London, 28 February 2006
Product name: **Exelon**
Procedure number: **EMEA/H/C/169/II/33**

SCIENTIFIC DISCUSSION

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1. INTRODUCTION

Currently, rivastigmine is indicated in Europe for the symptomatic treatment of patients with mild to moderately severe Alzheimer's Dementia (AD).

The scope of this variation application is to extend the therapeutic indication of rivastigmine to include the symptomatic treatment of mild to moderately severe dementia associated with Parkinson's disease (PDD).

Both types of dementia (AD and PDD) are thought to result from central neurodegeneration and associated with deficits in cholinergic activity. However, the neuropathology of AD and PDD differ, and the clinical picture is also different between AD and PDD. The principal differences are the presence of a retrieval type memory deficit in PDD compared to an amnestic type memory deficit in AD, a relative lack of language abnormalities in PDD compared to AD, and a predominance of executive deficits in PDD compared to AD.

Rivastigmine is a slowly reversible, carbamate-typed inhibitor of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Both enzymes play a role in cholinergic transmission.

2. CLINICAL EFFICACY

The efficacy and safety of rivastigmine monotherapy in the treatment of dementia in patients with Parkinson's disease (PDD) was examined in one placebo-controlled study (Study ENA713B2311), and its uncontrolled extension study (Study ENA713B2311E1).

A 4-week validation study (Study ENA713B2314) was conducted to evaluate and validate the efficacy assessment scales in patients with PDD, as compared to the sensitivity and reliability of these scales in AD patients.

The proposed clinical development and study designs were discussed twice with the SAWP at the EMEA. These advices were followed in this development program (Scientific Advice letter of 22-Feb-02, Scientific Advice letter of 29-April-03). The CHMP did not recommend re-exploring the dose-response relationship for Exelon as this was well-defined for the approved "mild to moderately severe dementia of the Alzheimer's type". Many cholinomimetic drugs, including cholinesterase inhibitors, have a potential to induce extrapyramidal symptoms. The SAWP/CHMP therefore required data to show that Exelon has no negative impact on the signs and symptoms of PD and no effect on the evolution of the disease.

Studies were conducted in accordance with the version of the Declaration of Helsinki and the principles of Good Clinical Practice applicable at the time. The MAH has also provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.1 Main study ENA713B2311

Study ENA713B2311 was a 24-week prospective, randomized, multicenter, double-blind, placebo-controlled, parallel-group study to assess the efficacy, tolerability, and safety of 3-12 mg/day of Exelon (Rivastigmine) capsules.

Design and Methods

The study was conducted in approximately 60 centers in Europe and Canada.
Approximately 540 patients with PDD were to be randomly assigned to treatment with either Exelon 3-12 mg/day, or placebo in an assignment ratio of 2:1 (i.e. approximately 360 patients on Exelon and 180 on placebo).

Phase	Pre-randomization		Double-blind treatment	
Period	Screening	Baseline	Titration	Maintenance
Time	week s -3 to -1	day 0	16 weeks	8 weeks
Visit	1	2	3 4 5 6	7 and 8
Treatment	None	None	Exelon (3-12 mg/d) or placebo	Exelon (12 mg/d or highest well-tolerated dose) or placebo

All patients were started on dose level 1, with increases to the next dose level after a minimum of 4 weeks. Dosage could be reduced to the next lower dose level in case of tolerability problems and then increased again by one dose level as clinically indicated (in case of re-increases, the minimum interval was 2 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.
If 6 consecutive doses or less were missed, patients were allowed to continue at the same dose level, or to restart at the next lower dose level. If patients missed more than 6 consecutive doses, they were to be re-titrated starting at dose level 1.

Study population

The study included patients of either sex aged 50 years or older with idiopathic PD according to UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria and a clinical diagnosis of PDD according to DSM IV criteria (Code 294.1) with the onset of dementia symptoms occurring at least 2 years after the first diagnosis of idiopathic PD, with an MMSE score of 10 to 24, and with a single, designated caregiver.
Excluded were patients with other primary neurodegenerative disorders and other causes of dementia (Alzheimer's disease, Frontotemporal dementia, Huntington's disease, dementia with Lewy bodies, Parkinson plus Syndromes other than PDD (progressive supranuclear palsy or olivopontocerebellar degeneration), a current diagnosis of probable or possible vascular dementia (according to the NINDS-AIREN criteria), a current diagnosis of major depressive episode (DSM IV- Code 296), and patients with conditions or circumstances likely to affect the patient's safety or compliance, the efficacy evaluations, or the conduct of the study.

Efficacy endpoints

Primary
Cognition: Alzheimer's Disease Assessment Scale-cognitive subscale (**ADAS-cog**).
Global clinical rating of change: The Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change (**ADCS-CGIC**).

Secondary
Cognitive Drug Research (**CDR**) Computerized Assessment System tests for the assessment of attention.
D-KEFS Verbal Fluency Test for the assessment of executive functioning.
Alzheimer's Disease Cooperative Study – Activities of Daily Living (**ADCS-ADL**) for the assessment of ability to perform activities of daily living.
Neuropsychiatric Inventory (**NPI**) for the assessment of behaviour including delusions, hallucinations, apathy, depression, irritability, agitation, disinhibition, euphoria, aberrant motor behaviour and anxiety.
NPI Caregiver Distress Scale (**NPI-D**) for the assessment of caregiver distress due to behavioural disturbances.
Ten Point Clock Test (**TPCT**).
Mini-Mental State Examination (**MMSE**).

The ADAS-cog, MMSE, CDR, D-KEFS and TPCT are direct patient performance scales whereas the ADCS-ADL, NPI and NPI-D are assessed through interview with the caregiver. The ADCS-CGIC is assessed through patient interview by a clinician who is blinded to the other assessments in the study.

Study ENA713B2314 was conducted to evaluate and validate the efficacy assessment scales used in the evaluation of AD patients in patients with PDD.

Statistical analysis

The primary objective of this study required demonstration of a statistically significant difference at the two-sided 5% level of significance between the group of patients randomized to Exelon and the group randomized to placebo for each of the two primary efficacy variables.

Primary efficacy variables included the ADAS-cog (analysis of covariance, ANCOVA, on mean change from baseline) and the CGIC (categorical analysis, Van Elteren test). ANCOVA analyses included country and baseline (when applicable) as stratification factor and covariates, respectively.
All statistical tests were 2-tailed and performed at the 0.05 significance level. Analyses were performed on several analysis data set to assess the biasing effects of discontinuation.

Populations

The primary population for comparing the treatment groups was the **Intent To Treat with Retrieved Dropouts (ITT+RDO).** This population includes all randomized patients who received at least one dose of study medication and had at least a pre-baseline assessment and a post-baseline assessment for one of the primary efficacy variables, either under treatment or not. The RDO population included patients who discontinued study treatment early and continued to attend scheduled visits for efficacy evaluations.

ITT-Last observation carried forward (LOCF)
This population included all randomized patients who received at least one dose of study medication and had at least a pre-baseline assessment and a post baseline assessment on study drug (i.e. not more than 2 days after the last known date of study drug) for one of the primary efficacy variables.

Observed Cases (OC)
This population included all randomized patients who received at least one dose of study medication and had at least a pre-baseline assessment and a post baseline assessment on study drug (i.e. not more than 2 days after the last known date of study drug) for one of the primary efficacy variables.
Data was reported only from randomized subjects who had an evaluation on treatment at the designated assessment time (either interim scheduled or endpoint). Evaluations done more than 2 days after the last known date of study drug were not included in the analysis.
No imputation occurs under this definition. Note that only the OC analysis population was used for tests which were only performed at selected sites (Delis Kaplan Executive Function tests and the TPCT).

Demographics and baseline characteristics

Baseline demographic characteristics for age, gender and race were comparable in both treatment groups. The overall demographic characteristics (87% age beyond 65, 65% male) were representative of patients with PD and PDD.

Duration of PD, duration of PDD, and time interval between diagnosis of PD and initial symptoms of PDD were well balanced between the treatment groups (the last one being a bit longer in the placebo group). The distribution of PD severity as measured by Hoehn and Yahr (UPDRS part V) staging was similar in the two groups and indicated a moderate to severe stage of PD for majority of patients.
The average MMSE scores in both treatment groups were comparable at study entry: 19.4 (3 – 30) in the Exelon group and 19.2 (8 – 27) in the placebo group. The inclusion criteria (MMSE score of 10 to

24) was not fulfilled for 6 patients in the Exelon group and 3 patients in the placebo group. This low MMSE score in some patients seems not compatible to carry out the ADAS-Cog test.

The CHMP raised concerns on these protocol violations and requested the MAH clarifications. In addition the CHMP requested the MAH to clarify the percentage of patients with mild and moderate dementia and a post-hoc analysis in the sub-groups.
The MAH clarified that these patients were assigned as protocol violators; however, they were included in the primary analysis population as was defined prospectively in the statistical analysis plan. When the 9 patients who were protocol violators for out of range MMSE scores were excluded, all three efficacy measures still maintained significant improvement in the Exelon group compared to placebo at week 24.
The MAH also clarified that the distribution of patients with mild and moderate dementia were similar in both treatment groups. A post-hoc analysis of ADAS-cog, ADCS-CGIC and ADCS-ADL in the subgroups of patients with mild and moderate PDD, showed favourable results for Exelon as compared to placebo, but they did not achieve statistical significance on some measures.

Primary Efficacy results

ADAS-Cog change from baseline
Patients with PDD in the Exelon treatment group achieved an improvement of 2.1 points on the ADAS-Cog at week 24, whereas patients in the placebo group deteriorated by 0.7 points at week 24 (ITT+RDO).
The difference was 2.5 points in Exelon group and -0.8 points in the placebo group in the LOCF population and 2.9 points and -1.0 in the Exelon and placebo groups respectively in the OC population.

The treatment group difference for the change from baseline was statistically significantly in favour of Exelon in all three analysis populations, both at week 24 and at week 16 ($p<0.001$).

ADAS-Cog categorical analysis - patients improving
The percentage of patients in whom the ADAS-Cog score improved by at least 4 points on study drug was consistently significantly higher in the Exelon group in analysis of populations at weeks 16 and 24. For the ITT+RDO population at week 24, the statistical significance level was close to statistical significance ($p=0.074$).

ADCS- CGI-C - categorical analysis at week 24
The percentage of patients in whom the ADCS CGI-C rating improved on study drug was significantly higher in the Exelon group in all analysis populations at week 24 than in the placebo group. At week 16 the ADCS CGI-C rating improved was also significantly higher in the Exelon group in all analysis populations.

ADCS CGI-C - patients improving and treatment effect
The treatment effect was consistently in favour of Exelon, with odds ratios for an improvement on Exelon between 1.6 and 2.1.
When adjusted for duration of PD (measured by time since diagnosis of PD) and severity of Parkinsonian motor symptoms (measured by baseline UPDRS part III total score, and change from baseline at week 24) CGIC scores at week 24 remained significant in favour of Exelon as compared to placebo.

Secondary Efficacy Results

ADCS-ADL total score change from baseline
Patients in the Exelon group demonstrated significantly less deterioration as measured by the ADCS-ADL mean scores at week 24 compared to the placebo group. The decline in ADCS-ADL total score was 3.6 points in the placebo group and 1.1 points in the Exelon group (ITT+RDO population). A statistically significant superiority of Exelon over placebo for the ADCS-ADL total score change from baseline for all three-analysis populations at week 24 was observed.

The assessment of activities of daily living by ADCS-ADL in patients who have reported 'AEs potentially associated with PD' did not show a less favourable outcome.

Supplementary sensitivity analysis including all randomized patients (even those without measures after baseline) with an imputation of missing data by LOCF method and by the hypothesis that ADAS-Cog score variation is similar to those observed in the placebo group, were requested to the MAH. Both analyses showed that the results are statistically significant, in favour of Exelon group.

NPI-10 total score change from baseline
The NPI-10 total composite scores decreased, indicating clinical improvement. The decrease from baseline was larger in the Exelon group than in the placebo group. At week 24, significance was observed in the ITT-RDO and LOCF populations. The percentage of patients with an improved NPI-10 total composite score at week 24 was also statistically significantly higher in the Exelon group compared to placebo in all three analysis populations. The difference in change from baseline also reached statistical significance in all three analysis populations at week 16.
The NPI-12 total score was decreased in the Exelon group compared to placebo group in the ITT+RDO and the LOCF population and was comparable for the OC population. Although the percentage of patients improving (at least 30% improvement over baseline) was higher in the Exelon group at all times points, the differences in all populations analysis were not statistically significant.

CDR - power of attention score change from baseline
The CDR attention battery scores at week 24 were statistically significantly lower in the Exelon group for the combined power of attention score (mean of simple reaction time, digit vigilance test and choice reaction time) and significant for choice reaction time but not for simple reaction time or for digit vigilance speed of detection test.

D-KEFS Letter fluency test change from baseline – total correct responses
On the D-KEFS Letter Fluency test, the mean scores for total correct responses improved in the Exelon group (1.7 points) and deteriorated (-1.1 points) in the placebo group at week 24. The treatment group difference was statistically significant at both weeks 16 and week 24.
The others D-KEFS executive functions tests were not performed in all study centres. D-KEFS Color-Word Interference tests show no statistically significance in mean change score. In the D-KEFS Card Sorting Test and Symbol Digit Modality test, a statistically significant improvement was observed in the Exelon group.

Ten point clock test change from baseline
Mean scores for this test at week 24 increased in the Exelon group and decreased in the placebo group. The difference in change from baseline was statistically significant at week 24.

MMSE
Mean MMSE scores increased by 0.8 points in the Exelon group, and decreased by 0.2 points in the placebo group (week 24, ITT+RDO population); the difference was statistically significant in favour of Exelon in all three analysis populations.

Composite responder analysis
A composite responder analysis was performed based on the criteria ADAS-Cog improvement of at least 4 points and no worsening on CGIC-C and ADCS-ADL (CGIC categories 1-4 and an ADCS-ADL change ≥ 0). For the primary analysis population ITT+RDO there was no statistically significant difference between rivastigmine and placebo at week 24 ($p=0.082$). For the LOCF population, the difference was statistically significant ($p=0.037$), and for the OC population close to statistical significance ($p=0.051$).
The CHMP acknowledged that the results for the primary efficacy parameters ADAS-cog and ADCS-CGIC were statistically significant in favour of rivastigmine. The secondary efficacy measure of ADL also improved significantly in the active group. However, the magnitude of the improvements for ADAS-cog were modest. In addition, the responder analysis measuring the proportion of clinically relevant responders did not show any difference from placebo at week 24 in the primary analysis population ITT+RDO. In the analysis of efficacy for the primary efficacy population (ITT + RDO),

only 23 patients (4.3 %) returned for efficacy assessment (retrieved dropouts), whereas the total number who discontinued was 131. For those patients who were missing, and no retrieved drop out was available, LOCF was used. The low number of retrieved drop outs in the ITT+RDO analysis entails a risk that the effect of rivastigmine is overestimated and the CHMP requested the MAH to discussed this issue.

The MAH conducted a post-hoc analysis taking into account the differential pattern of discontinuations over time. The analysis performed was the 'placebo results for all', which imputed the ITT+RDO placebo mean score (ADAS-cog total score/ADCS-CGIC) to the patients who were neither completer nor retrieved dropout (RDO) patients (80 Exelon and 28 placebo patients). For the ADAS-cog scale, the mean baseline total score of 24.3 and change at Week 24 of -0.7 were used; and for the ADCS-CGIC, the mode of the placebo result at week 24 (unchanged) was used.

In summary, the analyses in ADAS-cog total score resulted in statistically significant differences in favour of Exelon ($p<0.001$). The 'placebo results for all method' shows a treatment difference of 2.5 versus the difference of 2.8 achieved through the primary analysis method. This analysis also demonstrates consistent findings to ADAS-cog, which is cognitive benefit for Exelon-treated patients with PDD. The analysis of ADCS-CGIC using the 'placebo results for all' method also demonstrated the superiority of Exelon group over placebo group ($p=0.006$), and the result of this analysis was consistent to the primary analysis of the core study.

The CHMP considered that the imputation of placebo results for all missing values might still resulted in an overestimation since patients remaining on placebo are likely to have a better response than patients withdrawn due to intolerance. However, the uncertainty about the potential overestimation does not differ from that in Alzheimer trials.

Health economic parameters
NPI-D caregiver distress ratings were not significantly different between treatment groups; caregiver distress due to aberrant motor behaviour were in favour of Exelon at weeks 16 and 24, and sleep/night-time behaviour was in favour of placebo at week 16.

Overall efficacy conclusions on study ENA713B2311

Patients of either sex aged 50 years or older with idiopathic PD according to UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria and a clinical diagnosis of PDD according to DSM IV criteria with the onset of dementia symptoms occurring at least 2 years after the first diagnosis of idiopathic PD were included.

The average MMSE scores in both treatment groups were comparable at study entry: 19.4 (3 – 30) in the Exelon group and 19.2 (8 – 27) in the placebo group. The inclusion criteria (MMSE score of 10 to 24) was not fulfilled for 6 patients in the rivastigmine group and 3 patients in the placebo group. These patients were assigned as protocol violators; however, they were included in the primary analysis population as was defined prospectively in the statistical analysis plan. When the 9 patients who were protocol violators for out of range MMSE scores were excluded, all three efficacy measures still maintained significant improvement in the Exelon group compared to placebo at week 24.
The distribution of patients with mild and moderate dementia was similar in both treatment groups. A post-hoc analysis of ADAS-cog, ADCS-CGIC and ADCS-ADL in subgroups of patients with mild and moderate PDD, showed favourable results for Exelon as compared to placebo, but they did not achieve statistical significance on some measures. This could be explained due to reduced power as a result of decreased sample size.
Baseline demographic characteristics for age, gender and race were comparable in both treatment groups. The overall demographic characteristics (age and sex) were representative of patients with PD and PDD. Duration of PD, duration of PDD and time interval between diagnosis of PD and initial symptoms of PDD were well balanced between the treatment groups. The distribution of PD severity (as measured by Hoehn and Yahr staging) was similar in the two groups and indicated a moderate to severe stage of PD severity for majority of patients.

Of the 541 patients randomized, 410 (75.8 %) completed the study and were evaluated at week 24.

In the primary efficacy analysis, patients with PDD in the Exelon treatment group achieved an improvement of 2.1 points on the ADAS-Cog at week 24, whereas patients in the placebo group deteriorated by 0.7 points at week 24 (ITT+RDO). The difference was more pronounced in the LOCF (2.5 points in Exelon group and -0.8 points in the placebo group) and OC (2.9 points and -1.0 in the Exelon and placebo groups respectively) analysis populations. The treatment group difference for the change from baseline was statistically significant in favour of Exelon in all three analysis populations, both at week 16 and at week 24 ($p<0.001$). The percentage of patients in whom the ADAS-Cog score improved by at least 4 points did not achieve statistical significance in the primary efficacy analysis population (ITT + RDO) at week 24 ($p=0.074$).
The percentage of patients in whom the ADCS CGI-C rating improved was significantly higher in the Exelon group in all analysis populations at week 24 (ITT+RDO $p=0.007$; LOCF and OC $p<0.001$). The ADCS CGI-C rating improved was also significantly higher in the Exelon group in all analysis populations at week 16. The treatment effect was consistently in favour of Exelon (odds ratios for an improvement on Exelon between 1.6 and 2.1).
When adjusted for duration of PD and severity of Parkinsonian motor symptoms, CGIC scores at week 24 remained significantly in favour of Exelon as compared to placebo. There is no evidence that in patients who have reported 'AEs potentially associated with PD', the assessment of activities of daily living by ADCS-ADL scale has a less favourable outcome of functional assessment.

Secondary efficacy measures of activities of daily living, behaviour, attention and executive functioning showed statistically significant superiority for Exelon over placebo for the ITT+RDO population, the ITT (LOCF) and the OC population.
Mean MMSE scores difference between Exelon and placebo, was statistically significantly in favour of Exelon in all three analysis populations.

The categorical analysis of the percentage of overall responders was significantly in favour of Exelon at week 16 (LOCF, OC) and 24 (LOCF). The magnitude of the treatment effect in both primary efficacy criteria were in the range of magnitude of effect seen in studies for Alzheimer's Disease.

In summary, the two primary efficacy criteria were statistically significant in patients treated by Exelon compared to placebo. The magnitude of the treatment effect in both primary efficacy criteria were in the range of magnitude of effect seen in studies for Alzheimer's Disease.
All secondary efficacy criteria measuring activities of daily living, behaviour, attention, executive functions and quality of life were in favour of Exelon compared to placebo.

Parkinson's Disease motor signs assessed by the UPDRS motor score (the change scores of 0.3 and 0.4 at week 24 for the Exelon and placebo groups, respectively) and Hoehn-Yahr stage, were not aggravated neither in the Exelon nor in the placebo group.

2.2 Study ENA713B2311E1

This was a 24 week, prospective, multi-center, open-label, uncontrolled extension to the double-blind, placebo-controlled core study ENA713B2311. As in the core study, all patients had a 16-week titration period followed by an 8-week maintenance period.

The primary objectives of this 24-week extension study were to evaluate the safety and tolerability of Exelon (3 to 12 mg/day) and to provide access or continued access to Exelon for patients included in study ENA713B2311.
The planned overall duration of treatment was 24 weeks and consisted of a 16-week titration phase (with titration steps at 4 week intervals) and an 8-week maintenance phase.
Patients who have completed the double-blind (DB) core phase continued in the extension phase (OL) without any washout period. Study drug titration to the highest well-tolerated dose was restarted at 1.5 mg bid in all patients at the start of the extension period in order to preserve the blind for the core study.

Secondary objectives were to evaluate the effects of Exelon on cognition including executive function, on activities of daily living, behavioural symptoms and health economic parameters including caregiver distress and caregiver burden.

Criteria for evaluation

Safety
Safety assessments included the recording and monitoring for adverse events and serious adverse events, of vital signs and body weight, and the Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.

Efficacy
Efficacy was evaluated on similar assessment scales to those utilized in the core study.

Statistical methods
As this was an uncontrolled open-label study, no inferential statistics on efficacy were planned.
Descriptive summary statistics were used for all tests. The data include baseline (week 0) information and efficacy results obtained during the core period in those patients who participated in the extension.

Data were presented separately for each of the two pre-treatment groups; for patients exposed to Exelon in the core trial, and for patients exposed to placebo in the core trial, as well as for the combined pre-treatment groups.
Of the 433 patients who were eligible for the open-label extension, 334 consented to participate, in the extension phase (75% from the Exelon group vs 82% from the placebo group).

Demographic characteristics of patients who continued in the open-label extension phase were similar to those in the double-blind core phase with similar age distribution and male dominance.

The average time between diagnosis of PD and the first symptoms of dementia was 6.7 years. The majority of patients were at Hoehn and Yahr stages 2 to 3, with a similar distribution across both treatment groups in terms of severity of the disease.

Efficacy Results study ENA713B2311E1

One population was defined for analysis purposes, the Observed Cases (OC) population which included all patients who received at least one dose of open-label study drug and had at least one efficacy assessment on treatment during the open-label phase. At week 48, the mean ADAS-Cog score had improved by 2.0 points from baseline in the OC population. The evaluation by treatment phase and pre-treatment group showed that the improvement seen during Exelon exposure in placebo - pre-treated patients was comparable to that seen during exposure to Exelon in the double -blind phase (mean of +2.3, vs. +3.3).
At the end of the open-label phase, ADAS-Cog score, as compared to baseline, had improved by at least 4 points across both groups in 41% of patients.

An improvement of 0.4 points in ADCS-ADL scores 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 during the open-label extension. Patients in the DB-Placebo/OL-Exelon group, who received Exelon for 24 weeks in the open label phase also showed improvement in total ADCS-ADL scores, but remained below baseline level at week 48.

Patients had behavioural improvement on NPI-10 total composite score (2.4 points above their baseline level at week 0). Both groups remain above baseline at week 48 even if in the OL phase, DB-Exelon/OL-Exelon patients had slight deterioration from week 24.

Verbal fluency test also improved at week 48 in all patients. DB-placebo patients had some benefit in the OL-phase after receiving Exelon.

The mean MMSE score had increased by 1.4 points. Both group were above baseline (week 0) at week 48.
All this results should be considered as supportive taking into account the open nature of this study phase.

2.3 Study ENA713B2314

Study 2314 recruited patients diagnosed with 3 types of dementia, with the purpose of validating various assessment scales for their ability to differentiate between mild and moderate severity of PDD and Vascular Dementia (VaD). The study did not add any efficacy data in PDD. The scales evaluated were commonly used efficacy assessments in AD studies, and were used in the key study 2311. The presence of the AD arm in this validation study was to support the validity and reliability of the scales in PDD and VaD patients. For the indication sought in this submission (PDD), only the data for PDD and AD patients were required for assessment of validity and reliability, therefore an interim analysis of the data was performed, excluding the VaD patients.

This study was performed in accordance with the EMEA Scientific Advice of April, 28th 2003.

Objectives

Primary:
To assess the criterion-related validity through determination of the ability of the ADAS-Cog to differentiate between mild and moderate severity of PDD.
To assess the test-retest reliability of ADAS-cog in patients with PDD.

Secondary:
To assess the criterion-related validity through determination of the ability of other dementia rating scales/tests to differentiate between mild and moderate severity of PDD.

To assess the test-retest reliability of other dementia rating scales/tests.
To assess the convergent and divergent construct validity of ADAS-cog in patients with PDD.
To compare scores on dementia rating scales/tests in patients with AD with those in PDD.

These assessment scales include the Vascular Dementia Assessment Scale (VaDAS), Alzheimer Disease Assessment Scale, cognitive subscale (ADAS-cog), Neuropsychiatric Inventory (NPI) including the Distress subscale (NPI-D), Alzheimer Disease Cooperative Study Activities of Daily Living scale (ADCS-ADL), Delis-Kaplan Executive Function System (D-KEFS) verbal fluency test, Trail Making Test Part A (TMT-A), Ten Point Clock Test (TPCT) and Cognitive Drug Research (CDR) computerized assessment system for attention.

List of Scales/Tests to be validated by domain type

Domain	**Scales**
Cognition	ADAS -Cog (for PDD patients only)
Executive Function	Ten-point Clock Test (TPCT) Delis-Kaplan Executive Function System (D-KEFS) verbal fluency (letter fluency condition only)
Attention	Cognitive Drug Research (CDR) Computerized Assessment System tests for attention Trail Making Test Part A (TMT-A)
Behaviour	Neuropsychiatric Inventory (NPI), including NPI-D
Activities of Daily Living	Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL)

Methodology

It was planned to enrol approximately 150 patients; 50 patients with AD, 50 patients with VaD and 50 patients with PDD. The population used for the interim analysis are only the patients with AD and PDD. No patients with VaD were included in the analysis.

Patients were rated on a number of dementia rating scales at baseline, and 4 weeks later. The scales were assessed for their validity by comparing their ability to differentiate between mild and moderate severity stages of dementia in patients with AD and PDD, and for reliability by using test-retest procedures to compare the baseline and 4-week results for reproducibility.

Main criteria for inclusion

The study population were male or female patients aged 50 to 85, with a clinical diagnosis of PDD or AD according to DSM IV criteria, and with a severity of between 10 – 24 inclusive on MMSE at baseline. Patients were further divided into Mild (MMSE 18-24) or Moderate (MMSE 10 -17) severity groups.
Patients were on stable doses of existing therapy for at least 6 weeks prior to baseline and not expected to change doses/medications during the study (i.e. approximately 4 weeks after baseline).

Duration of treatment

No treatment was applied. After an initial 6-week screening period, a baseline visit was performed at least one week after the screening visit. A further single visit was performed 4 weeks after the baseline visit.

Statistical methods

Criterion-related validity was assessed on the basis of 'disease severity' as the external criterion. The patients were stratified by the MMSE into groups of mild or moderate severity and the performance of the two severity groups on the scales were compared by t-test.

Construct validity was demonstrated by evaluating the relative strengths of the correlations between the scales assessing similar symptom domains such as ADAS -cog and MMSE and the correlations between scales assessing different symptom domains, such as ADAS -cog and the NPI.

Test-retest reliability was assessed by comparing baseline scores with the scores on the same scales after a period of 4 weeks. Spearman correlation coefficient was calculated for both construct validity and reliability.

Results study ENA713B2314

The criterion-related validity was evaluated by the ability of the ADAS-Cog to differentiate between mild and moderate severity of PDD by performing a t-test on the ADAS-cog values achieved with mild vs. moderate patients within each dementia type. In both PDD and AD patients, mean ADAS-Cog at baseline showed a distinct separation between mild and moderate patients. In each dementia type and severity the variance associated with the mean was similar. The difference between mild and moderate was statistically significant for each dementia type.
The test-retest reliability of ADAS-cog was explored by obtaining a correlation coefficient between a patients ADAS-cog value at baseline and at 4 weeks. Mean values were similar between baseline and the assessment at week 4, and correlation coefficients were strongly positive for all dementia type/severity combinations.
The ability of other dementia rating scales to differentiate between mild and moderate severity of PDD and AD was explored by comparing the mean values obtained with each scale for mild vs. moderate patients with a t-test. In both PDD and AD patients, there was a statistically significant separation between mild and moderate patients for ADCS-ADL, TPCT, TMT-A, and D-KEFS. For the behavioural scales NPI 10 and NPI 12, and the associated scales for caregiver distress NPI-D-10 and NPI-D-12, the differences between severity strata were smaller and not statistically significant. The NPI scales were also inconsistent between the dementia types.
The test-retest reliability analysis showed moderate to high correlations in ADAS-cog, ADCS-ADL, and NPI-10 scores in both PDD and AD patients. The other scales were generally positively correlated, though several had less consistent results in the moderate severity patients in both populations.
These results showed that ADAS-Cog might be used for analysis of cognitive impairment in patients with PDD. The scale attributed statistically significantly different mean values to patients with mild severity disease compared to moderate severity disease patients.
The secondary outcomes selected to assess the other domains of the patients' dementia syndrome that may not have been adequately addressed by the ADAS-cog were: Cognitive Drug Research (CDR) attention battery for attention, Delis-Kaplan Executive Function System (D-KEFS), Verbal Fluency test for executive function, Ten-point clock test (TPCT) for executive and visuo-spatial function, Neuropsychiatric Inventory (NPI) for behavioural assessment. These outcomes showed statistically significant differences between Exelon treated patients as compared to placebo treated patients.

2.4 Dementia in Parkinson's disease population

The CHMP acknowledged that dementia in Parkinson's disease is a very complex topic and the MAH was questioned if the effect of rivastigmine on dementia in Parkinson's disease was dependent on the kind of cognitive impairment present. The MAH confirmed that the patient population included in the core study had mild to moderately severe dementia associated with Parkinson's disease (PDD), and the results in these patients may be generalised to this population in routine clinical practice.

PDD is aetiologically an homogenous dementia syndrome that develops in patients with a diagnosis of idiopathic Parkinson's disease (PD) as a result of the progression of the Lewy body pathology that characterises this disease. Converging evidence from recent studies indicates that, if concomitant Alzheimer pathology is present, it is generally no higher than in age-matched non-demented controls, insufficient to account for the dementia syndrome, and it is not considered to be the underlying cause of the dementia syndrome.

The MAH presented a review showing that risk factors, genetic, neuropathological, neuroimaging, neuropsychological, and non-neuropsychological evidence for PDD dementia differ from AD.

Risk Factors for Parkinson's Disease Dementia (PDD)

Several risk factors for dementia in patients with PD have been identified. The most significant risk factors are age, duration of PD, age at onset, akinetic-rigid form of the disease and the severity of motor symptoms. 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 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 or of dementia of the Alzheimer can be made. 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.

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

Neuropathologic Distinctions between 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

Neuroimaging

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.

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

Non-Cognitive Clinical Distinctions between 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 behaviour disorder	Common	Absent

Diagnostic 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

3 CLINICAL SAFETY

The main results for safety derive from the single pivotal core study with supportive data from the extension study. The key safety population consists of the 362 Exelon-treated and 179 placebo-treated patients examined in the core study. In addition, there were 334 patients in the extension study who were treated with Exelon.

Adverse events

In the core study, the overall incidence rate of AEs was higher with Exelon than with placebo. The most frequently affected system organ classes were the same as seen with Exelon in AD (gastrointestinal disorders, metabolism and nutrition disorders, and nervous system disorders).

Nausea and vomiting were the most common AEs, with incidence rates of 29% for nausea, and 16.6 % for vomiting. Tremor, diarrhoea, anorexia and dizziness were also more frequent with Exelon than placebo.

In the extension study, the overall incidence rate of AEs was the same in both groups of patients that were based on core study treatment assignments (i.e., core study Exelon patients re-treated with Exelon "Exe-Exelon" or placebo patients newly treated with Exelon "Plc-Exelon"). The frequency of nausea and tremor decreased in the Exe-Exelon group, but vomiting remained at the same level in the Exe-Exelon group as in the core study.
The higher incidence of tremor is not unexpected in the Exelon group.

Cardiac disorders

When all AEs that could be related to cardiac rhythm and conduction abnormalities in the core study are combined, the total incidence rate for the Exelon group was slightly higher at 3.3% compared to the placebo group at 2.2%. Moreover, 3 patients on Exelon (0.8%) developed acute cardiac syndromes (2 cases of myocardial infarction and one case of sudden death) compared to 2 patients (1.1%) on placebo (one case of acute coronary syndrome and one case of cardiac arrest).

In the core study, there were 3 (0.8%) premature study discontinuations for cardiac system AEs in the Exelon group compared to 2 (1.1%) in the placebo group. In the extension study, 5 (1.5%) patients discontinued due to cardiac system AEs.

Based on these findings, treatment with Exelon in patients with PDD did not seem to be associated with any new cardiovascular safety findings that indicated an additional risk other than the already known profile as described in Exelon product information.

Serious adverse events and deaths

The overall summary of SAEs, discontinuations, and deaths is the following:

*During the core study, the incidence rate of SAEs and the rate of discontinuations due to SAEs were less frequent in the Exelon group than placebo.

*AE discontinuations were found to be more frequent in the Exelon group due to the discontinuations for nausea, vomiting and tremor, which are known AEs associated with Exelon.

*The occurrence of SAEs and of AE discontinuations were as predicted, with higher rates of these events early in the study, during titration, and lower rates once maintenance doses had been achieved.

*Deaths were less frequent with Exelon than placebo and they reflected problems generally expected in the elderly population. There was no apparent relationship between the occurrence of death and the dose of study drug or the duration of therapy. None of the deaths reported were found to be related to the study medication.

*Importantly, in a disorder where parasympathetic and sympathetic drives may be altered, Exelon was not associated with any significantly increased incidence rate of cardiac or vascular SAEs and had a lower mortality rate compared to the placebo group.

Adverse events leading to treatment discontinuation

In the core study, a total of 27.3 % discontinued in the rivastigmine group compared with 17.9 % in the placebo group. The main reason for discontinuation in the rivastigmine group was adverse events (17.1 %). In the placebo group, 7.8 % discontinued due to adverse events. Adverse events that contributed to premature withdrawal from the study included nausea (3.6 % of patients in the rivastigmine group and 0.6 % in the placebo group, p=0.04), vomiting (in 1.9 % and 0.6 % respectively, ns), and tremor (in 1.7 % and 0 %, respectively, ns).
In the extension study, the frequency of patients discontinuing for safety/tolerability reasons was slightly higher in newly-treated Exelon patients.
The discontinuation rates due to adverse events potentially associated with PD in the core study was 4.7 % in the rivastigmine group relative to 1 .1 % in the placebo group.

Psychiatric disorders, including delusions and hallucinations

The MAH submitted a comprehensive safety review on psychiatric disorders and the findings did not indicate that Exelon treatment was associated with an increased incidence, severity, or discontinuation from overall or individual psychiatric AEs.

Severe constipation / abdominal obstructions

The MAH submitted a comprehensive safety review on severe constipation and abdominal obstructions and the findings do not indicate that the incidence rate of AEs of constipation, intestinal obstruction or fecaloma were higher than the expected rates in elderly PD patients.

Nausea / vomiting

Nausea and vomiting were the most common AEs, with incidence rates of 29% for nausea, and 16.6 % for vomiting. The supplementary data provided by the MAH indicate that the incidence rates for gastrointestinal side effects are highest during the dose-titration period and decrease with long-term treatment. These side effects are, however, common during a relatively long period because the dose titration is slow. It is not until week 16, i.e after 4 months of therapy, that the incidence rates show a more marked decrease.
Since nausea and vomiting are the main side effects of Exelon and Parkinson medication the MAH was asked to clarify if these enhance each other, making their combination less favourable for this specific patient group.
The MAH compared the incidence rates of AEs of nausea and vomiting in the placebo groups of studies in AD and PDD and similar frequencies were reported indicating that concomitant dopaminergic treatment in the PDD patients enrolled to the 2311 study did not appear to increase incidence rates of these events. This may be due to the chronic nature of most treatment with dopaminergic agents in the PDD patient population and the likely desensitization of their dopaminergic receptors. In addition, frequent concomitant use of antiemetics and antipsychotic medications could decrease the incidence rate of nausea and vomiting in this population.
Thus, there is no evidence that the incidence rates of AEs of nausea and vomiting, or discontinuations for these events, were more common in the patient population that was also receiving dopaminergic medication.

Laboratory findings

In the core study, the incidence of newly occurring laboratory abnormalities (clinical chemistry or hematology) was low, comparable for both treatments and were not regarded as clinically significant. There were no significant findings with urinalysis. There were a few cases of abnormally elevated prolactin, but the incidence was similar in both groups and mean values at 24 weeks were comparable.

However, there were changes in the special laboratory tests of amylase and lipase, examined as a part of safety evaluations, which revealed a mean increase from baseline greater with Exelon than with placebo. With Exelon, patients with normal baseline values of serum amylase (approximately 17%) or serum lipase (9%) showed elevated values atweek 24, with no indication of pancreatitis. Associated AEs included epigastric pain/discomfort and most frequently nausea, vomiting and anorexia. These events did not lead to discontinuation and patients generally completed the study and entered the extension. The cause for the increases in amylase and lipase is unclear and the MAH was requested to clarify this issue.

The MAH clarified that the pancreas is richly innervated by the autonomic nervous system. The stimulation of cholinergic system through the vagus nerve is involved in the cephalic phase of regulation of pancreatic secretions. There are multiple studies that show that cholinergic stimulation increases the serum level of pancreatic enzymes.
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 clinical significance. 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 scientific literature indicates that cholinergic stimulus may enhance secretion of pancreatic enzymes.
In summary, there is a possibility that amylase and lipase levels can be modestly elevated by cholinergic stimulation in some patients with PD. However, this study does not provide conclusive evidence that Exelon is the cause of these increases.

Cerebrovascular accidents

In the literature, there is no strong evidence of increased risk of cerebrovascular accidents with cholinergic treatment. The risk of cerebrovascular events is increased by age and vascular risk factors, such as hypertension.
Of 6 patients that experienced cerebrovascular AEs during the core study, 2 patients in the Exelon group and 3 of the 4 patients in the placebo group had either a previous cerebrovascular event or a cardiovascular risk factor. Of 8 patients that experienced cerebrovascular AEs during the extension study, 6 patients had either a previous cerebrovascular event or a cardiovascular risk factor.
These findings do not indicate that the incidence rate of cerebrovascular AEs is increased by Exelon treatment.

Adverse events reflecting worsening of Parkinson's disease, motor function scores, and use of medication for Parkinson's disease

In order to find out if treatment with Exelon could result in a worsening of PD symptoms, 3 sources of data were reviewed:

- Pre-defined AEs that could indicate a worsening of PD symptoms
- The motor score, collected from the UPDRS part III scale
- The usage of anti-parkinsonian medication

Adverse events associated with signs and symptoms of PD

Parkinsonian symptoms were reported as adverse events more frequently in the rivastigmine group than in the placebo group (27.3 % vs. 15.6 %, p=0.002). This was mainly due to a higher rate of tremor (3.9 % for placebo vs 10.2 % for Exelon, p=0.01). Other predefined adverse events with a trend to be more common in the Exelon group were bradykinesia, dyskinesia, worsening of parkinsonian symptoms, salivary hypersecretion, gait abnormality and musculoskeletal stiffness.

Thus, although tremor appears to be the main symptom of PD that is exacerbated by Exelon several other Parkinson-related symptoms were reported. Adverse events for tremor were mild to moderate in severity with one report of a severe case. Tremor led to discontinuation in 1.7% of Exelon-treated patients in the double-blind phase versus none in the placebo group.

Change in parkinsonian motor symptoms (UPDRS part III score)

Parkinsonian motor symptoms were evaluated (UPDRS part III subscale) at baseline, week 16 and/or at study endpoint, to detect any changes in motor symptoms caused by the use of Exelon in patients with PDD. The population from the main study and its extension study showed no significant change in any individual UPDRS sub items after treatment with Exelon, and no change in the total score.

The CHMP requested clarifications on the fact that risk of worsening of PD symptoms is well-known with rivastigmine, but the motor scores did not reveal any worsening of PD symptoms.

The majority of 'AEs potentially associated with PD' emerged and resolved before week 16, during the titration phase. Therefore, these events would not be recorded at the UPDRS part III assessment at week 16.

Use of anti-parkinsonian medication

Changes in the use of dopaminergic medications were examined to detect any worsening of PD symptoms.

In the core study, patients were required to keep their current dopaminergic treatment at constant doses through out the study and any dose increases resulted in protocol violations. At baseline, 100% of patients in the Exelon group and 99.4% of patients in the placebo group were on dopaminergic agents. During the core study, 5.5% of patients in the Exelon group and 4.5% of patients in the placebo group increased their dopaminergic agents. Also, 10.5% of patients in the Exelon group and 9.5% of patients in the placebo group started new dopaminergic agents during the study.

In summary, the most frequently affected system organ classes were gastrointestinal disorders, metabolism and nutrition disorders, and nervous system disorders. In the extension study (Exe-Exelon), there was a decrease in the incidence of nausea but vomiting remained at a frequency of 18 %. Parkinsonian symptoms were reported as adverse events significantly more frequent in the rivastigmine group than in the placebo group (27.3 % vs. 15.6 %, p=0.002). This was mainly due to a higher rate of tremor (3.9 % for placebo vs 10.2 % for Exelon, p=0.01) but there was a trend for an increase also of other Parkinson-related symptoms. The difference with regard to the incidence of parkinsononian symptoms was not reflected in significant difference in UPDRS scores between the two groups. Concomitant use of dopaminergic drugs that were newly introduced or increased in dose was slightly more common in the rivastigmine group during the double-blind core study, however, the MAH pointed out that the mean doses of dopaminergic medications in Exelon-treated patients during the core study and with long-term treatment were stable. The MAH was requested to provide supplementary information with regard to the frequency of tremor and other Parkinson-related symptoms over time.

The supplementary data provided by the MAH indicate that the incidence rates for adverse events associated with PD are highest during the dose-titration period and decrease with long-term treatment. However, because the dose titration is slow, adverse events associated with PD remain common during a relatively long time period. It is not until week 16, i.e after 4 months of therapy, that the incidence rates decrease.

Published safety information

Safety information from three open investigator-initiated studies of rivastigmine treatment in PDD is summarized below. In addition, there is a published case report with reversible worsening of motor function, mood and anxiety after ingestion of one 3-mg dose of oral rivastigmine.

Giladi et al (Acta Neurol Scand 108:368-373, 2003)
In the study by Giladi et al, 28 patients with PD and dementia were treated openly for 26 weeks with rivastigmine 1.5 -6 mg b.i.d. (mean daily dose 7.2 ± 3.3 mg/day). The most frequent adverse events were increased salivation (in 46 % of patients) and tremor (in 39 % of patients). Eleven patients had to decrease the rivastigmine daily dose due to side effects. Eight patients discontinued because of different reasons: three because of motor worsening, one developed a confusional state and one withdrew because of palpitations. One patient fell at week 25, had a minor brain concussion and developed acute psychosis, and rivastigmine was discontinued. One patient who had no history of heart disease was found dead in her bed after going to sleep with no special complaints while being on rivastigmine for 25 weeks. An autopsy was refused. Another patient with a long history of ischemic heart disease had an acute myocardial infarction at week 25.

Reading et al (Mov. Disorders 16, 1171-1195, 2001)
The study included 15 patients diagnosed with idiopathic PD. The key entry criterion for the study at screening was the presence of troublesome hallucinations for at least the previous 3 months. Rivastigmine was titrated from 1.5 mg twice daily with increases at 2-week intervals until either 6 mg twice daily of the highest tolerated dose was achieved. Rivastigmine was generally well tolerated although significant nausea was a dose-limiting side effect in most patients. Tremor was not reported

to worse, and the UPDRS scale (motor subscale) was unchanged. Three patients withdrew from the study. One died from septicemia thought not related to trial medication, one experienced side effects of severe nausea, and the third patients caregiver became unable to participate in the study due to ill health.

Bullock and Cameron (Curr. Med. Res. Opin. 18. 258-64, 2002)
Five patients with PD and dementia and/or hallucinations were treated with rivastigmine. Rivastigmine was generally well tolerated, although one patient had to reduce the dose due to the occurrence of dizziness, nausea, vomiting and abdominal pain.

Hegeman Richard et al., Clinical Neuropharmacology 25, 296-299 (2002)
A case report of a 71-year old woman with PD and cognitive impairment who developed a marked worsening of motor function, mood and anxiety after ingestion of one 3-mg dose of oral rivastigmine. The worsening was reversible. The patient had no previous exposure to acetylcholine inhibitors. The authors believe that the mechanism of the motor and perhaps psychiatric worsening was increased central cholinergic tone.

User consultation

The MAH did not conduct an assessment of the patient leaflet in cooperation with the target patient group for the following reasons:

1. The product has been on the market for more than 7 years. No difficulties have been encountered by patients and caregivers with respect to clarity and ease of use of the patient leaflet.

2. With this variation a new patient population is concerned, which however is very similar in terms of age (elderly), disease (neurodegenerative disorder) and treatment process (caregivers, same posology and method of administration with same pharmaceutical forms/strengths).

3. The package leaflet has only been changed by adding the proposed new indication. This has even been done by keeping the same language as with the current approved label namely "Symptomatic treatment of mild to moderately severe dementia in patients with Parkinson's disease".

4 BENEFIT-RISK ASSESSMENT

The scope of this variation is to extend the approved indication for rivastigmine currently indicated in the European Union for the symptomatic treatment of patients with mild to moderately severe Alzheimer's disease (AD) to include the treatment of symptomatic treatment of mild to moderately severe dementia associated with Parkinson's disease.

Following the evaluation of the dossier and the responses submitted by the MAH in the request for Supplementary Information, the MAH was asked to present in an oral explanation the risk/benefit of rivastigmine in the treatment of dementia in Parkinson's disease.

Further to the oral explanation, the CHMP still considered the risk/benefit of rivastigmine in the treatment of dementia in Parkinson's disease to be negative and therefore concluded on 13 October 2005 that the variation should be refused. The MAH requested a re-examination of the opinon and on 1 December 2005 provided the detailed grounds for this request. The MAH disagreed with the grounds for refusal of the variation and presented its arguments.

In order to assist the CHMP with this review, an expert meeting composed of experts in the fields of dementia in Parkinson disease and statistics took place.

During the re-examination the following issues were reassessed:

Issue 1: CHMP considered that the treatment with Exelon resulted in modestly statistically significant improvements in cognition, global ratings of dementia, ADL and behavioural symptoms. However, a responder analysis of the proportion of clinically relevant responders failed to show any statistically significant difference from placebo

The MAH claimed that the CHMP 'Note For Guidance On Medicinal Products In The Treatment Of Alzheimer's Disease' (CPMP/EWP/533/95 corrected) was followed for the design of study ENA713B2311. The study was designed to show significant differences in two protocol stipulated primary variables which evaluated cognition (Alzheimer's Disease Assessment Scale; ADAS-cog) and the overall dementia improvement which reflects the clinical relevance of improvement in combination of individual symptom domains (Alzheimer's Disease Cooperative Study Clinical Global Improvement of Change; ADCS-CGIC). The results of the study not only showed significance in these two domains, but also in functional activity (Alzheimer's Disease Cooperative Study Activities of Daily Living; ADCS-ADL) and in other symptom domains related to deficits that are known to be profoundly affected in dementia associated with PD (PDD), including executive functioning, attention and behaviour.

With regards to the failure to show statistical significance relative to placebo at Week 24 in the responder analysis, section 5 of the "CHMP Points to Consider document on multiplicity issues in clinical trials"(CPMP/EWP/908/99) clearly states that where responder analyses are being used to establish clinical significance following demonstration of statistical significance on the primary 'raw' endpoints, the level of statistical significance is best judged from the primary analysis i.e. the results of the responder analysis do not need to be statistical significant, and, the presence or absence of statistical significance between responder rates does not address whether the differences in responder rates are clinically important.

Some CHMP members highlighted that a considerable number of the patients would be treated without any benefit from the drug. But the majority concluded that even if the magnitude of the effect was modest, this effect is shown highly consistent in all three domains (cognitive, functional and global) and it was accepted that the modest mean effect size in PDD reflected an important effect in a fraction of patients.

In addition, it was acknowledged that the effect size in this population is in the range of the one seen in AD. The MAH agreed to recommend in the product information an early review of efficacy with discontinuation if ineffective. Therefore the CHMP concluded that although the effects are modest they are considered as clinically meaningful.

Issue 2: safety concerns in relation to the frequent occurrence of gastrointestinal side effects

Nausea and vomiting have been attributed to the central cholinergic-mediated release of dopamine in addition to the central effects of elevated acetylcholine (ACh). Vomiting is a complex process involving multiple neurotransmitters and organ systems, all coordinated by the central nervous system. Multiple neurotransmitters are involved in the emesis pathway, but dopamine, serotonin, histamine, and substance P are believed to play the largest roles. The stages of emesis are co-ordinated by the vomiting center (an area of the brainstem consisting of the area postrema, also known as the chemoreceptor trigger zone; the nucleus tractus solitarius; and the dorsal vagal complex. Coordination of these systems results in the activation of somatic and visceral impulses to effector organs such as the abdominal muscles, stomach, esophagus, and diaphragm, resulting in emesis.

The rapidity and maximal increases in brain levels of ACh and brain compensating mechanisms that increase dopamine may be responsible for acute adverse events of nausea and vomiting. Peripheral dopamine blockade and peripheral anticholinergics do not appreciably influence the incidence of these events. However, centrally acting dopamine blocking anti-emetics and concomitant antipsychotics appear to be effective at relieving cholinesterase inhibitor (ChEI) induced nausea and vomiting Evidence from animal models supports these. Vomiting in dogs following ChEI administration was

prevented by either centrally acting dopamine antagonists or muscarinic antagonists. Thus, acutely elevated brain ACh levels accompanying the initiation of ChEI therapy may induce elevations of brain dopamine levels and centrally mediated AEs attributable to these elevated brain levels of ACh and dopamine. Nausea and vomiting are transient in most patients treated with ChEIs indicating adjustment over time in the sensitivity of this mechanism. This mechanism is also blocked by concomitant dopamine receptor blockade and, perhaps also by chronic desensitization of dopamine receptors by chronic levodopa administration, explaining the lower incidence and severity of nausea and vomiting in the current Exelon study in PDD relative to similarly designed studies in AD.

The MAH argued that for patients who had received Exelon treatment during the core study, the incidence of nausea and vomiting decreased by approximately 50% during the extension study. The majority of adverse events (AEs) of nausea and vomiting reported for core-study Exelon patients occurred during the 16 week titration period, were single episodes of mild to moderate severity, were of 1 to 14 days duration, and only rarely resulted in discontinuation from the study.

The MAH highlighted that the incidence rates of AEs of nausea and vomiting, known cholinergic side effects, are consistent with the established safety profile of Exelon. Discontinuations due to these events were lower in patients with PDD than in patients with AD in placebo controlled pivotal studies. In patients with AD or PDD, the majority of these events occurred during the dose titration period and were of mild or moderate severity.

The MAH concluded that AEs of nausea and vomiting associated with Exelon treatment present no greater risk to patients with PDD than to those with AD.

The CHMP acknowledge that gastrointestinal AEs are known cholinergic effects with Exelon treatment. These events have been clearly described in the Summary of Product Characteristics (SPC Sections 4.4 and 4.8) and guidance on their management such as, slower titration, dose adjustments, discontinuations or administration with food, is provided when events are experienced (SPC Section 4.2).

Therefore the CHMP concluded that with the guidance introduced in the product information these AEs could be manageable and can be controlled by reduction or interruption of the treatment.

<u>Issue 3:</u> Safety concerns in relation to the risk for worsening of PD symptoms

According to the 'Acetylcholine/dopamine balance hypothesis of striatal function', ACh and dopamine exert opposing effects on striatal circuitry, and inhibition of ACh breakdown by ChEIs should exacerbate PD symptoms, such as tremor. However, several lines of reasoning and data from clinical studies suggest that ChEI therapy has little effect on motor function in most PD patients.Cholinergic and dopaminergic systems normally influence each other and modulate brain function in complex feed-forward and feedback loops. Cholinergic nuclei Ch5-6 (including pedunculopontine and dorsolateral tegmental nuclei) modulate basal ganglia and cerebellum, and nuclei Ch1-4 (including nucleus basalis of Meynert) modulate the cortex. Thus, the cholinergic system is normally involved in modulating different levels of motor function including simple movements, planning, timing, and coordination. Different motor symptoms in PD are thought to have different regional pathophysiologies. Together these observations suggest that the involvement of ACh in producing a particular motor symptom is dependent upon the local regional mix of ACh and dopamine dysfunction. Therefore, depending on the particular motor symptoms, ChEI therapy may have no effect, a positive effect, or a negative effect in different subgroups of PD patients. Furthermore, an immediate and often transient impact on motor symptoms, suggested by specific dose-titration related AEs, should be differentiated from any impact on the progression of the underlying PD-associated movement disorder, which should be demonstrated on the motor symptom and functional assessments and/or an altered pattern of concomitant dopaminergic drug use.

The MAH claimed that Exelon did not generally induce clinically significant exacerbation of movement disorder in patients with PDD. Nevertheless, AE reports of worsening of parkinsonian symptoms, mainly tremor, were more frequently reported in Exelon-treated patients than in placebo-treated patients. The peak incidence of these reports was between weeks 8 and 12, during Exelon-dose titration. These reports were not reflected in changes in overall or individual sub-items of UPDRS part III motor scale assessments at week 16 and at study termination, compared to baseline or placebo

indicating that the events were not prolonged or severe enough to result in a change on the scale. Tremor and other events related or potentially related to an exacerbation of PD in the double-blind and extension studies 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.

The CHMP had highlighted that there were slightly more patients in the Exelon group who started new dopaminergic agents or increased their dose during the core study. However, the MAH pointed out that the mean doses of dopaminergic medications in Exelon-treated patients during the core study and with long-term treatment were stable. Similar improvements in the symptoms of dementia were seen regardless of whether events related or possibly related to an exacerbation of PD were reported during the study, including assessments of the ability to perform activities of daily living.

The incidence of the AE of tremor appeared to be the main driver behind the higher incidence of "AEs potentially associated with PD" in Exelon-treated patients (10.2% out of 27.3%). Premature study discontinuations due to an AE of tremor were low (1.7%). Relative to patients receiving placebo in the overall study, Exelon-treated patients who reported the AE of tremor showed comparable changes in total UPDRS part III scores and improvements in the ability to perform activities of daily living assessed on the ADCS-ADL scale at the core study endpoint (week 24). A small increase in the AE of tremor was also seen in patients with mild to moderately severe AD receiving Exelon (4% versus <1% in those receiving placebo). These data are consistent with the view that, unlike other extrapyramidal symptoms, AEs of tremor may not be an indication of disease progression, but due rather to symptomatic response of enhanced cholinergic neurotransmission.

The MAH provided analysis of subgroups that may be more vulnerable to worsening of PD and these showed no increased risk of worsening with treatment of Exelon. However, increased incidence of AEs of worsening of parkinsonian symptoms and bradykinesia was observed in patients receiving concomitant antipsychotics, which may be related to the side effect profile of the antipsychotic and/or the combination of therapies. It should be noted that there was no increased incidence of tremor in patients receiving concomitant antipsychotics.

The MAH concluded that these findings did 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 stated in the SPC.

Following the expert meeting the CHMP acknowledged that PD motor symptoms are easily identifiable by clinical examination and clinicians would be able to deal with this problem since there are some good options to treat Parkinsonian tremor. In view of the post-hoc analyses performed by the MAH the CHMP concluded that no clinical relevant increase in dopaminergic treatment took place in these patients.

The CHMP discussed and concluded that physicians experienced in the diagnosis and treatment of dementia associated with Parkinson's disease would be able to differentiate these adverse event from the underlying progression rate of PD and these symptoms could be controlled in the worst cases by down-titration or interruption of the treatment which has been addressed in the SPC.

<u>Issue 4:</u> the benefit/risk assessment

The MAH claimed that the superior efficacy of Exelon treatment relative to placebo on both primary outcome measures (ADAS-cog and ADCS-CGIC) at study endpoint was robust. Statistically significant improvements were also demonstrated in Exelon-treated patients on all key secondary efficacy outcome measures assessing executive functioning, attention, behaviour and functioning.

Gastrointestinal AEs occurred mostly during Exelon dose titration, the majority were single events, 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 in the double-blind and extension studies were usually single episodes of mild or moderate severity, decreased in frequency after completion of the dose-titration periods of the core and extension studies, and resulted in few discontinuations.

Exposure to long-term treatment with Exelon (i.e. 48 weeks) was not associated with worsening of PD relative to patients who had received Exelon for a shorter period of time (i.e. 24 weeks), even in patients potentially more vulnerable to worsening of PD.

The MAH performed analysis of subgroups that may be more vulnerable to worsening of PD and these showed no increased risk of worsening with treatment of Exelon. However, an increased incidence of AEs of worsening of parkinsonian symptoms and bradykinesia was observed in patients receiving concomitant antipsychotics, which may be related to the side effect profile of the antipsychotic and/or the combination of therapies.

The MAH argued that there were less 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.

The MAH concluded that 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. In fact, data suggest that Exelon may have a favourable impact on the progression of underlying PD, particularly in patients who are progressing more rapidly, such as those with more advanced PDD.

The results of Number needed to treat (NNT) versus number needed to harm (NNH) analyses showed that the benefits of treatment with Exelon on cognition, overall dementia or functionality, outweigh potential risks associated with of PD or GI related side effects.

There is currently no approved treatment for patients with PD who suffer from dementia.

Following the evaluation of the grounds for the re-examination submitted by the MAH and the outcome of the expert meeting, the CHMP considered that the previous concerns raised by the CHMP had been addressed sufficiently by the MAH through the new changes introduced in the product information. In addition the MAH committed to conduct further analysis to identify prognostic factors for patients that would benefit most from the medicinal product and to perform a long-term safety study with particular focus on PD symptoms and the potential greater clinical benefit in the subpopulations identified by the data mining.

Therefore, the CHMP concluded that Exelon's benefits outweigh the potential risks in the proposed indication "Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease" due to the following reasons:

- The studies submitted to support the new indication showed modest efficacy in PDD, however this reflects an important benefit in a fraction of patients
- Exelon will be initiated and supervised by physicians with experience in PDD. Exelon will only be started if a caregiver is available to monitor drug intake by the patient
- The product information has been amended to recommend an early review of efficacy with discontinuation if ineffective
- The product information recommends appropriate measures for the management of gastro-intestinal and parkinsonian symptoms
- The MAH committed change the PSUR cycle and closely monitor nausea, vomiting, tremor and other adverse events associated with worsening of parkinsonian symptoms and to report these events to CHMP (every six months after the CD for a period of two years, then yearly for two years and then every three years thereafter)
- The MAH committed to conduct further analysis to identify prognostic factors for patients that would benefit most from rivastigmine
- The MAH committed to perform a long-term safety study with particular focus on PD symptoms and the potential greater clinical benefit in the subpopulations identified by the data mining

Pharmacovigilance measures

The CHMP having considered the data submitted in the variation application agreed on the following activities minimize potential risks associated with Exelon in the treatment of patients with PDD:

- **Changes to the Summary of Product Characteristics**

The changes to the SPC and PL are highlighted in the product information attached in Annex 10. The MAH introduced more detailed recommendations in the method of administration and special warnings and precautions for use in the SPC, which are described bellow:

4.2 Posology and method of administration

Dose titration: The starting dose is 1.5 mg twice a day. If this dose is well tolerated after a minimum of two weeks of treatment, the dose may be increased to 3 mg twice a day. Subsequent increases to 4.5 mg and then 6 mg twice a day should also be based on good tolerability of the current dose and may be considered after a minimum of two weeks of treatment at that dose level.

If adverse effects (e.g. nausea, vomiting, abdominal pain or loss of appetite), weight decrease *or* ***worsening of extrapyramidal symptoms (e.g. tremor) in patients with dementia associated with Parkinson's disease*** are observed during treatment, these may respond to omitting one or more doses. If adverse effects persist, the daily dose should be temporarily reduced to the previous well-tolerated dose ***or the treatment may be discontinued.***

Maintenance dose:

Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of rivastigmine should be reassessed on a regular basis, especially for patients treated at doses less than 3 mg twice a day. ***If after 3 months of maintenance dose treatment the patient's rate of decline in dementia symptoms is not altered favourably, the treatment should be discontinued.*** Discontinuation should also be considered when evidence of a therapeutic effect is no longer present.

Individual response to rivastigmine cannot be predicted. ***However, a greater treatment effect was seen in Parkinson's disease patients with moderate dementia. Similarly a larger effect was observed in Parkinson's disease patients with visual hallucinations (see section 5.1).***

4.4 Special warnings and special precautions for use

Dose titration: Adverse effects (e.g. hypertension ***and*** hallucinations ***in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated with Parkinson's disease***) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, Exelon has been discontinued (see ***section*** 4.8).

The use of rivastigmine in patients with severe ***dementia of*** Alzheimer's ***disease or associated with Parkinson's disease***, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated.

Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening ***(including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson's disease (see section 4.8). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse events.***

- **Classification for supply of the medicinal product**

Maintain the current Exelon classification for supply "Medicinal product subject to restricted medical prescription". Section 4.2 of the SPC is defined as follows:

Administration: Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia or dementia associated with Parkinson's disease. Diagnosis should be made according to current guidelines. Therapy with rivastigmine should only be started if a caregiver is available who will regularly monitor drug intake by the patient.

- **Change of PSUR cycle**

Additionally to routine pharmacovigilance, the MAH will submit PSURs every six months for a period of two years after the Commission Decision on the extension of the indication then yearly for two years and then every three years thereafter. The MAH also committed to closely monitor AEs of nausea, vomiting, tremor and other events associated with worsening of parkinsonian symptoms and report these events to CHMP with future PSURs.

- **Follow up measures**

In order to identify prognostic factors for patients who would most benefit from Exelon, the MAH committed to conduct further analysis of the existing Parkinson's disease dementia (PDD) database.
A detailed plan will be provided to the SAWP for further discussion prior to conduct of the analysis.
Findings of this data mining will be submitted to SAWP and will be taken into consideration in the design and analysis plan of the study proposed below.

The MAH also committed to perform a long term (≥12 months) open label safety study to investigate

- The safety of Exelon treatment in PDD patients with particular focus on worsening of parkinsonian symptoms
- The potential for greater clinical benefit in subpopulations identified by the data mining and in PDD patients with visual hallucinations (including the assessment of the reduction in the antipsychotics burden in treated patients)