7 ± 5.7	9.4 ± 5.9	9.0 ± 5.8
	Median (min-max)	7.0 (0.1 - 32)	7.9 (2.0 - 34.8)	7.6 (0.1 -34.8)
Time since first symptom of dementia was noticed by patient / caregiver (years)	n	360	178	538
	Mean ± SD	2.1 ± 1.7	2.3 ± 1.9	2.2 ± 1.7
	Median (min-max)	1.8 (0 – 9.6)	1.9 (0.1 – 15.6)	1.8 (0 – 15.6)
Time since PDD was first diagnosed by physician (years)	n	362	179	541
	Mean ± SD	1.1 ± 1.3	1.4 ± 1.8	1.2 ± 1.5
	Median (min-max)	0.6 (0 – 8.0)	0.7 (0 – 13.6)	0.7 (0 – 13.6)
Time between diagnosis of PD and first symptoms of dementia (years)	n	360	178	538
	Mean ± SD	6.6 ± 5.2	7.2 ± 5.2	6.8 ± 5.2
	Median (min-max)†	4.8 (0.4 – 27.9)	5.9 (1.5 – 30.5)	5 (0.4 – 30.5)
Modified Hoehn and Yahr staging	0	1 (0.3)	0	1 (0.2)
	1	7 (1.9)	4 (2.2)	11 (2.0)
	1.5	20 (5.5)	9 (5.0)	29 (5.4)
	2	65 (18.0)	31 (17.3)	96 (17.7)
	2.5	89 (24.6)	41 (22.9)	130 (24.0)
	3	114 (31.5)	63 (35.2)	177 (32.7)
	4	51 (14.1)	28 (15.6)	79 (14.6)
	5	15 (4.1)	2 (1.1)	17 (3.1)
Number of years of education	n	362	179	541
	Mean ± SD	8.8 ± 4.1	9.2 ± 3.9	9.0 ± 4.1
	Median (range)	8.0 (0-23)	9.0 (0-21)	8.0 (0-23)
MMSE score at baseline	Mean ± SD	19.4 ± 3.8	19.2 ± 4.1	19.3 ± 3.9
	Median	20.0	20.0	20.0
	Min-max‡	3 – 30	8 - 27	3 - 30
All Dopa & Dopa Derivatives	n	347	169	-
	Mean in mg/day* ± SD	663.4 ± 368.0	705.7 ± 349.9	-

*L Dopa doses were calculated for both standard and CR formulations of levodopa/carbidopa and levodopa/benserazide.

† one patient was excluded due to date recording error and 3 patients had missing dates for first symptoms of dementia. There were 17 patients (protocol violators with less than a 2 yr period between the first symptoms of dementia and the diagnosis of PD. For 9 of these patients, this period was greater than 1 year.

‡ There were 9 patients with MMSE scores outside the range of 10-24

Source: [Post-text table 7.4-2]

In the 24-week open-label extension study, there were no major differences between the patient population sub-groups with regard to baseline demographics and disease characteristics. The characteristics were relatively unchanged from those of the core study population. The average time between diagnosis of PD and the first symptoms of dementia was 6.7 years. The majority of patients were Hoehn and Yahr stages 2 to 3, with a similar distribution across both treatment groups in terms of severity of the PD. The only exception was an improvement in MMSE score at the extension study baseline compared to core study baseline in the Exe-Exelon group (i.e. patients who received Exelon during the core study and remained on Exelon in the extension study).

6.7.2 Dopa derivatives at baseline

During four weeks prior to the start of study medication, 95.9% of patients in the Exelon group and 94.4% of patients in the placebo group were receiving Dopa or dopa derivatives (i.e. sinemet, madopar, levodopa, levodopa with benserazide and carbidopa) (Table 6-8). The mean dose of these agents at baseline was comparable in the Exelon and placebo treatment groups. (Table 6-5).

6.8 Study Medication

6.8.1 Dosage

In this study, a titration phase of 16 weeks was followed by a maintenance phase of 8 weeks. The aim was to find the highest well-tolerated dose for each individual patient within the 16 week titration period. The highest well-tolerated dose for each individual patient was then to be maintained for the remaining 8 weeks, although dose adjustments were allowed at any time during this maintenance period.

Patients were started on Exelon 3 mg/day (1.5 mg b.i.d) and were titrated up to the maximum tolerated dose by 4 week intervals. The target maintenance dose range for Exelon was 6-12 mg/day. Patients who could not tolerate higher doses were allowed to stay on lower doses.

The average daily Exelon dose over 4-week intervals is shown in Table 6-6. The mean dose of Exelon taken at 24 weeks was 8.7 mg/day. Seventy-six percent (n=277) of patients received 6-12 mg/day of Exelon during the last three days of the core study (Report 2311, Appendix 8.1, Table 1-5)

Table 6-6 Average daily Exelon dose per treatment interval

	Exposure interval	n	Average daily dose (mg/day) ± SD
	Any exposure	362	6.3 ± 2.3
Titration phase	≤ week 4	362	3.0 ± 0.2
	> week 4 to week 8	343	5.4 ± 1.2
	> week 8 to week 12	324	7.2 ± 2.4
	> week 12 to week 16	301	8.6 ± 3.4
Maintenance phase	> week 16 to week 20	281	8.7 ± 3.4
	> week 20 to week 24	271	8.7 ± 3.4

Source: Post-text table 8.1-1

6.8.2 Patient exposure

The cumulative duration of patient exposure is summarized by treatment group in Table 6-7. The average duration of exposure was 20.6 weeks in the Exelon group and 22.1 weeks in the placebo group. Over half of patients in both groups were treated for at least 24 weeks.

Table 6-7 Overall exposure to study drug by treatment group – Safety population

	Exelon	Placebo
Exposure statistics (weeks)		
Mean ± SD	20.6 ± 7.1	22.1 ± 6.2
Median	24.0	24.1
Range	0.6 – 28.1	0.3 – 28.0

Source: Post-text table 8.1-2

6.9 Concomitant Medication

6.9.1 Dopaminergic agents

In the core study, dopaminergic medications were required to be kept at stable doses, unless changes in dosage were clinically indicated. Unlike many other chronic neurodegenerative disorders where treatment regimens may be stable over long periods of time, the routine clinical management of patients with PD often requires relatively frequent changes in dopaminergic drug doses due to fluctuations in symptom expression in the disease.

Within four weeks prior to the start of study medication 95.9% of Exelon-treated patients and 94.4% of placebo-treated patients were receiving Dopa or dopa derivatives. Dopamine agonists were being administered to 45.6% of the Exelon group and 46.4% of the placebo group (Table 6-8).

Table 6-8 Baseline and concomitant usage of dopaminergic agents (core study population)

	Core study	
Anatomical Therapeutic Chemical Class	**Exelon** (N = 362) n (%)	**Placebo** (N = 179) n (%)
Prior to core study baseline	347 (95.9)	169 (94.4)
Adamantane derivatives	38 (10.5)	17 (9.5)
Dopa and dopa derivatives*	347 (95.9)	169 (94.4)
Dopamine agonists	165 (45.6)	83 (46.4)
Monoamine oxidase B inhibitors	19 (5.2)	11 (6.1)
Other dopaminergic agents	70 (19.3)	55 (30.7)

	Core study	
Anatomical Therapeutic Chemical Class	**Exelon** (N = 362)	**Placebo** (N = 179)
Prolactin inhibitors**	43 (11.9)	21 (11.7)
New use during study	38 (10.5)	17 (9.5)
Adamantane derivatives	2 (0.6)	0 (0.0)
Dopa and dopa derivatives*	28 (7.7)	12 (6.7)
Dopamine agonists	9 (2.5)	5 (2.8)
Monoamine oxidase B inhibitors	0 (0.0)	1 (0.6)
Other dopaminergic agents	4 (1.1)	3 (1.7)
Prolactin inhibitors**	2 (0.6)	0 (0.0)
Increased dose during study***	23 (6.4)	8 (4.5)
Dopa and dopa derivatives*	20 (5.5)	8 (4.5)
Dopamine agonists	3 (0.8)	1 (0.6)
Other dopaminergic agents	2 (0.6)	0 (0.0)
Prolactin inhibitors**	0 (0.0)	0 (0.0)

* includes sinemet, madopar, levodopa, levodopa with benserazide and carbidopa

** includes cabergoline, bromocriptine and lisuride

***Increased dose = dose at last visit compared to dose at first visit of study

Source: [Report 2311 – Table 8-3], [Report 2311E1 – Table 8-3]

The data indicate that treatment with Exelon did not result in any clinically meaningful increase in new use of dopaminergic medication or an increase in dose of existing dopaminergic medication that would affect the interpretation of study results.

6.9.2 Antipsychotics

Patients were required to keep concomitant medications affecting the central nervous system unchanged for 4 weeks before starting study drug.

The percentage of Exelon- and placebo-treated patients on antipsychotics at baseline was comparable (27% and 25%, respectively). Although antipsychotics are used in treatment of psychosis in patients with PD, they should be prescribed with caution and patients need to be monitored closely due to extrapyramidal side effects. Analysis of antipsychotic use during the study showed that there were less newly introduced antipsychotics in the Exelon treatment group than in the placebo group (7.7% vs. 11.2%, respectively), dose increases were less frequent in the Exelon treatment group (2.5% vs. 3.9%) and dose decreases were comparable in both treatment groups (1.4% vs. 1.7%) (Table 6-9).

Table 6-9 Rate of new introduction, dose increases and dose decreases of antipsychotics (core study)

	Exelon N=362	**Placebo** N=179
Antipsychotics		
Newly introduced	28 (7.7%)	20 (11.2%)
Increased dose	9 (2.5%)	7 (3.9%)
Decreased dose	5 (1.4%)	3 (1.7%)

	Exelon N=362	Placebo N=179

Source: [Report 2311 PTT 8.2-4], [Report 2311 Appendix 8.1 Table 1-2]

Although the duration and dose of antipsychotic treatment have not been accounted for in the analysis, the data suggests that Exelon treatment may decrease the need for antipsychotic use in patients with PDD. Patients with visual hallucinations represent a subgroup of PD patients who often require antipsychotic treatment. For the patients in this study with visual hallucinations at baseline, there were less newly introduced, or increased doses of, antipsychotics in the Exelon treatment group than in the placebo group (11.9% vs. 20.0%, respectively [Appendix 2, Table 4a3]).

6.10 Efficacy results

6.10.1 Primary efficacy

The primary efficacy analyses were performed on change from baseline scores on ADAS-cog and ADCS-CGIC at week 24.

ADAS-cog

For ADAS-cog, the analysis variable was the change from baseline in the sum score of the 11 items included in scale. Results of ADAS-cog scores for baseline and for weeks 16 and 24 are presented in Figure 6-2 and Table 6-10.

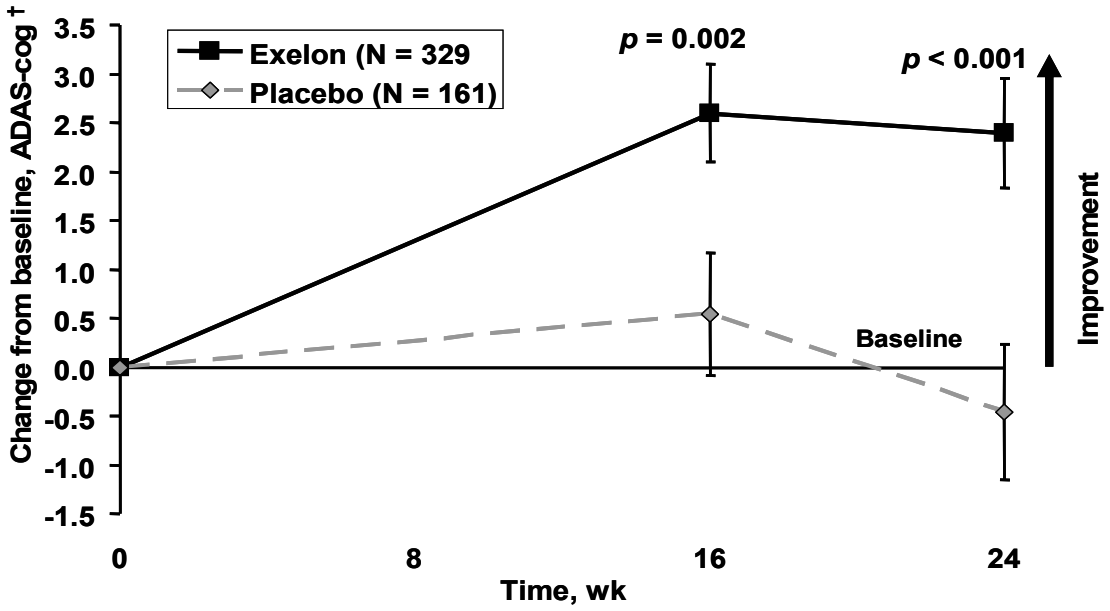


Figure 6-2 ADAS-cog change from baseline (ITT+RDO population, core study 2311)

† Least square means ± Standard Error. Least square means have been adjusted for baseline and country

Source: [Post-hoc Analyses Table 1-114]

In the primary analysis population (ITT+RDO), the Exelon treatment group achieved a arithmetic mean improvement on ADAS-cog of 2.1 points at week 24, whereas the placebo group deteriorated by a arithmetic mean change from baseline of -0.7 points. The difference was even more pronounced in the LOCF and OC analysis populations. The treatment group difference for the change from baseline was statistically significant in favor of Exelon in all three analysis populations, both at week 16 and at week 24. In addition, the treatment effect of 2.88 points (ITT+RDO population) for Exelon on ADAS-cog in the core study was comparable to that shown in placebo-controlled studies, with similar duration (26 weeks) and dose (3-12mg/day) in the approved indication of AD (2.1 points) (Birks, et al. 2000).

Table 6-10 ADAS-cog change from baseline (core study 2311)

	Exelon		Placebo				
Population† / Visit	n	mean (SD)	n	mean (SD)	LS MEANS difference	p-value*	95% CI‡
ITT+RDO							
Baseline	329	23.8 (10.2)	161	24.3 (10.5)			
Change at week 16	329	2.3 (7.3)	161	0.3 (6.8)	2.06	**0.002**	0.78; 3.34
Change at week 24	329	2.1 (8.2)	161	-0.7 (7.5)	2.88	**<0.001**	1.44; 4.31
LOCF							
Baseline	287	24.0 (10.3)	154	24.5 (10.6)			
Change at week 16	287	2.8 (7.4)	154	0.3 (6.7)	2.74	**<0.001**	1.42; 4.06
Change at week 24	287	2.5 (8.4)	154	-0.8 (7.5)	3.54	**<0.001**	2.05; 5.04
Observed Cases							
Baseline for week 16	284	23.9 (10.3)	150	24.5 (10.6)			
Change at week 16	284	2.8 (7.4)	150	0.3 (6.8)	2.78	**<0.001**	1.43; 4.12
Baseline for week 24	256	23.7 (10.4)	139	23.4 (9.8)			
Change at week 24	256	2.9 (8.3)	139	-1.0 (7.6)	3.80	**<0.001**	2.22; 5.37

Positive change in score indicates an improvement on the ADAS-cog scale
† ITT+RDO=intent-to-treat population, including retrieved drop-outs; LOCF=last observation carried forward; OC=observed cases
*P-value based on Analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
‡ 95% confidence interval calculated for the difference between Least Squares Means (LS MEANs).
Source: [Report 2311-Table 9-1]

ADCS-CGIC

For the ADCS-CGIC, the analysis variable was the overall clinical rating of change from baseline measured on a 7-point scale. Both the recorded value or category of the ADCS-CGIC and the dichotomized version of the ADCS-CGIC were used for statistical analysis. The ADCS-CGIC was dichotomized by the following scheme: Scores of 1, 2, and 3 (marked, moderate, and minimal improvement) were coded as "1" and interpreted as a positive response to study treatment, and scores of 4, 5, 6, and 7 (no change, minimal, moderate, and marked worsening) were coded as "0" and interpreted as no response to study treatment.

Results from this categorical analysis of the ADCS-CGIC ratings at week 24 are presented in Table 6-11 where a lower score (<4) indicates improvement, and a higher one (≥4) indicates no change or a deterioration. Mean values reflect the distribution of scores across all patients.

Table 6-11 ADCS-CGIC - categorical analysis at week 24 (core study 2311)

	ITT+RDO		LOCF		Observed Cases	
	Exelon	**Placebo**	**Exelon**	**Placebo**	**Exelon**	**Placebo**
N	329	165	289	158	252	145
Mean (SD) at week 24	3.8 (1.4)	4.3 (1.5)	3.7 (1.4)	4.3 (1.5)	3.7 (1.4)	4.2 (1.5)
Change						
Markedly improved (1)	4%	2%	5%	2%	6%	2%
Moderately improved (2)	16%	12%	16%	12%	18%	12%
Minimally improved (3)	21%	15%	23%	16%	23%	15%
Unchanged (4)	26%	28%	25%	28%	25%	29%
Minimally worse (5)	21%	19%	20%	19%	19%	19%
Moderately worse (6)	11%	16%	9%	17%	8%	17%
Markedly worse (7)	2%	7%	2%	6%	2%	6%
P-value*	**0.007**		**<0.001**		**<0.001**	

* P-value (Exelon vs. placebo) based on van Elteren test blocking for country.
Source: [Report 2311-Table 9-3]

Additional analyses of ADAS-cog

The percentage of patients in whom the ADAS-cog score improved on study drug by at least 4 points relative to baseline is summarized by categorical analysis in Table 6-12.

Table 6-12 ADAS-cog categorical analysis - patients improving >/= 4 points (core study 2311)

		Exelon		Placebo		
Population	**Visit**	**N**	**% improved‡**	**N**	**% improved‡**	**p-value***
ITT+RDO	week 16	329	36%	161	25%	**0.022**
	week 24	329	37%	161	29%	**0.074**
LOCF	week 16	287	39%	154	26%	**0.005**
	week 24	287	40%	154	29%	**0.015**
OC	week 16	284	39%	150	27%	**0.006**
	week 24	256	42%	139	29%	**0.008**

‡ Improvement was defined as at least 4 points improvement relative to baseline.
* P-values are based on CMH test blocking for country.
Source: [Report 2311-Table 9-2]

Improvement was statistically significant in favor of Exelon treatment in all analysis populations at weeks 16 and 24, except for the ITT+RDO population at week 24, where the statistical significance level was borderline (p=0.074).

As noted in [Report 2311-Section 9.1.1], when adjusted for duration of PD and severity of parkinsonian motor symptoms (UPDRS- part III score), the change from baseline in ADAS-cog scores at week 24 for Exelon remained significantly superior to placebo in all three analyses populations (ITT+RDO, LOCF and OC).

Table 6-13 Percentage of patients improved based on change from baseline on ADAS-cog total score at week 24 (core study 2311, ITT+RDO population)

	Change from baseline at week 24 in ADAS-cog		
	≥7	**≥4**	**≥0**
Exelon (N=329)	25.5%	37.4%	60.8%
Placebo (N=161)	12.4%	29.2%	53.4%

Source: [Post-hoc Analyses- Figure 1-1]

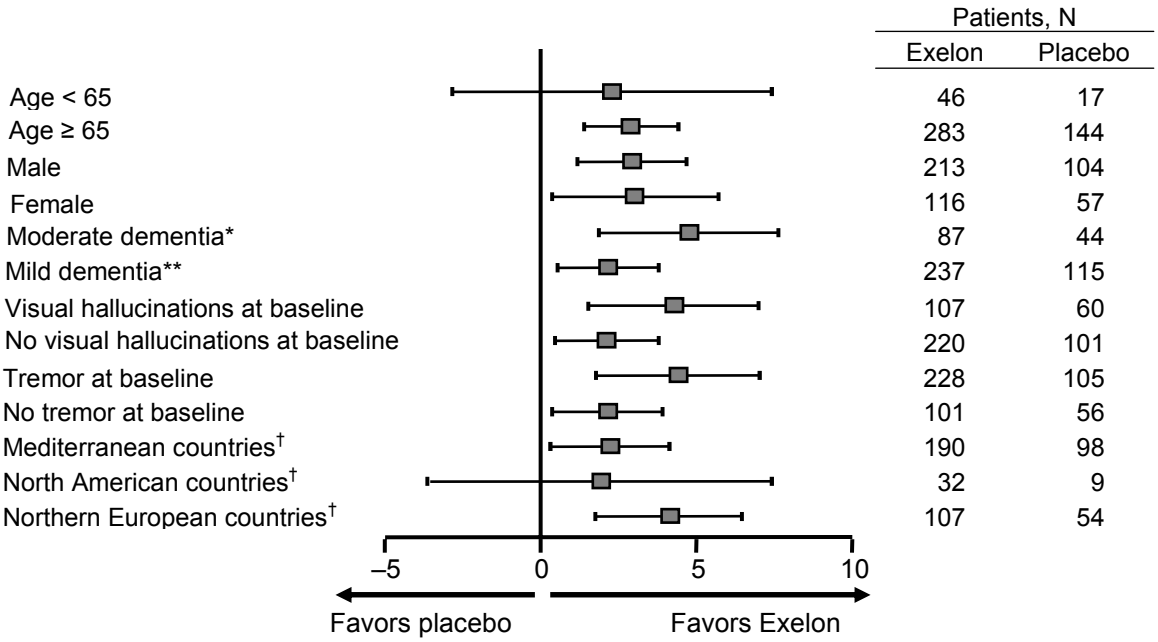
Table 6-13 shows that in the ITT+RDO population, a greater percentage of Exelon-treated patients improved based on change from baseline in total scores on the ADAS-cog compared to placebo-treated patients at week 24. Improvement on ADAS-cog of ≥7 points was observed for 25.8% of the Exelon-treated patients compared to 12.4% of the placebo group. Improvement of ≥4 points was observed for 37.4% of the Exelon group and 29.2% of the placebo group.

6.10.1.1 Consistency of Results across Subgroups

Post-hoc subgroup analysis of treatment difference between the Exelon and placebo groups in cognition (ADAS-cog) at week 24, showed consistency across all subgroups. Noteworthy, is the treatment difference in patients with visual hallucinations at baseline, a subgroup which presents clinicians with one of the greatest challenges in the management of patients with PDD (Figure 6-3).

The subgroups selected in Figure 6-3 represent a cross section of baseline demographics and disease characteristics. Detailed, post-hoc analysis for other efficacy and safety outcomes for patients with and without visual hallucinations at baseline are provided in [Appendix 2].

Figure 6-3 Treatment difference (95% CI) in ADAS-cog by subgroup at Wk 24



* MMSE score = 18-24

** MMSE score = 10-17

† Mediterranean countries: Italy, Turkey, Portugal, France and Spain
North America: Canada
Northern Europe: Austria, Germany, Great Britain, Belgium, Netherlands, and Norway.

Source: [Post-hoc Analyses Tables 1-25, 1-26, 1-29, 9.1-4c, 1-78, 1-114]

6.10.1.2 Sensitivity analysis (ADAS-cog)

A total of 40 patients (27 Exelon and 13 placebo) were not included in the ITT+RDO population. In addition, eleven patients (6 Exelon and 5 placebo) in the ITT+RDO population the total ADAS-cog scores could not be computed at baseline and post-baseline due to missing subitem values at all visits. Therefore, 51 patients were not included in the ADAS-cog analysis in the ITT+RDO population.

A post-hoc sensitivity analysis, 'placebo results for all', was performed using the placebo results from the ITT+RDO population (mean baseline total score of 24.3 and change from baseline of -0.7) to impute the missing data for those 51 patients regardless which treatment group the patients were randomized to.

Table 6-14 shows that the mean ADAS-cog total scores at baseline were 24.0 and 23.9 for Exelon and placebo groups, respectively, and the treatment difference in changes from baseline at week 24 was approximately 2.5 (LS mean difference).

The result was statistically significant, in favor of the Exelon group. This sensitivity analysis demonstrated that the superiority of Exelon over placebo was robust and consistent with the primary analysis results.

Table 6-14 Sensitivity analyses in ADAS-cog analysis for all randomized patients (core study)

	Exelon (N=362)	*Placebo* (N=179)	*p-value*
	mean±SD	mean±SD	
'Placebo results for all' method			
Baseline	24.0±10.2	23.9±10.5	
Change at Week 24	1.9±7.8	-0.7±7.1	**< 0.001***

p-value based on analysis of covariance model (ANCOVA) using treatment and country as factors and baseline ADAS-cog score as covariate.

Positive change score on ADAS-cog indicates improvement.

* p-value < 0.05

Source: [Post-hoc analysis 1-59]

Additional analyses of ADCS-CGIC

The categorical analysis of the ADCS-CGIC ratings at week 24 was statistically significant in favor of Exelon, a higher percentage of patients on active treatment demonstrated an improvement and a higher percentage of patients on placebo demonstrated a worsening.

The percentage of patients in whom the ADCS-CGIC rating improved (i.e., showed a response with a score <4) on study drug is summarized in Table 6-15.

Table 6-15 ADCS-CGIC — percentage of patients improving (core study 2311)

	Exelon		Placebo		
Population† / Visit	N	**% impr.**	N	**% impr.**	**p-value***
ITT+RDO					
Week 16	318	42%	159	31%	**0.028**
Week 24	329	41%	165	30%	**0.025**
LOCF					
Week 16	282	46%	153	31%	**0.007**
Week 24	289	44%	158	30%	**0.006**
Observed Cases					
Week 16	282	46%	153	31%	**0.007**
Week 24	252	46%	145	30%	**0.002**

† ITT+RDO=intent-to-treat population, including retrieved drop-outs; LOCF=last observation carried forward
* P-values are based on a CMH test blocking for country.

impr.=improving. Improving is defined as markedly, moderately or minimally improved.

Source: [Report 2311-Table 9-4]

Improvement ratings were significantly higher in the Exelon group in all analysis populations at weeks 16 and 24. The treatment effect was consistently in favor of Exelon, with odds ratios for an improvement on Exelon between 1.5 and 2.0 [Report 2311-Table 9-4].

As noted in [Report 2311-section 9.1.2], when adjusted for duration of PD and severity of parkinsonian motor symptoms (UPDRS part III score), ADCS-CGIC scores at week 24 remained significantly in favor of Exelon compared to placebo.

Table 6-16 shows that in the ITT+RDO population, based on the clinical global assessment of change scale (ADCS-CGIC), patients treated with Exelon demonstrated greater improvement from baseline compared to placebo-treated patients at week 24. Patients with ADCS-CGIC scores of ≤2 were 19.8% in the Exelon-treated group and 14.5% in the placebo-treated group, and patients with scores ≤3 on ADCS-CGIC were 40.7% in the Exelon-treated group and 29.7% in the placebo-treated group.

Table 6-16 Percentage of patients improved based on the scores in ADCS-CGIC at week 24 (core study 2311, ITT+RDO population)

	Change from baseline at week 24 in ADCS-CGIC		
	≤2	**≤3**	**≤4**
Exelon (N=329)	19.8%	40.7%	66.3%
Placebo (N=165)	14.5%	29.7%	57.6%

Source: [Post-hoc Analyses- Figure 1-2]

6.10.1.3 Sensitivity analysis (ADCS-CGIC)

The sensitivity analysis for ADCS-CGIC used 'placebo results for all' analysis, which imputed the median score of ADCS-CGIC at week 24 from the ITT+RDO population in the placebo group to the patients who did not have the evaluation of ADCS-CGIC at week 24 regardless which treatment group the patients were randomized to.

The results of this analysis demonstrated the superiority of Exelon over placebo (p=0.006), which was consistent with the results of the primary analysis of the core study.

6.10.2 Secondary efficacy results

Statistically significant superiority for Exelon over placebo for all key secondary outcome variables was shown (ITT + RDO population), indicating that measurable benefits in all cognitive, executive, attentional and behavioral domains were achieved (Table 6-17).

Table 6-17 Change from baseline in overall scores for key secondary outcome measures.

Scale	n	Mean change at Wk 24[§]	*p* value
ADCS-ADL[†]			
Exelon	333	–1.1	**0.023**
Placebo	165	–3.6	
NPI-10[†]			
Exelon	334	2.0	**0.015**
Placebo	166	0	
CDR-Attention battery[†]			
Exelon	328	–30.5	**0.009**
Placebo	158	142.7	
MMSE[†]			
Exelon	335	0.8	**0.028**
Placebo	166	–0.2	

Scale	n	Mean change at Wk 24§	*p* value
D-KEFS-Verbal fluency‡			
Exelon	258	1.7	**< 0.001**
Placebo	144	–1.1	
Ten-point clock‡			
Exelon	49	0.6	**0.015**
Placebo	30	–0.6	

§ On CDR-Attention Battery and NPI-10, negative change indicates improvement. On all other scales positive change indicates improvement.

†Analysis performed ITT+RDO population.

‡ Analysis performed on OC population only.

Source: [Report 2311- PTT 9.2-4, 9.2-22, 9.2-10, 9.2-35, 9.2-30, 9.2-34]

Caregiver distress measured by individual item changes on NPI-D did not reveal a significant difference between the treatment groups, however 10 of 12 items on the scale were numerically in favor of the Exelon group.

6.10.3 Long-term efficacy

Long-term efficacy data comes from the open-label extension study. No primary efficacy objectives were defined for this long-term extension study, the primary aim being to evaluate the safety and tolerability of long-term exposure to Exelon. Three hundred thirty-four patients entered the extension study, 211 patients who had received Exelon (Exe-Exelon) and 123 patients who had received placebo (Plc-Exelon) during the core study. Key efficacy analyses (ADAS-cog and ADCS-ADL) that were performed as secondary extension-study objectives are presented below.

Change from core-study baseline in ADAS-cog scores after 24 weeks of extension study treatment showed that the improvement was maintained for up to 48 weeks. Statistically significant improvement, similar to that seen for Exelon-treated patients during the core study, was seen for patients who received Exelon treatment *de novo* during the extension study (Table 6-18).

Table 6-18 Summary of changes in cognitive score (ADAS-cog) (extension study, OC populations compared to core study ITT+RDO population)

		Extension study (ADAS-cog)			
		Exe-Exelon		Plc-Exelon	
OC population	**Wk**	n	mean ± SD	n	mean ± SD
Core study Baseline	**0**	176	22.5 ± 9.6	97	23.3 ± 10.3
Extension study baseline	**24**	174	19.3 ± 9.6	95	23.6 ± 11.7
Mean change from week 24	**48**	162	-1.4 ± 6.9	93	**2.8 ± 6.8**
Mean change from week 0	**48**	162	**2.0 ± 7.3**	93	**2.2± 8.2**

Higher baseline score indicates greater impairment, positive change score indicates improvement

	Extension study (ADAS-cog)	
	Exe-Exelon	**Plc-Exelon**

Source: [Summary of Clinical Efficacy -Table 3-11]

An improvement relative to core study baseline of 0.4 points was maintained in the patient group treated with Exelon for 48 weeks. The decline observed during placebo treatment in the double-blind phase (-2.1 points at week 24) was reversed to some extent in the open-label extension (Table 6-19).

Table 6-19 ADCS-ADL total score - summary of changes (extension study 2311E1, OC population)

		Exe-Exelon	Plc-Exelon
Change from core study baseline (Wk 0) at wk 24	N	178	96
	Mean (SD)	1.5 (12.6)	-2.1 (10.6)
	Median (min-max)	1.5 (-40 to 47)	-1 (-33 to 37)
	95% CI	[-0.3, 3.4]	[-4.3, 0.0]
Change from extension study baseline (wk 24) at wk 48	N	169	93
	Mean (SD)	-1.1 (11.1)	1.4 (11.3)
	Median (min-max)	0 (-46 to 35)	1 (-37 to 30)
	95% CI	[-2.8, 0.5]	[-1.0, 3.7]
Change from core study baseline (Wk 0) at week 48	N	171	95
	Mean (SD)	0.4 (14.1)	-0.8 (13.7)
	Median (min-max)	1 (-57 to 50)	-1 (-39 to 42)
	95% CI	[-1.7, 2.6]	[-3.6, 2.0]

Positive change indicates an improvement.
Source: [Summary of Clinical Efficacy Table 3-24]

Change from core-study baseline in most other key secondary efficacy measures after 24 weeks of extension study treatment showed improvement was maintained for up to 48 weeks (Report 2311E1-Tables 9-3, 9-4, 9-5).

6.10.4 Efficacy summary and conclusions

Summary

Superior efficacy of Exelon treatment relative to placebo was demonstrated on both primary outcome measures at study endpoint.. The treatment differences between Exelon and placebo groups consistently achieved a high level of statistical significance of $p<0.001$ for both ADAS-cog and CGIC assessments in ITT+RDO, ITT-LOCF and OC populations, except for the treatment difference on CGIC assessment in the ITT+RDO population ($p=0.007$). The consistent, statistically significant, superior efficacy of Exelon over placebo was also evident at the week 16 assessments. Post-hoc subgroup analysis of treatment difference between the Exelon and placebo groups in cognition (ADAS-cog) at week 24, showed consistency across

all subgroups. Noteworthy, is the treatment difference in patients with visual hallucinations at baseline, a subgroup which presents clinicians with one of the greatest challenges in the management of patients with PDD

The treatment effect of 2.88 points (ITT+RDO population) for Exelon on ADAS-cog in the core study was comparable to that shown in placebo-controlled studies, with similar duration (26 weeks) and dose (3-12mg/day) in the approved indication of AD (2.1 points). (Birks, et al. 2000). ADCS-CGIC is a global assessment tool for dementia and the treatment difference demonstrated on this measure - showing more improvement and less worsening with Exelon treatment - reflects the contribution of Exelon efficacy in all dementia symptom domains in addition to those that are assessed on ADAS-cog.

The secondary efficacy outcome measures in this study assessed the efficacy of Exelon in other domains of dementia symptomatology that are not fully assessed by the ADAS-cog. Statistically significant improvements were demonstrated in Exelon-treated patients on the secondary efficacy outcome measures assessing executive functioning, attention, behavior, and functional activity which complement the improvement in cognition assessment of dementia symptoms. seen on the ADAS-cog scale. All of these symptom domains contribute to disabilities characteristic of patients with PDD, and the significant improvements seen in all of these domains contribute to the global impression of efficacy seen on the ADCS-CGIC.

Conclusions

In the core study, Exelon treatment showed statistically significant benefits over placebo in both primary outcome measures and in the key secondary measures. Additionally, the results of post-hoc sensitivity analyses supported the robustness of the primary outcomes.

In the extension study, improvement from core-study baseline (week 0) was maintained in the main efficacy variable that measured cognition (ADAS-cog), in activities of daily living (ADCS-ADL), and in most other secondary variables that were assessed in this extension study.

6.11 Safety results

6.11.1 Adverse Events

The overall incidence of AEs and the most frequently affected organ systems in all study groups is shown in Table 6-20.

Overall the incidence of patients with AEs in the core study was higher for Exelon-treated patients than for the placebo group (83.7% and 70.9%, respectively).

The system organ classes most frequently affected in all Exelon-treated groups in the double-blind core and open-label extension studies were gastrointestinal and nervous system disorders. This pattern is identical (with slightly lower incidence of AEs of nausea and vomiting in PDD) to that seen with Exelon treatment in AD patients treated with a similar Exelon regimen, dosage and for a similar time period (Exelon Prescribing Information). The incidence of psychiatric AEs was similar in both treatment groups. Vascular and cardiac AEs were less frequent in the Exelon treatment group. AEs classified as metabolism and nutritional disorders were more frequently affected in the Exelon-treated patients in the core study

compared to placebo. The individual AEs in this system organ class, including anorexia, were frequently related to AEs reported under gastrointestinal system organ class. AEs classified as musculoskeletal and connective tissue, and eye disorders for Exelon-treated patients consisted of a variety of infrequent individual events that make no significant contribution to the safety profile of Exelon. The AE profile in the core and extension studies was similar.

Table 6-20 AE incidence rate overall and by system organ class (all events) (core and extension populations)

	Core study		*Extension study*	
	Exelon n (%)	**Placebo** n (%)	**Exe-Exelon** n (%)	**Plc-Exelon** n (%)
Total patients studied	362 (100)	179 (100)	211 (100)	123 (100)
Total patients with AE(s)	303 (83.7)	127 (70.9)	159 (75.4)	93 (75.6)
System organ class				
Gastrointestinal disorders	183 (50.6)	48 (26.8)	58 (27.5)	47 (38.2)
Nervous system disorders	122 (33.7)	47 (26.3)	49 (23.2)	38 (30.9)
Psychiatric disorders	86 (23.8)	41 (22.9)	51 (24.2)	23 (18.7)
General disorders & administrative site conditions	45 (12.4)	20 (11.2)	15 (7.1)	17 (13.8)
Infections & infestations	43 (11.9)	22 (12.3)	32 (15.2)	18 (14.6)
Metabolism & nutritional disorders	38 (10.5)	9 (5.0)	14(6.6)	10 (8.1)
Injury, poison. & procedures	37 (10.2)	18 (10.1)	15 (7.1)	14 (11.4)
Musculoskeletal & connective Tissues	36 (9.9)	9 (5.0)	7 (3.3)	10 (8.1)
Vascular disorders	30 (8.3)	31 (17.3)	19 (9.0)	16 (13.0)
Investigations	19 (5.2)	10 (5.6)	5 (2.4)	7 (5.7)
Cardiac disorders	16 (4.4)	12 (6.7)	10 (4.7)	2 (1.6)
Skin & subcutaneous tissue	16 (4.4)	6 (3.4)	6 (2.8)	2 (1.6)
Renal & urinary disorders	13 (3.6)	7 (3.9)	6 (2.8)	3 (2.4)
Ear & labyrinth disorders	10 (2.8)	3 (1.7)	1 (0.5)	3 (2.4)
Eye disorders	10(2.8)	1 (0.6)	6 (2.8)	2 (1.6)
Respiratory, thoracic. & mediastinal	10 (2.8)	6 (3.4)	4 (1.9)	2 (1.6)
Blood & lymphatic system	5 (1.4)	2 (1.1)	0 (0.0)	0 (0.0)
Surgical & medical procedure	4 (1.1)	5 (2.8)	1 (0.5)	0 (0.0)
Reproductive System & breast	3 (0.8)	0 (0.0)	3 (1.4)	1 (0.8)
Endocrine disorders	1 (0.3)	0 (0.0)	1 (0.5)	1 (0.8)
Neoplasms benign, malign.	1 (0.3)	0 (0.0)	1 (0.5)	1 (0.8)
Congenital, familial & genetic	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Social circumstances	0 (0.0)	1 (0.6)	2 (0.9)	0 (0.0)

Sorted by descending frequency of AEs in the core study Exelon group.
Source: [Report 2311- PTT 10.1-1] and [Report 2311E1- PTT 10.1-1]

6.11.1.1 Most frequently occurring AEs

The overall incidence of AEs and the frequency of the individual events in all study groups are shown in Table 6-21.

The hierarchy of frequently reported AEs for Exelon-treated patients was similar in the core and extension populations. The most frequently reported AEs were nausea, vomiting, tremor diarrhea and anorexia. For patients who had received Exelon treatment during the core study (Exe-Exelon), the incidence of these events decreased by approximately 50% during the extension. The majority of these events were transient and occurred during the required re-titration of Exelon during the first 16 weeks of the extension study.

It was also observed that the rates hallucination, hypotension, confusional state, constipation and orthostatic hypotension were lower with Exelon than with placebo in the core study population.

This frequency of AEs was, in general, identical to that seen with Exelon treatment in AD patients treated with same regimen, similar doses and for the same period. The only exceptions were less frequent reports of nausea and vomiting and slightly more frequent reports of tremor in PDD patients [Exelon Prescribing Information].

Table 6-21 Frequent AEs (>/= 5% patients in any group) (core and extension populations).

	Core study		*Extension study*	
	Exelon n (%)	**Placebo** n (%)	**Exe-Exelon** n (%)	**Plc-Exelon** n (%)
Total patients studied	362	179	211	123
Total patients with AE(s)	303 (83.7)	127 (70.9)	159 (75.4)	93 (75.6)
AE preferred term				
Nausea	105 (29.0)	20 (11.2)	29 (13.7)	33 (26.8)
Vomiting	60 (16.6)	3 (1.7)	17 (8.1)	20 (16.3)
Tremor	37 (10.2)	7 (3.9)	8 (3.8)	15 (12.2)
Diarrhea	26 (7.2)	8 (4.5)	4 (1.9)	4 (3.3)
Anorexia	22 (6.1)	5 (2.8)	6 (2.8)	6 (4.9)
Fall	21 (5.8)	11 (6.1)	7 (3.3)	9 (7.3)
Dizziness	21 (5.8)	2 (1.1)	5 (2.4)	3 (2.4)
Hypotension	19 (5.2)	14 (7.8)	8 (3.8)	5 (4.1)
Hallucination	17 (4.7)	17 (9.5)	9 (4.3)	7 (5.7)
Constipation	17 (4.7)	12 (6.7)	4 (1.9)	2 (1.6)
Confusional state	13 (3.6)	10 (5.6)	10 (4.7)	7 (5.7)
Somnolence	13 (3.6)	5 (2.8)	5 (2.4)	7 (5.7)
Urinary tract infection	12 (3.3)	6 (3.4)	4 (1.9)	7 (5.7)
Orthostatic hypotension	6 (1.7)	9 (5.0)	5 (2.4)	4 (3.3)

Sorted by descending frequency of AEs in the core study Exelon group.
Source: [Report 2311- PTT 10.1-4] and [Report 2311E1- PTT 10.1-4]

Table 6-22 Frequent AEs in patients that completed the core study and entered the extension study.

	Core Study	*Extension Study*
	Exelon N = **211** n (%)	**Exe-Exelon** N = **211** n (%)
Total patients with AE(s)	170 (80.6)	159 (75.4)
AE preferred term		
Nausea	56 (26.5)	29 (13.7)
Vomiting	36 (17.1)	17 (8.1)
Tremor	21 (10.0)	8 (3.8)
Anorexia	16 (7.6)	6 (2.8)
Diarrhea	14 (6.6)	4 (1.9)
Fall	11(5.2)	7 (3.3)
Dizziness	11 (5.2)	5 (2.4)
Hypotension	11 (5.2)	8 (3.8)
Somnolence	11 (5.2)	5 (2.4)
Constipation	7(3.3)	4 (1.9)
Urinary tract infection	7(3.3)	4 (1.9)
Hallucination	7 (3.3)	9 (4.3)
Confusional state	4 (1.9)	10 (4.7)
Orthostatic hypotension	3 (1.4)	5 (2.4)

Source: Post-hoc analysis table 2-101

Post-hoc analysis was performed on the AE data for the 211 Exelon-treated patients who completed the core study and continued treatment during the extension. Table 6-22 shows that for this subgroup of patients, the incidence rates and hierarchy of the most frequently events reported during the core study were very similar to those reported for the total core-study Exelon population (Table 6-21). This demonstrates that the much lower rate of AEs reported in the extension study compared to the core study, was a real reduction and not the result of the 211 patients experiencing a lower rate of AEs during the core study.

6.11.1.2 Severity of AEs

In the Exelon treatment group compared to the placebo group, there was a slightly lower frequency of mild AEs and a slightly higher frequency of moderate AEs in the double-blind core study. Severe AEs were equally common in all groups comprising the core and extension studies and were similarly distributed across system organ classes and events (Table 6-23).

Table 6-23 Frequent AEs rated as severe (>/=1% in any group) (core and extension populations)

	Core study		*Extension study*	
	Exelon n (%)	**Placebo** n (%)	**Exe - Exelon** n (%)	**Plc – Exelon** n (%)
Total patients studied	362	179	211	123
Total patients with AE(s)	303 (83.7)	127 (70.9)	159 (75.4)	93 (75.6)
Patients with mild AE(s)	94 (26.0)	54 (30.2)	53 (25.1)	31 (25.2)
Patients with moderate AE(s)	150 (41.4)	46 (25.7)	76 (36.0)	43 (35.0)
Patients with severe AE(s)	59 (16.3)	27 (15.1)	30 (14.2)	19 (15.4)
System Organ class AE pref. term (severe)				
Gastrointestinal disorders	17 (4.7)	3 (1.7)	6 (2.8)	3 (2.4)
Nausea	2 (0.6)	0 (0.0)	2 (0.9)	1 (0.8)
Vomiting	4 (1.1)	0 (0.0)	1 (0.5)	1 (0.8)
Nervous system disorders	10 (2.8)	9 (5.0)	4 (1.9)	5 (4.1)
Tremor	1 (0.3)	0 (0.0)	1 (0.5)	3 (2.4)
Injury, poisoning & procedures comp.	9 (2.5)	3 (1.7)	1 (0.5)	2 (1.6)
Psychiatric disorders	8 (2.2)	5 (2.8)	5 (2.4)	3 (2.4)
Hallucination	5 (1.4)	1 (0.6)	0 (0.0)	0 (0.0)
Vascular disorders	5 (1.4)	2 (1.1)	1 (0.5)	2 (1.6)
Hypotension	4 (1.1)	1 (0.6)	0 (0.0)	0 (0.0)
Infections & infestations	4 (1.1)	5 (2.8)	7 (3.3)	2 (1.6)
Pneumonia	3 (0.8)	1 (0.6)	2 (0.9)	2 (1.6)
Urinary tract infections	0 (0.0)	2 (1.1)	1 (0.8)	0 (0.0)
Cardiac disorders	4 (1.1)	5 (2.8)	4 (1.9)	1 (0.8)
Musculoskeletal. & connective tissue	3 (0.8)	0 (0.0)	0 (0.0)	2 (1.6)
Respiratory, thoracic & mediastinal	1 (0.3)	2 (1.1)	0 (0.0)	2 (1.6)

Sorted by descending frequency of system organ class in the core study Exelon group.
Source: [Report 2311- PTT 10.1-3] and [Report 2311E1- PTT 10.1-3]

6.11.1.3 Serious AEs

The overall incidence of SAEs, frequently affected system organ classes and events by preferred term are shown for all study groups in Table 6-24. The total number of patients with SAEs during the double-blind core study was slightly lower in the Exelon group compared to the placebo group (13% in the Exelon group versus 14.5 % in the placebo group).

During the core study the most commonly affected system organ classes were nervous system, psychiatric disorders and infections and infestations. In all three system organ classes, the total incidence of SAEs was higher in the placebo group compared to the Exelon group. System organ classes where the total incidence of SAEs were higher in the Exelon group included gastrointestinal system, nutritional and metabolism disorders, injury, poisoning and procedural complications and vascular disorders. The incidence of SAEs reported in cardiac

system organ class were more frequent in the placebo group compared to the Exelon-treated patients.

The system organ classes affected by SAEs were not noticeably different among the treatment groups in the core and extension studies. During the open-label extension study, the total incidence of patients reporting SAEs increased slightly in both Exe-Exelon and Plc-Exelon groups, but no new unexpected events emerged (Table 6-24).

Table 6-24 SAEs by system organ class and frequent events (>/=1% in any group) (core and extension populations)

	Core study		*Extension study*	
	Exelon n (%)	**Placebo** n (%)	**Exe-Exelon** n (%)	**Plc- Exelon** n (%)
Total patients studied	362	179	211	123
Total patients with SAE(s)	47 (13.0)	26 (14.5)	37 (17.5)	20 (16.3)
System Organ Class				
AE Preferred Term				
Injury, poisoning and procedural complications	10 (2.8)	4 (2.2)	5 (2.4)	3 (2.4)
Hip fracture	3 (0.8)	0 (0.0)	1 (0.5)	0 (0.0)
Gastrointestinal Disorders	9 (2.5)	4 (2.2)	4 (1.9)	3 (2.4)
Vomiting	1 (0.3)	0 (0.0)	1 (0.5)	2 (1.6)
Metabolism & nutrition disorders	7 (1.9)	2 (1.1)	3 (1.4)	0 (0.0)
Dehydration	5 (1.4)	2 (1.1)	3 (1.4)	0 (0.0)
Psychiatric disorders	7 (1.9)	6 (3.4)	7 (3.3)	3 (2.4)
Confusional state	2 (0.6)	2 (1.1)	2 (0.9)	2 (1.6)
Nervous system disorders	6 (1.7)	8 (4.5)	7 (3.3)	7 (5.7)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Syncope	0 (0.0)	2 (1.1)	1 (0.5)	1 (0.8)
Infections & infestations	5 (1.4)	7 (3.9)	8 (3.8)	7 (5.7)
Pneumonia	3 (0.8)	1 (0.6)	2(0.9)	5(4.1)
Urinary tract infection	1 (0.3)	1 (0.6)	2 (0.9)	2 (1.6)
Investigations	4 (1.1)	0 (0.0)	1 (0.5)	0 (0.0)
Vascular Disorders	4 (1.1)	1 (0.6)	1 (0.5)	2 (1.6)
Cardiac Disorders	3 (0.8)	3 (1.7)	5 (2.4)	1 (0.8)
General Disorders & administrative site conditions	1 (0.3)	1 (0.6)	0 (0.0)	3 (2.4)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	2 (1.1)	0 (0.0)	1 (0.8)

Sorted by descending frequency of AEs in the core study Exelon group.

Source: [Report 2311- PTT 10.2-1] and [Report 2311E1- PTT 10.2-1]

* Source: Derived from [Report 2311- PTT 10.2-1, PTL 10.2-2], and [Report 2311E1- PTT 10.2-1, PTL 10.2-2]

**One patient who died in the Exe-Exelon group did not have any SAEs.

6.11.2 AEs leading to treatment discontinuation

AEs leading to discontinuation of study drug are shown by system organ class and preferred term (≥1% incidence) for core and extension studies in Table 6-25.

Table 6-25 Discontinuations due to AEs (>/= 1% in any group) (core and extension populations)

	Core study		*Extension study*	
	Exelon n (%)	**Placebo** n (%)	**Exe-Exelon** n (%)	**Plc- Exelon** n (%)
Total patients studied	362	179	211	123
Total patients with AE(s)	303 (83.7)	127 (70.9)	159 (75.4)	93 (75.6)
Discontinuations due to AEs	66 (18.2)	20 (11.2)	21 (10.0)	17 (13.8)
Nausea	13 (3.6)	1 (0.6)	1 (0.5)	5 (4.1)
Vomiting	7 (1.9)	1 (0.6)	0 (0.0)	3 (2.4)
Tremor	6 (1.7)	0 (0.0)	1 (0.5)	2 (1.6)

Sorted by descending frequency of AEs in the core study Exelon group.
Source:[Report 2311- PTT 10.2-1], and [Report 2311E1- PTT 10.2-1]

The rates of discontinuation (including death) for all AEs were higher in the Exelon group than the placebo group in the core study. The most common event leading to discontinuation was nausea (13[3.6%]) followed by vomiting (7[1.9%]) and tremor (6[1.7%]). AE discontinuations in other system organ classes were comparable for both treatment groups during the core study.

In the extension study, the discontinuation rates due to these events for patients who had previously taken Exelon in the core study (Exe-Exelon) was very low (one case of nausea and one case of tremor). These findings suggest that these events did not persist.

The highest rates of discontinuations due to AEs in the Exelon treatment group were mostly seen during the dose titration phase, with few discontinuations occurring during the dose maintenance phase.

6.11.3 Effects on motor symptoms of PD

The cardinal extrapyramidal symptoms of PD include tremor, bradykinesia and muscle rigidity. In the core study (2311), AEs potentially associated with these Parkinsonian symptoms – that may have been due to treatment-emergence of one or a combination of the cardinal extrapyramidal symptoms - were generally mild or moderate in severity with only four reports of severe events in the Exelon-treated patients (1.1%) versus one severe event in those receiving placebo (0.6%) (Table 6-26).

Table 6-26 Profile of AEs potentially associated with cardinal parkinsonian symptoms (core study)

	Tremor		**Muscle rigidity**		**Bradykinesia**	
	Exelon	Placebo	Exelon	Placebo	Exelon	Placebo
N	362	179	362	179	362	179
Incidence	37 (10.2%)	7 (3.9%)	1 (0.3%)	0 (0.0%)	9 (2.5%)	3 (1.7%)

	Tremor		Muscle rigidity		Bradykinesia	
Total events	40	7	1	0	10	5
Severity[1]						
Mild	18 (5.0%)	5 (2.8%)	0 (0.0%)	0 (0.0%)	4 (1.1%)	1 (0.6%)
Moderate	18 (5.0%)	2 (1.1%)	1 (0.3%)	0 (0.0%)	4 (1.1%)	1 (0.6%)
Severe	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	1 (0.6%)
Serious (SAEs)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Resulted in DC[2]	6 (1.7%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	2 (0.6%)	0 (0.0%)
Con. Meds. Added[3]	5 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (20.0%)	0 (0.0%)
Resolved[3]	22 (55.0%)	3 (42.9%)	1 (100%)	0 (0.0%)	6 (60.0%)	1 (20.0%)
1 episode	34 (91.9%)	7(100%)	1(100%)	0 (0.0%)	8 (88.9%)	2 (66.7%)
>1 episode	3 (8.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	1 (33.3%)

[1]For patients with more than one event, the most severe event was used

[2] discontinued

[3] Percentages calculated on number of events

Source: [Report 2311 PTT 10.1-1, 10.1-3, 10.2-2, 10.2-3], [Report 2311 Appendix 7.1 Listing 1-19], [Post-hoc analysis Table 2-99]

Tremor had the highest incidence among AEs associated with PD, occurring in 10.2% of the Exelon group. These AEs were not recurrent (91.9% of patients reported a single episode) and led to discontinuation in only 1.7% of patients (Details concerning the patients' whose tremor was reported to be unresolved are provided in Section 6.11.3.1, p 49). The incidence of bradykinesia, rigidity, were both less than 5% in the core and extension studies.

To detect any worsening effect on motor symptoms of PD potentially associated with the use of Exelon, post-hoc analyses were performed on data from the following 3 sources:

- Pre-defined AEs potentially associated with PD
- The motor symptom assessment score, collected from the UPDRS part III scale
- The use of dopaminergic medication

6.11.3.1 AEs pre-defined as 'potentially associated with PD'

Twenty-two AE preferred terms were prospectively defined as 'potentially associated with PD' (Table 6-28). This grouping included preferred terms such as musculoskeletal stiffness, gait abnormality, fall and dysarthria, which could have been associated with conditions other than PD.

In the core study, 99 (27.3%) patients in the Exelon group and 28 (15.6%) in the placebo group reported 'AEs potentially associated with PD'. It should be noted that in most cases these AEs were not directly associated with worsening of PD by the investigators.

For patients reporting one or more AEs 'potentially associated with PD', the baseline characteristics including age, gender, duration of PD, duration of dementia, and dementia severity, were very similar to those of the total study population (Table 6-27).

Table 6-27 Baseline demographic characteristics of patients with 'AEs potentially associated with PD' and the core study population

	Patients with 'AEs potentially associated with PD'			*Core study population*		
Characteristic	**Exelon** N=99	**Placebo** N=28	**Total** N=127	**Exelon** N=362	**Placebo** N=179	**Total** N=541
Age (yrs.)	71.5	74.6	72.2	72.8	72.4	72.7
Sex						
Male (%)	62.6	64.3	63.0	64.6	65.4	64.9
Female (%)	37.4	35.7	37.0	35.4	34.6	35.1
Duration of PD (yrs.)	8.6	9.2	8.7	8.7	9.4	8.9
Duration of Dementia (yrs.)	1.0	1.3	1.1	1.1	1.4	1.2
MMSE (mean score)	19.4	19.8	19.5	19.4	19.2	19.3

Source: [Report 2311-Table 7-4], [Report 2311- Table 7-5], [Post-hoc analysis-Table 2-38]

Table 6-28 shows the overall rate of these pre-defined AEs was higher with Exelon than placebo in the core study. This was mainly driven by the higher rate of tremor 10.2% in the Exelon group and 3.9% in the placebo group. However, the incidence rate of tremor in the extension study in patients who previously received Exelon during the core study (Exe-Exelon) decreased to 3.8%, while in those who previously received placebo (Plc-Exelon) the rate was 12.2%. Among 37 Exelon-treated patients who reported tremor as an AE, only six discontinued during the double-blind core study (Table 6-30). Of the remaining 30 patients who reported tremor as an AE during the core study, 15 had worsening, 4 remained unchanged and 11 had improvement in their total UPDRS part III score at the final visit compared to baseline. In regards to the 'postural tremor of hands' sub-item, 8 patients had worsening, 12 remained unchanged and 10 improved. For the sub-item 'tremor at rest' 16 patients had worsening, 5 remained unchanged and 9 patients improved. The number of patients reported to have experienced an AE of "worsening of PD" or "parkinsonism" during the double-blind core study was low, however these AEs were reported more frequently for patients in the Exelon group than in the placebo group (20 [5.5%] vs. 3 [1.7%], respectively). For both bradykinesia and rigidity the incidence rates, although higher in the Exelon treated core population than in the placebo group, were less than 5% in the Exelon-treated patients during both the core and extension studies.

Table 6-28 Number (%) of patients with pre-defined events possibly reflecting worsening of PD (core and extension populations)

	Core study		*Extension study*	
	Exelon n (%)	**Placebo** n (%)	**Exe-Exelon** n (%)	**Plc-Exelon** n (%)
Total patients studied	362	179	211	123
Any pre-defined AE(s)	99 (27.3)	28 (15.6)	28 (13.3)	32 (26.0)
Pre-defined AEs possibly reflecting worsening of PD				
Tremor	37 (10.2)	7 (3.9)	8 (3.8)	15 (12.2)
Fall	21 (5.8)	11 (6.1)	7 (3.3)	9 (7.3)
Parkinson's dis.(worsening)	12 (3.3)	2 (1.1)	7 (3.3)	5 (4.1)
Bradykinesia	9 (2.5)	3 (1.7)	1 (0.5)	0 (0.0)
Parkinsonism (worsening)	8 (2.2)	1 (0.6)	2 (0.9)	0 (0.0)
Salivary hypersecretion	5 (1.4)	0 (0.0)	2 (0.9)	2 (1.6)
Dyskinesia	5 (1.4)	1 (0.6)	3 (1.4)	0 (0.0)
Gait abnormality	5 (1.4)	0 (0.0)	0 (0.0)	1 (0.8)
Balance disorder	3 (0.8)	2 (1.1)	0 (0.0)	1 (0.8)
Dystonia	3 (0.8)	1 (0.6)	1 (0.5)	0 (0.0)
Musculoskeletal stiffness	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Drooling	2 (0.6)	2 (1.1)	0 (0.0)	1 (0.8)
On and off phenomenon	1 (0.3)	1 (0.6)	0 (0.0)	2 (1.6)
Hypokinesia	1 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)
Movement disorder	1 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)
Muscle rigidity	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)
Motor dysfunction	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rigors	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Freezing phenomenon	0 (0.0)	1 (0.6)	2 (0.9)	1 (0.8)
Akinesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Hypertonia	0 (0.0)	1 (0.6)	1 (0.5)	0 (0.0)
Dysarthria	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)

Source: [Report 2311 – PTT 10-2.3], [Report 2311- PTT 10-1.1], [Report 2311E1- PTT 10-2.3], [Summary of Clinical Safety - PTT 10.2-3]

To demonstrate the relationship between duration of therapy and the incidence rate of AEs, the frequency of AEs of tremor and total 'AEs potentially associated with PD' are presented for both treatment groups, in 4-week periods throughout the core study (Table 6-29). In the Exelon group, the incidence rates of 'AEs potentially associated with PD', as well as the AE of tremor occurred most frequently at 8-12 weeks of the titration period. The incidence rates for all these AEs decreased during the maintenance period (i.e., after week 16).

Table 6-29 Number (%) of patients with AEs of tremor and AEs 'potentially associated with PD' over time (core safety population)

	Exelon			*Placebo*		
	N	Tremor n (%)	PD* n (%)	N	Tremor n (%)	PD* n (%)
Titration Period						
Wk ≤ 4	362	7 (1.9)	27 (7.5)	179	3 (1.7)	12 (6.7)
Wk >4 – 8	343	9 (2.6)	27 (7.9)	168	0 (0.0)	3 (1.8)
Wk >8 – 12	324	15 (4.6)	35 (10.8)	165	1 (0.6)	9 (5.5)
Wk >12 – 16	301	6 (2.0)	14 (4.7)	162	2 (1.2)	7 (4.3)
Maintenance Period						
Wk >16 – 20	281	2 (0.7)	10 (3.6)	158	1 (0.6)	3 (1.9)
Wk >20 – 24	271	1 (0.4)	6 (2.2)	151	0 (0.0)	5 (3.3)

*PD= total patients with 'AEs potentially associated with PD'
Source: [Post-hoc Analyses Table 2-25] [Post-hoc Analyses Table 2-27]

Consequences of 'AEs potentially associated with PD'

The discontinuation rates due to 'AEs potentially associated with PD' in the core and extension studies were low (Table 6-30). Of the 99 Exelon-treated patients who had 'AEs potentially associated with PD', 17 (4.7% of the Exelon-treated double-blind study population relative to 1.1 % in the placebo group) patients discontinued the double-blind study due to these events, and 53 (54%) entered the extension study and 47 (89%) of these 53 patients completed the extension study (Table 6-31).

Table 6-30 Discontinuations due to 'AEs potentially associated with PD' (core and extension safety populations)

	Core study		*Extension study*		
	Exelon n (%)	**Placebo** n (%)	**Exe-Exelon** n (%)	**Plc-Exelon** n (%)	**Total** n (%)
Total patients studied	362	179	211	123	334
Preferred term					
Tremor	6 (1.7)	0 (0.0)	1 (0.5)	2 (1.6)	3 (0.9)
Patients with 'AEs potentially associated with PD'	17 (4.7)	2 (1.1)	1 (0.5)	3 (2.4)	4(1.1)

Total 'AEs potentially associated with PD' is based on a prospectively defined group of individual AEs that are in listed in [Report 2311-PTT 10.2-3].
Source: [Post-hoc Analyses Table 2-29, 2-30]

The discontinuation rates due to the AE of tremor for Exelon-treated patients were low, 1.7 % and 0.9%, in the double-blind and extension studies, respectively (Table 6-30). Of the 37 Exelon-treated patients who experienced the AE of tremor, 6 (1.7% of the Exelon-treated

double-blind study population relative to 0% in the placebo group) patients discontinued the double-blind study due to these events, and 21(57% compared to 58% of all Exelon-treated patients) entered the extension study and 19 (90%) of these 21 patients completed the extension study (Table 6-30). Total discontinuations due to the AE of tremor in the extension study was 0.9%.

Of 18 Exelon-treated patients whose tremor was not reported to have resolved during the core study, three discontinued. Of the remaining 15 patients, 12 continued in the extension with no action taken to treat the event (Post-text listings 10.2-3, 10.2-4, Appendix 7.1, Listing 1-1.).

Of the 37 patients that experienced AEs of tremor, 8 patients were taking less than 6mg of Exelon at the time of the event. Of these 8 patients, Exelon daily dose was decreased in 2 patients and one of the dose decreases resulted in resolution of the AE. The other patient never reported resolution of the AE, but completed the core study and entered the extension. The additional 29 patients who experienced AEs of tremor were taking 6mg of more of Exelon at the time of the event. Of these 29 patients, Exelon daily dose was decreased in 11 patients which resulted in resolution of the AE.

Of the 9 Exelon-treated patients who had an AE of bradykinesia 4(44%) entered the extension study and 3 (75%) of these 4 patients completed the extension study (Table 6-31).

The fact that the majority of patients with these AEs consented to enter the open label study to receive Exelon, is a strong indicator that the AEs were not disabling, permanent or significant enough for the patients to stop treatment with Exelon.

Table 6-31 Patients with 'AEs potentially associated with PD' who entered and completed the Extension study

	Entered Extension		Completed Extension	
	N	n (%)	N	n (%)*
All Exelon-treated patients	362	211(58%)	211	177(84%)
Patients with AEs of:				
Tremor	37	21 (57%)	21	19 (90%)
Bradykinesia	9	4 (44%)	4	3 (75%)
Muscle rigidity	1	0 (0%)	0	0 (0%)
All predefined AEs 'potentially associated with PD'	99	53 (54%)	53	47 (89%)

*percentage of patients who entered the extension

Source: Derived from [Report 2311E1 Appendix 7.1 Listing 1-1], [Report 2311 Appendix 7.1 Listing 1-19], [Post-hoc Analyses Table 2-29, 2-30]

Of the 362 patients, who were randomized to the core study and received double-blind Exelon treatment, 263 completed the core study, 211 patients entered the extension study and 177 of these patients completed the extension study. Table 6-32 presents the incidence rates, in 4-week intervals, of total 'AEs potentially associated with PD' and the AE of tremor in these 177 patients who received Exelon treatment for 48 weeks.

In this group of 177 patients, who received Exelon treatment for 48 weeks, the incidence rate of 'AEs potentially associated with PD', decreased after week 16 (completion of dose-titration phase). The slight increase in the incidence rates around weeks 28-40 corresponded to the dose re-titration phase of Exelon in the open-label extension study. After week 40, the incidence rates again decreased for the remaining 8-weeks of open-label treatment.

Table 6-32 Number (%) of Exelon- treated patients who remained in the study for 48 weeks and experienced 'AEs potentially associated with PD' and the AE of tremor

Study period (weeks)	Patients with 'AEs potentially associated with PD' (N=177) n (%)	Patients with AE of tremor (N=177) n (%)
Wk ≤ 4	11 (6.2)	3 (1.7)
Wk >4 – 8	12 (6.8)	4 (2.3)
Wk >8 – 12	17 (9.6)	6 (3.4)
Wk >12 – 16	10 (5.6)	5 (2.8)
Wk >16 – 20	6 (3.4)	2 (1.1)
Wk >20 – 24	4 (2.3)	1 (0.6)
Wk >24 – 28	2 (1.1)	0 (0.0)
Wk >28 – 32	10 (5.6)	3 (1.7)
Wk >32 – 36	9 (5.1)	3 (1.7)
Wk >36 – 40	11 (6.2)	1 (0.6)
Wk >40 – 44	1 (0.6)	0 (0.0)
Wk >44 – 48	0 (0.0)	0 (0.0)

Source: [Post-hoc Analyses Table 2-44]

Functional outcome in patients with AE of tremor and all 'AEs potentially associated with PD'

In patients who reported the AE of tremor, the ability to perform activities of daily living assessed on the ADCS-ADL scale showed improvement with Exelon treatment at core study endpoint (week 24). This contrasted with a decline in this assessment in those reporting the AE of tremor who received placebo (Table 6-33). In this sub-population, the changes in mean ADL scores in both the Exelon and placebo groups, and the difference between treatment groups, was comparable to that seen in the overall core study population. The same was true for patients with 'AEs potentially associated with PD' (Table 6-33).

Table 6-33 ADCS-ADL total score - summary of changes at week 24 for patients with AE of tremor and 'AEs potentially associated with PD' in the core study (ITT+RDO population)

	Patients with AE of tremor		Patients with predefined 'AEs potentially associated with PD'		Total core study population	
Efficacy Measure	**Exelon**	**Placebo**	**Exelon**	**Placebo**	**Exelon**	**Placebo**
ADCS-ADL						
N	37	7	97	25	333	165
Mean at baseline* ±SD	44.6±16.2	42.3± 0.4	40.0±16.3	41.0±14.8	41.6±18.6	41.2±17.7
Mean at endpoint ±SD	46.0± 6.1	39.9± 8.5	39.1±18.7	37.9±16.1	40.7±20.0	37.7±18.3
Change from baseline ±SD	1.4± 1.7	-3.5±4.3	-0.9±14.1	-3.5±6.6	-1.1±12.6	-3.6±10.3
P value**	-		-		0.023	

*Baseline is week 0 for the core and the extension studies. Endpoint is week 24 for the core and week 48 for the extension studies.

Positive change scores indicate improvement.

**p-values were based on an analysis of covariance model using treatment and country as factors and baseline assessment score as a covariate.

Source: [Post-hoc analyses Table 1-42, 1-49], [Study 2311 PTT 9.1-1, 9.1-4, 9.1-8, 9.2-1 9.2-4, 9.2-19 and 9.2-22]

Improvement or the absence of decline in functional activity at study endpoint was observed for 65% of patients with the AE of tremor, for 40% of patients with AEs of worsening of PD/parkinsonism and 48% of patients with predefined 'AEs potentially associated with PD' (Table 6-34).

Table 6-34 ADCS-ADL outcome in patients with 'AEs potentially associated with a worsening of PD' at study endpoint relative to baseline (Exelon treated, core study)

	Tremor	Bradykinesia	Muscle rigidity	'AEs potentially associated with PD'
Activities of daily living	N=37 n (%)	N=9 n (%)	N=1 n (%)	N=99 n (%)
Improved or unchanged	24 (65%)	3 (33%)	1(100%)	48(48%)

Source: Derived from [Report 2311 PTT 10.2-3, PTL 10.2-4], [Report 2311 Appendix 7.1 Listing 1-14]

The efficacy outcomes (in global dementia assessment, cognition and functional activity) in the sub-population of Exelon-treated patients who experienced 'AEs potentially associated with PD' were similar to those in the overall core study population, indicating that patients who experienced 'AEs potentially associated with PD' derived comparable efficacy benefits from treatment with Exelon. Neither tremor nor 'AEs potentially associated with PD' appear

to have negatively affected the overall functional outcome in this sub-population (Post-text tables 1-28, 1-35, 1-49).

6.11.3.2 Change in parkinsonian motor symptoms (UPDRS part III score)

In the core and extension studies the UPDRS part III scale was used to assess changes in motor symptoms of associated the underlying PD. The UPDRS scale has been used as the gold standard for assessment of disease progression in many clinical trials conducted in patients with PD. PD is a chronic progressive neurodegenerative disorder, with an estimated annual decline of 1.5 to 3.3 points on the UPDRS part III scale in patients where baseline UPDRS scores ranged from 28.5 (15.8) to 29.6 (SD 15.1) (Louis et al. 1999, Jankovic and Kapadia 2001, Alves, et al. 2005) in L-dopa treated patients.

Table 6-35 presents the mean UPDRS part III scores at baseline and mean changes from baseline at study endpoint for patients who reported 'AEs potentially associated with PD' during the core study. In this sub-population mean baseline scores were worse than in the overall core study population. Exelon-treated patients who reported 'AEs potentially associated with PD' during the core study showed a slight deterioration in their total and 'tremor at rest' sub-item scores and a slight improvement in the 'postural tremor' sub-item score. Patients in this sub-population who received placebo had an improvement in total and the tremor related sub-item scores. In the overall core study population, Exelon-treated patients showed similar mean changes from baseline on UPDRS part III scale scores to patients in the placebo group.

Table 6-35 Mean values and changes from baseline at week 24 in motor symptoms (UPDRS part III total score and sub-item scores) for patients with 'AEs potentially associated with PD' (core and extension safety populations)

	Baseline values[1] mean ± SD		Change from baseline[2] mean ± SD	
Patients with 'AEs potentially associated with PD'				
UPDRS part III score:	**Exelon** (n=69)	**Placebo** (n=22)	**Exelon** (n=69)	**Placebo** (n=22)
total score	35.5 ± 13.5	38.0 ± 14.2	0.8 ± 10.6	-1.2 ± 12.9
tremor at rest[4]	2.3 ± 2.9	2.9 ± 3.8	0.4 ± 2.6	-1.5± 3.8
postural tremor[4]	1.5 ± 1.7	1.3 ± 1.8	-0.1 ± 1.6	-0.3 ± 1.9
Core study population				
UPDRS part III score:	**Exelon** (n=263)	**Placebo** (n=146)	**Exelon** (n=263)	**Placebo** (n=146)
total score[3]	32.9 ± 14.2	32.5 ± 13.0	- 0.3 ± 9.5	- 0.4 ± 8.5
tremor at rest[4]	2.0 ± 2.8	1.7 ± 2.6	0.1 ± 2.6	0.0 ± 2.1
postural tremor[4]	1.3±1.4	1.1±1.5	-0.1±1.4	0.0±1.2
Extension study population				
UPDRS part III score:	**Exe-Exelon** (n=209)	**Plc-Exelon** (n=122)	**Exe-Exelon** (n=171)	**Plc-Exelon** (n=96)
total score	31.9 ± 14.8	32.3 ± 13.5	1.5 ± 8.8	2.3 ± 10.9
tremor at rest[4]	1.9 ± 2.6	1.9 ± 2.8	-0.1 ± 2.0	0.5 ± 2.7
postural tremor[4]	1.1±1.4	1.2±1.4	0.1±1.2	0.0±1.3

Total 'AEs potentially associated with PD' is based on a prospectively defined group of individual AEs that are in listed in [Report 2311-PTT 10.2-3].

Positive change scores indicate worsening of PD motor symptoms on UPDRS part III scale

[1] baseline is week 0 in core study, week 24 in extension study.

[2] Week 0-24 core study, week 24-48 extension study

[3] total score at baseline for the core study has been calculated only for patients who had week 24 evaluation

[4] Some patients may not have both baseline and week 24 assessments.

Source: [Report 2311– PTT 10.6-2, 10.6-3], [Report 2311E1– PTT 10.4-1, 10.4-2], [Post-hoc Analyses-Table 2-32, 2-33, 2-34]

6.11.3.3 Concomitant dopaminergic therapy

In the core study, dopaminergic medications were required to be kept at stable doses, unless changes in dosage were clinically indicated. Unlike many other chronic neurodegenerative disorders where treatment regimens may be stable over long periods of time, the routine clinical management of patients with PD often requires relatively frequent changes in dopaminergic drug doses due to fluctuations in symptom expression in the disease.

Table 6-36 presents mean doses of dopaminergic medications for both treatment groups in all core study patients and in the patient sub-population who reported 'AEs potentially associated with PD' during the core study. Mean daily doses of dopaminergic medications in patients who received Exelon treatment for 48 weeks are also presented in this table. In the core study,

all patients in the placebo group had higher mean daily doses of dopa and dopa derivatives at baseline (705.7 mg/d) than all Exelon-treated patients (663.4 mg/d). This was also the case for dopamine agonists (Summary of Clinical Safety Table 8-7). In both treatment groups, there was a slight increase in the mean daily doses of dopa and dopa derivatives at study endpoint from baseline (17.5 mg/d and 7.2/d mg in the Exelon and placebo groups, respectively). However, considering that the usual minimum starting dose of L-dopa treatment is 375-500mg/day, the amount of the change in the daily L-dopa dose were not considered clinically significant increases.

In the sub-population of patients with 'AEs potentially associated with PD', the mean daily dose of dopa and dopa derivatives in the placebo group (833.6 mg/day) was higher than that in the Exelon-treated patients (665.2 mg/day). The mean daily doses of dopa and dopa derivatives at baseline and study endpoint were comparable with those in the core study population. In patients who reported 'AEs potentially associated with PD', there was a slight increase from baseline in mean daily doses of dopa and dopa derivatives at study endpoint in both treatment groups (24.9 mg and 8.9 mg/day in the Exelon and placebo groups, respectively). In addition, there was also a slight increase in mean equivalent doses of dopamine agonists in both the Exelon and placebo groups (Summary of Clinical Safety Table 8-7).

Table 6-36 Baseline and endpoint mean doses of dopaminergic medications for patients with 'AEs potentially associated with PD', core study population, and patients who received Exelon for 48 weeks

	Exelon		***Placebo***	
	Mean (SD) value at baseline	Mean (SD) value at endpoint	Mean (SD) value at baseline	Mean (SD) value at endpoint
Patients with 'AEs potentially associated with PD'*				
All Dopa and Dopa Derivatives** (mg/day)	(n=96) 665.2 (360.4)	(n=95) 690.1 (381.9)	(n=28) 833.6 (437.9)	(n=28) 842.5 (436.1)
Core study population				
All Dopa and Dopa Derivatives** (mg/day)	(n=347) 663.4 (368.0)	(n=346) 680.9 (470.2)	(n=169) 705.7 (349.9)	(n=169) 712.9 (390.2)
Patients who received Exelon for 48 weeks				
All Dopa and Dopa Derivatives** (mg/day)	(n=167) 678.6 (408.8)	(n=169) 745.9 (564.1)	-	-

*Total 'AEs potentially associated with PD' is based on a prospectively defined group of individual AEs that are in listed in [Report 2311-PTT 10.2-3]

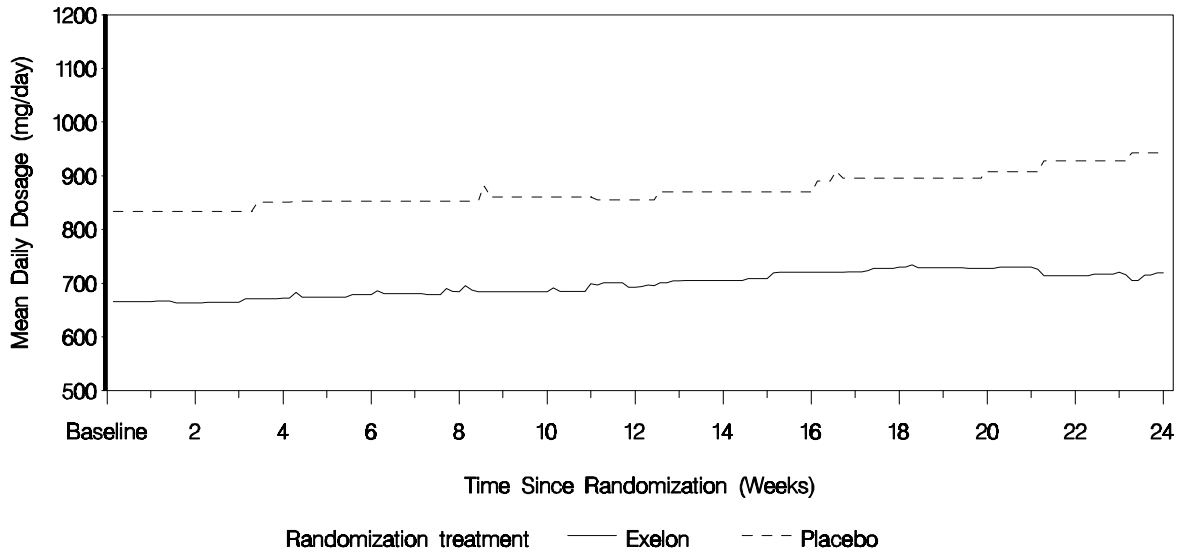
** Doses were calculated for combination of carbidopa/levodopa.

Source: [Post-hoc Analyses- Table 2-39], [Post-hoc analyses- Table 2-5a], [Post-hoc analyses- Table 2-37a], [Post-hoc analyses- Table 2-39a], [Post-hoc analyses- Table 2-37-b]

Figure 6-4 shows mean daily doses of dopa and dopa derivatives in patients who experienced 'AEs potentially associated with PD', throughout the core study. The findings show that there was no significant change in the mean doses of L-dopa and dopa derivatives, particularly in

response to increased incidence rates of 'AEs potentially associated with PD' that peaked during weeks 8-12 of the titration period of Exelon study medication.

Figure 6-4 Mean daily doses of dopa and dopa derivatives in patients who experienced 'AEs potentially associated with PD' (core study)



Source: Post-hoc analyses Figure 2-4

Among the 177 Exelon-treated core study patients who also completed the extension study, receiving 48 weeks of Exelon treatment, the percentage of patients who started new dopaminergic medications was 4.5%, indicating that dopaminergic medications were usually stable during long-term treatment. During the extension study there was a slight increase in mean doses of dopa and dopa derivatives (67.3 mg) in Exelon-treated patients who remained in the study for 48 weeks (Table 6-36). It should be noted that there was no placebo control group for comparison of long-term treatment and during the extension study it was encouraged, but not required to keep dopaminergic medications stable.

Overall summary and conclusions regarding effects on motor symptoms of PD

'AEs potentially associated with PD', mainly tremor, were more frequent in Exelon-treated patients than in placebo-treated patients. These AEs were usually mild or moderate in severity, decreased in frequency after completion of the dose-titration periods of the core and extension studies, and resulted in few discontinuations.

These AE reports were not reflected in changes in overall UPDRS part III motor scale assessments compared to baseline or placebo at week 16 or at study termination, indicating that the events were neither prolonged nor severe enough to result in a change on the scale. Mean changes in UPDRS part III scores with the long-term Exelon treatment in the extension study, was comparable to the expected annual change of 1.5 to 3.3 points reported in previous PD studies (Louis et al. 1999, Jankovic and Kapadia 2001, Alves, et al. 2005). In the extension study, patients who continued to receive Exelon (Exe-Exelon) had less worsening

on the UPDRS part III scale, than patients in the extension study who had received placebo during the core study.

The mean doses of dopaminergic medications in Exelon-treated patients during the core study and with long-term treatment were stable. Throughout the study, the Exelon treatment group received a lower mean daily dose of L-dopa and dopa derivatives than did the placebo group (in both the total core population and patients who reported 'AEs associated with PD'). There was no indication that the decrease in incidence rate of 'AEs potentially associated with PD' observed in Exelon-treated patients during the maintenance period of the core study was associated with increased doses of dopaminergic medications.

The efficacy outcomes (in global dementia assessment, cognition and functional activity) in the sub-population of Exelon-treated patients who experienced 'AEs potentially associated with PD' were similar to those in the overall core study population, indicating that patients who experienced 'AEs potentially associated with PD' derived comparable efficacy benefits from treatment with Exelon. Neither tremor nor 'AEs potentially associated with PD' appear to have negatively affected the overall functional outcome in this sub-population.

These data are consistent with the view that the frequency or severity of tremor in patients with PD is not associated with progression of the underlying disease (Deuschl 2000). The increased incidence of the AE of tremor in the core study may reflect enhanced central cholinergic neurotransmission. In patients with mild to moderate AD receiving Exelon, a small increase in the AE of tremor was also seen (4% versus <1% in those receiving placebo, Exelon Product Information).

These findings do not indicate that Exelon is associated with effects that increase the underlying progression rate of PD beyond the expected rate of decline and suggest that symptoms potentially associated with the worsening of PD are manageable through clinical monitoring and advice as stated in the proposed Exelon Product Information.

6.11.4 Clinical chemistry, hematology, urinalysis

In the core study (2311), all laboratory evalutions were performed twice; one at the screening visit and the final study visit (i.e. week 24 or premature study discontinuation).

In the core study, the incidence of newly occurring abnormalities in clinical chemistry or hematology was low, comparable for both treatments and not clinically significant. There were no significant findings with urinalysis.

There was a slight increase in mean prolactin, which was slightly higher in the Exelon-treated patients compared with the placebo group. However, the mean changes in both groups did not seem to represent clinically significant increases [Summary of Clinical Safety - Table 5-3].

The mean changes from baseline at week 24 in amylase and lipase levels in the Exelon group were higher than those observed in the placebo group.

Summary of findings in patients with elevated amylase and lipase levels

The central laboratory normal range for serum amylase was 1-88 U/L and for serum lipase was 0-63 U/L. In the Exelon group, the maximum level at the final visit was 196 U/L for

serum amylase and 342 U/L for serum lipase. With placebo, maximum level for serum amylase at the final visit was 122U/L and 86U/L for serum lipase.

Table 6-37 shows the mean serum levels of amylase and lipase at baseline and mean changes at week 24. The mean changes in amylase and lipase levels in the Exelon group were higher than those observed in the placebo group.

Table 6-37 Mean amylase and lipase values and changes from baseline (core study)

		Baseline values mean ± SD			Change from baseline mean ± SD	
	N	**Exelon**	**N**	**Placebo**	**Exelon**	**Placebo**
Amylase (U/L)	257	65.98 ± 31.72	139	66.94 ± 25.54	13.23 ± 30.50	3.97 ± 17.21
Lipase (blood) (U/L)	255	33.14 ± 18.38	138	33.59 ± 19.69	13.23 ± 58.75	-0.34 ± 18.69

The central laboratory normal range for serum amylase is 1-88 U/L and 0-63 U/L for serum lipase.
Source: [Study 2311 PTT 10.3-3]

Of the patients with normal baseline values for amylase, 44 (17.1%) patients in the Exelon group and 14 (10.1%) patients in the placebo group had abnormal elevation of amylase at study completion (Report 2311 PTT 10.3-2). Of patients with normal baseline values for lipase, abnormal elevations were observed in 23 (9.0%) in the Exelon group and 5 (3.6%) in the placebo group at study completion (Report 2311 PTT 10.3-2).

The mean dose of Exelon in patients who had normal amylase values at baseline, and elevated levels at endpoint was 9.6 mg/day during weeks 16-20 and 10mg/day during weeks 20-24.

Of patients with normal baseline values for both amylase and lipase, abnormal elevation was observed in 12 (3.3%) patients in the Exelon group and 1 (0.5%) patient in the placebo group at study completion.

Increased levels of amylase have been shown to be associated with pancreatitis. Therefore, for patients with normal baseline and elevated amylase levels at endpoint, AEs reported in the gastrointestinal, metabolism and nutritional system classes that might indicate the presence of pancreatitis were analyzed (Table 6-38). The most frequently reported AEs in the Exelon group include nausea, vomiting, diarrhea and abdominal pain. These AEs had very similar incidence rates to those seen in the total study population. In addition, of the 21 patients that reported gastrointestinal AEs 13 patients' events were resolved before study endpoint when lab samples were obtained. Of the patients in the core study, that had elevations in amylase levels and experienced gastrointestinal AEs, only one patient discontinued early due to an AE of sick sinus syndrome.

There were no reports of 'pancreatitis' as an AE or as a reason for discontinuation.

Table 6-38 Number (%) of patients with gastrointestinal system related AEs and normal amylase level at baseline with abnormal elevations at study endpoint (core study)

	Patients with elevation in amylase from baseline		Core study population	
	Exelon N= 44	Placebo N= 14	Exelon N= 362	Placebo N= 179
Preferred term	n(%)	n(%)	n(%)	n(%)
Nausea	13 (29.5)	2 (14.2)	105 (29.0)	20 (11.2)
Vomiting	7 (16.0)	0 (0.0)	60 (16.6)	3 (1.7)
Diarrhea	4 (9.0)	1 (7.1)	26 (7.2)	8 (4.5)
Abdominal pain	2 (4.5)	1 (7.1)	15 (4.1)	1 (0.8)
Constipation	2 (4.5)	2 (14.2)	17 (4.7)	12 (6.7)
Anorexia	2 (4.5)	0 (0.0)	22 (6.1)	5 (2.8)
Intestinal obstruction	1 (2.3)	0 (0.0)	2 (0.6)	1 (0.6)
Fecaloma	1 (2.3)	0 (0.0)	3 (0.8)	0 (0.0)
Epigastric Discomfort	1 (2.3)	0 (0.0)	1 (0.3)	0 (0.0)
Decreased Appetite	0 (0.0)	1 (7.1)	6 (1.7)	3 (1.7)
Hemorrhoids	0 (0.0)	1 (7.1)	0 (0.0)	1 (0.6)
Rectal hemorrhage	0 (0.0)	1 (7.1)	0 (0.0)	1 (0.6)
Rectal polyp	0 (0.0)	1 (7.1)	0 (0.0)	1 (0.6)
Gastroesophageal reflux	0 (0.0)	1 (7.1)	0 (0.0)	1 (0.6)

Source: [Report 2311-PTT 10.1-1]and Derived from [Post-hoc Analyses-PTL 2-1]

In acute pancreatitis, along with elevations in serum and amylase levels, elevations in calcium, glucose and lactate dehydrogenase (LDH) are expected. Of the patients who had elevations in both serum amylase and lipase levels, none had associated changes in serum calcium, glucose or LDH levels. Table 6-39 shows the laboratory evaluations for patients with elevated amylase levels. The laboratory profile of these patients were similar to that of the complete study population and did not indicate an association with pancreatitis.

Table 6-39 Serum calcium, glucose and LDH levels for patients with normal amylase level at baseline and abnormal elevations at endpoint (core study)

	Patients with amylase elevations from baseline		Core study population	
Laboratory assessment at week 24	Exelon	Placebo	Exelon	Placebo
Calcium (2.1-2.57mmol/L*)				
N	44	14	258	139
Mean at baseline ±SD	2.34±0.12	2.42±0.11	2.36±0.11	2.37±0.10
Mean at endpoint ±SD	2.37±0.10	2.38±0.10	2.36±0.10	2.37±0.10
Change from baseline ±SD	0.03±0.11	-0.04±0.15	-0.004±0.10	-0.002±0.11
Glucose (3.9-6.7mmol/L*)				
N	43	14	251	138
Mean at baseline ±SD	5.90±1.02	5.64±0.75	5.78±1.23	5.99±1.61

	Patients with amylase elevations from baseline		Core study population	
Laboratory assessment at week 24	Exelon	Placebo	Exelon	Placebo
Mean at endpoint ±SD	5.52±1.17	5.44±0.87	5.67±1.22	5.92±1.45
Change from baseline ±SD	-0.38±0.91	-0.20±0.86	-0.11±1.18	-0.06±1.70
LDH** (53-234 U/L*)				
N	37	12	218	123
Mean at baseline ±SD	162.70±37.29	161.83±29.32	159.34±33.88	160.55±35.84
Mean at endpoint ±SD	153.19±26.46	154.75±21.76	156.09±37.42	157.46±32.37
Change from baseline ±SD	-9.51±30.04	-7.08±28.09	-3.26±28.90	-3.09±22.71

*Normal ranges are based on Covance central laboratory ranges.

**LDH: Lactate dehydrogenase

Source: [Post –hoc Analyses Listing 2-3] and [Report 2311- PTT 10.3-3]

Because laboratory evaluations were limited to the core study, follow-up laboratory assessment of these patients is not available beyond the last visit date of the core study. However, 10 of 12 patients with both elevated amylase and lipase levels continued in the extension study and all 10 completed the extension study. This may indicate, along with the absence of any other associations, that these patients did not experience clinically significant complications associated with the elevation of amylase and/or lipase levels.

Discussion and conclusions

There is some evidence that suggests an increased incidence rate of modest elevations of amylase and lipase in Exelon-treated patients. These elevations do not appear to be associated with any clinically significant findings. In the core study, patients with elevated amylase in the Exelon group had a very similar AE profile to Exelon-treated patients in the overall study population. Importantly, there is no evidence that elevations in amylase and/or lipase are due to pancreatitis. None of the patients with abnormal elevations of amylase or lipase reported 'pancreatitis' as an AE and the majority completed the core study and continued in the extension study.

A possible explanation for these modest increases in amylase and lipase in a small number of patients may be the cholinergic effects on the autonomic nervous system innervation of the salivary and/or pancreatic glands. The stimulation of the cholinergic system through the vagus nerve is involved in the cephalic phase of regulation of pancreatic and salivary gland secretions. Acetylcholine is essential for parasympathetic and pre-ganglionic sympathetic neural transmission. The literature indicates that cholinergic stimulus may enhance secretion of pancreatic enzymes (Field, et al. 1987, Humphries, et al. 1987). Autonomic dysfunction, which is frequent in patients with PD, has been shown to induce changes in pancreatic amylase and lipase secretion in animal models (Tiscornia, et al. 2000) and disrupted salivary acinar cell function has been described in dysautonomia (Wolff, et al. 2002). Hypersalivation is a common symptom in patients with PD which may be associated with increased salivary enzymes. In addition, elevations of amylase and lipase in the serum might be due to concomitant dopaminergic or antipsychotic medications (Pinter, et al. 1998).

There is a possibility that amylase and lipase levels can be modestly elevated by cholinergic stimulation in some patients with PDD; however, this study does not provide conclusive evidence that Exelon is the cause of these increases.

Pancreatitis is labeled as an infrequent adverse event in the current Exelon product label. To our knowledge amylase and lipase levels were not evaluated in trials in the AD population.

6.11.5 Cardiac and vascular safety

Peripheral effects of raised cholinergic activity may lead to a slowing of heart rate (bradycardia), and could be a risk factor for patients with sick sinus syndrome or other supraventricular conduction conditions. Thus, the information in the core population, in which ECG measurements were obtained, and in the extension population with no ECG measurements, were reviewed carefully for signs of any significant changes in cardiac rate or rhythm abnormalities.

When all AEs associated with rhythm and conduction abnormalities in the core study were combined, the total incidence rate for the Exelon group was slightly higher than the placebo group (12 [3.3%] vs. 4[2.2%], respectively). In addition, the incidence rate of combined AEs of acute cardiac syndromes in the Exelon treatment group, was 0.8% compared to 1.1% in the placebo group [Report 2311-Appendix 8.1 Table 1-3].

Based on analyses of these data, treatment with Exelon in patients with PDD did not seem to be associated with any new cardiovascular safety findings that indicated a risk beyond that described in the Exelon prescribing information for patients with AD. Furthermore, current post marketing surveillance data do not indicate any increased risk for cardiovascular events or mortality beyond that already described in the Exelon label.

During the core study, 2 of the 4 patients who died in the Exelon group reported a cardiac event as the primary cause of death. Both of these patients reported a cardiac or vascular system related medical history at baseline. During the extension study, 3 patients died due to cardiac system related events and all presented with cardiac or vascular disorders at baseline. None of these events were judged to be related to study medication by the investigator. Except for one patient, all patients who died due to cardiovascular reasons were male. Cardiac system related deaths are common in males above age 65, particularly in patients with PD who are prone to autonomic dysfunction and conduction abnormalities (Kaufmann, et al. 2004).

The number of deaths, and the distribution of reported causes, observed in the Exelon group do not indicate any increased risk for cardiac system related mortality.

6.11.6 Deaths

During the double-blind core study, there were 11 deaths, four in the Exelon group and seven in the placebo group (includes the two cardiac-related deaths described above). Two additional deaths were reported after study completion (1 death beyond 30 days after study discontinuation in the Exelon group and 1 death, 3 weeks after study completion in the placebo group). During the extension phase, there were 7 deaths (5 in Exe-Exelon and 2 in the Plc-Exelon group).

The incidence of deaths in the core study treatment was 1.1% (4 in 362) for Exelon and 3.9% (7 in 179). In the extension phase, the incidence was 2.4 % for Exe/Exelon group (5 in 211) and 1.7 % for the Plc-Exelon group (2 in 123). These findings provide no indication that Exelon is associated with an increased incidence of death. Noteworthy is the fact that the frequency of deaths in patients who were exposed to Exelon was lower than the incidence in

the placebo group. [Report 2311- Post-text Table 10.2-1 and Report 2311E1- Post-text Table 10.2-1].

The causes of death were typical for the elderly patients with underlying PD enrolled in these studies and were not attributed to the use of study drug by the investigator in any case (Table 6-40). Pneumonia (including aspiration pneumonia), a common cause of death in PD, was frequently reported in both Exelon and placebo groups, and occurred in similar frequencies in both groups, indicating that there was no treatment-related differences in the incidence of pneumonia, as a cause of death.

Table 6-40 Causes of deaths, associated circumstances and attribution to study drug (core and extension populations)

Patient no. (age/sex)	Main cause of death (preferred term)	Day of last dose/death	Drug Relation	Comment
Core study				
Exelon				
BEL/0002/00003 (77/M)	Myocardial infarction	68 / 69	unrelated	prior arterial hypertension
ESP/0074/00004 (76/M)	Sudden cardiac death	88 / 88	unrelated	prior edema in both legs
FRA/0012/00003 (82/F)	Dehydration	141 / 142	unrelated	dehydration in heat wave
GBR/0087/00003 (79/F)	Pneumonia aspiration	121 / 127	unrelated	prior hospitalization due to depression (not eating)
Placebo				
BEL/0003/00001 (74/M)	Cerebral hemorrhage	74 / 82	unrelated	prior transient ischemic attack
ESP/0073/00005 (76/M)	Neuroleptic malignant syndrome	19 / 34	unrelated	due to withdrawal of levodopa
ESP/0075/00002 (82/M)	Cardiac arrest	114 / 115	unrelated	prior hypertensive cardiopathy
FRA/0016/00005 (82/M)	Cardiac failure	11 / 19	unrelated	history of 1st degree AV block
GBR/0085/00001 (72/M)	Pneumonia	49 / 50	unrelated	history of asthma
GBR/0089/00007 (63/M)	Pulmonary embolism	88 / 88	unrelated	history of sinus bradycardia
GBR/0094/00002 (76/M)	Bronchopneumonia	148 / 149	unrelated	prior history of pneumonias
Extension study				
Exe-Exelon				
ESP/0075/00001 (86/M)	Pneumonia	181 /188	unrelated	prior hospitalization (pneumonia, sinus bradycardia)
ESP/0075/00007 (70/M)	Myocardial infarction	291 / 291	unrelated	prior cardiac ischemia, 1° block
FRA/0017/00003 (81/M)	Cardiac failure	335 / 336	unrelated	no relevant prior history
ITA/0043/00004 (67/F)	Myocardial infarction	315 / 316	unrelated	history of hypertension
TUR/0123/00001 (74/M)	Pneumonia	288 / 205	unrelated	no relevant prior history
Plc-Exelon				
NLD/0061/00005 (72/F)	Cerebrovascular accident	285 / 325	unrelated	prior cerebrovascular accident
TUR/0122/00024 (87/M)	Cardio-respiratory arrest	222 / 224	unrelated	prior diabetes & abnormal electrocardiogram

Source: [Report 2311-PTL 10.2-1], [Report 2311E1-PTL 10.2-1]

6.11.7 Safety conclusions

- The most frequent AEs and affected body systems in the Exelon-treated patients both in the core and extension studies were nausea, vomiting and diarrhea (gastrointestinal system). This AE profile is similar to that observed in studies of Exelon in patients with AD. Tremor (nervous system) was the most common AE related to the underlying PD, however, it was rarely severe and led to discontinuation from the core study of only 6 (1.7%) patients.
- The overall incidence of AEs and in particular, the incidence of the most frequent AEs observed (nausea, vomiting, tremor), increased as the dose of Exelon was titrated, decreased at the end of titration phase and continued to decrease during the maintenance phase in both the core and extension studies. No increase in the frequency of AEs associated with non-motor symptoms of PD such as syncope, hypotension or hallucinations were observed.
- AEs leading to discontinuation occurred in 18% of the Exelon-treated patients during the 24-week, double-blind, core study and in 10% of patients in the 24-week open-label extension phase who had received Exelon during the core study.
- In the subset of patients with vomiting or diarrhea, there was no evidence of an increase in PD symptoms or any significantly increased use of dopaminergic medication, to suggest diminished dopaminergic drug absorption.
- Analysis of 'AEs potentially associated with PD' showed that there was mild, transient, dose-increment related exacerbation of tremor and total 'AEs potentially associated with PD'. However, neither the total score or any of the subscores for the UPDRS part III scale nor the new use or increase in dose of anti-parkinsonian medications indicated notable worsening of PD with Exelon treatment.
- Analyses of heart rate (vital signs), ECG and cardiac system AEs showed that treatment with Exelon was not associated with any new cardiovascular safety findings. A slight decrease in cardiac heart rate, similar to that observed in Exelon-treated AD patients, was noted in this population.
- The incidence and nature of deaths and SAEs in this study reflected events generally affecting elderly patients with PD. Deaths were not considered by investigators to be study drug related and were not related to dose or duration of treatment. SAEs except for the ones related to gastrointestinal organ system, did not indicate a relationship to the dose or duration of study medication.
- There were no new or unexpected events, except for the laboratory finding of occasional mild increases in serum amylase and lipase values, which were not associated with clinical diagnosis of pancreatitis. The reason for elevation of amylase and lipase was thought to be related to the cholinergic stimulation of secretion of these enzymes either from pancreas or salivary glands.

Other than a slight increase in the incidence of AEs of tremor or an occasional asymptomatic rise in serum amylase or lipase, not associated with pancreatitis, the safety and tolerability profile observed in PDD was similar to the profile in AD, with no new or unexpected safety findings. It is concluded that Exelon is well tolerated in PDD.

7 Risk/Benefit profile

Dementia is common in patients with PD. It presents with cognitive impairment, including, amnestic or retrieval-type memory deficit, executive dysfunction and attentional impairment, deterioration in activities of daily living and behavior. Early changes associated with dementia may go unrecognized, but the later decline of cognition and functional activity often lead to institutionalization.

PDD, for which there is currently no approved therapy, is a condition that causes considerable burden and distress to patients, relatives and healthcare professionals, increases the risk of mortality and has serious economic implications.

The current study (2311) is the first large, double-blind, placebo-controlled study with a long-term extension to demonstrate the efficacy and safety of Exelon in patients with mild to moderate PDD.

7.1 Benefits of Exelon treatment in PDD

- Both primary efficacy measures (ADAS-cog and ADCS-CGIC) showed statistically significant and clinically relevant improvement in overall dementia and cognition.
- In placebo-controlled dementia trials with cholinesterase inhibitors, the mean treatment difference on ADAS-cog ranges from 2 to 4 points (Corey-Bloom, et al 1998; Rogers, et al. 1998; Rosler, et al. 1999; Burns, et al. 1999; Geldmacher 2004)**.** In the core study (2311), the treatment effect of 2.88 points for Exelon on ADAS-cog was comparable to that shown in placebo-controlled Exelon studies (2.1 points), with similar duration (26 weeks) and dose (3-12mg/day) in the approved indication of AD (Birks et al, 2000).
- Statistically significant and clinically relevant improvements were also demonstrated on the secondary efficacy outcome measures assessing functional activity, executive function, visuospatial function, attention, and behavior.
- Benefit, in cognition (ADAS-cog) at week 24 was consistently in favor of Exelon across all analyzed subgroups.
    - Noteworthy, is the benefit shown in the subgroup of patients with visual hallucinations at baseline, patients who presents clinicians with one of the greatest challenges in the management of patients with PDD.
- There were fewer newly introduced antipsychotics and fewer increases in doses of these drugs in Exelon-treated patients, particularly in patients with visual hallucinations at baseline, suggesting that Exelon treatment may decrease the need for antipsychotic use in patients with PDD.
- In PDD, symptomatic improvement above baseline appeared to drive the treatment effect, whereas in AD, it was mostly the stabilization of cognitive function.

7.2 Risks of Exelon treatment in PDD

- Gastrointestinal AEs occurred mostly during Exelon dose titration, the majority were of mild or moderate severity, were lower in incidence and less likely to result in discontinuation than in previous Exelon studies in AD, and thus present no greater risk to patients with PDD than to those with AD.
- Tremor and other events related or potentially related to an exacerbation of PD were of mild or moderate severity, did not induce significant increases in use of dopaminergic therapy, and resulted in few discontinuations. Newly emergent episodes of these events decreased in frequency after completion of the dose-titration periods of the core and extension studies.
- No new cardiac or vascular system related safety findings that indicated a risk beyond that described in the Exelon prescribing information for patients with AD.
- No increased frequency of non-motor symptoms of PD including autonomic nervous system related symptoms or hallucinations.
- There are no known pharmacokinetic drug interactions associated with Exelon, which is especially important in an elderly population that is generally taking concomitant medication for a variety of co-existing medical conditions.
- There were fewer deaths in the Exelon treatment group compared to the placebo treatment group.
- Exposure to long-term treatment with Exelon in the extension study (i.e. 48 weeks) revealed a similar AE profile to that observed during Exelon treatment in the core study (i.e. 24 weeks).
- An increase in the frequency or severity of tremor in patients with PD is not associated with progression of the underlying disease (Deuschl 2000).
- The results from this study do not indicate that Exelon is associated with effects that increase the underlying progression rate of PD, beyond the expected rate of decline.

7.2.1 NNT and NNH

To further assess the clinical relevance of the benefit/risk ratio of Exelon treatment in PDD, NNT and NNH analyses were performed (Table 7-1). NNT was calculated using three different efficacy criteria and NNH was calculated using criteria (i.e. discontinuations due to AEs of concern) which are considered to be consequences of treatment that most appropriately represent intolerance to Exelon.

The NNT analysis, calculated on the basis of improvement in cognition, overall improvement in dementia or functionality, was favorable (12.2 and 9.3, respectively) as were the results of NNH analysis for discontinuations due to an AE of tremor, AE(s) potentially associated with PD and nausea/vomiting (60.3, 27.9, and 22.7, respectively). The NNT analysis was based on criteria that involve improvement or no change from baseline in a 6-month study of a progressive disorder where attenuated decline may also constitute a therapeutic effect. Thus, the NNTs, though highly favorable, are conservative estimates.

Table 7-1 NNT vs. NNH

Criteria	NNT*	NNH*
ADAS-cog: improvement of at least 4 points at week 24	12.2	-
CGIC: improved at week 24	9.1	-
ADCS-ADL: change ≥ 0 points at week 24	9.3	
Discontinuation due to AE of Tremor	-	60.3
Discontinuation due to AE(s) potentially associated with PD†	-	27.9
Discontinuation due to AE of nausea/vomiting	-	22.7

*NTT is the number of patients needed to be treated to achieve an improvement in outcome relative to placebo. NNH is the number of patients to be treated that would lead to one additional patient being harmed relative to placebo.

NNT or NNH = $1/(P_{Exelon} - P_{placebo})$ where P = % of event

† includes AE of Tremor

Source: Derived from [Report 2311 PTT 9.1-7 9.1-8, 9.2-2, 10.2-2], [Report 2311 Appendix 7.1 Listing 1-14]

8 Single Study Submission

The supplemental New Drug Application (NDA 20823; SE1-016) submitted on August 31, 2005 was based on the study EXPRESS. The data from this single study should be sufficient to expand the indication of Exelon to include "treatment of mild to moderate dementia associated with Parkinson's disease" for the following reasons:

- Exelon is approved for mild to moderate dementia of the Alzheimer's type. Both Alzheimer's dementia and Parkinson's disease dementia, share a common cholinergic deficit resulting in cognitive, behavioral and functional impairment. The pharmacologic rationale for the efficacy of Exelon in both dementias is the inhibition of the cholinesterase enzymes involved in the breakdown of acetylcholine.
- The post-marketing exposure to Exelon is estimated at 2.1 million patient years. Therefore, the safety profile of Exelon, mainly in AD, is well established.
- EXPRESS was a large prospective, randomized, double-blind, placebo-controlled, multicenter study that evaluated the efficacy and safety of Exelon in PD patients with mild to moderate dementia, whose onset of dementia occurred at least two years after a clinical diagnosis of PD.
- Exelon-treatment in the EXPRESS study appeared to be safe with no unexpected treatment-emergent safety issues.
- Exposure to long-term treatment with Exelon in the extension study (i.e. 48 weeks) revealed a similar AE profile to that observed during Exelon treatment in the core study (i.e. 24 weeks).
- AEs potentially associated with PD were of mild or moderate severity, did not induce significant increases in use of dopaminergic therapy, were not reflected in changes in overall UPDRS part III motor scale assessments, and resulted in few discontinuations. These results do not indicate that Exelon is associated with effects that increase the underlying progression rate of PD.

- Other than a slightly higher incidence of AEs of tremor, the safety and tolerability profile of Exelon in the EXPRESS study was similar to the established profile for Exelon in patients with AD.
- The EXPRESS data and current post marketing surveillance data do not indicate any increased risk for cardiovascular events or mortality beyond that described in the Exelon prescribing information for patients with AD.
- Exelon-treatment demonstrated statistically significant and clinically relevant improvements compared to placebo, in the two prospectively declared primary endpoints (cognitive and global scales), and in secondary efficacy outcome measures assessing functional activity, executive function, visuospatial function, attention, and behavior.
- The consistency of the efficacy results across primary and secondary endpoints in all three analysis populations and across demographic and disease-characteristic subgroups, as well as the results of post-hoc sensitivity analyses, demonstrate the robustness of the study's efficacy findings.

The results of the EXPRESS study, which have been recently published in The New England Journal of Medicine (Emre, et al. 2004), provide compelling evidence that Exelon therapy meets a currently unmet medical need. Novartis believes that approval of the proposed new indication would provide a safe and efficacious treatment option for patients with PDD, for whom there are currently no approved dementia therapies.

The EXPRESS study results were submitted to EMEA in Europe in February 2005 to support the inclusion of "mild to moderate dementia associated with PD" in the labeled indications. The application was recently approved in the EU (March 2006). To date, this new indication has been approved in 39 countries worldwide.

Novartis believes that the EXPRESS study data, in combination with the evidence that PDD is a distinct disease entity which can be differentiated from AD in routine clinical practice, are sufficient to support the proposed extension of the indication for Exelon.

9 Overall Conclusions

- There is currently no approved treatment for patients with PD who suffer from dementia.
- PDD is a distinct disease entity, with neuropathologic evidence that it is distinct from that underlying AD. It is also an entity that may be relatively easily, and unambiguously, diagnosed in routine clinical practice.
- Exelon demonstrated statistically significant and clinically relevant benefit on cognition, executive function, activities of daily living and behavior in patients with this unmet medical need.
- Except for a greater incidence of treatment-emergent tremor, the type and frequency of AEs were consistent with the established safety profile for Exelon. All AEs, including tremor are considered manageable through the advice stated in the proposed product label.

- No new cardiovascular system related safety findings indicate a risk beyond that described in the Exelon prescribing information for patients with AD.
- No new safety issues in non-motor symptoms of PD.
- The benefits of Exelon-treatment in patients with PDD outweigh the risks.

The results of EXPRESS show that Exelon is safe and effective for the treatment of mild to moderate dementia associated with Parkinson's disease. The supplemental New Drug Application (NDA 20823; SE1-016) based on the EXPRESS study should be approved for the indication "treatment of mild to moderate dementia associated with Parkinson's disease".

10 List of Appendices

Appendix 1: Additional Post-hoc Analyses Post-text Tables and Listings

Appendix 2: Additional Analyses for Patients with and without Visual Hallucinations

Appendix 3: Expert report by Cummings, Emre and Olanow

11 List of references

[Aarsland D, Andersen K, Larsen JP, et al.(2001)] Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology;56:730-736.

[Aarsland D, Andersen K, Larsen JP, et al.(2003)] Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol.;60:387-392.

[Aarsland D, Cummings JL, Larsen JP (2001)] Neuropsychiatric differences between Parkinson's disease with dementia and Alzheimer's disease. Int J Geriatr Psychiatry;16:184-191.

[Aarsland D, Larsen JP, Karlsen K, et al.(1999)] Mental symptoms in Parkinson's disease are important contributers to caregiver distress. Int J Geriatr Psychiatry.;14:866-874.

[Alves G, Wentzel-Larsen T, Aarsland D et al (2005)] Progression of motor impairment and disability in Parkinson disease: A population–based study. Neurol.; 65:1436-1441.

[Apaydin H, Ahlskog E, Parisi JE, et al.(2002)] Parkinson Disease Neuropathology: Later-developing dementia and loss of the levodopa response. Arch Neurol.;59:102-112.

[Arendt T, Bigl V, Arendt A, et al. (1983)] Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans and Korsakoff's disease. Acta Neuropathol (Berl).;61:101-108.

[Birks J, Grimley Evans J, Iakovidou V, et al (2000)] Rivastigmine for Alzheimer's disease. The Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD001191. DOI: 10.1002/14651858.CD001191.

[Bohnen NI, Kaufer DI, Ivanco LS, et al.(2003)] Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo Positron Emission Tomographic Study. Arch Neurol.;60:1745-1748.

[Braak H, Del Tredici K, Rüb U, et al.(2003)] Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging.;24:197-211.

[Braak H, Rüb U, Jansen Seur ENH, et al. (2005)] Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology;64:1404-1410.

[Bullock R, Cameron A.(2002)] Rivastigmine for the treatment of dementia and visual hallucinations associated with Parkinson's disease: a case series. Curr Med Res and Opin.;18(5):258-264.

[Burns A, Rossor M, Hecker J, et al.(1999)] The effects of donepezil in Alzheimer's disease – results from a multinational trial. Dem Geriatr Cog Disord.;10:237-244.

[Corey-Bloom J, Anand R, Veach J.(1998)] A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol.;1:55-65.

[Cummings JL. (1998)] Intellectual impairment in Parlinson's Disease: Clinical, pathologic, and biochemical correlates. J Geriatr Psychiatry Neurol,;1:24-36.

[Deuschl G, Raethjen J, Baron R,et al (2000)] The pathophysiology of parkinsonian tremor: a review. J Neurol 247:Suppl 5, V/33-V/48.

[Emre M, Aarsland D, Albanese A, et al.(2004)] Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med.;351:2509-2518.

[Fernandez HH, Lapane KL.(2002)] Predictors of mortality among nursing home residents with a diagnosis of Parkinson's disease. Med Sci Monit.;8(4):CR241-246.

[Field RB, Hand AR. (1987)] Secretion of lingual lipase and amylase from rat lingual serous glands. Am J Physiol Gastrointest Liver Physiol.;253:G217-G225.

[Gaspar P, Gray F. (1984)] Dementia in idiopathic Parkinson's disease: a neuropathological study of 32 cases. Acta Neuropathol (Berl).;64:43-52.

[Geldmacher DS.(2004)] Differential diagnosis of dementia syndromes. Clin Geriatr Med.;20:27-43.

[Giladi N, Shabtai H, Gurevich T, et al.(2003)] Rivastigmine (Exelon) for dementia in patients with Parkinson's disease. Acta Neurol Scand.;108:368-373.

[Goetz CG, Stebbins GT. (1993)] Risk factors for nursing home placement in advanced Parkinson's disease. Neurology.;43(11):2227-2229.

[Hughes TA, Ross HF, Mindham RHS, et al.(2004)] Mortality in Parkinson's disease and its association with dementia and depression. Arch Neurol Scand.;110:118-123.

[Hughes TA, Ross HF, Musa S, et al. (2000)] A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. Neurology ;54:1596-1602.

[Humphries LL, Adams LJ, Eckfeldt JH, et al.(1987)] Hyperamylasemia in patients with eating disorders. Ann Int Med.; 106:50-52.

[Hurtig HI, TRojanowski JQ, Galvin J, et al.(2000)] Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology;54:1916-1921.

[Jankovic J and Kapadia AS (2001)] Functional decline in Parkinson disease. Arch Neurol; 58(10):1611-5.

[Jellinger K. (1988)] The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry;51 (4):540-543.

[Kaufmann H, Nahm K, Purohit D, et al.(2004)] Autonomic failure as the initial presentation of Parkinson disease and dementia with Lewy bodies. Neurology;63:1093-1095.

[Kuhl DE, Minoshima S, Fessler JA (1996)] In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. Ann Neurol.;40:399-410.

[Leech RW, Brumback RA, Poduslo SE, et al.(2001)] Dementia: the University of Oklahoma autopsy experience. J Okla State Med Assoc.;94(11):507-511.

[Levy G, Tang M-X, Louis ED, et al.(2002)] The association of incident dementia with mortality in PD. Neurology.;59:1708-1713.

[Louis ED, Marder K, Cote L, et al.(1997)] Mortality from Parkinson disease. Arch Neurol.;54(3):260-264.

[Louis ED, Tang MX, Cote L, et al. (1999)] Progresssion of parkinsonian signs in Parkinson's disease. Arch Neurol.;56: 334-337

[National Parkinson's Foundation] About Parkinson Disease (Internet) Available from: http://www.parkinson.org/site/pp.asp?c=9dJFJLPwB7b=71125 (Accessed 6 April 2006).

[Perry EK, Curtis M, Dick DJ, et al.(1985)] Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. J Neurol, Neurosurg Psychiatry.;48:413-421.

[Pinter MM, Helscher RJ, Mundsperger N, et al.(1998)] Transient increase of pancreatic enzymes evoked by apomorphine in Parkinson's disease. J Neural Transm.;105:1237-1244.

[Reading PJ, Luce AK, McKeith IG (2001)] Rivastigmine in the treatment of Parkinsonian psychosis and cognitive impairment: preliminary findings from an open trial. Movement Disord.;16(6):1171-1195.

[Rinne JO, Rummukainen J, Paljärvi L, et al.(1989)] Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. Ann Neurol.;26:47-50.

[Rogers SL, Farlow MR, Doody RS, et al. (1998)] A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzhimer's disease. Donepezil Study Group. Neurology;50(1):136-145.

[RöslerM, Anand R, Cicin-Sain A, et al.(1999)] Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. Brit Med J.;318:633-638.

[Tanner CM, Hubble JP, Chan P. (1997)] Epidemiology and genetics of Parkinson's disease. In: Watts RL, Loller WC (eds). Neurologic Principles and Practice. New York: McGraw-Hill. p. 137-152.

[Tiscornia MO, Lehmann E, De Hamamura SS, et al.(2000)] [Autonomic nervous system and pancreas (Analysis of the influence of different types of autonomic denervation in glandular

regeneration phenomena and the interactions of the exocrine-endocrine-Axis).] Acta Gastroenerol Latinoam.; 30(4):253-265.

[Whitehouse PJ, Hedreen JC, White CL III, et al. (1983)] Basal forebrain neurons in the dementia of Parkinson disease. Ann Neurol.;13:243-248.

[Wolff A, Harell D, Gadoth N, et al.(2002)] Submandibular and sublingual salivary gland function in familial dysautonomia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod.; 94:315-319.

[Zarow C, Lyness SA, Mortimer JA, et al. (2003)] Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Arch Neurol.;60:337-341.

[Zweig RM, Cardillo JE, Cohen M, et al.(1993)] The locus ceruleus and dementia in Parkinson's disease. Neurology;43:986-991.

NOVARTIS

Clinical Development

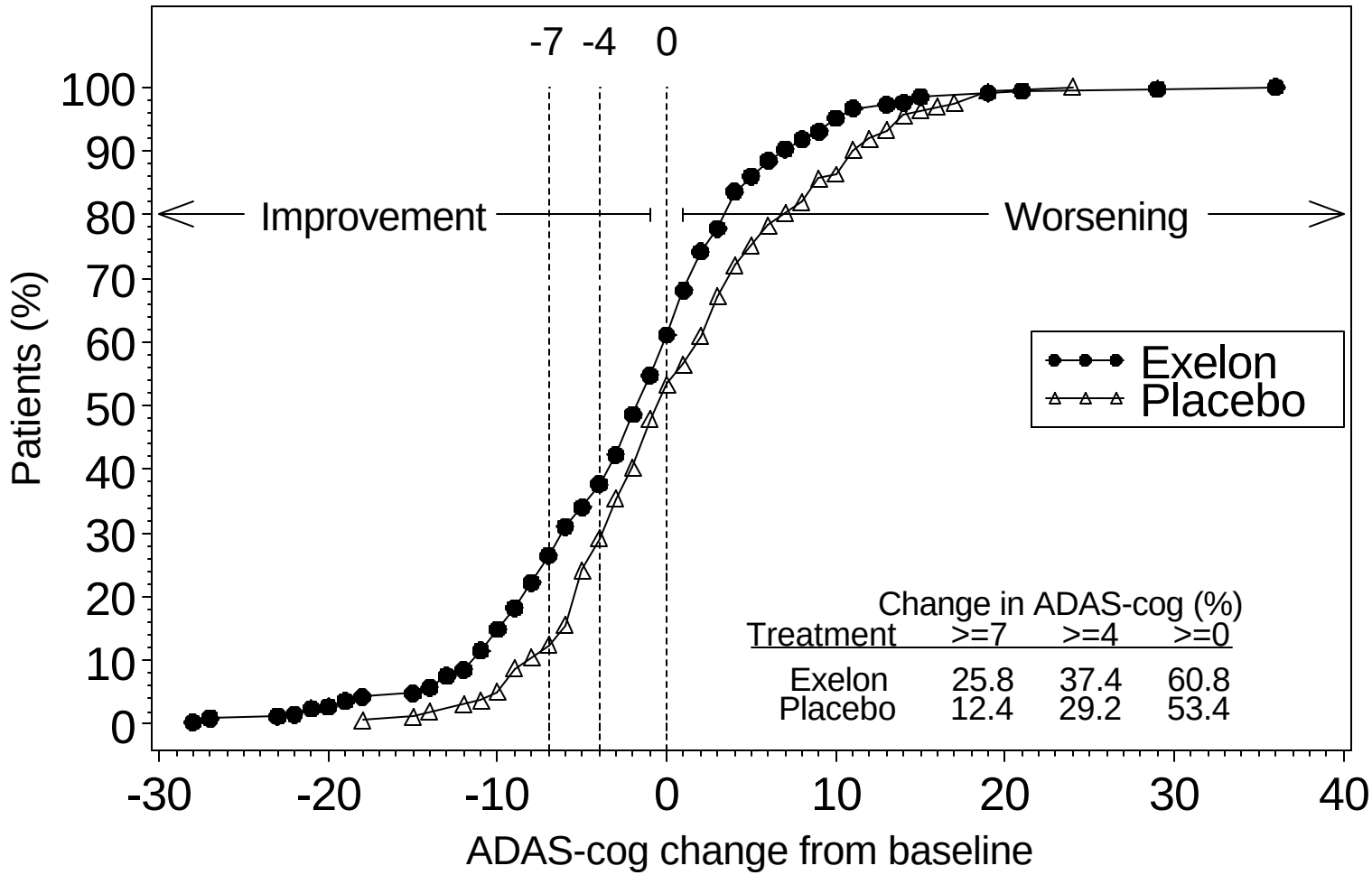
Exelon® (rivastigmine tartrate)

Briefing Document for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting of May 17, 2006

Appendix 1: Additional Post-hoc Analyses Post-text Tables and Listings

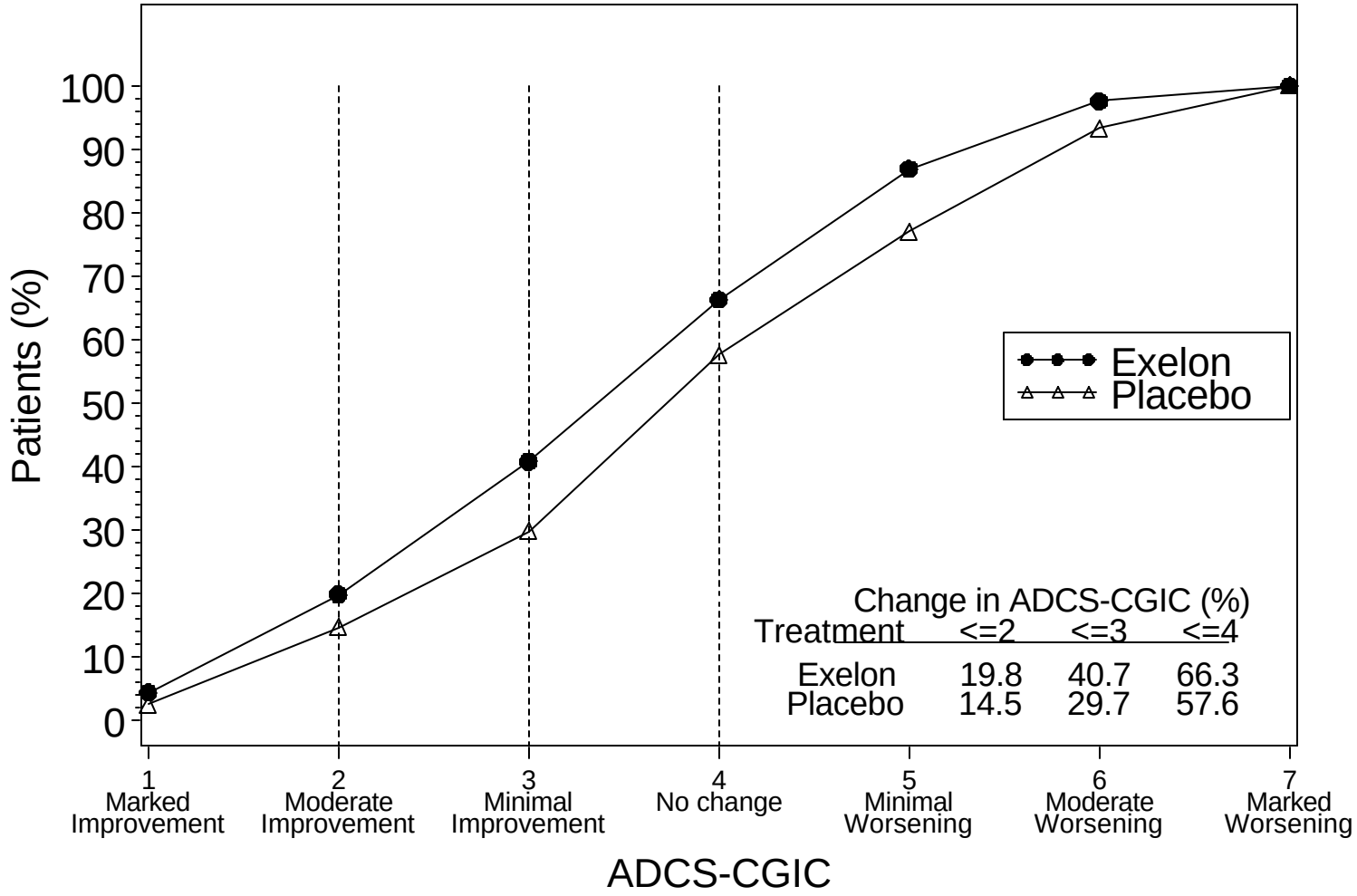
Document type:	Briefing Document
Release date:	17 April 2006
Number of pages:	115

Post-hoc analyses Figure 1-1
Percentage of patients improved based on change from baseline
on ADAS-cog total score
ITT-RDO population



Program Source: /vob/CENA713B/CENA713B2311/report/pgm_eff/ada_graph.sas

Post-hoc analyses figure 1-2
Percentage of patients improved based on the scores in ADCS-CGIC
ITT-RDO population



Program Source: /vob/CENA713B/CENA713B2311/report/pgm_eff/cgi_graph.sas

Post-hoc Analyses Table 1-53 (Page 1 of 1)
ADAS-cog – change from baseline – summary statistics at week 24
All randomized patients imputing missing baseline or change

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
All randomized patients	Baseline	362	24.0	10.2	23.0	179	23.9	10.5	23.0			
Week 24	Change	362	1.9	7.8	0.7	179	-0.4	7.1	1.0	2.24	<0.001*	(0.93, 3.55)

- For patients randomized to Exelon and no baseline or no change value, baseline=24.3 and change=-0.7
- For patients randomized to Placebo and no baseline or change value, baseline=23.8 and change=2.1
- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea13a.sas/Final Version (20JUN2005 9:24:07)

Post-hoc Analyses Table 1-58 (Page 1 of 1)
ADAS-cog – change from baseline – summary statistics at week 24
All randomized patients using LOCF method for patients randomized but not in ITT+RDO population

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
All randomized patients	Baseline	362	24.0	10.2	22.8	179	23.9	10.6	23.0			
Week 24	Change	362	1.9	7.8	0.7	179	-0.6	7.1	0.0	2.50	<0.001*	(1.20, 3.80)

- For patients randomized but not in ITT+RDO and with no change value, the LOCF method will be used to impute post-baseline score at week 24
- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea16a.sas/Final Version (24JUN2005 7:49:59)

Post-hoc Analyses Table 1-59 (Page 1 of 1)
ADAS-cog – change from baseline – summary statistics at week 24
All randomized patients using "Placebo result for all" imputation method

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
All randomized patients	Baseline	362	24.0	10.2	23.0	179	23.9	10.5	23.0			
Week 24	Change	362	1.9	7.8	0.7	179	-0.7	7.1	-0.7	2.52	<0.001*	(1.22, 3.83)

- For patients randomized but not in ITT+RDO and no baseline or no change value, baseline will be the baseline mean of placebo group (24.3) and change at week 24 will be the change mean of placebo group at week 24 (-0.7)
- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea16b.sas/Final Version (20JUN2005 9:12:25)

Post-hoc Analyses Table 2-99 (Page 1 of 1)
Summary of SAE in patients with potential PD related-AEs of interest
by preferred term and treatment
Safety population

Preferred term	Exelon	Placebo
Bradykinesia	0	0
Muscle rigidity	0	0
Parkinson's disease/Parkinsonism	2	0
Tremor	0	0

Post-hoc Analyses Table 2-38 (Page 1 of 2)
Summary of baseline characteristics
by treatment
Safety population
Patients with AE's of worsening of PD

Background Variable	Exelon N=99	Placebo N=28	Total N=127
Age (Years)			
n	99	28	127
Mean	71.5	74.6	72.2
SD	7.0	6.6	7.0
Median	72.0	76.0	73.0
Min	50.0	61.0	50.0
Max	91.0	87.0	91.0
Sex			
Male	62(62.6%)	18(64.3%)	80(63.0%)
Female	37(37.4%)	10(35.7%)	47(37.0%)
Time since idiopathic PD was first diagnosed by physician (years)			
n	99	28	127
Mean	8.6	9.2	8.7
SD	5.0	6.0	5.2
Median	7.8	8.4	7.9
Min	2.0	2.0	2.0
Max	21.6	29.7	29.7

Post-hoc Analyses Table 2-38 (Page 2 of 2)
Summary of baseline characteristics
by treatment
Safety population
Patients with AE's of worsening of PD

Background Variable	Exelon N=99	Placebo N=28	Total N=127
Time since Parkinson disease dementia was first diagnosed by physician (years)			
n	99	28	127
Mean	1.0	1.3	1.1
SD	1.2	1.9	1.4
Median	0.6	0.6	0.6
Min	0.0	0.0	0.0
Max	6.6	9.4	9.4
Mini-Mental State Examination (MMSE)			
n	99	28	127
Mean	19.4	19.8	19.5
SD	4.0	3.6	3.9
Median	20.0	20.0	20.0
Min	10.0	11.0	10.0
Max	30.0	24.0	30.0

Post-hoc Analyses Table 2-27 (Page 1 of 6)
Summary of Worsening of Parkinson's disease by study period
for core Exelon patients
Safety population

Preferred term	Week 0 - 4 N=362 n (%)	Week 4 - 8 N=343 n (%)	Week 8 - 12 N=324 n (%)	Week 12 - 16 N=302 n (%)	Week 16 - 20 N=283 n (%)	Week 20 - 24 N=273 n (%)
-Any preferred term	27(7.5)	27(7.9)	35(10.8)	14(4.6)	10(3.5)	6(2.2)
Fall	7(1.9)	5(1.5)	5(1.5)	4(1.3)	3(1.1)	3(1.1)
Tremor	7(1.9)	9(2.6)	15(4.6)	6(2.0)	2(0.7)	1(0.4)
Gait abnormal	3(0.8)	1(0.3)	0(0.0)	0(0.0)	0(0.0)	1(0.4)
Parkinsonism	3(0.8)	0(0.0)	4(1.2)	0(0.0)	0(0.0)	1(0.4)
Bradykinesia	2(0.6)	5(1.5)	1(0.3)	0(0.0)	1(0.4)	0(0.0)
Dystonia	2(0.6)	0(0.0)	0(0.0)	1(0.3)	0(0.0)	0(0.0)
Parkinson's disease	2(0.6)	6(1.7)	3(0.9)	1(0.3)	0(0.0)	1(0.4)
Dyskinesia	1(0.3)	1(0.3)	1(0.3)	0(0.0)	2(0.7)	0(0.0)
Extrapyramidal disorder	1(0.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Motor dysfunction	1(0.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Muscle rigidity	1(0.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Salivary hypersecretion	1(0.3)	1(0.3)	2(0.6)	1(0.3)	0(0.0)	0(0.0)
Balance disorder	0(0.0)	0(0.0)	3(0.9)	0(0.0)	0(0.0)	0(0.0)
Drooling	0(0.0)	0(0.0)	0(0.0)	1(0.3)	1(0.4)	0(0.0)
Freezing phenomenon	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Hyperkinesia	0(0.0)	0(0.0)	1(0.3)	0(0.0)	0(0.0)	0(0.0)
Hypertonia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Hypokinesia	0(0.0)	0(0.0)	1(0.3)	0(0.0)	0(0.0)	0(0.0)
Movement disorder	0(0.0)	0(0.0)	1(0.3)	0(0.0)	0(0.0)	0(0.0)
Musculoskeletal stiffness	0(0.0)	0(0.0)	2(0.6)	1(0.3)	0(0.0)	0(0.0)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_04.sas - 29JUN2005:1:23

Post-hoc Analyses Table 2-27 (Page 2 of 6)
Summary of Worsening of Parkinson's disease by study period
for core Exelon patients
Safety population

Preferred term	Week 24 - 28 N=248 n (%)	Week 28 - 32 N=206 n (%)	Week 32 - 36 N=202 n (%)	Week 36 - 40 N=195 n (%)	Week 40 - 44 N=191 n (%)	Week 44 - 48 N=177 n (%)
-Any preferred term	4(1.6)	10(4.9)	9(4.5)	12(6.2)	1(0.5)	1(0.6)
Fall	0(0.0)	3(1.5)	2(1.0)	3(1.5)	0(0.0)	0(0.0)
Tremor	0(0.0)	3(1.5)	3(1.5)	1(0.5)	0(0.0)	1(0.6)
Gait abnormal	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Parkinsonism	0(0.0)	1(0.5)	0(0.0)	1(0.5)	0(0.0)	0(0.0)
Bradykinesia	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Dystonia	0(0.0)	0(0.0)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
Parkinson's disease	1(0.4)	1(0.5)	2(1.0)	4(2.1)	1(0.5)	0(0.0)
Dyskinesia	0(0.0)	1(0.5)	1(0.5)	1(0.5)	0(0.0)	0(0.0)
Extrapyramidal disorder	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Motor dysfunction	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Muscle rigidity	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Salivary hypersecretion	0(0.0)	1(0.5)	0(0.0)	1(0.5)	0(0.0)	0(0.0)
Balance disorder	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Drooling	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Freezing phenomenon	0(0.0)	0(0.0)	1(0.5)	1(0.5)	0(0.0)	0(0.0)
Hyperkinesia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Hypertonia	0(0.0)	0(0.0)	0(0.0)	1(0.5)	0(0.0)	0(0.0)
Hypokinesia	1(0.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Movement disorder	1(0.4)	0(0.0)	1(0.5)	0(0.0)	0(0.0)	0(0.0)
Musculoskeletal stiffness	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_04.sas - 29JUN2005:1:23

Post-hoc Analyses Table 2-27 (Page 3 of 6)
Summary of Worsening of Parkinson's disease by study period
for core Exelon patients
Safety population

Preferred term	>Week 48 N=99 n (%)
-Any preferred term	1(1.0)
Fall	0(0.0)
Tremor	1(1.0)
Gait abnormal	0(0.0)
Parkinsonism	0(0.0)
Bradykinesia	0(0.0)
Dystonia	0(0.0)
Parkinson's disease	0(0.0)
Dyskinesia	0(0.0)
Extrapyramidal disorder	0(0.0)
Motor dysfunction	0(0.0)
Muscle rigidity	0(0.0)
Salivary hypersecretion	0(0.0)
Balance disorder	0(0.0)
Drooling	0(0.0)
Freezing phenomenon	0(0.0)
Hyperkinesia	0(0.0)
Hypertonia	0(0.0)
Hypokinesia	0(0.0)
Movement disorder	0(0.0)
Musculoskeletal stiffness	0(0.0)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_04.sas - 29JUN2005:1:23

Post-hoc Analyses Table 2-27 (Page 4 of 6)
Summary of Worsening of Parkinson's disease by study period
for core Exelon patients
Safety population

Preferred term	Week 0 - 4 N=362 n (%)	Week 4 - 8 N=343 n (%)	Week 8 - 12 N=324 n (%)	Week 12 - 16 N=302 n (%)	Week 16 - 20 N=283 n (%)	Week 20 - 24 N=273 n (%)
On and off phenomenon	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.4)	0(0.0)
Rigors	0(0.0)	1(0.3)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_04.sas - 29JUN2005:1:23

Post-hoc Analyses Table 2-27 (Page 5 of 6)
Summary of Worsening of Parkinson's disease by study period
for core Exelon patients
Safety population

Preferred term	Week 24 - 28 N=248 n (%)	Week 28 - 32 N=206 n (%)	Week 32 - 36 N=202 n (%)	Week 36 - 40 N=195 n (%)	Week 40 - 44 N=191 n (%)	Week 44 - 48 N=177 n (%)
On and off phenomenon	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Rigors	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_04.sas - 29JUN2005:1:23

Post-hoc Analyses Table 2-27 (Page 6 of 6)
Summary of Worsening of Parkinson's disease by study period
for core Exelon patients
Safety population

Preferred term	>Week 48 N=99 n (%)
On and off phenomenon	0(0.0)
Rigors	0(0.0)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_04.sas - 29JUN2005:1:23

Post-hoc Analyses Table 2-29 (Page 1 of 2)
Discontinuation due to the worsening of Parkinson's disease
by treatment
Safety population

Primary system organ class Preferred term	Exelon N=362 n (%)	Placebo N=179 n (%)
-Any primary system organ class		
-Total	17(4.7)	2(1.1)
General disorders and administration site conditions		
-Total	2(0.6)	0(0.0)
Gait abnormal	2(0.6)	0(0.0)
Injury, poisoning and procedural complications		
-Total	0(0.0)	1(0.6)
Fall	0(0.0)	1(0.6)
Musculoskeletal and connective tissue disorders		
-Total	2(0.6)	0(0.0)
Muscle rigidity	1(0.3)	0(0.0)
Musculoskeletal stiffness	1(0.3)	0(0.0)
Nervous system disorders		
-Total	16(4.4)	1(0.6)
Tremor	6(1.7)	0(0.0)
Parkinson's disease	3(0.8)	0(0.0)

- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one randomization group is counted only once in the AE category for that randomization group.
- Only adverse events that caused study drug to be permanently discontinued are displayed.
- A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

report/pgm_saf/emea_aev_06.sas - 14JUL2005:8:27

Post-hoc Analyses Table 2-29 (Page 2 of 2)
Discontinuation due to the worsening of Parkinson's disease
by treatment
Safety population

Primary system organ class Preferred term	Exelon N=362 n (%)	Placebo N=179 n (%)
Nervous system disorders		
Bradykinesia	2(0.6)	0(0.0)
Parkinsonism	2(0.6)	0(0.0)
Balance disorder	1(0.3)	1(0.6)
Drooling	1(0.3)	0(0.0)
Dystonia	1(0.3)	0(0.0)

- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one randomization group is counted only once in the AE category for that randomization group.
- Only adverse events that caused study drug to be permanently discontinued are displayed.
- A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

report/pgm_saf/emea_aev_06.sas - 14JUL2005:8:27

CENA713B 2311E1

Post-hoc Analyses Table 2-30 (Page 1 of 1)
Discontinuation due to the worsening of Parkinson's disease
by double-blind treatment
Extension safety population

Primary system organ class Preferred term	Exelon N=211 n (%)	Placebo N=123 n (%)
-Any primary system organ class		
-Total	1(0.5)	3(2.4)
Nervous system disorders		
-Total	1(0.5)	3(2.4)
Tremor	1(0.5)	2(1.6)
Parkinson's disease	0(0.0)	1(0.8)

- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A patient with multiple occurrences of an AE under one randomization group is counted only once in the AE category for that randomization group.
- Only adverse events that caused study drug to be permanently discontinued are displayed.
- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

report/pgm_saf/emea_aev_07.sas - 14JUL2005:10:36

Post-hoc Analyses Table 2-44 (Page 1 of 3)
Summary of AE's of interest (nausea, vomiting, tremor and PD) by study period
for core Exelon patients who completed extension
Safety population

Preferred term	Week 0 - 4 N=177 n (%)	Week 4 - 8 N=177 n (%)	Week 8 - 12 N=177 n (%)	Week 12 - 16 N=177 n (%)	Week 16 - 20 N=177 n (%)	Week 20 - 24 N=177 n (%)
-Any preferred term	18(10.2)	30(16.9)	33(18.6)	25(14.1)	15(8.5)	8(4.5)
PD	11(6.2)	12(6.8)	17(9.6)	10(5.6)	6(3.4)	4(2.3)
Nausea	7(4.0)	13(7.3)	13(7.3)	11(6.2)	6(3.4)	4(2.3)
Tremor	3(1.7)	4(2.3)	6(3.4)	5(2.8)	2(1.1)	1(0.6)
Vomiting	2(1.1)	12(6.8)	11(6.2)	9(5.1)	6(3.4)	1(0.6)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_10.sas - 01JUL2005:11:22

Post-hoc Analyses Table 2-44 (Page 2 of 3)
Summary of AE's of interest (nausea, vomiting, tremor and PD) by study period
for core Exelon patients who completed extension
Safety population

Preferred term	Week 24 - 28 N=177 n (%)	Week 28 - 32 N=177 n (%)	Week 32 - 36 N=177 n (%)	Week 36 - 40 N=177 n (%)	Week 40 - 44 N=177 n (%)	Week 44 - 48 N=168 n (%)
-Any preferred term	7(4.0)	17(9.6)	21(11.9)	20(11.3)	5(2.8)	1(0.6)
PD	2(1.1)	10(5.6)	9(5.1)	11(6.2)	1(0.6)	0(0.0)
Nausea	5(2.8)	4(2.3)	12(6.8)	6(3.4)	1(0.6)	0(0.0)
Tremor	0(0.0)	3(1.7)	3(1.7)	1(0.6)	0(0.0)	0(0.0)
Vomiting	1(0.6)	3(1.7)	2(1.1)	5(2.8)	3(1.7)	1(0.6)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_10.sas - 01JUL2005:11:22

Post-hoc Analyses Table 2-44 (Page 3 of 3)
Summary of AE's of interest (nausea, vomiting, tremor and PD) by study period
for core Exelon patients who completed extension
Safety population

Preferred term	>Week 48 N=97 n (%)
-Any preferred term	0(0.0)
PD	0(0.0)
Nausea	0(0.0)
Tremor	0(0.0)
Vomiting	0(0.0)

- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria; Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Week 0 - 4 column.
- A patient with multiple occurrences of an AE in a time period is counted only once in each period.

report/pgm_saf/emea_aev_10.sas - 01JUL2005:11:22

Post-hoc Analyses Table 1-42 (Page 1 of 1)
ADCS-ADL - summary statistics across time
All patients who had worsening parkinsonism from ITT+RDO population

Visit	Statistics	Exelon N=97	Placebo N=26
Baseline	n	97	25
	Mean	40.0	41.0
	SD	16.3	14.8
	Median	39.0	39.0
	Min	6.0	18.0
	Max	73.0	72.0
Week 16	n	97	26
	Mean	39.6	40.7
	SD	18.5	14.9
	Median	40.0	39.5
	Min	2.0	7.0
	Max	77.0	70.0
Week 24	n	97	26
	Mean	39.1	37.9
	SD	18.7	16.1
	Median	40.0	37.0
	Min	2.0	8.0
	Max	75.0	75.0

Post-hoc Analyses Table 1-49 (Page 1 of 1)
ADCS-ADL - change from baseline - summary statistics across time
All patients who had worsening parkinsonism from ITT+RDO population

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	97	40.0	16.3	39.0	25	41.0	14.8	39.0			
Week 16	Change	97	-0.5	12.1	0.0	25	-0.3	6.2	1.0	-0.34	0.895	(-5.42, 4.74)
Week 24	Change	97	-0.9	14.1	0.0	25	-3.5	6.6	-5.0	2.59	0.364	(-3.04, 8.22)

- p-value based on analysis of covariance model using treatment and country and as factors and baseline ADCS-ADL as covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea11e.sas/Final Version (20JUN2005 9:12:11)

Post-hoc Analyses Table 2-32 (Page 1 of 1)
UPDRS part III total score - summary statistics across time
Safety population
Patients with AE's of worsening of PD

Visit	Statistics	Exelon N=99	Placebo N=28
Baseline	n	99	28
	Mean	36.7	34.2
	SD	13.9	15.1
	Median	35	34
	Min	2	4
	Max	70	69
Week 16	n	79	24
	Mean	35.7	35.2
	SD	14.1	14.6
	Median	34	34.5
	Min	4	14
	Max	72	69
Week 24	n	69	22
	Mean	36.2	36.8
	SD	15.3	15.2
	Median	37	35.5
	Min	5	11
	Max	80	77

Post-hoc Analyses Table 2-33 (Page 1 of 1)
UPDRS part III total scores - summary of change
Safety population
Patients with AE's of worsening of PD

Visit		Exelon N=99 n	Mean	SD	Median	Placebo N=28 n	Mean	SD	Median	Difference in LSMEANS	P-value	95% CI for Exelon - Placebo
Week 16	Baseline	79	36.0	14.2	35.0	24	37.1	13.9	37.0			
	Change	79	-0.3	8.4	0.0	24	-1.9	10.6	0.0	1.21	0.560	(-2.91, 5.33)
Week 24	Baseline	69	35.5	13.5	34.0	22	38.0	14.2	37.5			
	Change	69	0.8	10.6	1.0	22	-1.2	12.9	1.5	1.78	0.524	(-3.76, 7.32)

Post-hoc Analyses Table 2-34
UPDRS part III item scores - summary of change
Safety population
Patients with AE's of worsening of PD

	Exelon						Placebo						
	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max	P-value
Speech													
Baseline	99	1.7	0.8	0.0	2.0	3.0	28	1.6	0.7	0.0	2.0	3.0	
Week 16	79	1.7	0.9	0.0	2.0	4.0	24	1.8	0.9	0.0	2.0	3.0	
Week 24	69	1.7	0.9	0.0	2.0	4.0	22	2.1	0.8	1.0	2.0	4.0	
Change from baseline													
Week 16	79	0.1	0.7	-2.0	0.0	2.0	24	0.0	0.7	-2.0	0.0	1.0	0.539
Week 24	69	0.1	0.8	-2.0	0.0	2.0	22	0.3	0.6	-1.0	0.0	1.0	0.501
Facial expression													
Baseline	99	2.0	1.0	0.0	2.0	4.0	28	2.1	1.0	0.0	2.0	3.0	
Week 16	79	1.9	0.9	0.0	2.0	4.0	24	2.3	0.9	1.0	2.5	4.0	
Week 24	69	2.0	0.9	0.0	2.0	4.0	22	2.1	0.8	0.0	2.0	3.0	
Change from baseline													
Week 16	79	0.0	0.7	-2.0	0.0	2.0	24	0.0	0.6	-1.0	0.0	1.0	0.646
Week 24	69	0.0	0.9	-2.0	0.0	2.0	22	-0.1	0.8	-2.0	0.0	1.0	0.864
Tremor at rest													
Baseline	99	2.3	2.9	0.0	1.0	13.0	28	3.1	3.9	0.0	2.0	13.0	
Week 16	79	2.5	3.1	0.0	2.0	14.0	24	2.3	3.6	0.0	0.0	12.0	
Week 24	69	2.4	2.9	0.0	1.0	14.0	22	2.2	3.5	0.0	0.0	11.0	
Change from baseline													
Week 16	79	0.3	2.4	-6.0	0.0	10.0	24	-1.3	3.9	-13.0	0.0	6.0	0.092
Week 24	69	0.4	2.6	-5.0	0.0	14.0	22	-1.5	3.8	-13.0	0.0	3.0	0.111

report/pgm_saf/emea_updrs_cor3.sas - 14JUL05:08:24

Post-hoc Analyses Table 2-34
UPDRS part III item scores - summary of change
Safety population
Patients with AE's of worsening of PD

	Exelon						Placebo						
	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max	P-value
Action or postural tremor of hands													
Baseline	99	1.6	1.6	0.0	2.0	6.0	28	1.4	1.8	0.0	1.0	8.0	
Week 16	79	1.4	1.7	0.0	1.0	7.0	24	1.5	1.5	0.0	1.5	6.0	
Week 24	69	1.4	1.7	0.0	1.0	8.0	22	1.2	1.4	0.0	0.5	4.0	
Change from baseline													
Week 16	79	-0.1	1.4	-5.0	0.0	4.0	24	0.1	2.0	-4.0	0.0	6.0	0.863
Week 24	69	-0.1	1.6	-5.0	0.0	6.0	22	-0.3	1.9	-4.0	0.0	4.0	0.845
Rigidity													
Baseline	98	7.1	4.2	0.0	7.0	18.0	28	6.0	3.3	1.0	5.5	15.0	
Week 16	79	6.4	4.1	0.0	6.0	16.0	24	5.9	3.8	0.0	5.0	15.0	
Week 24	69	6.6	4.4	0.0	6.0	18.0	22	6.3	3.8	0.0	7.0	15.0	
Change from baseline													
Week 16	78	-0.9	3.0	-10.0	0.0	5.0	24	-0.7	3.7	-10.0	0.0	9.0	0.786
Week 24	68	-0.6	3.1	-10.0	0.0	6.0	22	-0.6	4.2	-10.0	0.0	7.0	0.342
Finger taps													
Baseline	99	3.4	1.7	0.0	3.0	8.0	28	3.3	1.8	0.0	3.0	8.0	
Week 16	79	3.4	1.6	0.0	3.0	8.0	24	3.3	1.8	0.0	3.0	7.0	
Week 24	69	3.5	1.8	0.0	3.0	8.0	22	3.4	1.6	1.0	3.0	8.0	
Change from baseline													
Week 16	79	0.1	1.6	-4.0	0.0	4.0	24	-0.2	1.1	-2.0	0.0	2.0	0.408
Week 24	69	0.2	1.6	-3.0	0.0	5.0	22	0.1	1.2	-2.0	0.0	2.0	0.697

Post-hoc Analyses Table 2-34
UPDRS part III item scores - summary of change
Safety population
Patients with AE's of worsening of PD

	Exelon						Placebo						
	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max	P-value
Hand movement													
Baseline	99	3.1	1.4	0.0	3.0	6.0	28	3.0	1.6	0.0	3.0	7.0	
Week 16	78	2.9	1.4	0.0	3.0	6.0	24	3.1	1.9	0.0	3.0	8.0	
Week 24	69	3.1	1.6	0.0	3.0	6.0	22	3.2	1.7	0.0	3.0	8.0	
Change from baseline													
Week 16	78	0.0	1.3	-3.0	0.0	3.0	24	0.0	1.1	-2.0	0.0	3.0	0.748
Week 24	69	0.2	1.5	-3.0	0.0	4.0	22	0.1	1.6	-2.0	0.0	3.0	0.654
Rapid alternating movements of hands													
Baseline	99	3.5	1.5	0.0	4.0	7.0	28	3.4	1.6	0.0	3.5	6.0	
Week 16	79	3.2	1.5	0.0	3.0	8.0	24	3.3	1.6	1.0	3.0	6.0	
Week 24	69	3.3	1.6	0.0	3.0	6.0	22	3.6	1.6	2.0	3.0	8.0	
Change from baseline													
Week 16	79	-0.1	1.4	-3.0	0.0	3.0	24	-0.2	1.2	-3.0	0.0	3.0	0.788
Week 24	69	0.0	1.5	-4.0	0.0	4.0	22	0.2	1.6	-3.0	0.0	4.0	0.447
Leg agility													
Baseline	99	3.4	1.8	0.0	3.0	8.0	28	3.0	1.6	0.0	3.0	7.0	
Week 16	79	3.3	1.8	0.0	3.0	8.0	24	3.3	1.8	0.0	3.0	7.0	
Week 24	69	3.4	2.0	0.0	4.0	8.0	22	3.3	2.0	0.0	3.5	8.0	
Change from baseline													
Week 16	79	0.0	1.6	-4.0	0.0	4.0	24	0.0	1.3	-2.0	0.0	3.0	0.762
Week 24	69	0.1	1.8	-5.0	0.0	6.0	22	-0.2	1.8	-2.0	-0.5	5.0	0.377

Post-hoc Analyses Table 2-34
UPDRS part III item scores - summary of change
Safety population
Patients with AE's of worsening of PD

	Exelon						Placebo						
	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max	P-value
Arising from chair													
Baseline	99	1.6	1.2	0.0	1.0	4.0	28	1.3	1.0	0.0	1.0	4.0	
Week 16	79	1.6	1.3	0.0	1.0	4.0	24	1.7	1.2	0.0	2.0	4.0	
Week 24	69	1.7	1.3	0.0	2.0	4.0	22	1.7	1.2	0.0	2.0	4.0	
Change from baseline													
Week 16	79	0.1	1.1	-3.0	0.0	3.0	24	0.3	1.0	-2.0	0.0	3.0	0.215
Week 24	69	0.2	1.1	-3.0	0.0	3.0	22	0.2	0.8	-1.0	0.0	2.0	0.643
Posture													
Baseline	99	1.8	0.9	0.0	2.0	4.0	28	1.3	0.9	0.0	1.5	3.0	
Week 16	79	1.8	1.0	0.0	2.0	4.0	23	1.7	1.0	0.0	2.0	3.0	
Week 24	69	1.9	0.9	0.0	2.0	4.0	22	2.0	0.9	0.0	2.0	4.0	
Change from baseline													
Week 16	79	0.0	0.7	-2.0	0.0	2.0	23	0.3	0.8	-1.0	0.0	2.0	0.154
Week 24	69	0.0	0.7	-2.0	0.0	2.0	22	0.4	0.7	-1.0	1.0	1.0	0.027*
Gait													
Baseline	99	1.6	0.9	0.0	1.0	4.0	28	1.5	0.9	0.0	2.0	3.0	
Week 16	79	1.7	0.9	0.0	2.0	4.0	23	1.7	0.8	0.0	2.0	3.0	
Week 24	69	1.7	0.9	0.0	2.0	4.0	22	1.7	0.9	0.0	2.0	3.0	
Change from baseline													
Week 16	79	0.1	0.7	-2.0	0.0	2.0	23	0.0	0.6	-2.0	0.0	1.0	0.888
Week 24	69	0.1	0.7	-2.0	0.0	2.0	22	0.0	0.8	-2.0	0.0	1.0	0.526

Post-hoc Analyses Table 2-34
UPDRS part III item scores - summary of change
Safety population
Patients with AE's of worsening of PD

	Exelon						Placebo						
	n	Mean	SD	Min	Median	Max	n	Mean	SD	Min	Median	Max	P-value
Postural stability													
Baseline	99	1.5	0.9	0.0	1.0	4.0	28	1.3	1.1	0.0	1.0	3.0	
Week 16	79	1.6	1.1	0.0	2.0	4.0	23	1.4	1.0	0.0	1.0	4.0	
Week 24	69	1.6	1.1	0.0	1.0	4.0	22	1.7	0.9	0.0	2.0	3.0	
Change from baseline													
Week 16	79	0.1	0.7	-2.0	0.0	2.0	23	0.0	1.2	-3.0	0.0	3.0	0.563
Week 24	69	0.1	0.8	-2.0	0.0	3.0	22	0.2	1.0	-1.0	0.0	2.0	0.718
Body bradykinesia and hypokinesia													
Baseline	99	2.1	0.9	0.0	2.0	4.0	28	2.0	0.9	0.0	2.0	4.0	
Week 16	79	2.2	0.9	0.0	2.0	4.0	23	2.2	0.6	1.0	2.0	3.0	
Week 24	69	2.2	0.9	0.0	2.0	4.0	22	2.2	0.9	0.0	2.0	4.0	
Change from baseline													
Week 16	79	0.0	0.8	-3.0	0.0	2.0	23	0.0	0.6	-1.0	0.0	1.0	0.774
Week 24	69	0.1	0.8	-2.0	0.0	2.0	22	0.0	0.7	-1.0	0.0	1.0	0.709

Post-hoc Analyses Table 2-39 (Page 1 of 2)
Summary of Concomitant medication in L-Dopa, Dopamine agonist and Adamantine
by double-blind treatment
Extension safety population

Dosage (Weeks)	Exelon N=211	Placebo N=123
DOPA AND DOPA DERIVATIVES (L-DOPA)		
Baseline		
n	144	83
Mean	1240.4	1327.0
SD	811.84	640.74
Minimum	187.5	250.0
Maximum	6700.0	3625.0
Median	1122.5	1200.0
End of study		
n	151	90
Mean	1246.7	1286.9
SD	801.53	642.79
Minimum	125.0	250.0
Maximum	6500.0	3900.0
Median	1150.0	1200.0
DOPAMINE AGONISTS		
Baseline		
n	79	45
Mean	7.1	4.9
SD	24.48	5.37
Minimum	0.4	0.4
Maximum	198.8	26.2
Median	2.5	3.3

Post-hoc Analyses Table 2-39 (Page 2 of 2)
Summary of Concomitant medication in L-Dopa, Dopamine agonist and Adamantine
by double-blind treatment
Extension safety population

Dosage (Weeks)	Exelon N=211	Placebo N=123
End of study		
n	84	48
Mean	7.1	4.5
SD	23.86	5.18
Minimum	0.1	0.3
Maximum	198.8	26.2
Median	2.6	3.0
ADAMANTANE DERIVATIVES		
Baseline		
n	10	7
Mean	410.0	457.1
SD	207.90	395.21
Minimum	100.0	200.0
Maximum	700.0	1200.0
Median	400.0	200.0
End of study		
n	10	7
Mean	425.0	442.9
SD	196.14	407.66
Minimum	100.0	100.0
Maximum	700.0	1200.0
Median	400.0	200.0

Post-hoc Analyses Table 2-5a (Page 1 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by treatment
Safety population

Dosage (Weeks)	Exelon N=362	Placebo N=179
DOPA AND DOPA DERIVATIVES (L-DOPA)		
Baseline		
n	347	169
Mean	663.4	705.7
SD	368.02	349.85
Minimum	4.0	0.8
Maximum	2875.0	2100.0
Median	600.0	625.0
End of study		
n	346	169
Mean	680.9	712.9
SD	470.15	390.16
Minimum	4.0	0.8
Maximum	6100.0	3115.0
Median	600.0	625.0
DOPAMINE AGONISTS		
Baseline		
n	165	83
Mean	3.1	5.6
SD	6.80	19.37
Minimum	0.1	0.2
Maximum	75.0	163.6
Median	1.6	2.1

Post-hoc Analyses Table 2-5a (Page 2 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by treatment
Safety population

Dosage (Weeks)	Exelon N=362	Placebo N=179
End of study		
n	164	79
Mean	3.1	5.9
SD	6.81	19.83
Minimum	0.1	0.2
Maximum	75.0	163.6
Median	1.6	2.1
ADAMANTANE DERIVATIVES		
Baseline		
n	38	16
Mean	200.7	231.3
SD	85.12	195.68
Minimum	50.0	100.0
Maximum	350.0	800.0
Median	200.0	200.0
End of study		
n	39	15
Mean	196.8	240.0
SD	87.39	199.28
Minimum	50.0	100.0
Maximum	350.0	800.0
Median	200.0	200.0

Post-hoc Analyses Table 2-5a (Page 3 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by treatment
Safety population

Dosage (Weeks)	Exelon N=362	Placebo N=179
PRAMIPEXOLE		
Baseline		
n	46	28
Mean	1.7	1.8
SD	1.20	1.16
Minimum	0.2	0.2
Maximum	7.0	4.5
Median	1.4	2.1
End of study		
n	46	27
Mean	1.7	1.9
SD	1.24	1.48
Minimum	0.2	0.2
Maximum	7.0	7.1
Median	1.5	2.1

Post-hoc Analyses Table 2-37a (Page 1 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by treatment
Safety population
Patients with AE's of worsening of PD

Dosage (Weeks)	Exelon N=99	Placebo N=28
DOPA AND DOPA DERIVATIVES (L-DOPA)		
Baseline		
n	96	28
Mean	665.2	833.6
SD	360.40	437.87
Minimum	5.0	250.0
Maximum	1950.0	2100.0
Median	612.5	756.3
End of study		
n	95	28
Mean	690.1	842.5
SD	381.90	436.07
Minimum	4.0	250.0
Maximum	1950.0	2100.0
Median	625.0	862.5
DOPAMINE AGONISTS		
Baseline		
n	52	12
Mean	4.3	22.1
SD	10.93	48.46
Minimum	0.2	0.2
Maximum	75.0	163.6
Median	2.1	1.4

Post-hoc Analyses Table 2-37a (Page 2 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by treatment
Safety population
Patients with AE's of worsening of PD

Dosage (Weeks)	Exelon N=99	Placebo N=28
End of study		
n	51	11
Mean	4.2	24.1
SD	11.04	50.30
Minimum	0.2	0.2
Maximum	75.0	163.6
Median	2.0	1.6
ADAMANTANE DERIVATIVES		
Baseline		
n	10	2
Mean	210.0	100.0
SD	84.33	0.00
Minimum	100.0	100.0
Maximum	350.0	100.0
Median	200.0	100.0
End of study		
n	11	1
Mean	195.5	100.0
SD	93.42	
Minimum	50.0	100.0
Maximum	350.0	100.0
Median	200.0	100.0

Post-hoc Analyses Table 2-37a (Page 3 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by treatment
Safety population
Patients with AE's of worsening of PD

Dosage (Weeks)	Exelon N=99	Placebo N=28
PRAMIPEXOLE		
Baseline		
n	15	3
Mean	1.4	0.5
SD	1.04	0.24
Minimum	0.2	0.3
Maximum	3.0	0.7
Median	1.1	0.6
End of study		
n	15	2
Mean	1.4	0.5
SD	1.04	0.32
Minimum	0.2	0.3
Maximum	3.0	0.7
Median	1.1	0.5

Post-hoc Analyses Table 2-39a (Page 1 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by double-blind treatment
Extension safety population

Dosage (Weeks)	Exelon N=211	Placebo N=123
DOPA AND DOPA DERIVATIVES (L-DOPA)		
Baseline		
n	144	83
Mean	1240.4	1327.0
SD	811.84	640.74
Minimum	187.5	250.0
Maximum	6700.0	3625.0
Median	1122.5	1200.0
End of study		
n	151	90
Mean	1246.7	1286.9
SD	801.53	642.79
Minimum	125.0	250.0
Maximum	6500.0	3900.0
Median	1150.0	1200.0
DOPAMINE AGONISTS		
Baseline		
n	79	45
Mean	7.1	4.9
SD	24.48	5.37
Minimum	0.4	0.4
Maximum	198.8	26.2
Median	2.5	3.3

Post-hoc Analyses Table 2-39a (Page 2 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by double-blind treatment
Extension safety population

Dosage (Weeks)	Exelon N=211	Placebo N=123
End of study		
n	84	48
Mean	7.1	4.5
SD	23.86	5.18
Minimum	0.1	0.3
Maximum	198.8	26.2
Median	2.6	3.0
ADAMANTANE DERIVATIVES		
Baseline		
n	10	7
Mean	410.0	457.1
SD	207.90	395.21
Minimum	100.0	200.0
Maximum	700.0	1200.0
Median	400.0	200.0
End of study		
n	10	7
Mean	425.0	442.9
SD	196.14	407.66
Minimum	100.0	100.0
Maximum	700.0	1200.0
Median	400.0	200.0

Post-hoc Analyses Table 2-39a (Page 3 of 3)
Summary of Concomitant medication in L-Dopa, Dopamine agonist, adamantine and pramipexole
by double-blind treatment
Extension safety population

Dosage (Weeks)	Exelon N=211	Placebo N=123
PRAMIPEXOLE		
Baseline		
n	26	15
Mean	2.8	2.9
SD	1.69	2.17
Minimum	0.4	0.4
Maximum	6.0	6.8
Median	2.8	2.1
End of study		
n	27	16
Mean	2.8	2.6
SD	1.67	1.81
Minimum	0.4	0.4
Maximum	6.0	5.9
Median	2.8	2.3

Post-hoc Analyses Table 2-37-b (Page 1 of 4)
Summary of the CNS group Dopaminergic Medication
by ATC class
Extension safety population
DB-Exelon patients who have completed the Extension phase

Dosage (Weeks)	Exelon N=177
ADAMANTANE DERIVATIVES	
Baseline	
n	14
Mean	214.3
SD	86.44
Minimum	50.0
Maximum	350.0
Median	200.0
End of study	
n	15
Mean	206.7
SD	88.37
Minimum	50.0
Maximum	350.0
Median	200.0
DOPA AND DOPA DERIVATIVES (L-DOPA)	
Baseline	
n	167
Mean	678.6
SD	408.78
Minimum	100.0
Maximum	3700.0
Median	600.0

Post-hoc Analyses Table 2-37-b (Page 2 of 4)
Summary of the CNS group Dopaminergic Medication
by ATC class
Extension safety population
DB-Exelon patients who have completed the Extension phase

Dosage (Weeks)	Exelon N=177
End of study	
n	169
Mean	745.9
SD	564.07
Minimum	100.0
Maximum	5300.0
Median	625.0
DOPAMINE AGONISTS	
Baseline	
n	86
Mean	9.2
SD	31.75
Minimum	0.2
Maximum	265.0
Median	3.0
End of study	
n	88
Mean	11.1
SD	35.40
Minimum	0.1
Maximum	265.0
Median	3.0

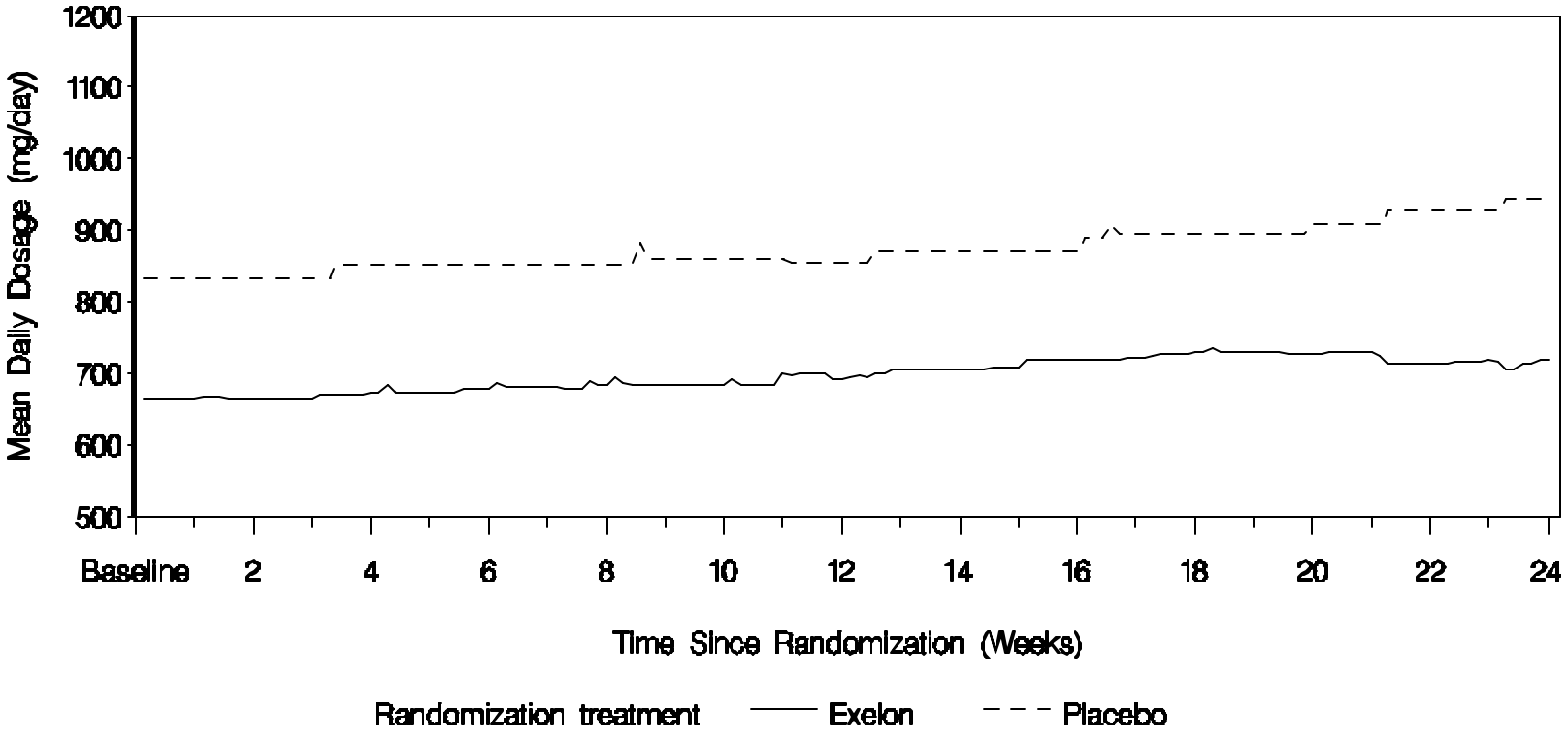
Post-hoc Analyses Table 2-37-b (Page 3 of 4)
Summary of the CNS group Dopaminergic Medication
by ATC class
Extension safety population
DB-Exelon patients who have completed the Extension phase

Dosage (Weeks)	Exelon N=177
MONOAMINE OXIDASE B INHIBITORS	
Baseline	
n	13
Mean	27.4
SD	71.76
Minimum	1.3
Maximum	265.0
Median	5.0
End of study	
n	12
Mean	28.9
SD	74.76
Minimum	1.3
Maximum	265.0
Median	5.0
OTHER DOPAMINERGIC AGENTS	
Baseline	
n	29
Mean	820.8
SD	317.71
Minimum	1.0
Maximum	1400.0
Median	800.0

Post-hoc Analyses Table 2-37-b (Page 4 of 4)
Summary of the CNS group Dopaminergic Medication
by ATC class
Extension safety population
DB-Exelon patients who have completed the Extension phase

Dosage (Weeks)	Exelon N=177
End of study	
n	31
Mean	829.1
SD	345.57
Minimum	1.0
Maximum	1400.0
Median	800.0
PROLACTINE INHIBITORS	
Baseline	
n	14
Mean	8.0
SD	12.60
Minimum	1.0
Maximum	45.0
Median	2.5
End of study	
n	16
Mean	7.7
SD	11.77
Minimum	1.0
Maximum	45.0
Median	3.5

Post-hoc Analyses Graph 2-4
Mean daily dose (mg/day) of the concomitant medication Dopa and dopa derivatives (L-dopa)
in treatment period over time
(Safety population)
Patients with AE's of worsening of PD



report/export/pgm_saf/cmd_graph_04.sas 14JUL2005:7:51 '

Post-hoc Analyses Table 2-25 (Page 1 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:baseline (included) to week 4 (included)

Preferred term	Exelon N=362 n (%)	Placebo N=179 n (%)
-Total	27(7.5)	12(6.7)
Fall	7(1.9)	5(2.8)
Tremor	7(1.9)	3(1.7)
Gait abnormal	3(0.8)	0(0.0)
Parkinsonism	3(0.8)	1(0.6)
Bradykinesia	2(0.6)	0(0.0)
Dystonia	2(0.6)	1(0.6)
Parkinson's disease	2(0.6)	0(0.0)
Dyskinesia	1(0.3)	1(0.6)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

Post-hoc Analyses Table 2-25 (Page 2 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:baseline (included) to week 4 (included)

Preferred term	Exelon N=362 n (%)	Placebo N=179 n (%)
Extrapyramidal disorder	1(0.3)	0(0.0)
Motor dysfunction	1(0.3)	0(0.0)
Muscle rigidity	1(0.3)	0(0.0)
Salivary hypersecretion	1(0.3)	0(0.0)
Balance disorder	0(0.0)	1(0.6)
Drooling	0(0.0)	1(0.6)
Dysarthria	0(0.0)	1(0.6)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

Post-hoc Analyses Table 2-25 (Page 3 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:week 4 (excluded) to week 8 (included)

Preferred term	Exelon N=343 n (%)	Placebo N=168 n (%)
-Total	27(7.9)	3(1.8)
Tremor	9(2.6)	0(0.0)
Parkinson's disease	6(1.7)	1(0.6)
Bradykinesia	5(1.5)	1(0.6)
Fall	5(1.5)	1(0.6)
Dyskinesia	1(0.3)	0(0.0)
Gait abnormal	1(0.3)	0(0.0)
Rigors	1(0.3)	0(0.0)
Salivary hypersecretion	1(0.3)	0(0.0)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

Post-hoc Analyses Table 2-25 (Page 4 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:week 8 (excluded) to week 12 (included)

Preferred term	Exelon N=324 n (%)	Placebo N=165 n (%)
-Total	35(10.8)	9(5.5)
Tremor	15(4.6)	1(0.6)
Fall	5(1.5)	4(2.4)
Parkinsonism	4(1.2)	0(0.0)
Balance disorder	3(0.9)	1(0.6)
Parkinson's disease	3(0.9)	0(0.0)
Musculoskeletal stiffness	2(0.6)	0(0.0)
Salivary hypersecretion	2(0.6)	0(0.0)
Bradykinesia	1(0.3)	1(0.6)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

Post-hoc Analyses Table 2-25 (Page 5 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:week 8 (excluded) to week 12 (included)

Preferred term	Exelon N=324 n (%)	Placebo N=165 n (%)
Dyskinesia	1(0.3)	0(0.0)
Hyperkinesia	1(0.3)	0(0.0)
Hypokinesia	1(0.3)	0(0.0)
Movement disorder	1(0.3)	0(0.0)
Drooling	0(0.0)	1(0.6)
On and off phenomenon	0(0.0)	1(0.6)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

Post-hoc Analyses Table 2-25 (Page 6 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:week 12 (excluded) to week 16 (included)

Preferred term	Exelon N=301 n (%)	Placebo N=162 n (%)
-Total	14(4.7)	7(4.3)
Tremor	6(2.0)	2(1.2)
Fall	4(1.3)	4(2.5)
Drooling	1(0.3)	0(0.0)
Dystonia	1(0.3)	0(0.0)
Musculoskeletal stiffness	1(0.3)	0(0.0)
Parkinson's disease	1(0.3)	0(0.0)
Salivary hypersecretion	1(0.3)	0(0.0)
Bradykinesia	0(0.0)	1(0.6)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

Post-hoc Analyses Table 2-25 (Page 7 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:week 16 (excluded) to week 20 (included)

Preferred term	Exelon N=281 n (%)	Placebo N=158 n (%)
-Total	10(3.6)	3(1.9)
Fall	3(1.1)	1(0.6)
Dyskinesia	2(0.7)	0(0.0)
Tremor	2(0.7)	1(0.6)
Bradykinesia	1(0.4)	0(0.0)
Drooling	1(0.4)	0(0.0)
On and off phenomenon	1(0.4)	0(0.0)
Parkinson's disease	0(0.0)	1(0.6)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

Post-hoc Analyses Table 2-25 (Page 8 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:week 20 (excluded) to week 24 (included)

Preferred term	Exelon N=271 n (%)	Placebo N=151 n (%)
-Total	6(2.2)	5(3.3)
Fall	3(1.1)	3(2.0)
Gait abnormal	1(0.4)	0(0.0)
Parkinson's disease	1(0.4)	0(0.0)
Parkinsonism	1(0.4)	0(0.0)
Tremor	1(0.4)	0(0.0)
Freezing phenomenon	0(0.0)	1(0.7)
Hypertonia	0(0.0)	1(0.7)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

Post-hoc Analyses Table 2-25 (Page 9 of 9)
Summary of worsening of Parkinson's disease
Regardless of study drug relationship
by study period, preferred term and treatment
Safety population

Study Period:week 24 (excluded) to last date on study drug +2 days(included)

Preferred term	Exelon N=158 n (%)	Placebo N=96 n (%)
-Total	2(1.3)	0(0.0)
Bradykinesia	1(0.6)	0(0.0)
Parkinson's disease	1(0.6)	0(0.0)

- If day in start date is missing then day is set to 01 (e.g. JAN2002 becomes 01JAN2002).
- Worsening of Parkinson's disease symptoms were pre-defined: Parkinsonian Rest Tremor; Cogwheel rigidity; Parkinsonian Gait and Parkinsonian Crisis; Parkinson's disease NOS; Extrapyramidal disorder; Tremor; Rigors; Muscle rigidity; Nuchal rigidity; Parkinsonism; Akathisia; Dystonia; Dyskinesia; Gait abnormal; Balance Disorder; Bradykinesia; Hypokinesia; Akinesia; Fall; Dysarthria;Salivary Hypersecretion; Drooling; Musculoskeletal stiffness; Hyperkinesia; Motor dysfunction; On and Off phenomenon; Freezing phenomenon; Hypertonia; Movement Disorder.
- Preferred terms are sorted in descending frequency, as reported in the Exelon column.
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

-/vob/CENA713B/CENA713B2311/report/pgm_saf/emea_aev_02.sas - 14JUL05:08:54

CENA713B 2311

Post-hoc Analyses Listing 2-1 (Page 1 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
AUT/0116/00009	73/M/Ca		DETERIORATION OF PARKINSON SYMPTOMS / Parkinson's disease / Nervous system disorders	29MAY2003/8	23JUL2003/63	1
			LEG OEDEMA / Oedema peripheral / General disorders and administration site conditions	29MAY2003/8	23JUL2003/63	None
			RESTLESSNESS (IN THE EVENING AND DURING NIGHT) / Restlessness / Psychiatric disorders	29MAY2003/8	30SEP2003/ 132	3
			VISUAL HALLUCINATIONS / Hallucination, visual / Psychiatric disorders	18AUG2003/89	Continuing	None
			GASTROENTERITIS / Gastroenteritis / Infections and infestations	21OCT2003/ 153	04NOV2003/ 167	None
BEL/0001/00008	66/F/Ca		AGGRAVATION OF PARKINSON SYMPTOMS / Parkinson's disease / Nervous system disorders	31JUL2003/ 108	05SEP2003/ 144	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 2 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
BEL/0001/00008	66/F/Ca	*	WEIGHT LOSS / Weight decreased / Investigations	31JUL2003/ 108	02SEP2003/ 141	5
BEL/0001/00014	80/M/Ca	*	WORSENING OF THE PARKINSON SYMPTOMS / Parkinson's disease / Nervous system disorders	20AUG2003/30	Continuing	5
			NAUSEA / Nausea / Gastrointestinal disorders	30AUG2003/40	Continuing	3
		*	IATROGEN HAEMOTHORAX / Haemothorax / Injury, poisoning and procedural complications	04OCT2003/75	Continuing	3,4,5
		*	SICK-SINUS SYNDROME / Sick sinus syndrome / Cardiac disorders	04OCT2003/75	Continuing	2,4,5
BEL/0002/00004	70/M/Ca		NAUSEA / Nausea / Gastrointestinal disorders	10JUL2003/29	30SEP2003/ 111	1,3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
SAE: * defines a serious adverse event
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 3 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
BEL/0002/00004	70/M/Ca		NAUSEA / Nausea / Gastrointestinal disorders	01OCT2003/ 112	10DEC2003/ 182	None
CAN/0104/00001	76/F/Ca		OCCASIONAL NECK DIAPHORESIS / Hyperhidrosis / Skin and subcutaneous tissue disorders	19JUN2003/49	Continuing	None
			NAUSEA / Nausea / Gastrointestinal disorders	11JUL2003/71	31JUL2003/91	3
			HEMATOMA RIGHT ARM / Haematoma / Vascular disorders	24JUL2003/84	26SEP2003/ 148	None
			LOST OF APPETITE / Anorexia / Metabolism and nutrition disorders	01AUG2003/92	26SEP2003/ 148	1
			NAUSEA / Nausea / Gastrointestinal disorders	01AUG2003/92	28AUG2003/ 119	1,3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 4 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
CAN/0104/00001	76/F/Ca		EXACERBATION OF PARKINSONISM / DYSKINESIA / Dyskinesia / Nervous system disorders	22AUG2003/ 113	04SEP2003/ 126	None
			NAUSEA / Nausea / Gastrointestinal disorders	17SEP2003/ 139	18SEP2003/ 140	1
CAN/0105/00008	67/M/Ca		PAIN IN RIGHT LEG / Pain in extremity / Musculoskeletal and connective tissue disorders	10AUG2003/66	20SEP2003/ 107	None
			WORSENING PARKINSON'S DISEASE / Parkinson's disease / Nervous system disorders	15AUG2003/71	Continuing	None
			DIARRHEA / Diarrhoea / Gastrointestinal disorders	28OCT2003/ 145	31OCT2003/ 148	None
			NAUSEA / Nausea / Gastrointestinal disorders	28OCT2003/ 145	15NOV2003/ 163	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 5 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
CAN/0105/00012	86/M/Ca		FALL / Fall / Injury, poisoning and procedural complications	01AUG2003/17	01AUG2003/17	None
			WORSENING PARKINSON'S DISEASE / Parkinson's disease / Nervous system disorders	20AUG2003/36	Continuing	1,3
			NAUSEA / Nausea / Gastrointestinal disorders	15OCT2003/92	Continuing	1,3
			DAYTIME DROWSINESS / Somnolence / Nervous system disorders	11NOV2003/ 119	Continuing	None
			FALL / Fall / Injury, poisoning and procedural complications	03DEC2003/ 141	03DEC2003/ 141	None
			CAVITIES IN TEETH / Dental caries / Infections and infestations	22DEC2003/ 160	07JAN2004/ 176	3,4

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

CENA713B 2311

Post-hoc Analyses Listing 2-1 (Page 6 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
DEU/0034/00007	67/M/Ca		HYPERHIDROSIS / Hyperhidrosis / Skin and subcutaneous tissue disorders	25APR2003/16	17JUN2003/69	None
			NAUSEA / Nausea / Gastrointestinal disorders	25APR2003/16	17JUN2003/69	None
			VERTIGO / Vertigo / Ear and labyrinth disorders	25APR2003/16	Continuing	None
		*	FALLING DOWN / Fall / Injury, poisoning and procedural complications	28APR2003/19	08MAY2003/29	None
			ILL STOMAGE / Stomach discomfort / Gastrointestinal disorders	15AUG2003/ 128	19AUG2003/ 132	None
DEU/0035/00002	73/M/Ca		GRIPPAL INFECTION / Influenza / Infections and infestations	14JUL2003/68	23JUL2003/77	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
SAE: * defines a serious adverse event
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 7 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
DEU/0035/00006	86/M/Ca		HEADACHE / Headache / Nervous system disorders	03SEP2003/89	23OCT2003/ 139	1
			UNREST / Anxiety / Psychiatric disorders	03SEP2003/89	23OCT2003/ 139	1
DEU/0038/00007	80/M/Ca		NONE			
ESP/0072/00001	70/M/Ca		MALAISE / Malaise / General disorders and administration site conditions	14MAR2003/4	20MAR2003/10	1
			DYSPNEA / Dyspnoea / Respiratory, thoracic and mediastinal disorders	19MAY2003/70	26MAY2003/77	3
			BRONCOSPASM / Bronchospasm / Respiratory, thoracic and mediastinal disorders	10JUN2003/92	24JUN2003/ 106	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 8 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ESP/0072/00001	70/M/Ca		WORSENING OF URINARY INCONTINENCE / Urinary incontinence / Renal and urinary disorders	04JUL2003/ 116	Continuing	None
			DYSPNEA / Dyspnoea / Respiratory, thoracic and mediastinal disorders	22JUL2003/ 134	28JUL2003/ 140	3
			WORSENING OF PARKINSONISM / Parkinsonism / Nervous system disorders	05AUG2003/ 148	Continuing	None
ESP/0074/00002	72/F/Ca		VOMIT / Vomiting / Gastrointestinal disorders	11MAY2003/62	12MAY2003/63	None
			VOMIT / Vomiting / Gastrointestinal disorders	05JUN2003/87	08JUN2003/90	None
			HYPERTENSION EPISODE / Hypertension / Vascular disorders	16JUN2003/98	16JUN2003/98	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 9 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ESP/0074/00002	72/F/Ca		VOMIT / Vomiting / Gastrointestinal disorders	22JUN2003/ 104	22JUN2003/ 104	None
			URINARY INFECTION / Urinary tract infection / Infections and infestations	01JUL2003/ 113	08AUG2003/ 151	3
			NAUSEAS / Nausea / Gastrointestinal disorders	11AUG2003/ 154	13AUG2003/ 156	None
			HYPERTENSION EPISODE / Hypertension / Vascular disorders	18AUG2003/ 161	20AUG2003/ 163	3
			VOMIT / Vomiting / Gastrointestinal disorders	19AUG2003/ 162	19AUG2003/ 162	None
			HYPERTENSION EPISODE / Hypertension / Vascular disorders	22AUG2003/ 165	22AUG2003/ 165	3
			HYPERPROLACTINEMIA / Hyperprolactinaemia / Endocrine disorders	28AUG2003/ 171	Continuing	None

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 10 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ESP/0075/00005	78/F/Ca		DIARRHEA / Diarrhoea / Gastrointestinal disorders	17APR2003/86	14MAY2003/ 113	4
			VOMITING / Vomiting / Gastrointestinal disorders	17APR2003/86	14MAY2003/ 113	4
ESP/0075/00014	81/F/Ca		DIZZINESS / Dizziness / Nervous system disorders	25MAY2003/45	28MAY2003/48	None
		*	INTESTINAL SUBOCCLUSION / Intestinal obstruction / Gastrointestinal disorders	11JUL2003/92	17JUL2003/98	4,5
			URINARY INFECTION / Urinary tract infection / Infections and infestations	17JUL2003/98	23JUL2003/ 104	3
			FALL / Fall / Injury, poisoning and procedural complications	19AUG2003/ 131	19AUG2003/ 131	None

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
SAE: * defines a serious adverse event
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 11 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ESP/0075/00014	81/F/Ca		FACIAL CONTUSION / Contusion / Injury, poisoning and procedural complications	19AUG2003/ 131	19AUG2003/ 131	None
ESP/0077/00005	76/F/Ca		INSOMNIA / Insomnia / Psychiatric disorders	26APR2003/24	02MAY2003/30	None
			ANOREXIA / Anorexia / Metabolism and nutrition disorders	01JUN2003/60	Continuing	None
ESP/0078/00003	81/F/Ca		ENDOMETRIAL HIPERTROPHY / Endometrial hypertrophy / Reproductive system and breast disorders	19MAR2003/7	Continuing	None
			OVARIAN CYST / Ovarian cyst / Reproductive system and breast disorders	19MAR2003/7	Continuing	None

Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 12 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ESP/0078/00003	81/F/Ca		WORSENING OF PARKINSON SYMPTOMS / Parkinson's disease / Nervous system disorders	08MAY2003/57	05JUN2003/85	1,3
			WORSENING SYMTOMS OF PARKINSON DISEASE / Parkinson's disease / Nervous system disorders	02SEP2003/ 174	Continuing	3
ESP/0078/00007	79/F/Ca		ISCHAEMIC CARDIOPATHY / Ischaemic cardiomyopathy / Cardiac disorders	23OCT2003/ 120	Continuing	3
			INSOMNIA / Insomnia / Psychiatric disorders	02DEC2003/ 160	Continuing	None
FRA/0012/00008	72/F/Ca	*	AGITATION / Agitation / Psychiatric disorders	16OCT2003/98	Continuing	3,5
		*	CONFUSIONAL SYNDROME / Confusional state / Psychiatric disorders	16OCT2003/98	Continuing	3,5

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
SAE: * defines a serious adverse event
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 13 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
FRA/0012/00008	72/F/Ca		EPIGASTRALGIA / Abdominal pain upper / Gastrointestinal disorders	17OCT2003/99	17OCT2003/99	3
			THORACIC PAIN / Chest pain / General disorders and administration site conditions	19OCT2003/ 101	19OCT2003/ 101	3
			CONSTIPATION / Constipation / Gastrointestinal disorders	12DEC2003/ 155	Continuing	3
			HYPOTENSION / Hypotension / Vascular disorders	12DEC2003/ 155	Continuing	3
FRA/0014/00013	76/M/Ca		NONE			
FRA/0014/00019	72/M/Ca		EPIGASTRALGIA / Abdominal pain upper / Gastrointestinal disorders	15OCT2003/ 100	01NOV2003/ 117	1,3
			INCREASE OF THE TREMOR / Tremor / Nervous system disorders	15OCT2003/ 100	Continuing	None

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 14 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
FRA/0014/00019	72/M/Ca		NAUSEA / Nausea / Gastrointestinal disorders	15OCT2003/ 100	01NOV2003/ 117	1,3
			VOMITING / Vomiting / Gastrointestinal disorders	15OCT2003/ 100	01NOV2003/ 117	1,3
FRA/0016/00004	66/F/Ca		COSTAL FRACTURE DUE TO FALL / Rib fracture / Injury, poisoning and procedural complications	18FEB2003/41	18FEB2003/41	None
			FALL / Fall / Injury, poisoning and procedural complications	18FEB2003/41	18FEB2003/41	None
			INSOMNIA / Insomnia / Psychiatric disorders	15MAR2003/66	Continuing	3
			FALL / Fall / Injury, poisoning and procedural complications	28MAR2003/79	28MAR2003/79	4

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 15 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
FRA/0016/00004	66/F/Ca	*	FECALOMA / Faecaloma / Gastrointestinal disorders	22APR2003/ 104	30APR2003/ 112	5
		*	DEHYDRATATION / Dehydration / Metabolism and nutrition disorders	12JUN2003/ 155	18JUN2003/ 161	5
FRA/0019/00004	71/M/Ca		NONE			
GBR/0085/00004	77/M/Ca		CONSTIPATION / Constipation / Gastrointestinal disorders	28JUL2003/31	Continuing	3
			EPIGASTRIC DISCOMFORT / Epigastric discomfort / Gastrointestinal disorders	09OCT2003/ 104	10OCT2003/ 105	None
GBR/0091/00004	75/M/Ca		SLEEPINESS - DAYTIME / Somnolence / Nervous system disorders	13APR2003/30	05JUN2003/83	None

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
SAE: * defines a serious adverse event
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 16 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ITA/0046/00012	75/M/Ca		BRADIKINESIA / Bradykinesia / Nervous system disorders	04APR2003/1	28MAY2003/55	None
			RESTLESSNESS / Restlessness / Psychiatric disorders	30APR2003/27	17JUL2003/ 105	None
			BRADIKINESIA / Bradykinesia / Nervous system disorders	29MAY2003/56	04JUN2003/62	1
ITA/0046/00017	79/M/Ca		NAUSEA / Nausea / Gastrointestinal disorders	04JUL2003/29	06JUL2003/31	1
ITA/0049/00019	73/M/Ca		VOMITING / Vomiting / Gastrointestinal disorders	28AUG2003/43	06SEP2003/52	1
			VOMITING / Vomiting / Gastrointestinal disorders	18SEP2003/64	21SEP2003/67	1

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 17 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ITA/0049/00034	65/M/Ca		DIRRHEA / Diarrhoea / Gastrointestinal disorders	25AUG2003/40	30AUG2003/45	1
ITA/0051/00012	63/M/Ca		NONE			
ITA/0051/00013	65/M/Ca		NONE			
NLD/0061/00006	63/F/Ca		VARICELLA ZOSTER INFECTION / Herpes zoster / Infections and infestations	01MAY2003/23	15JUN2003/68	None
			NAUSEA / Nausea / Gastrointestinal disorders	01JUN2003/54	10AUG2003/ 124	1
			VOMITING / Vomiting / Gastrointestinal disorders	01JUN2003/54	10AUG2003/ 124	1
			CHALAZION LEFT EYE / Chalazion / Eye disorders	29AUG2003/ 143	Continuing	None

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 18 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
NLD/0061/00006	63/F/Ca		NAUSEA / Nausea / Gastrointestinal disorders	01OCT2003/ 176	Continuing	1
NLD/0061/00011	74/M/Ca		NONE			
NLD/0061/00012	76/M/Ca		NONE			
NOR/0131/00002	84/M/Ca		NONE			
NOR/0131/00011	62/F/Ca		PAIN IN LEGS / Pain in extremity / Musculoskeletal and connective tissue disorders	01SEP2003/76	Continuing	3
			INCREASED SALIVA PRODUCTION / Salivary hypersecretion / Gastrointestinal disorders	18SEP2003/93	Continuing	1
			INCREASED SLIME SECRESION FROM NOUSE AND MOUTH / Secretion discharge / General disorders and administration site conditions	18SEP2003/93	Continuing	1

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 19 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
NOR/0131/00011	62/F/Ca		INCREASED TREMOR / Tremor / Nervous system disorders	18SEP2003/93	Continuing	1
			INCREASED TREMOR / Tremor / Nervous system disorders	18SEP2003/93	Continuing	1
PRT/0137/00006	67/M/Ca		BEHAVIOUR DISTURBANCE / Abnormal behaviour / Psychiatric disorders	13SEP2003/85	14OCT2003/ 116	1,3
TUR/0121/00003	75/M/Ca		NONE			
TUR/0121/00008	72/M/Ca		NONE			
TUR/0122/00009	53/M/Ca		NONE			
TUR/0122/00015	50/F/Ca		HALLUCINATIONS / Hallucination / Psychiatric disorders	15JUL2003/79	Continuing	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 20 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
TUR/0122/00015	50/F/Ca		DAYTIME SLEEPINESS / Somnolence / Nervous system disorders	11AUG2003/ 106	Continuing	None
			BRADYKINESIA / Bradykinesia / Nervous system disorders	01SEP2003/ 127	Continuing	None
TUR/0122/00018	60/M/Ca		NAUSEA / Nausea / Gastrointestinal disorders	04AUG2003/92	Continuing	1
			VOMITING / Vomiting / Gastrointestinal disorders	04AUG2003/92	05AUG2003/93	1
			DIAREA / Diarrhoea / Gastrointestinal disorders	24AUG2003/ 112	Continuing	1
			NAUSEA / Nausea / Gastrointestinal disorders	11SEP2003/ 130	13SEP2003/ 132	1
			VOMITING / Vomiting / Gastrointestinal disorders	11SEP2003/ 130	Continuing	1

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 21 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
TUR/0122/00023	69/M/Ca		POSTURAL HYPOTENTION / Orthostatic hypotension / Vascular disorders	04JUL2003/52	06AUG2003/85	None
		*	RIGHT HEMIPARESIS DUE TO LEFT THALAMIC HEMORRAGE / Hemiparesis / Nervous system disorders	23AUG2003/ 102	Continuing	1,3,4, 5
			HYPOCROM MICROCYTER ANEMIA / Hypochromic anaemia / Blood and lymphatic system disorders	31AUG2003/ 110	Continuing	3
TUR/0122/00033	69/M/Ca		WEIGHT LOSS / Weight decreased / Investigations	02SEP2003/58	23OCT2003/ 109	3
			HYPERSALIVATION / Salivary hypersecretion / Gastrointestinal disorders	24SEP2003/80	Continuing	3
			LOSS OF APPETITE / Anorexia / Metabolism and nutrition disorders	24SEP2003/80	Continuing	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
SAE: * defines a serious adverse event
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 22 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
TUR/0122/00033	69/M/Ca		VISUAL HALLUCINATIONS / Hallucination, visual / Psychiatric disorders	24SEP2003/80	Continuing	3
			WEIGHT LOSS / Weight decreased / Investigations	24SEP2003/80	Continuing	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 23 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Placebo

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
BEL/0003/00004	66/M/Ca	*	FRACTURE RIGHT SHOULDER / Upper limb fracture / Injury, poisoning and procedural complications	16MAR2003/28	01APR2003/44	4,5
			HYPOTENSION / Hypotension / Vascular disorders	02APR2003/45	15JUL2003/ 149	3,4
			HYPOTENSION / Hypotension / Vascular disorders	15JUL2003/ 149	Continuing	3,4
CAN/0103/00003	72/M/Ca		CONSTIPATION / Constipation / Gastrointestinal disorders	04SEP2003/ 177	Continuing	None
DEU/0028/00010	72/M/Ca		NONE			
DEU/0037/00001	76/F/Ca		NONE			

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
SAE: * defines a serious adverse event
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 24 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Placebo

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ESP/0075/00010	79/M/Ca		INTERNAL HEMORRHOID / Haemorrhoids / Gastrointestinal disorders	27JUL2003/ 158	27JUL2003/ 158	None
			RECTAL BLEENDING / Rectal haemorrhage / Gastrointestinal disorders	27JUL2003/ 158	27JUL2003/ 158	4
			RECTAL POLYP / Rectal polyp / Gastrointestinal disorders	27JUL2003/ 158	27JUL2003/ 158	None
ESP/0077/00006	78/M/Ca		NAUSEA / Nausea / Gastrointestinal disorders	21SEP2003/ 110	23SEP2003/ 112	None
			PAIN IN RIGHT HIP / Arthralgia / Musculoskeletal and connective tissue disorders	14OCT2003/ 133	Continuing	3
ESP/0078/00009	81/M/Ca		CONFUSION / Confusional state / Psychiatric disorders	21OCT2003/ 112	22OCT2003/ 113	None

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 25 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Placebo

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ESP/0078/00009	81/M/Ca		INCISED WOUND / Wound drainage / Surgical and medical procedures	14NOV2003/ 136	14NOV2003/ 136	4
			CONFUSION / Confusional state / Psychiatric disorders	06DEC2003/ 158	11DEC2003/ 163	None
FRA/0014/00002	73/M/Ca		NONE			
FRA/0014/00008	66/M/Ca		NONE			
FRA/0017/00010	83/F/Ca		GASTRIC REFLUX / Gastrooesophageal reflux disease / Gastrointestinal disorders	01SEP2003/56	Continuing	3
			DIARRHEA / Diarrhoea / Gastrointestinal disorders	03SEP2003/58	03SEP2003/58	None
GBR/0087/00004	75/F/Ca		URINARY TRACT INFECTION / Urinary tract infection / Infections and infestations	07AUG2003/29	15AUG2003/37	3

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 26 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Placebo

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
GBR/0094/00001	70/F/Ca		CELLULITIS / Cellulitis / Infections and infestations	19MAY2003/-1	16JUN2003/27	3
			DIZZINESS / Dizziness / Nervous system disorders	02JUN2003/13	30JUN2003/41	None
			DECREASED APPETITE / Decreased appetite / Metabolism and nutrition disorders	15JUL2003/56	Continuing	None
			DIZZYNESS / Dizziness / Nervous system disorders	15JUL2003/56	Continuing	None
			NAUSEA / Nausea / Gastrointestinal disorders	15JUL2003/56	Continuing	None
			DROP IN SYSTOLIC BLOOD PRESSURE TO 78MMHG / Blood pressure systolic decreased / Investigations	11AUG2003/83	18AUG2003/90	4

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-1 (Page 27 of 27)
Adverse events, regardless of study drug relationship
by primary system organ class, preferred term and treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Placebo

Country/ Center/ Subject	Age/ Sex/ Race	SAE	Adverse Event (REPORTED / Preferred / System organ class)	Start date/ day	End date/ day	Action taken
ITA/0052/00001	64/M/Ca		VISUAL HALLUCINATION / Hallucination, visual / Psychiatric disorders	01JUL2003/15	02JUL2003/16	1
			VISUAL HALLUCINATION / Hallucination, visual / Psychiatric disorders	07JUL2003/21	08JUL2003/22	1
TUR/0122/00017	54/M/Ca	*	CONSTIPATION / Constipation / Gastrointestinal disorders	10MAY2003/6	Continuing	1,5
		*	ABDOMINAL PAIN / Abdominal pain / Gastrointestinal disorders	15MAY2003/11	Continuing	1,5
			CONSTIPATION / Constipation / Gastrointestinal disorders	19MAY2003/15	Continuing	1

Action taken: 1=Study drug dosage adjusted/temporarily interrupted, 2=Study drug permanently discontinued due to this AE
3=Concomitant medication taken, 4=Non-drug therapy given, 5=Hospitalization/Prolonged hospitalization
SAE: * defines a serious adverse event
Note: Day is relative to the first day of treatment (day 1)

report/pgm_saf/l_amyl.sas - 14JUL2005:8:47

Post-hoc Analyses Listing 2-3 (Page 1 of 7)
Subject laboratory profile for calcium, LDH and glucose
by treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	Study phase	Calcium mmol/L	Glucose mmol/L	LDH U/L
AUT/0116/00009	73/M/Ca	Baseline	2.35	7.1 H	128.0
		Endpoint	2.33	5.7	122.0
BEL/0001/00008	66/F/Ca	Baseline	2.47	6.1	
		Endpoint	2.34	4.7	
BEL/0001/00014	80/M/Ca	Baseline	2.38	4.6	178.0
		Endpoint	2.44	4.6	158.0
BEL/0002/00004	70/M/Ca	Baseline	2.47	6.1	
		Endpoint	2.46	4.4	
CAN/0104/00001	76/F/Ca	Baseline	2.45	5.8	189.0
		Endpoint	2.45	7.5 H	179.0
CAN/0105/00008	67/M/Ca	Baseline	2.35	4.2	177.0
		Endpoint	2.37	3.7 L	157.0
CAN/0105/00012	86/M/Ca	Baseline	2.42	5.3	183.0
		Endpoint	2.52	4.6	207.0
DEU/0034/00007	67/M/Ca	Baseline	2.20	9.0 H	270.0 H
		Endpoint	2.32	7.0 H	197.0
DEU/0035/00002	73/M/Ca	Baseline	2.36	5.1	172.0
		Endpoint	2.27	5.7	132.0
DEU/0035/00006	86/M/Ca	Baseline	2.29	6.3	148.0
		Endpoint	2.29	5.8	122.0
DEU/0038/00007	80/M/Ca	Baseline	2.24	8.4 H	161.0

L/H denotes a value below/above normal range and are calculated on the data prior to conversion to standard unit.
Note: Day is relative to the first day of treatment (day 1).

report/pgm_saf/l_amy_pan.sas - 14JUL2005:8:46

Post-hoc Analyses Listing 2-3 (Page 2 of 7)
Subject laboratory profile for calcium, LDH and glucose
by treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	Study phase	Calcium mmol/L	Glucose mmol/L	LDH U/L
DEU/0038/00007	80/M/Ca	Endpoint	2.21	8.3 H	153.0
ESP/0072/00001	70/M/Ca	Baseline	2.28	6.4	292.0 H
		Endpoint	2.35	5.6	164.0
ESP/0074/00002	72/F/Ca	Baseline	2.41	7.1 H	
		Endpoint	2.31	6.8 H	
ESP/0075/00005	78/F/Ca	Baseline	2.25	7.8 H	112.0
		Endpoint	2.37	6.6	134.0
ESP/0075/00014	81/F/Ca	Baseline	2.50	6.2	183.0
		Endpoint	2.36	5.7	162.0
ESP/0077/00005	76/F/Ca	Baseline	2.46	5.3	155.0
		Endpoint	2.41	4.5	146.0
ESP/0078/00003	81/F/Ca	Baseline	2.48	6.4	215.0
		Endpoint	2.36	5.8	183.0
ESP/0078/00007	79/F/Ca	Baseline	2.48	7.2 H	184.0
		Endpoint	2.69 H	7.9 H	174.0
FRA/0012/00008	72/F/Ca	Baseline	2.21	6.2	124.0
		Endpoint	2.28	6.3	121.0
FRA/0014/00013	76/M/Ca	Baseline	2.44	5.8	175.0
		Endpoint	2.37	5.5	212.0
FRA/0014/00019	72/M/Ca	Baseline	2.24	5.6	138.0
		Endpoint	2.33	4.6	134.0

L/H denotes a value below/above normal range and are calculated on the data prior to conversion to standard unit.
Note: Day is relative to the first day of treatment (day 1).

report/pgm_saf/l_amy_pan.sas - 14JUL2005:8:46

Post-hoc Analyses Listing 2-3 (Page 3 of 7)
Subject laboratory profile for calcium, LDH and glucose
by treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	Study phase	Calcium mmol/L	Glucose mmol/L	LDH U/L
FRA/0016/00004	66/F/Ca	Baseline	2.44	5.3	139.0
		Endpoint	2.50	5.1	114.0
FRA/0019/00004	71/M/Ca	Baseline	2.53	6.2	166.0
		Endpoint	2.37	6.6	182.0
GBR/0085/00004	77/M/Ca	Baseline	2.27	6.1	
		Endpoint	2.31	5.4	
GBR/0091/00004	75/M/Ca	Baseline	2.36	5.3	167.0
		Endpoint	2.34	4.0	141.0
ITA/0046/00012	75/M/Ca	Baseline	2.45	4.8	163.0
		Endpoint	2.42	4.9	180.0
ITA/0046/00017	79/M/Ca	Baseline	1.86 L		
		Endpoint	2.26		
ITA/0049/00019	73/M/Ca	Baseline	2.17	4.9	146.0
		Endpoint	2.24	4.9	133.0
ITA/0049/00034	65/M/Ca	Baseline	2.27	5.3	140.0
		Endpoint	2.46	4.9	177.0
ITA/0051/00012	63/M/Ca	Baseline	2.35	5.0	149.0
		Endpoint	2.20	5.0	129.0
ITA/0051/00013	65/M/Ca	Baseline	2.30	5.6	137.0
		Endpoint	2.32	2.5 L	131.0
NLD/0061/00006	63/F/Ca	Baseline	2.39	6.0	145.0

L/H denotes a value below/above normal range and are calculated on the data prior to conversion to standard unit.
Note: Day is relative to the first day of treatment (day 1).

report/pgm_saf/l_amy_pan.sas - 14JUL2005:8:46

Post-hoc Analyses Listing 2-3 (Page 4 of 7)
Subject laboratory profile for calcium, LDH and glucose
by treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	Study phase	Calcium mmol/L	Glucose mmol/L	LDH U/L
NLD/0061/00006	63/F/Ca	Endpoint	2.45	5.6	141.0
NLD/0061/00011	74/M/Ca	Baseline	2.38	5.4	174.0
		Endpoint	2.33	7.3 H	183.0
NLD/0061/00012	76/M/Ca	Baseline	2.33	5.9	
		Endpoint	2.37	4.7	
NOR/0131/00002	84/M/Ca	Baseline	2.38	5.4	197.0
		Endpoint	2.41	5.1	161.0
NOR/0131/00011	62/F/Ca	Baseline	2.29	5.7	161.0
		Endpoint	2.25	5.0	145.0
PRT/0137/00006	67/M/Ca	Baseline	2.26	5.2	
		Endpoint	2.34	4.1	
TUR/0121/00003	75/M/Ca	Baseline	2.35	4.8	144.0
		Endpoint	2.48	5.5	146.0
TUR/0121/00008	72/M/Ca	Baseline	2.34	5.3	122.0
		Endpoint	2.37	5.5	112.0
TUR/0122/00009	53/M/Ca	Baseline	2.21	5.5	142.0
		Endpoint	2.23	5.5	147.0
TUR/0122/00015	50/F/Ca	Baseline	2.47	5.0	165.0
		Endpoint	2.48	5.4	179.0
TUR/0122/00018	60/M/Ca	Baseline	2.36	6.6	128.0
		Endpoint	2.53	6.1	159.0

L/H denotes a value below/above normal range and are calculated on the data prior to conversion to standard unit.
Note: Day is relative to the first day of treatment (day 1).

report/pgm_saf/l_amy_pan.sas - 14JUL2005:8:46

Post-hoc Analyses Listing 2-3 (Page 5 of 7)
Subject laboratory profile for calcium, LDH and glucose
by treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Exelon

Country/ Center/ Subject	Age/ Sex/ Race	Study phase	Calcium mmol/L	Glucose mmol/L	LDH U/L
TUR/0122/00023	69/M/Ca	Baseline	2.26	4.7	122.0
		Endpoint	2.29	5.5	122.0
TUR/0122/00033	69/M/Ca	Baseline	2.37	7.7 H	129.0
		Endpoint	2.49	7.6 H	129.0

L/H denotes a value below/above normal range and are calculated on the data prior to conversion to standard unit.
Note: Day is relative to the first day of treatment (day 1).

report/pgm_saf/l_amy_pan.sas - 14JUL2005:8:46

Post-hoc Analyses Listing 2-3 (Page 6 of 7)
Subject laboratory profile for calcium, LDH and glucose
by treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Placebo

Country/ Center/ Subject	Age/ Sex/ Race	Study phase	Calcium mmol/L	Glucose mmol/L	LDH U/L
BEL/0003/00004	66/M/Ca	Baseline	2.57	5.1	199.0
		Endpoint	2.26	4.8	174.0
CAN/0103/00003	72/M/Ca	Baseline	2.50	5.3	
		Endpoint	2.40	5.7	
DEU/0028/00010	72/M/Ca	Baseline	2.40	6.4	156.0
		Endpoint	2.40	4.6	140.0
DEU/0037/00001	76/F/Ca	Baseline	2.31	4.1	212.0
		Endpoint	2.42	4.2	183.0
ESP/0075/00010	79/M/Ca	Baseline	2.44	5.2	156.0
		Endpoint	2.35	5.2	169.0
ESP/0077/00006	78/M/Ca	Baseline	2.34	5.7	134.0
		Endpoint	2.36	5.4	129.0
ESP/0078/00009	81/M/Ca	Baseline	2.36	6.6	187.0
		Endpoint	2.58 H	5.4	149.0
FRA/0014/00002	73/M/Ca	Baseline	2.49	6.0	
		Endpoint	2.34	6.3	
FRA/0014/00008	66/M/Ca	Baseline	2.63 H	5.8	164.0
		Endpoint	2.40	5.8	183.0
FRA/0017/00010	83/F/Ca	Baseline	2.24	6.8 H	147.0
		Endpoint	2.16	5.3	124.0
GBR/0087/00004	75/F/Ca	Baseline	2.45	5.0	120.0

L/H denotes a value below/above normal range and are calculated on the data prior to conversion to standard unit.
Note: Day is relative to the first day of treatment (day 1).

report/pgm_saf/l_amy_pan.sas - 14JUL2005:8:46

Post-hoc Analyses Listing 2-3 (Page 7 of 7)
Subject laboratory profile for calcium, LDH and glucose
by treatment
Safety population
Patients with amylase values normal at baseline but abnormal at endpoint

Treatment: Placebo

Country/ Center/ Subject	Age/ Sex/ Race	Study phase	Calcium mmol/L	Glucose mmol/L	LDH U/L
GBR/0087/00004	75/F/Ca	Endpoint	2.47	5.3	132.0
GBR/0094/00001	70/F/Ca	Baseline	2.44	5.9	167.0
		Endpoint	2.32	5.7	152.0
ITA/0052/00001	64/M/Ca	Baseline	2.41	4.9	180.0
		Endpoint	2.41	4.7	144.0
TUR/0122/00017	54/M/Ca	Baseline	2.29	6.2	120.0
		Endpoint	2.48	7.8 H	178.0

L/H denotes a value below/above normal range and are calculated on the data prior to conversion to standard unit.
Note: Day is relative to the first day of treatment (day 1).

report/pgm_saf/l_amy_pan.sas - 14JUL2005:8:46

Post-hoc Analyses Table 1-25 (Page 1 of 2)
ADAS-cog - change from baseline - summary statistics, by age group
ITT+RDO population

Age < 65

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	46	20.6	9.0	19.3	17	20.1	8.1	19.0			
Week 16	Change	46	2.1	6.6	1.2	17	-2.4	6.8	-0.3	3.95	0.078	(-0.45, 8.35)
Week 24	Change	46	1.9	9.4	1.2	17	-1.9	5.7	-2.0	2.26	0.378	(-2.85, 7.38)

- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea8b.sas/Final Version (20JUN2005 9:11:21)

Post-hoc Analyses Table 1-25 (Page 2 of 2)
ADAS-cog - change from baseline - summary statistics, by age group
ITT+RDO population

Age >= 65

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	283	24.4	10.3	22.3	144	24.8	10.6	23.8			
Week 16	Change	283	2.3	7.4	2.0	144	0.6	6.7	0.7	1.83	0.009*	(0.47, 3.20)
Week 24	Change	283	2.1	8.0	1.7	144	-0.6	7.7	0.5	2.88	<0.001*	(1.36, 4.40)

- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea8b.sas/Final Version (20JUN2005 9:11:21)

Post-hoc Analyses Table 1-26 (Page 1 of 2)
ADAS-cog - change from baseline - summary statistics, by gender
ITT+RDO population

Male

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	213	23.0	10.3	21.0	104	23.2	9.7	21.8			
Week 16	Change	213	2.4	7.1	1.7	104	0.1	6.9	0.0	2.27	0.005*	(0.71, 3.83)
Week 24	Change	213	2.2	8.1	2.0	104	-0.6	7.2	0.5	2.91	0.001*	(1.17, 4.64)

- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea8c.sas/Final Version (20JUN2005 9:11:23)

Post-hoc Analyses Table 1-26 (Page 2 of 2)
ADAS-cog - change from baseline - summary statistics, by gender
ITT+RDO population

Female

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	116	25.3	10.0	24.8	57	26.3	11.7	25.7			
Week 16	Change	116	2.2	7.7	1.3	57	0.6	6.5	0.7	1.67	0.166	(-0.70, 4.04)
Week 24	Change	116	1.9	8.4	1.0	57	-0.9	8.0	0.3	3.00	0.027*	(0.34, 5.67)

- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea8c.sas/Final Version (20JUN2005 9:11:23)

Post-hoc Analyses Table 1-29 (Page 1 of 2)
ADAS-cog - change from baseline - summary statistics, by MMSE severity group
ITT+RDO population

Mild (MMSE 18 - 24)

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	237	20.6	7.9	19.3	115	20.7	7.9	19.0			
Week 16	Change	237	1.9	6.8	1.7	115	0.3	6.5	0.3	1.69	0.022*	(0.25, 3.14)
Week 24	Change	237	1.9	7.7	2.0	115	-0.2	7.5	1.0	2.14	0.010*	(0.52, 3.77)

- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea8f.sas/Final Version (20JUN2005 9:11:29)

Post-hoc Analyses Table 1-29 (Page 2 of 2)
ADAS-cog - change from baseline - summary statistics, by MMSE severity group
ITT+RDO population

Moderate (MMSE 10 - 17)

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	87	32.6	10.4	30.3	44	33.7	10.3	31.8			
Week 16	Change	87	3.1	8.5	1.3	44	0.4	7.6	0.2	3.23	0.023*	(0.45, 6.02)
Week 24	Change	87	2.6	9.4	0.3	44	-1.8	7.2	-0.8	4.73	0.002*	(1.84, 7.61)

- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea8f.sas/Final Version (20JUN2005 9:11:29)

Post-text Table 9.1-4c (Page 1 of 3)
ADAS-cog - change from baseline - summary statistics by visual hallucination at baseline

Visual hallucination at baseline: information unavailable

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	2	24.5	5.4	24.5							
Week 16	Change	2	11.7	0.9	11.7							(,)
Week 24	Change	2	8.3	1.4	8.3							(,)
LOCF	Baseline	2	24.5	5.4	24.5							
Week 16	Change	2	11.7	0.9	11.7							(,)
Week 24	Change	2	8.3	1.4	8.3							(,)
OC												
Week 16	Baseline	2	24.5	5.4	24.5							
	Change	2	11.7	0.9	11.7							(,)
Week 24	Baseline	2	24.5	5.4	24.5							
	Change	2	8.3	1.4	8.3							(,)

- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate.
- 95% confidence interval calculated for the difference between LSMEANS.
- * p < 0.05.
- /ptt91_4c.sas - 12OCT2004:09:11

Post-text Table 9.1-4c (Page 2 of 3)
ADAS-cog - change from baseline - summary statistics by visual hallucination at baseline

Patients who had visual hallucination at baseline

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	107	25.4	9.9	24.7	60	27.4	10.4	26.5			
Week 16	Change	107	2.2	7.7	1.7	60	-0.5	7.7	-0.2	3.76	0.001*	(1.47, 6.05)
Week 24	Change	107	1.0	9.2	0.3	60	-2.1	8.3	-0.3	4.27	0.002*	(1.59, 6.96)
LOCF	Baseline	96	25.9	10.0	25.3	57	27.7	10.4	26.7			
Week 16	Change	96	2.7	7.8	2.2	57	-0.8	7.7	-0.3	4.72	<0.001*	(2.33, 7.12)
Week 24	Change	96	1.7	9.1	0.8	57	-2.2	8.5	-2.7	5.28	<0.001*	(2.44, 8.12)
OC												
Week 16	Baseline	96	25.9	10.0	25.3	56	27.6	10.4	26.5			
	Change	96	2.7	7.8	2.2	56	-0.9	7.7	-0.5	4.74	<0.001*	(2.32, 7.15)
Week 24	Baseline	88	25.6	10.2	25.0	52	26.9	9.7	26.5			
	Change	88	2.2	9.3	2.0	52	-2.4	8.4	-1.5	5.53	<0.001*	(2.52, 8.54)

- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate.
- 95% confidence interval calculated for the difference between LSMEANS.
- * p < 0.05.
- /ptt91_4c.sas - 12OCT2004:09:11

Post-text Table 9.1-4c (Page 3 of 3)
ADAS-cog - change from baseline - summary statistics by visual hallucination at baseline

Patients who did not have visual hallucination at baseline

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	220	23.1	10.4	21.0	101	22.5	10.1	20.7			
Week 16	Change	220	2.3	7.1	1.7	101	0.8	6.1	0.7	1.14	0.146	(-0.40, 2.68)
Week 24	Change	220	2.6	7.6	2.0	101	0.1	6.9	1.0	2.09	0.015*	(0.41, 3.77)
LOCF	Baseline	189	23.0	10.4	20.7	97	22.6	10.2	21.0			
Week 16	Change	189	2.7	7.1	2.0	97	0.9	6.1	0.7	1.64	0.042*	(0.06, 3.23)
Week 24	Change	189	2.9	8.0	2.0	97	0.1	6.8	1.0	2.51	0.005*	(0.75, 4.26)
OC												
Week 16	Baseline	186	22.9	10.3	21.0	94	22.6	10.3	21.3			
	Change	186	2.7	7.2	2.2	94	1.0	6.2	0.7	1.67	0.043*	(0.06, 3.28)
Week 24	Baseline	166	22.6	10.5	20.0	87	21.3	9.2	19.3			
	Change	166	3.1	7.8	2.3	87	-0.2	7.0	0.7	2.65	0.005*	(0.82, 4.48)

- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate.
- 95% confidence interval calculated for the difference between LSMEANS.
- * p < 0.05.
- /ptt91_4c.sas - 12OCT2004:09:11

Post-hoc Analyses Table 1-78 (Page 1 of 2)
ADAS-cog - change from baseline - summary statistics, by tremor at baseline
ITT+RDO population

No tremor at baseline

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	101	25.4	10.8	23.3	56	23.0	10.1	20.8			
Week 16		101	22.1	10.7	19.0	56	24.5	9.2	24.2			
	Change	101	3.3	7.1	2.7	56	-1.5	7.5	-1.0	4.16	<0.001*	(1.90, 6.43)
Week 24		101	22.8	11.3	20.7	56	25.1	11.3	24.3			
	Change	101	2.6	8.1	1.3	56	-2.1	7.6	-2.3	4.39	0.001*	(1.75, 7.02)

- Tremor at baseline was defined using UPDRS part III sub-items as either tremor at rest >0 or action or postural tremor at hands >0.
- Only patients having both baseline and the respective post-baseline assessment are considered.
- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea29.sas/Final Version (27SEP2005 4:02:43)

Post-hoc Analyses Table 1-78 (Page 2 of 2)
ADAS-cog - change from baseline - summary statistics, by tremor at baseline
ITT+RDO population

Tremor at baseline

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	228	23.1	9.9	21.7	105	25.0	10.7	24.0			
Week 16		228	21.2	10.6	18.3	105	23.7	11.1	21.7			
	Change	228	1.9	7.3	1.3	105	1.3	6.2	1.0	0.86	0.289	(-0.73, 2.45)
Week 24		228	21.2	10.4	18.3	105	25.0	12.1	23.3			
	Change	228	1.9	8.2	1.7	105	0.1	7.3	1.0	2.14	0.018*	(0.36, 3.91)

- Tremor at baseline was defined using UPDRS part III sub-items as either tremor at rest >0 or action or postural tremor at hands >0.
- Only patients having both baseline and the respective post-baseline assessment are considered.
- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea29.sas/Final Version (27SEP2005 4:02:43)

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog on ITT-RDO population (same as PTT 9.1-4)

The GLM Procedure

Class Level Information

Class	Levels	Values
TGP1A	2	A B
COU1A	12	AUT BEL CAN DEU ESP FRA GBR ITA NLD NOR PRT TUR

Number of observations 501

NOTE: Due to missing values, only 490 observations can be used in this analysis.

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog on ITT-RDO population (same as PTT 9.1-4)

The GLM Procedure

Dependent Variable: TOTACHG

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	13	4750.59652	365.43050	6.44	<.0001
Error	476	27003.30575	56.72963		
Corrected Total	489	31753.90227			

R-Square	Coeff Var	Root MSE	TOTACHG Mean
0.149607	635.9509	7.531908	1.184354

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TGP1A	1	862.508496	862.508496	15.20	0.0001
COU1A	11	891.439896	81.039991	1.43	0.1564
TOTABS	1	2996.648129	2996.648129	52.82	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TGP1A	1	884.631790	884.631790	15.59	<.0001
COU1A	11	1392.471991	126.588363	2.23	0.0121
TOTABS	1	2996.648129	2996.648129	52.82	<.0001

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog on ITT-RDO population (same as PTT 9.1-4)

The GLM Procedure
Least Squares Means

TGP1A	TOTACHG LSMEAN	Standard Error	H0:LSMEAN=0 Pr > |t|	H0:LSMean1= LSMean2 Pr > |t|
A	2.41647374	0.56123247	<.0001	<.0001
B	-0.45906073	0.70388429	0.5146	

TGP1A	TOTACHG LSMEAN	95% Confidence Limits	
A	2.416474	1.313674	3.519273
B	-0.459061	-1.842165	0.924044

Least Squares Means for Effect TGP1A

i	j	Difference Between Means	95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	2.875534	1.444678	4.306391

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=Mediterranean

The GLM Procedure

Class Level Information

Class	Levels	Values
TGP1A	2	A B

Number of observations 294

NOTE: Due to missing values, only 288 observations can be used in this analysis.

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=Mediterranean

The GLM Procedure

Dependent Variable: TOTACHG

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	2158.30666	1079.15333	17.71	<.0001
Error	285	17366.39550	60.93472		
Corrected Total	287	19524.70216			

R-Square	Coeff Var	Root MSE	TOTACHG Mean
0.110542	2932.367	7.806070	0.266204

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TGP1A	1	275.336079	275.336079	4.52	0.0344
TOTABS	1	1882.970585	1882.970585	30.90	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TGP1A	1	316.406892	316.406892	5.19	0.0234
TOTABS	1	1882.970585	1882.970585	30.90	<.0001

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=Mediterranean

The GLM Procedure
Least Squares Means

TGP1A	TOTACHG LSMEAN	Standard Error	H0:LSMEAN=0 Pr > |t|	H0:LSMean1= LSMean2 Pr > |t|
A	1.01926330	0.56638565	0.0730	0.0234
B	-1.19380979	0.78873145	0.1312	

TGP1A	TOTACHG LSMEAN	95% Confidence Limits	
A	1.019263	-0.095566	2.134093
B	-1.193810	-2.746288	0.358668

Least Squares Means for Effect TGP1A

i	j	Difference Between Means	95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	2.213073	0.301453	4.124693

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=North Amrican

The GLM Procedure

Class Level Information

Class	Levels	Values
TGP1A	2	A B

Number of observations 41

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=North Amrican

The GLM Procedure

Dependent Variable: TOTACHG

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	35.800852	17.900426	0.35	0.7048
Error	38	1926.172047	50.688738		
Corrected Total	40	1961.972900			

R-Square	Coeff Var	Root MSE	TOTACHG Mean
0.018247	280.6766	7.119602	2.536585

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TGP1A	1	19.92081640	19.92081640	0.39	0.5345
TOTABS	1	15.88003608	15.88003608	0.31	0.5790

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TGP1A	1	25.45172217	25.45172217	0.50	0.4829
TOTABS	1	15.88003608	15.88003608	0.31	0.5790

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=North Amrican

The GLM Procedure
Least Squares Means

TGP1A	TOTACHG LSMEAN	Standard Error	H0:LSMEAN=0 Pr > |t|	H0:LSMean1=LSMean2 Pr > |t|
A	2.95991565	1.26222659	0.0244	0.4829
B	1.03141103	2.39756094	0.6695	

TGP1A	TOTACHG LSMEAN	95% Confidence Limits	
A	2.959916	0.404672	5.515160
B	1.031411	-3.822197	5.885019

Least Squares Means for Effect TGP1A

i	j	Difference Between Means	95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	1.928505	-3.581005	7.438014

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=North European

The GLM Procedure

Class Level Information

Class	Levels	Values
TGP1A	2	A B

Number of observations 166

NOTE: Due to missing values, only 161 observations can be used in this analysis.

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=North European

The GLM Procedure

Dependent Variable: TOTACHG

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1557.589739	778.794870	15.15	<.0001
Error	158	8120.610399	51.396268		
Corrected Total	160	9678.200138			

R-Square	Coeff Var	Root MSE	TOTACHG Mean
0.160938	288.7977	7.169119	2.482402

Source	DF	Type I SS	Mean Square	F Value	Pr > F
TGP1A	1	647.0256640	647.0256640	12.59	0.0005
TOTABS	1	910.5640752	910.5640752	17.72	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
TGP1A	1	614.0642768	614.0642768	11.95	0.0007
TOTABS	1	910.5640752	910.5640752	17.72	<.0001

ENA713B 2311, Post-hoc Analyses Table 1-114

ANCOVA analysis (wk 24) of ADAS-cog by Country Region

cou_reg=North European

The GLM Procedure
Least Squares Means

TGP1A	TOTACHG LSMEAN	Standard Error	H0:LSMEAN=0 Pr > |t|	H0:LSMean1= LSMean2 Pr > |t|
A	3.87011541	0.69311893	<.0001	0.0007
B	-0.26732746	0.97574423	0.7845	

TGP1A	TOTACHG LSMEAN	95% Confidence Limits	
A	3.870115	2.501142	5.239089
B	-0.267327	-2.194512	1.659857

Least Squares Means for Effect TGP1A

i	j	Difference Between Means	95% Confidence Limits for LSMean(i)-LSMean(j)	
1	2	4.137443	1.773275	6.501610

Post-hoc Analyses Table 1-28 (Page 1 of 1)
ADAS-cog - change from baseline - summary statistics across time
All patients who had worsening parkinsonism from ITT+RDO population

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	94	23.8	9.8	22.0	24	24.2	10.2	22.8			
Week 16	Change	94	2.2	6.6	1.3	24	0.4	8.1	0.3	1.80	0.235	(-1.19, 4.80)
Week 24	Change	94	2.3	8.3	1.7	24	-1.9	8.8	-1.3	4.71	0.009*	(1.20, 8.21)

- A positive change indicated an improvement from baseline.
- p-value based on analysis of covariance model using treatment and country as factors and baseline ADAS-cog as a covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea8e.sas/Final Version (20JUN2005 9:11:27)

Post-hoc Analyses Table 1-35 (Page 1 of 1)
ADCS CGI-C - categorical analysis
All patients who had worsening parkinsonism from ITT+RDO population

Visit		Exelon N=97 n	%	Placebo N=26 n	%	p-value
Week 16	Markedly improved (1)	5	(5)	1	(4)	0.964
	Moderately improved (2)	9	(9)	4	(16)	
	Minimally improved (3)	20	(21)	3	(12)	
	Unchanged (4)	25	(26)	6	(24)	
	Minimally worse (5)	21	(22)	9	(36)	
	Moderately worse (6)	10	(11)	2	(8)	
	Markedly worse (7)	5	(5)	0	(0)	
	n	95		25		
	Mean	4.0		4.0		
	SD	1.5		1.4		
	Median	4.0		4.0		
Week 24	Markedly improved (1)	3	(3)	0	(0)	0.717
	Moderately improved (2)	14	(15)	6	(23)	
	Minimally improved (3)	18	(19)	4	(15)	
	Unchanged (4)	25	(26)	5	(19)	
	Minimally worse (5)	20	(21)	3	(12)	
	Moderately worse (6)	13	(14)	7	(27)	
	Markedly worse (7)	3	(3)	1	(4)	
	n	96		26		
	Mean	4.0		4.2		
	SD	1.5		1.6		
	Median	4.0		4.0		

- p-value based on van Elteren test blocking for country
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea9e.sas/Final Version (20JUN2005 9:11:40)

Post-hoc Analyses Table 1-49 (Page 1 of 1)
ADCS-ADL - change from baseline - summary statistics across time
All patients who had worsening parkinsonism from ITT+RDO population

Population/ Visit		Exelon n	Exelon Mean	Exelon SD	Exelon Median	Placebo n	Placebo Mean	Placebo SD	Placebo Median	Difference in LSMEANS	p-value	95% CI for Exelon - Placebo
ITT+RDO	Baseline	97	40.0	16.3	39.0	25	41.0	14.8	39.0			
Week 16	Change	97	-0.5	12.1	0.0	25	-0.3	6.2	1.0	-0.34	0.895	(-5.42, 4.74)
Week 24	Change	97	-0.9	14.1	0.0	25	-3.5	6.6	-5.0	2.59	0.364	(-3.04, 8.22)

- p-value based on analysis of covariance model using treatment and country and as factors and baseline ADCS-ADL as covariate
- 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS)
- * p < 0.05

- /vob/CENA713B/CENA713B2311/report/pgm_eff/emea11e.sas/Final Version (20JUN2005 9:12:11)

NOVARTIS

Clinical Development

Exelon® (rivastigmine tartrate)

Briefing Document for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting of May 17, 2006

Appendix 2: Additional Analyses for Patients with and without Visual Hallucinations

Document type:	Briefing Document
Release date:	17 April 2006
Number of pages:	5

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE 1. *Patient characteristics at baseline*

Variable	Visual hallucinators		Non-hallucinators	
	Rivastigmine (*n* = 118)	Placebo (*n* = 70)	Rivastigmine (*n* = 239)	Placebo (*n* = 109)
Age, years				
Mean (SD)	72.0 (6.5)	73.0 (5.8)	73.1 (6.8)	72.0 (6.8)
Gender				
% women	31.4%	32.9%	37.2%	35.8%
Years of Education				
Mean (SD)	8.7 (4.3)	9.5 (4.3)	8.9 (4.1)	9.1 (3.6)
PD duration, years				
Mean (SD)	10.6 (6.4)	10.6 (5.7) ¶¶	7.8 (5.0)	8.9 (6.0)
Dementia duration, years				
Mean (SD)	1.3 (1.6)¶ ¶	2.0 (2.3)** ¶	1.0 (1.2)	0.9 (1.3)
MMSE score				
Mean (SD)	18.9 (3.7)	17.9 (4.3) ¶¶	19.6 (3.9)	20.1 (3.7)
CNS Medications (%)				
L-dopa	99.2¶	95.7	94.1	93.6
Dopamine agonists	51.7	44.3	42.7	47.7
Benzodiazepines	19.5	21.4	21.8	18.3
Antidepressants	33.1	21.4	25.9	24.8
Antipsychotics	44.1¶¶	37.1 ¶	20.5	20.2
Hoehr & Yahr (%)				
≤2	15.2%	17.2%	31.3%	29.4%
2.5–3	63.5%	62.9%	52.3%	55.1%
4	18.6%	18.6%	11.3%	13.8%
5	2.5%	1.4%	5.0%	0.9%
UPDRS Part III				
Mean (SD)	35.1 (15.0)	32.6 (14.4)	33.3 (14.3)	31.9 (12.3)

*$p < 0.05$ and **$p \leq 0.001$, rivastigmine *versus* placebo (within the same subgroup)
¶$p < 0.05$ and ¶¶$p \leq 0.001$ visual hallucinators *versus* non-hallucinators (within the same treatment group) Source: Burn et al. submitted

TABLE 2. *Results of the primary efficacy variables*

	Visual hallucinators				Non-hallucinators			
	n	**Baseline Mean (SD) scores**	**Week 24 Mean (SD) change**	**Week 24 treatment difference (95% CI shown for ADAS-cog)**	***n***	**Baseline score Mean (SD)**	**Week 24 change Mean (SD)**	**Treatment difference (95% CI shown for ADAS-cog)**
ADAS-cog								
ITT+RDO				**4.27**‡				**2.09**‡
Rivastigmine	107	25.4 (9.9)	-1.0 (9.2)	(1.59, 6.96)	220	23.1 (10.4)	-2.6 (7.6)	(0.41, 3.77)
Placebo	60	27.4 (10.4)	2.1 (8.3)	*p* = 0.002*	101	22.5 (10.1)	-0.1 (6.9)	*p* = 0.015*
LOCF				**5.28**‡				**2.51**‡
Rivastigmine	96	25.9 (10.0)	-1.7 (9.1)	(2.44, 8.12)	189	23.0 (10.4)	-2.9 (8.0)	(0.75, 4.26)
Placebo	57	27.7 (10.4)	2.2 (8.5)	*p* < 0.001*	97	22.6 (10.2)	-0.1 (6.8)	*p* = 0.005*
OC				**5.53**‡				**2.65**‡
Rivastigmine	88	25.6 (10.2)	-2.2 (9.3)	(2.52, 8.54)	166	22.6 (10.5)	-3.1 (7.8)	(0.82, 4.48)
Placebo	52	26.9 (9.7)	2.4 (8.4)	*p* < 0.001*	87	21.3 (9.2)	0.2 (7.0)	*p* = 0.005*
ADCS-CGIC								
ITT+RDO								
Rivastigmine	109	-	4.0 (1.5)	**0.5**	218	-	3.8 (1.4)	**0.3**
Placebo	64	-	4.5 (1.6)	*p* = 0.030**	101	-	4.1 (1.4)	*p* = 0.111**
LOCF								
Rivastigmine	97	-	3.9 (1.5)	**0.7**	190	-	3.7 (1.4)	**0.4**
Placebo	60	-	4.6 (1.5)	*p* = 0.017**	98	-	4.1 (1.4)	*p* = 0.031**
OC								
Rivastigmine	84	-	3.9 (1.5)	**0.7**	166	-	3.6 (1.3)	**0.4**
Placebo	55	-	4.6 (1.6)	*p* = 0.022**	90	-	4.0 (1.4)	*p* = 0.017**

ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale (negative changes on the ADAS-cog indicate improvements)
ADCS-CGIC: Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change (there are no baseline scores for the ADCS-CGIC because this tool assesses change, and there was no comparator at baseline on which to base a 'change' score)
‡Modeled treatment difference (difference of least square means)
* *p*-value based on ANCOVA model using treatment and country as factors and baseline ADAS-cog as covariate
** *p*-value based on van Elteren test, blocking for country Source: Burn et al. submitted

TABLE 3. *Results of the secondary efficacy variables (ITT+RDO population)*

	Visual hallucinators				Non-hallucinators			
		Baseline score	Week 24 change	Treatment difference		Baseline score	Week 24 change	Treatment difference
	n	Mean (SD)	Mean (SD)		*n*	Mean (SD)	Mean (SD)	
ADCS-ADL								
Rivastigmine	110	37.1 (16.4)	- 2.2 (10.7)	3.93‡	221	43.8 (19.3)	- 0.6 (13.5)	1.72‡
Placebo	64	37.3 (15.7)	- 5.4 (9.8)	*p* = 0.013*	101	43.7 (18.6)	- 2.4 (10.4)	*p* = 0.247*
MMSE								
Rivastigmine	110	18.9 (3.7)	0.6 (4.2)	1.00	223	19.7 (3.8)	0.9 (3.7)	1.0
Placebo	64	17.9 (4.1)	-0.4 (3.8)	*p* = 0.072	102	20.0 (3.6)	-0.1 (3.4)	*p* = 0.144
NPI-10								
Rivastigmine	110	19.8 (12.7)	- 4.2 (11.6)	- 4.19‡	223	9.1 (9.5)	- 0.9 (9.0)	- 0.37‡
Placebo	64	19.3 (15.4)	0.9 (11.5)	*p* = 0.013*	102	9.3 (9.5)	- 0.5 (9.7)	*p* = 0.713*
Choice Reaction Time (msec)								
Rivastigmine	105	1063.7 (725.0)	-65.4 (648.9)	-345.70‡	216	957.0 (804.9)	-67.7 (582.6)	-290.03‡
Placebo	58	1627.5 (2487.6)	37.1 (1668.0)	*p* = 0.028*	98	878.7 (619.0)	254.8 (1163.2)	*p* = 0.002*
Power of Attention (msec)								
Rivastigmine	106	2305.9 (1102.3	7.7 (1222.5)	-273.97‡	220	2141.4 (1201.9)	-52.5 (862.0)	-284.12
Placebo	58	3096.9 (3324.02)	-12.4 (2136.8)	*p* = 0.261*	100	2138.7 (1340.0)	232.6 (1541.0)	*p* = 0.022*
D-KEFS Verbal Fluency (total correct responses)								
Rivastigmine	87	13.1 (8.9)	2.0 (5.8)	3.5	169	14.3 (9.8)	1.4 (7.3)	2.3
Placebo	55	13.0 (8.6)	-1.5 (5.4)	*p* < 0.001**	89	15.4 (9.7)	- 0.9 (6.8)	*p* = 0.003**

ADCS-ADL: Alzheimer's Disease Cooperative Study Activities of Daily Living; MMSE: Mini-Mental State Examination; NPI-10: 10-item Neuropsychiatric Inventory; D-KEFS: Delis-Kaplan Executive Function System
‡Modeled treatment difference (difference of least square means)
*ITT+RDO analyses
**OC analyses*; n* values show numbers of patients providing week 24 data
p-values based on ANCOVA model using treatment and country as factors and baseline score as a covariate, except for D-K-KEFS Verbal Fluency Total Correct Responses based on van Elteren test, blocking for country Source: Burn et al. submitted

TABLE 4. *Most frequently reported adverse events (in at least 5% of any group)*

Adverse events	**Visual hallucinators**		**Non-hallucinators**	
	Rivastigmine (*n* = 118)	**Placebo (*n* = 70)**	**Rivastigmine (*n* = 239)**	**Placebo (*n* = 109)**
Any adverse event	77.1%	75.7%	87.0%	67.9%
Nausea	30.5%	15.7%	28.0%	8.3%
Vomiting	15.3%	1.4%	17.6%	1.8%
Tremor	10.2%	2.9%	10.5%	4.6%
Hallucinations	9.3%	15.7%	2.5%	5.5%
Anorexia	7.6%	2.9%	5.4%	2.8%
Diarrhea	6.8%	2.9%	7.1%	5.5%
Fall	6.8%	8.6%	5.4%	4.6%
Dizziness	5.1%	0.0%	6.3%	1.8%
Constipation	4.2%	8.6%	5.0%	5.5%
Weight decreased	4.2%	8.6%	2.5%	1.8%
Urinary tract infection	3.4%	5.7%	3.3%	1.8%
Hypotension	2.5%	10.0%	6.7%	6.4%
Confusional state	0.8%	5.7%	5.0%	5.5%
Orthostatic hypotension	0.8%	4.3%	2.1%	5.5%

NOVARTIS

Clinical Development

Exelon® (rivastigmine tartrate)

Briefing Document for the Peripheral and Central Nervous System Drugs Advisory Committee Meeting of May 17, 2006

Appendix 3: Diagnosing Dementia Associated with Parkinson's Disease and Distinguishing It from Alzheimer Disease

Document type: Briefing Document

Release date: 17 April 2006

Number of pages: 16

Diagnosing Dementia Associated with Parkinson's Disease and Distinguishing It from Alzheimer Disease

Prof. J. Cummings, Prof. M. Emre, Prof. C.W. Olanow

At the request of Novartis Pharmaceuticals, we have prepared this report providing our opinion regarding whether the dementia associated with PD (PDD) is a different disease entity from the dementia of Alzheimer's disease (AD), and whether practitioners can differentiate these conditions.

Upon a review of all available evidence, it is our opinion that 1) there is a distinction between PDD and AD; 2) operational criteria permit the two conditions to be readily distinguished; and 3) the operational criteria can be applied by community practitioners so that they can readily differentiate between these conditions. A summary of the evidence in support of these positions is provided below.

1 Prevalence and Incidence of PDD

The prevalence and incidence of dementia in patients with PD are substantially higher than the prevalence and incidence of dementia seen in age-matched controls. Variable prevalence rates have been reported, but a meta-analysis of 27 studies revealed a prevalence of dementia in patients with PD of approximately 40% (Cummings, 1988). Population based studies reveal similar results in different geographical areas and ethnic groups. The prevalence of dementia in PD patients was in 29% in a study in southern Finland (Marttila and Rinne, 1976), 41% in a study of 180,000 inhabitants in a New York-based study, (Mayeux *et al*, 1992) and 28% in a community-based study of 220,000 inhabitants in a Norwegian study (Aarsland *et al*, 1996).

Dementia in PD is associated with increased mortality, and is likely under-represented in cross-sectional studies or in longitudinal studies not accounting for differential mortality (Levy *et al*, 2002; Marder *et al*, 1991). Incidence studies, which are relatively free of survival bias, reported a 4-6 times higher incidence of dementia in PD patients followed for 3 to 5 years in comparison to controls or expected numbers (Mindham *et al*, 1982; Rajput *et al*, 1987; Aarsland *et al*, 2001c). In a prospective follow-up study, the incidence of dementia in PD patients after 5 years was 69 per 1000 person-years, and by the age of 85 the risk of dementia was 65% (Mayeux *et al*, 1990). Other long-term follow-up studies of sizable cohorts of PD patients in different countries had comparable results: After 5 years of follow-up, dementia was diagnosed in 62% of PD patients *versus* 17% in controls in an Australian study (Reid *et al*, 1996); prospective follow-up over 8 years revealed a cumulative incidence of 78% in a study in Norwegian patients with PD (Aarsland *et al*, 2003c); and in a study of PD patients from the UK, the cumulative incidence was 38% after 10 and 53% after 14 years

1.

(Hughes *et al*, 2000; Read *et al*, 2001). Indeed, in a recent UK study 36% of newly diagnosed PD patients showed evidence of cognitive impairment with appropriate neuropsychological testing (Foltynie *et al*, 2004). This evidence of cognitive deficits in cognitively asymptomatic early PD patients strongly suggests that cognitive deficits are an integral part of PD.

Conclusion

The frequency of dementia is 4 to 6 times higher in patients with PD compared to age-matched controls. The frequency of dementia in the control populations probably represents the occurrence of AD or other degenerative and symptomatic dementias in the population. The increased occurrence of dementia in the PD population likely represents the excess of dementia that is directly attributable to PD.

2 Risk Factors for PDD

Several risk factors for dementia in patients with PD have been identified (for a review see Emre 2003). The most significant risk factors are old age (Aarsland *et al*, 1996; Hughes *et al*, 2000; Levy *et al*, 2002; Tison *et al*, 1995), duration of PD (Aarsland *et al*, 1996), age at onset (Mayeux *et al*, 1992), akinetic-rigid form of the disease (Hershey *et al*, 1991; Huber *et al*, 1991), and the severity of motor symptoms (Aarsland *et al*, 2001; Hughes *et al*, 2000; Levy *et al*, 2002; Marder *et al*, 1995). Levy and colleagues (Levy *et al*, 2002) observed that older PD patients with higher motor symptom severity at baseline had an almost 10-fold increase in risk of incident dementia, compared with younger patients with lower motor symptom severity. The presence of subtle involvement of executive functions in non-demented PD patients predicts the emergence of dementia at subsequent follow-up evaluation (Woods and Troster, 2003). Dementia becomes more common as PD advances. and most patients are affected late in the disease when age and severity of PD are highest (Aarsland *et al*, 2003c).

Conclusion

Risk factors for PDD differ from those in AD and include gait disturbances, postural instability, and executive function abnormalities. The principal risk factor for developing PDD is the presence of PD. The diagnosis of AD is excluded in the presence of PD by the requirement that other central nervous system disease that may cause dementia be excluded before the diagnosis of probable AD (McKhann *et al*, 1984) or of dementia of the Alzheimer type (American Psychiatric Association, 1994) can be made. Thus, a diagnosis of AD cannot be made if PD is present. The diagnosis of PDD can thus be diagnosed in an individual with PD and dementia in whom other etiologies of dementia (hypothyroidism, B12 deficiency, cerebrovascular disease) have been excluded.

3 Genetic Distinctions between PDD and AD

There is no excess of AD among probands with PD (Levy *et al*, 2004), as might be anticipated if there were major shared genetic contributions to their etiology. Just as for late onset AD, the majority of cases of PD occur sporadically and are not known to be associated with any genetic mutation. However, genetic mutations have been identified in some PD and AD patients (see Table 3-1). Interestingly, genetic defects that are associated with PD differ from genetic defects associated with AD, and no gene mutation has yet been identified that causes both AD and PD. Indeed, genetic forms of AD tend to be associated with disorders of amyloid production and metabolism while some genetic forms of PD are associated with mutations

and increased deposition of alpha-synuclein. (Singleton and Gwinn-Hardy, 2004; Farrer *et al*, 2001). Interestingly, PD can be seen with additional copies of the normal alpha-synuclein gene, and as the gene load increase from duplication to triplication, the age of onset of PD and the likelihood of developing PDD but not AD increases (Singleton *et al* , 2003; Chartier-Harlin *et al*, 2004; Farrer *et al*, 2004; Ibanez *et al*, 2004). This evidence indicates that increased expression of alpha-synuclein protein (the major component of Lewy bodies and a cause of PD), alone can result in dementia, and that the type and the severity of the neurodegenerative phenotype is related to the dose of the SNCA gene. Similar observations are noted with respect to AD, where in Down's syndrome an extra copy of the gene encoding amyloid-precursor protein leads to progressive dementia and Alzheimer's pathology, but not a phenotype or pathology indicative of PD, (Eriksen *et al*, 2003; Singleton and Gwinn-Hardy, 2004).

Results of APOE genotyping also serve to differentiate PDD and AD. A systematic review and meta-analysis of apolipoprotein E (APOE) genotype frequencies has recently been reported from case-control studies that provided clear clinical or pathologic criteria for PD (Huang *et al*, 2004). Unlike AD, for which the APOE-epsilon4 (APOE e4) allele increases the prevalence and the APOE e2 allele is protective, the APOE e2 allele, but not the APOE e4 allele, was shown to be positively associated with sporadic PD. The APOE-2 allele increased the likelihood of dementia in patients with PD while the APOE-4 allele increased the risk of dementia but not in excess of the influence of E-4 in normal controls (Harhangi *et al*, 2000). Similarly, in neuropathologically verified PD, the APOE ε4 allele frequency is increased only in the cases with concomitant AD pathology. Likewise, in dementia associated with Lewy bodies (DLB), , cases without AD-type pathology have an APOE e4 allele frequency similar to that of healthy age matched controls (Huckvale *et al*, 2003). These findings indicate that possession of an APOE e4 allele *per se* does not contribute to the development of PD or Lewy body pathology although its presence may induce additional AD-type pathology.

Table 3-1 summarizes the genetic distinctions between PDD and AD.

Table 3-1 Genetic distinctions between PDD and AD

Genetic Feature	Dementia Associated with Parkinson's Disease	Alzheimer's Disease
Causative mutations	Alpha-synuclein, PARKIN, UCH-L1, PARK-8, PINK-1, DJ-1	PS1, PS2, APP
APOE-4 influence	No effect on PDD; increases age-related or AD-type pathology	Major risk factor
APOE-2 influence	Increases PDD	Decreases AD

Conclusion

Genetic evidence indicates that the genetic etiologies and risk factors differ in PDD and AD.

4 Neuropathologic Distinctions between PDD and AD

The pathology of PDD is increasingly well understood. The advent of stains that is more specific and sensitive for detecting Lewy body and neurite pathology has facilitated investigation of the contribution of Lewy-type pathology to the PDD. The pathology with the highest correlation with the occurrence of dementia in patients with PD is the presence of cortical Lewy bodies (Apaydin *et al*, 2002; Hurtig *et al*, 2000; Kovari *et al*, 2003; Mattila *et al*, 2000; Zweig *et al*, 1993). The abundance of Lewy neurites in the CA2 region of the

3.

hippocampus also shows a strong correlation with the severity of cognitive impairment (Churchyard and Lees, 1997). Senile plaques are frequently present in PD cases with advanced dementia, but are often absent in PD cases with mild cognitive impairment and have low sensitivity for diagnosis (Hurtig *et al*, 2000). Many studies have shown some association between AD-type pathology and dementia in PD (Boller *et al*, 1980; de la Monte *et al*, 1989; Hakim *et al*, 1979; Paulus and Jellinger, 1991); these observations indicate that AD-type changes are commonly present when dementia is advanced but they do not account for all or even a majority of cases of PDD whereas Lewy-type pathology correlates much better with the presence of a dementia syndrome in a PD patient. Recent pathologic studies have staged the involvement of cerebral structures in patients with advancing PD, and provide a plausible correlate with the emergence of dementia in the course of PD. These studies demonstrate Lewy changes that are initially found in the lower brain stem and gradually ascend to involve limbic and neocortical areas. These findings may explain why cognitive changes and dementia usually appear relatively late in the course of patients with classic PD (Braak *et al*, 2003).

A unique pathological feature of dementia associated with PD is marked nigro-striatal dopaminergic neuronal degeneration. This finding compares to no significant change in AD patients (Piggot *et al*, 1999). Cell loss in the medial substantia nigra is associated with the presence of dementia in PDD (Rinne *et al*, 1989). Extranigral pathology in the locus ceruleus may also contribute to cognitive deterioration in PDD (Cash *et al*, 1987; Zweig *et al*, 1993). There is also cell loss of cholinergic neurons in the nucleus basalis of Meynert and a marked cholinergic deficiency in patients with PD (Zarow *et al*, 2003). These changes are most pronounced in patients with PDD (Arendt *et al*, 1983; Gaspar and Gray, 1984; Whitehouse *et al*, 1983). Indeed, the severity of the cholinergic deficiency in PDD is greater than what occurs in AD, and these deficits may occur earlier in the clinical course of PDD (Aubert *et al*, 1992; Bohnen *et al*, 2003; Kuhl *et al*, 1996; Perry *et al*, 1985). In contrast to AD, PDD is also associated with neuronal loss in the striatum and pediculopontine cholinergic pathways that project to structures such as thalamus (Rub *et al*, 2002).

Table 4-1 summarizes the differences between the neuropathology of PDD and AD.

Table 4-1 Neuropathology of PDD and AD

Pathological Feature	Dementia Associated with Parkinson's Disease	Alzheimer's Disease
Lewy bodies	Correlate highly with cognitive impairment	Rare
Senile plaques	Low sensitivity for dementia	Present in all cases
Neurofibrillary tangles	Low sensitivity for dementia	Present in nearly all cases
Cholinergic deficit	More marked	Less marked
Dopaminergic deficit	Present	Absent
Noradrenergic deficit	Present	Present

Conclusion

The neuropathology of PDD and of AD differs. The dementia of PDD correlates most highly with the presence of cortical Lewy bodies and is associated with degeneration of the nigrostriatal dopamine system; the dementia of AD correlates best with the presence of cortical senile plaques and neurofibrillary tangles, which are frequently no different than aged matched controls in PD.

4.

5 Neuroimaging

Relatively few neuroimaging studies have been done in patients with PDD. Preliminary magnetic resonance imaging (MRI) observations suggest that whereas temporal lobe atrophy including the hippocampus and parahippocampal gyrus is more severe in AD patients, there is more severe atrophy of the thalamus and occipital lobe in dementia associated with PD (Burton *et al*, 2004). Functional imaging studies using ligands which provide a measure of pre-synaptic dopaminergic neurons and terminals (F-Dopa-PET; FP-CIT SPECT) consistently reveal significant reductions in striatal uptake or binding as compared to those with AD and controls (O'Brien *et al*, 2004, Arch Neurol, 61 (6): 919-25)

Conclusion

Neuroimaging evidence supports a distinction between PDD and AD based on differences in the distribution of atrophy on MRI and degree of involvement of nigro-striatal dopaminergic function on PET or SPECT in the two disorders.

6 Neuropsychological Differences between PDD and AD

PDD and AD can be distinguished on the basis of their neuropsychological profiles (Pillon *et al*, 2001; Emre 2003). The principal differences are the presence of a retrieval deficit type memory abnormality in PDD compared to an amnestic type memory deficit in AD, the relative lack of language abnormalities in PDD compared to AD, and the predominance of executive deficits in PDD compared to AD.

An amnestic type of memory disorder with abnormalities of storage leading to disturbances of free recall and recognition is the key neuropsychological feature of AD (Zec, 1993). This contrasts with the memory deficit of PDD that features a deficit in recall with preserved recognition. In this disorder, information storage is achieved but timely recall is compromised; when structured clues are provided or multiple choices provided, retrieval is facilitated (Helkala *et al*, 1988; Noe *et al*, 2004; Pillon *et al*, 1993).

Executive function refers to choosing, planning, programming, implementing, and adjusting action plans. Executive function results in the realization of goal-directed, adaptive behavior in response to new, challenging environmental situations, including attention, response-inhibition, task management, planning, monitoring, and coding (Smith, 1999). It is assessed through tests of abstraction, set shifting, generative intellectual function, attention and concentration, planning, strategy development, and motor programming (Lezak, 1995). Executive function abnormalities occur early in the course of PDD and are prominent throughout the course of the illness (Appollonio *et al*, 1994; Cahn-Weiner *et al*, 2002; Freedman *et al*, 1986; Huber *et al*, 1986; Litvan *et al*, 1991; Marinus *et al*, 2003; Piat *et al*, 1999; Pillon *et al*, 1986; Pillon *et al*, 2001). In AD, executive function disturbances are relatively minor compared to the profound change in memory and the marked abnormalities in language and visuospatial function (Zec, 1993).

Visuospatial deficits are prominent in both PDD and AD. However, in PDD they appear early and are disproportionately severe (Levin *et al*, 1991). This may be in part because of the executive function deficits (Bondi *et al*, 1993; Crucian and Okun, 2003) as executive strategies are required for the performance of most visuospatial tests.

Language changes in PDD are minimal and consist of mild anomia in the more advanced phases of the dementia. In contrast, aphasic-type language abnormalities are a prominent

5.

early feature in AD and increase throughout the course of the illness. Indeed, in AD the anomia typically progresses to a transcortical type aphasia with disease progression (Cummings *et al*, 1988).

Cognitive slowing (bradyphrenia) is more prominent in PDD patients as compared to patients with AD (Pate *et al*, 1994).

Fluctuating attention is common in PDD and uncommon AD. Patients with PDD exhibit deficits in reaction time, vigilance and attentional fluctuation that are unusual in AD (Ballard *et al*, 2002). Rating scales of attention and EEG measures of vigilance support the observation that fluctuating cognition is greater in PDD than in AD (Walker *et al*, 2000).

There have been several recent direct comparisons of dementia profiles in patients with PD and AD that have largely confirmed the aforementioned profiles (Cahn-Weiner *et al*, 2002; Galvin *et al*, 2003; Aarsland *et al*, 2003b; Noe *et al*, 2004). These studies suggested that although the burden of global cognitive dysfunction and behavioral disturbance may appear similar in patients with AD to that found in PDD, specific measures of the functions described above are sensitive to the underlying neuropathology found in each of these diseases and differs significantly between them. Specifically, these studies revealed that patients with PDD, relative to those with AD, had better memory performance, but performed worse on executive function tests. PDD patients had lower scores on tests of initiation as well as worse preservation and reduced construction subscores.

Table 6-1 summarizes the principal neuropsychological differences between PDD and AD.

Table 6-1 Principal neuropsychological differences between PDD and AD

Neuropsychological Domain	Dementia Associated with Parkinson's Disease	Alzheimer's Disease
Memory	Retrieval deficit syndrome	Amnestic type
Executive function	Prominent	Moderate
Language changes	Limited	Prominent
Visuospatial deficits	Prominent, may be attributable to executive abnormalities	Milder, Independent of executive changes
Bradyphrenia	Present	Absent
Fluctuation attention	Characteristic	Uncommon

Conclusion

PDD and AD have contrasting clinical profiles. Executive function deficits, bradyphrenia, and a retrieval deficit type of memory disturbance are prominent in PDD. In contrast, AD is associated with an amnestic type of memory change with prominent language alterations and only mild-moderate executive function changes. Attentional fluctuation is characteristic of PDD and rare in AD.

7 Non-Cognitive Clinical Distinctions between PDD and AD

The major noncognitive difference between PDD and AD is the presence of PD. Patients with PD exhibit a progressive extrapyramidal syndrome with bradykinesia, rigidity, rest tremor, and typically show a beneficial response to treatment with dopaminergic agents. Patients with AD my have progressive rigidity as their disease advances but lack the typical levodopa responsive motor features of PD (Gnanalingham *et al*, 1997). As noted above, the diagnoses

6.

of PDD and AD are definitionally exclusive, since the diagnosis of AD or dementia of the Alzheimer's type require the exclusion of other brain disorders capable of causing a dementia syndrome (McKhann *et al*, 1984; American Psychiatric Association, 1994).

Autonomic dysfunction with orthostatic and postprandial hypotension resulting in syncope and falls, bowel and bladder disturbances, reduced heart rate variability predisposing to ventricular arrhythmias, and sexual dysfunction may be frequent, disabling features in patients with dementia associated with PD (Kaufman and Biaggioni 2003), while these are not features of AD.

Neuroleptic sensitivity is another clinical feature which differentiates AD from PDD (Aarsland *et al*, 2003c; Gnanalingham *et al*, 1997). AD patients are not known to have sensitivity to classical neuroleptics whereas this is a prominent feature which can be life-threatening in PD.

Rapid eye movement (REM) sleep behavior disorder is common as a concomitant feature in PDD which can antedate the onset of the PD (Boeve *et al*, 1998, 2004). REM sleep behavior disorder is not associated with AD.

Table 7-1 presents the non-cognitive features that distinguish PDD and AD.

Table 7-1 Non-cognitive features that distinguish PDD and AD

Non-cognitive Feature	Dementia Associated with Parkinson's Disease	Alzheimer's Disease
PD motor features	Present	Absent (parkinsonism may emerge late)
Neuroleptic sensitivity	Present	Absent
Autonomic dysfunction	Common	Uncommon
REM sleep behavior disorder	Common	Absent

Conclusion

Noncognitive clinical features differ between PDD and AD. The levodopa-responsive motor features of PD are the principal differences between the two disorders and are central to the diagnosis of PDD. Autonomic changes, REM sleep behavior disorder, and neuroleptic sensitivity are all more common in PDD than AD and assist in distinguishing these two disorders.

8 PDD can be distinguished from AD by a Practitioner

Currently available diagnostic criteria for PDD are those described in the Diagnostic and statistical Manual of Mental Disorders, 4th edition (DSM IV) (American Psychiatric Association, 1994). They require that a PD is present, a dementia syndrome is present (as defined in DSM IV), the patient evidenced PD prior to the onset of dementia, and alternate causes of dementia have been excluded (Table 8-1). These criteria can be applied by a medical practitioner who is not a dementia specialist. Once disorders such as hypothyroidism or B12 deficiency have been excluded as recommended by the American Academy of Neurology in the evaluation of dementia (Knopman *et al*, 2002), the diagnosis of dementia in

the patient with PD is most likely PDD. Based on incidence studies this diagnosis is 4-6 times more likely than AD in this population. If further differentiation is required, the absence of an amnestic type memory deficit or prominent language changes would further support the diagnosis of PDD and distinguish the syndrome from AD. Thus, the practitioner can achieve a diagnosis of PDD based on a clinical diagnosis of PD followed by the development of dementia with other causes being excluded. This is feasible in a practice setting.

Table 8-1 Criteria for dementia associated with Parkinson's disease

Criteria for PDD
All major criteria must be present.
Parkinson's disease
Dementia
Memory impairment
Impairment of at least one other cognitive domain
Impairment represents a decline from a previous level of function
Impairment sufficient to cause occupational or social disability
Impairment not present exclusively during a delirium
Onset of Parkinson's disease preceded the onset of dementia
Alternate causes of dementia have been excluded

References

[Aarsland D, Cummings JL, Larsen JP (2001a)]. Neuropsychiatric differences between Parkinson's disease with dementia and Alzheimer's disease. Int J Geriatr Psychiatry 16:184-91.

[Aarsland D, Ballard C, Larsen JP, McKeith I (2001b)]. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. Int J Geriatr Psychiatry 16:528-36.

[Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P (2001c)]. Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology 56:730-36.

[Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P (2003a)]. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 60:387-92.

[Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP (2003b)]. Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. J Neurol Neurosurg Psychiatry 74:1215-20.

[Aarsland D, Ballard CG, Larsen JP, McKeith IG, O'Brien J, Perry R (2003c)]. Marked neuroleptic sensitivity in dementia with Lewy bodies and Parkinson's disease. Nord J Psychiatry. 57:94.

[Aarsland D, Laake K, Larsen JP, Janvin C (2002)]. Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. J Neurol Neurosurg Psychiatry 72:708-12.

[Aarsland D, Mosimann UP, McKeith IG (2004)]. Role of Cholinesterase Inhibitors in Parkinson's Disease and dementia with Lewy Bodies. J Geriatr Psychiatry Neurol 17:164-71.

8.

[Aarsland D, Tandberg E, Larsen JP, Cummings JL (1996)]. Frequency of dementia in Parkinson's disease. Arch Neurol 53:538-42.

[Ala TA, Hughes LF, Kyrouac GA, Ghobrial MW, Elble RJ (2002)]. The Mini-Mental State exam may help in the differentiation of dementia with Lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry 17:503-9.

[American Psychiatric Association (1994)]. Diagnostic and statistical manual of mental disorders, 4th ed. Washington DC: American Psychological Association.

[American Psychiatric Association (2000)]. Diagnostic and statistical manual of mental disorders, 4th ed., Text Revision. Washington DC: American Psychological Association.

[Anand R, Messina J, Hartman R (2000)]. Dose-response effect of rivastigmine in the treatment of Alzheimer's disease. Int J Geriatr Psychopharm 2:68-72.

[Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW (2002)]. Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. Arch Neurol 59:102-12.

[Aubert I, Araujo DM, Cecyre D, Robitaille Y, Gauthier S, Quirion R (1992)]. Comparative alterations of nicotinic and muscarinic binding sites in Alzheimer's and Parkinson's diseases. J Neurochem. 58(2):529-41.

[Baba M, Nakajo S, Tu PH, Tomita T, Nakaya K, Lee VM, Trojanowski JQ, Iwatsubo T (1998)]. Aggregation of alpha-synuclein in Lewy bodies of sporadic Parkinson's disease and dementia with Lewy bodies. Am J Pathol 152(4):879-84.

[Bartus RT (2000)]. On neurodegenerative diseases, models, and treatment strategies: lessons learned and lessons forgotten a generation following the cholinergic hypothesis. Exp Neurol 163:495-529.

[Boeve BF, Silber MH, Parisi JE, Dickson DW, Ferman TJ, Benarroch EE, Schmeichel GE, Petersen RC, Ahlskog JE, Matsumoto JY, Knopman DS, Schenck CH, Mahowald MW (2003)]. Synucleinopathy pathology and REM sleep behavior disorder plus dementia or parkinsonism. Neurology 61:40-45.

[Bohnen NI, Kaufer DI, Ivanco LS, Lopresti B, Koeppe RA, Davis JG, Mathis CA, Moore RY, DeKosky ST (2003)]. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol 60:1745-8.

[Bondi MW, Kaszniak AW, Bayles KA, Vance KT (1993)]. Contribution of frontal system dysfunction to memory and perceptual abilities in Parkinson's disease. Neuropsychology 7:89-102.

[Braak H, Braak E, Yilmazer D, de Vos RA, Jansen EN, Bohl J (1996)]. New aspects of pathology in Parkinson's disease with concomitant incipient Alzheimer's disease. J Neural Transm Suppl 48:1-6. Review.

[Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E (2003)]. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197-211.

[Burn DJ, Rowan EN, Minett T, Sanders J, Myint P, Richardson J, Thomas A, Newby J, Reid J, O'Brien JT, McKeith IG (2003a)]. Extrapyramidal features in Parkinson's disease with and without dementia and dementia with Lewy bodies: a cross-sectional comparative study. Mov Disord 18:884-9.

9.

[Burn DJ, McKeith IG (2003b)]. Current treatment of dementia with Lewy bodies and dementia associated with Parkinson's disease. Mov Disord 18 Suppl 6:S72-9.

[Burton EJ, Karas G, Paling SM, Barber R, Williams ED, Ballard CG, McKeith IG, Scheltens P, Barkhof F, O'Brien JT (2004)]. Patterns of cerebral atrophy in dementia with Lewy bodies using voxel-based morphometry. Neuroimage 17:618-30.

[Cahn-Weiner DA, Grace J, Ott BR, Fernandez HH, Friedman JH (2002)]. Cognitive and behavioral features discriminate between Alzheimer's and Parkinson's disease. Neuropsychiatry Neuropsychol Behav Neurol 15:79-87.

[Chartier-Harlin MC, Kachergus J, Roumier C, Mouroux V, Douay X, Lincoln S, Levecque C, Larvor L, Andrieux J, Hulihan M, Waucquier N, Defebvre L, Amouyel P, Farrer M, Destee A (2004)]. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. Lancet 364:1167-9.

[Colosimo C, Hughes AJ, Kilford L, Lees AJ (2003)]. Lewy body cortical involvement may not always predict dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 74:852-8856.

[Corey-Bloom J, Anand R, Veach J (1998)]. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1:55-65.

[Court JA Piggott MA, Lloyd S, Cookson N, Ballard CG, McKeith IG, Perry RH, Perry EK (2000)]. Nicotine binding in human striatum: elevation in schizophrenia and reductions in dementia with Lewy bodies, Parkinson's disease and Alzheimer's disease and in relation to neuroleptic medication. Neuroscience 98:79-87.

[Crucian GP, Okun MS (2003)]. Visual-spatial ability in Parkinson's disease. Front Biosci 8:s992-7.

[Cummings JL (1998)]. Intellectual impairment in Parkinson's disease: clinical, pathologic, and biochemical correlates. J Geriatr Psychiatry Neurol 1:24-36.

[Dickson DW, Ruan D, Crystal H, Mark MH, Davies P, Kress Y, Yen SH (1991)]. Hippocampal degeneration differentiates diffuse Lewy body disease (DLBD) from Alzheimer's disease: light and electron microscopic immunocytochemistry of CA2-3 neurites specific to DLBD. Neurology 41:1402-9.

[Dubois B, Pillon B (1999)]. Dementia in Parkinson's disease. In: Wolters EC, Sheltens P, Berendse HW (eds) Mental dysfunction in Parkinson's disease II. Utrecht: Academic Pharmaceutical Productions 165-176.

[Emre M (2003)]. Dementia associated with Parkinson's disease. Lancet Neurol 2:229-37.

[Eriksen JL, Dawson TM, Dickson DW, Petrucelli L (2003)]. Caught in the act: alpha-synuclein is the culprit in Parkinson's disease. Neuron 40:453-6.

[Farde L, Suhara T, Nyberg S, Karlsson P, Nakashima Y, Hietala J, Halldin C (1997)]. A PET-study of [11C] FLB 457 binding to extrastriatal D2-dopamine receptors in healthy subjects and antipsychotic drug-treated patients. Psychopharmacology (Berl) 133:396-404.

[Farlow M, Lane R, Kudaravalli S, He Y]. Differential qualitative responses to rivastigmine in APOE 4 carriers and noncarriers. Pharmacogenomics online publication 3 August 2004

10.

[Farrer M, Kachergus J, Forno L, Lincoln S, Wand DS, Hulihan M, Maraganore D, Gwinn-Hardy K, Wszolek Z, Dickson D, Langston JW (2004)]. Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. Ann Neurol 55:174-9.

[Farrer M, Maraganore DM, Lockhart , Lesnick TG, de Andrade M, West A, de Silva R, Hardy J, Hernandez D (2001)]. apha-Synuclein gene haplotypes are associated with Parkinson's disease. Hum Mol Genet 10:1847-51.

[Foltynie T, Brayne CEG, Robbins TW, Barker RA (2004)]. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 127:550-560.

[Gauthier S, Gélinas I, Gauthier L (1997)]. Functional disability in Alzheimer's disease. Int Psychogeriatr 9(Suppl 1):163-5.

[Gelb DJ, Oliver E, Gilman S (1999)]. Diagnostic criteria for Parkinson disease. Arch Neurol. 56:33-9.

[Gibb WR, Lees AJ (1998)]. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 51:745-52.

[Gnanalingham KK, Smith LA, Hunter AJ, Jenner P, Marsden CD (1993)]. Alterations in striatal and extrastriatal D-1 and D-2 dopamine receptors in the MPTP-treated common marmoset: an autoradiographic study. Synapse 14:184-94.

[Gomez-Tortosa E, Newell K, Irizarry MC, Albert M, Growdon JH, Hyman BT (1999)]. Clinical and quantitative pathological correlates of dementia with Lewy bodies. Neurology 53:1284-91.

[Hansen, L.A., E. Masliah, D. Galasko & R.D. Terry (1993)]. Plaque-only Alzheimer disease is usually the lewy body variant, and vice versa. J. Neuropathol. Exp. Neurol. 52:648-54.

[Harding AJ, Halliday GM (2001)]. Cortical Lewy body pathology in the diagnosis of dementia. Acta Neuropathol (Berl) 102:355-63.

[Hardy, J. (1994)]. Lewy bodies in Alzheimer's disease in which the primary lesion is a mutation in the amyloid precursor protein. Neurosci. Lett. 180:290-1.

[Hardy J (2003)]. The Relationship between Lewy Body Disease, Parkinson's Disease, and Alzheimer's Disease. Annals of the New York Academy of Sciences 991:167-70.

[Hausdorff JM, Balash J, Giladi N (2003)]. Effects of cognitive challenge on gait variability in patients with Parkinson's disease. J Geriatr Psychiatry Neurol 16:53-8.

[Helkala EL, Laulumaa V, Soininen H, Riekkinen PJ (1988)]. Recall and recognition memory in patients with Alzheimer's and Parkinson's diseases. Ann Neurol 24:214-7.

[Huang X, Chen PC, Poole C (2004)]. APOE-epsilon2 allele associated with higher prevalence of sporadic Parkinson disease. Neurology 62(12):2198-202.

[Huckvale C, Richardson AM, Mann DM, Pickering-Brown SM (2003)]. Debrisoquine hydroxylase gene polymorphism (CYP2D6*4) in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 74:135-6.

[Hughes TA, Ross HF, Musa S, Bhattacherjee S, Nathan RN, Mindham RH, Spokes EG (2000)]. A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. Neurology 54:1596-602.

[Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, Lee VM, Clark CM, Glosser G, Stern MB, Gollomp SM, Arnold SE (2000)]. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. Neurology 54:1916-21.

11.

[Ibanez P, Bonnet AM, Debarges B, Lohmann E, Tison F, Pollak P, Agid Y, Durr A, Brice A (2004)]. Causal relation between alpha-synuclein gene duplication and familial Parkinson's disease. Lancet 364:1169-71.

[Ince PG, Perry EK, Morris CM (1998)]. Dementia with Lewy bodies. A distinct non-Alzheimer dementia syndrome? Brain Pathol 8:299-324.

[Janvin C, Aarsland D, Larsen JP, Hugdahl K (2003)]. Neuropsychological profile of patients with Parkinson's disease without dementia. Dement Geriatr Cogn Disord 15:126-31.

[Jellinger KA, Paulus W (1992)]. Clinico-pathological correlations in Parkinson's disease. Clin Neurol Neurosurg 94(Suppl):S86-8.

[Kaasinen V, Nagren K, Hietala J, Oikonen V, Vilkman H, Farde L, Halldin C, Rinne JO (2000)]. Extrastriatal dopamine D2 and D3 receptors in early and advanced Parkinson's disease. Neurology 54:1482-7.

[Kaufmann H, Biaggioni I (2003)]. Autonomic failure in neurodegenerative disorders. Semin Neurol 23(4):351-63.

Klatka LA, Louis ED, Schiffer RB (1996). Psychiatric features in diffuse Lewy body disease: a clinicopathologic study using Alzheimer's disease and Parkinson's disease comparison groups. Neurology 47:1148-52.

[Kosaka K, Tsuchiya K, Yoshimura M (1988)]. Lewy body disease with and without dementia: a clinicopathological study of 35 cases. Clin Neuropathol 7:299-305.

[Kovari E, Gold G, Herrmann FR, Canuto A, Hof PR, Bouras C, Giannakopoulos P (2003)]. Lewy body densities in the entorhinal and anterior cingulate cortex predict cognitive deficits in Parkinson's disease. Acta Neuropathol (Berl) 106:83-8.

[Kuhl DE, Minoshima S, Fessler JA, Frey KA, Foster NL, Ficaro EP, Wieland DM, Koeppe RA (1996)]. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease, and Parkinson's disease. Ann Neurol 40:399-410.

[Kuzuhara S, Mori H, Izumiyama N, Yoshimura M, Ihara Y (1988)]. Lewy bodies are ubiquinated: a light and electron microscopic immunocytochemical study. Acta Neuropathol (Berl) 75:345-53.

[Leech RW, Brumback RA, Poduslo SE, Schiffer R, Adesina A (2001)]. Dementia: the University of Oklahoma autopsy experience. J Oklahoma State Med Assoc 94:507-11.

[Leverenz JB, Tsuang DW, Larson EB, Montine T, Kraybill M, Nochlin D (2004)]. Parkinson's disease dementia in a community-based autopsy sample of dementia. Movement Disorders 19(suppl 9):S402.

[Levy G, Schupf N, Tang MX, cote LJ, Louis ED, Mejia H, Stern Y, Marder K (2002)]. Combined effect of age and severity on the risk of dementia in Parkinson's disease. Ann Neurol 51:722-9.

Levy G, Louis ED, Mejia-Santana H, Cote L, Andrews H, Harris J, Waters C, Ford B, Frucht S, Fahn S, Ottman R, Marder K (2004). Lack of familial aggregation of Parkinson disease and Alzheimer disease. Arch Neurol 61:1033-39.

[Lippa CF, Fujiwara H, Mann DM, Giasson B, Baba M, Schmidt ML, Nee LE, O'Connell B, Pollen DA, St George-Hyslop P, Ghetti B, Nochlin D, Bird TD, Cairns NJ, Lee VM, Iwatsubo T, Trojanowski JQ (1998)]. Lewy bodies contain altered alpha-synuclein in brains of many

familial Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes. Am. J. Pathol 153:1365-70.

[Litvan I, Mohr E, Williams J, Gomez C, Chase TN (1991)]. Differential memory and executive functions in demented patients with Parkinson's and Alzheimer's disease. J Neurol Neurosurg Psychiatry 54:25-9.

[Litvan I, Bhatia KP, Burn DJ, Goetz CG, Lang AE, McKeith I, Quinn N, Sethi KD, Shults C, Wenning GK (2003)]. Movement Disorders Society Scientific Issues Committee. Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. Mov Disord 18:467-86.

[Marttila RJ, Rinne UK (1976)]. Epidemiology of Parkinson's disease in Finland. Acta Neurol Scand 53:81-102.

[Mattila PM, Rinne JO, Helenius H, Dickson DW, Roytta M (2000)]. Alpha-synuclein-immunoreactive cortical Lewy bodies are associated with cognitive impairment in Parkinson's disease. Acta Neuropathol (Berl) 100:285-90.

[Mattila PM, Koskela T, Roytta M, Lehtimaki T, Pirttila TA, Ilveskoski E, Karhunen P, Rinne JO (1998a)]. Apolipoprotein E epsilon4 allele frequency is increased in Parkinson's disease only with co-existing Alzheimer pathology. Acta Neuropathol (Berl) 96:417-20.

[Mattila PM, Roytta M, Torikka H, Dickson DW, Rinne JO (1998b)]. Cortical Lewy bodies and Alzheimer-type changes in patients with Parkinson's disease. Acta Neuropathol (Berl) 95:576-82.

[Mattila PM, Roytta M, Lonnberg P, Marjamaki P, Helenius H, Rinne JO (2001)]. Choline acetytransferase activity and striatal dopamine receptors in Parkinson's disease in relation to cognitive impairment. Acta Neuropathol (Berl) 102:160-6.

[Mayeux R, Chen J, Mirabello E, Marder K, Bell K, Dooneief G, Cote L, Stern Y (1990)]. An estimate of the incidence of dementia in idiopathic Parkinson's disease. Neurology 40:1513-17.

[Mayeux R, Denaro J, Hemenegildo N, Marder K, Tang MX, Cote LJ, Stern Y (1992)]. A population-based investigation of Parkinson's disease with and without dementia. Relationship to age and gender. Arch Neurol 49:492-7.

[McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH (1996)]. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 47:1113-24.

[Miller D, Hague SM, Clarimon J, Baptista M, Cookson MR, Singleton AB (2004)]. alpha-Synuclein in blood and brain from familial Parkinson disease with SNCA locus triplication. Neurology 62:1835-8.

[Mindham RH, Ahmed SW, Clough CG (1982)]. A controlled study of dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 45:969-74.

[Noe E, Marder K, Bell KL, et al (2004)]. Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia. Mov Disord 19:60-7.

[Parkinson J (1817)]. An essay on shaking palsy. London: Sherwood, Neely and Jones.

13.

[Parsian A, Racette B, Goldsmith LJ, Perlmutter JS (2002)]. Parkinson's disease and apolipoprotein E: possible association with dementia but not age at onset. Genomics 79:458-61.

[Pate DS, Margolin DI (1994)]. Cognitive slowing in Parkinson's and Alzheimer's patients: distinguishing bradyphrenia from dementia. Neurology 44:669-74 .

[Perry EK, Curtis M, Dick DJ, Candy JM, Atack JR, Bloxham CA, Blessed G, Fairbairn A, Tomlinson BE, Perry RH (1985)]. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparison with Alzheimer's disease. J Neurol Neurosurg Psychiatry 48:413-21.

[Perry EK, Marshall E, Perry RH, Irving D, Smith CJ, Blessed G, Fairbairn AF (1990)]. Cholinergic and dopaminergic activities in senile dementia of Lewy body type. Alzheimer Dis Assoc Disord 4:87-95.

[Perry E, Walker M, Grace J, Perry R (1999)]. Acetylcholine in mind: a neurotransmitter correlate of consciousness? Trends Neurosci 22:273-80.

[Piggott MA, Marshall EF, Thomas N, Lloyd S, Court JA, Jaros E, Burn D, Johnson M, Perry RH, McKeith IG, Ballard C, Perry EK (1999)]. Striatal dopaminergic markers in dementia with Lewy bodies, Alzheimer's and Parkinson's diseases: rostrocaudal distribution. Brain 122:1449-68.

[Pillon B, Boller F, Levy R, Dubois B (2001)]. Cognitive deficits and dementia in Parkinson's disease. In: Boller F, Cappa S, eds. Handbook of Neuropsychology, 2 ed. Amsterdam: Elsevier Science 311-71.

[Pillon B, Deweer B, Agid Y, Dubois B (1993)]. Explicit memory in Alzheimer's, Huntington's, and Parkinson's diseases. Arch Neurol 50:374-9.

[Rainer M, Mucke HAM (1998)]. Long-term cognitive benefits from galanthamine in Alzheimer's disease. Int J Geriatr Psychopharmacol 1:197-201.

[Rajput AH, Offord KP, Beard CM, Kurland LT (1987)]. A case-control study of smoking habits, dementia, and other illnesses in idiopathic Parkinson's disease. Neurology 37:226-32.

[Read NL, Hughes TA, Dunn EM, Nirodi P, Branton T, Mindham RHS, Spokes EGS (2001)]. Dementia in Parkinson's disease: incidence and associated factors at 14-years of follow up. Parkinsonism Relat Disord 7(suppl):S109.

[Reid WG, Hely MA, Morris JG, Broe GA, Adena M, Sullivan DJ, Williamson PM (1996)]. A longitudinal study of Parkinson's disease: clinical and neuropsychological correlates of dementia. J Clin Neurosci 3:327-33.

[Rosenstein LD (1998)]. Differential diagnosis of the major progressive dementias and depression in middle and late adulthood: a summary of the literature of the early 1990s. Neuropsychol Rev 8:109-67.

[Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stahelin HB, Hartman R, Gharabawi M (1999)]. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. Br Med J 318:633-40.

[Rub U, Del Tredici K, Schultz C, Ghebremedhin E, de Vos RA, Jansen Steur E, Braak H (2002)]. Parkinson's disease: the thalamic components of the limbic loop are severely impaired by alpha-synuclein immunopositive inclusion body pathology. Neurobiol Aging 23:245-54.

[Rybicki BA, Johnson CC, Gorell JM (1995)]. Demographic differences in referral rates to neurologists of patients with suspected Parkinson's disease: implications for case-control study design. Neuroepidemiology 14:72-81.

[Saint-Cyr JA, Taylor AE, Lang AE (1988)]. Procedural learning and neostriatal dysfunction in man. Brain 111:941-59.

[Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y (1983)]. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Res 275:321-8.

[Schaafsma JD, Giladi N, Balash Y, Bartels AL, Gurevich T, Hausdorff JM (2003)]. Gait dynamics in Parkinson's disease: relationship to Parkinsonian features, falls and response to levodopa. J Neurol Sci 212:47-53.

[Singleton A, Gwinn-Hardy K (2004)]. Parkinson's disease and dementia with Lewy bodies: a difference in dose? Lancet 364:1105-7.

[Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K (2003)]. alpha-Synuclein locus triplication causes Parkinson's disease. Science 302:841.

[Smith EE, Jonides J (1999)]. Storage and executive processes in the frontal lobes. Science 283:1657-61.

[Spillantini MG, Crowther RA, Jakes R, Hasegawa M, Goedert M (1998)]. a-Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. Proc Natl Acad Sci U S A. 95:6469-73.

[Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C (2000)]. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 54:2269-76.

[Verghese J, Buschke H, Viola L, Katz M, Hall C, Kuslansky G, Lipton R (2002)]. Validity of divided attention tasks in predicting falls in older individuals: a preliminary study. J Am Geriatr Soc 50:1572-6.

[Winblad B, Brodaty H, Gauthier S, Morris JC, Orgogozo JM, Rockwood K, Schneider L, Takeda M, Tariot P, Wilkinson D (2001)]. Pharmacotherapy of Alzheimer's disease: is there a need to redefine treatment success? Int J Geriatr Psychiatry 16:653-66.

[Wooten GF, Currie LJ, Bovbjerg VE, Lee JK, Patrie J (2004)]. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry 75:637-9.

[Zareparsi S, Camicioli R, Sexton G, Bird T, Swanson P, Kaye J, Nutt J, Payami H (2002)]. Age at onset of Parkinson disease and apolipoprotein E genotypes. Am J Med Genet 107:156-61.

[Zgaljardic DJ, Borod JC, Foldi NS, Mattis P (2003)]. A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. Cogn Behav Neurol 16:193-210.

[Ziabreva I, Ballard CG, Aarsland D, Larsen JP, McKeith IG, Perry RH, Perry EK (2004)]. Cortical and thalamic cholinergic activity in Lewy body disease in relation to dementia and parkinsonism. Presented at: MDS-Conference, Rome, Italy.

15.