**Review and Evaluation of Clinical Data**

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|---|---|
| **NDA (Serial Number)** | **20823 (SE1-016)** |
| **Sponsor:** | **Novartis** |
| **Drug:** | **Exelon® (rivastigmine tartrate)** |
| **Proposed Indication:** | **Dementia Associated With Parkinson's Disease** |
| **Material Submitted:** | **Supplemental New Drug Application** |
| **Correspondence Date:** | **8/31/05** |
| **Date Received / Agency:** | **9/1/05** |
| **Date Review Completed** | **4/18/06** |
| **Reviewer:** | **Ranjit B. Mani, M.D.** |

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# Executive Summary

## *Recommendation*

Deferred, pending discussion of this application at a scheduled meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee

## *Proposed Indication*

"Treatment of mild to moderate dementia associated with Parkinson's Disease"

## *Summary Of Clinical Findings*

Exelon® is currently approved for marketing in this country, as both capsule and oral solution formulations, for the treatment of mild to moderate dementia of the Alzheimer's type.

The sponsor has provided evidence from two completed clinical studies in support of the efficacy and safety of Exelon® for the proposed new indication. These are:

- Study 2311, which was randomized, double-blind, placebo-controlled, and parallel-arm in design
- Study 2311E1, the open-label uncontrolled extension to Study 2311

In addition, the sponsor has performed a non-interventional study (Study 2314) of the validity of a number of assessment scales in the Parkinson's Disease Dementia (and vascular dementia); partial results for this study have been submitted in this application.

The data for these studies as they pertain to the efficacy and safety of Exelon® in this population are summarized below, as are the results of the non-interventional validation study listed above.

### *Efficacy*

The results of a single randomized, double-blind, placebo-controlled study (also referred to as the EXPRESS Study) of the efficacy of rivastigmine in the proposed entity of dementia associated with Parkinson's Disease (also referred to interchangeably as Parkinson's Disease Dementia) have been submitted in this application. The main features of this study were as follows

- This was a randomized (2:1 [Exelon®:Placebo]), double-blind, placebo-controlled, parallel-arm study

- The key inclusion criteria for the study were as follows

  - Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria
  - Clinical diagnosis of Parkinson's Disease Dementia according to DSM-IV criteria (Code 294.1) with onset of symptoms of dementia within at least 2 years of the first diagnosis of idiopathic Parkinson's Disease
  - Mini-Mental Status Examination score of 10 – 24 at entry

- The study was of 24 weeks' duration

- The 2 parallel treatment arms were

  - Rivastigmine 3 to 12 mg/day (flexible dose) as BID dosing
  - Placebo

- The primary efficacy measures were the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and Alzheimer's Disease Cooperative Study – Clinician's Global Impression Of Change (ADCS-CGIC).

- The secondary efficacy measures were the following: Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL); Neuropsychiatry Inventory-10; Mini-Mental Status Examination; Cognitive Drug Research Computerized Assessment System; Delis-Kaplan Executive Functioning System (D-KEFS) Verbal Fluency Test; and Ten Point Clock-Drawing Test

- Safety was assessed through adverse events, vital signs, safety laboratory tests, electrocardiograms, and Unified Parkinson's Disease Rating Scale motor score

- The sponsor's primary efficacy analysis was performed on the intent-to-treat plus retrieved dropouts dataset using the following statistical models

  - The change from baseline to endpoint in the ADAS-Cog score was to be compared between the treatment groups using an analysis of covariance with treatment, country, and baseline ADAS-Cog score as explanatory variables
  - The ADCS-CGIC score at endpoint was to be analyzed using a Cochran-Mantel-Haenszel test with modified ridits scores and with country as a stratification variable

Key results for this study were as follows.

541 patients were randomized, of whom 442 patients completed the study. Their distribution by treatment group was as follows:

| Treatment Group | Exelon® | Placebo |
|---|---|---|
| Number randomized | 362 | 179 |
| Number completed | 263 | 147 |

The main efficacy results of this study were as follows

- The primary efficacy analysis, using Study Week 24 as the endpoint, revealed statistically significant differences between the treatment groups on the ADAS-

Cog (difference in mean change from baseline score at endpoint: 2.90; $p < 0.001$) and ADCS-CGIC (difference in mean score between treatment groups at endpoint: 0.5; $p = 0.007$). Note that an Agency statistical reviewer has judged the distribution of ADAS-Cog data not to be normal and therefore in violation of the assumptions of the analysis of covariance model proposed; however, even with the use of a non-parametric model, the Wilcoxon rank sum test, the Exelon® group showed a statistically significant superiority over placebo on this measure

- Nominally statistically significant differences were seen between the treatment groups on all secondary efficacy variables at Week 24 in the same dataset as that used for the primary efficacy analysis

- Analyses of the primary efficacy parameters using other datasets (intent-to-treat last-observation-carried-forward, and observed cases) yielded similar results.

## *Safety*

### *Study 2311*

This study has already been summarized above. Salient safety findings for this study were as follows.

- The incidence of nausea, vomiting, and tremor was appreciably higher in the rivastigmine group than in the placebo group; a similar adverse event profile was seen in the key controlled clinical trials of Exelon® in Alzheimer's Disease
- Several treatment-emergent adverse events that may have represented a worsening in the motor manifestations of Parkinson's Disease, and tremor in particular, were more frequent in those treated with Exelon® than in those treated with placebo. However, changes in UPDRS total and individual motor scores, probably a more objective measure of change in the motor manifestations of Parkinson's Disease than the incidence of treatment-emergent adverse events, showed no meaningful difference between treatment groups.

### *Study 2311E1*

This was a 24-week open-label uncontrolled extension to Study 2311 intended primarily to evaluate the safety and tolerability of Exelon® in the study population. Patients given the option of enrolling in this study had either completed the double-blind treatment phase of Study 2311 or discontinued early during that study, but returned for all the remaining scheduled efficacy assessments without significant protocol violations. Regardless of their previous treatment assignment, patients enrolled in the extension study were all re-titrated to a flexible dose of Exelon® that ranged from 1.5 mg BID to 6.0 mg BID, based on tolerability.

433 patients enrolled in Study 2311 were eligible to enroll in Study 2311E1, of whom 334 patients actually consented to participate in, and 273 patients, completed the latter study.

The adverse event profile of Exelon® in Study 2311 was broadly similar to that seen in Study 2311E1.

*Non-Interventional Validation Study (Study 2314)*

This 4-week cross-sectional study was intended to evaluate the validity and reliability of several measures of cognition, activities of daily living, executive function and behavior in patients with Parkinson's Disease Dementia and vascular dementia, and to compare the performance of the same measures in those conditions with their performance in Alzheimer's Disease. This submission contains an interim report that only pertains to Parkinson's Disease Dementia.

The interim report indicates that 55 patients with Parkinson's Disease Dementia (diagnosed using the DSM-IV criteria) and 58 patients with Alzheimer's Disease (diagnosed using the NINCDS-ADRDA criteria) were enrolled in the study; patients with each diagnosis were further grouped into mild and moderate categories based on Mini-Mental Status Examination scores of 18 to 24 and 10 to 17, respectively, at study entry. The efficacy instruments evaluated were the ADAS-Cog, Global Deterioration Scale, ADCS-ADL, D-KEFS Verbal Fluency Test, Ten-Point Clock Test, Trailmaking Tests A and B, Neuropsychiatry Inventory, including Neuropsychiatry Inventory-Distress, and Cognitive Drug Research Computerized Assessment System tests for the assessment of attention. Each enrolled patient was to be evaluated using these measures at baseline and Week 4; all but 2 patients, both in the Parkinson's Disease Dementia group, completed their evaluations.

The results of this study have been interpreted as demonstrating the following:

- That the ADAS-Cog score can differentiate between dementia associated with Parkinson's Disease of mild and moderate severities, as can the scores for several of the other instruments evaluated in this study
- That the ADAS-Cog and several other efficacy measures had test-retest reliability in dementia associated with Parkinson's Disease
- That the ADAS-Cog scores correlated with those of several other efficacy instruments in dementia associated with Parkinson's Disease, whether the latter measures assessed cognition or other domains
- A factor analysis that compared populations with Parkinson's Disease Dementia and Alzheimer's Disease on ADAS-Cog sub-item scores had indicated that the sub-items grouped differently in each population, suggesting that the cognitive and behavioral profiles in these populations might differ

### *Conclusions*

Deferred, pending discussion of this application at a scheduled meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee

## 1. Background

This submission, a Supplemental New Drug Application, seeks the approval of Exelon® (rivastigmine tartrate) for the treatment of "mild to moderate dementia associated with Parkinson's Disease."

The data supporting this application are stated to be derived entirely from the results of the EXPRESS ("Rivastigmine for Dementia Associated with Parkinson's Disease") Study, also referred to as Study 2311. An open-label uncontrolled extension to that Study 2311, designated as Study 2311E1 has also bee completed.

A meeting to discuss this submission and the results of the EXPRESS Study was held between the Division and sponsor on May 18, 2005, and is summarized later in this review.

Exelon® (rivastigmine tartrate) is an acetylcholinesterase inhibitor drug approved by this Agency on April 21, 2000, for the treatment of mild to moderate dementia of the Alzheimer's type, as immediate-release capsule and oral solution formulations. Please refer to the primary reviews of NDAs #s 20823 (for the immediate-release capsule formulation) and 21025 (for the oral solution formulation) for full details.

In this review, the terms "Exelon®" and "rivastigmine" are used interchangeably. Also note that "dementia associated with Parkinson's Disease" is also referred to, apparently interchangeably, as Parkinson's Disease Dementia (PDD) in the sponsor's submission.

The Biometrics Reviewer of this submission is Dr Juan (Joanne) Zhang.

## 2. Contents Of Submission

This submission has been provided in accordance, as per the sponsor, with the guidance for industry entitled Providing Regulatory Submissions In Electronic Format-NDAs (January 1999)

The key items in this application are:

- Cover letter
- Proposed product labeling
- Application summary
- Clinical and statistical section, containing the following:

- Tabular listing of all clinical study reports
- Reports of efficacy and safety studies: Study 2311 and Study 2311E1
- Report of Study 2314 (non-interventional validation study)
- Publication references
- Tables for Summary of Clinical Safety
- Tables and appendices for Summary of Clinical Efficacy

- Case Report Tabulations
- Case Report Forms
- Patent Information
- Debarment Certification
- Use Fee Cover Sheet
- Financial Disclosure Information
- Confidentiality Statement

## 3. Contents Of Review

The contents of this submission will be addressed under the following principal headings and in the same order as below

- Key diagnostic instruments used in efficacy study (Study 2311)
- Efficacy outcome measures and selected additional instruments used in efficacy study
- Summary of efficacy study
- Description of efficacy study
- Study 2311E1 (open-label uncontrolled extension to Study 2311)
- Study 2314 (non-interventional validation study)
- Summary of earlier meeting between Division and sponsor regarding this application
- Sponsor's current view of dementia associated with Parkinson's Disease, and appropriateness of ADAS-Cog and ADCS-ADL for evaluating treatment effects in dementia associated with Parkinson's Disease
- Financial disclosure certification
- Site inspection report
- Review of proposed labeling
- Comments
- Conclusion
- Recommendation

# 4. Key Diagnostic Instruments Used in Efficacy Study (Study 2311)

The criteria for 2 diagnostic instruments used in the efficacy study are listed below:

## *4.1 UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria For Parkinson's Disease*

Step 1 Diagnosis of Parkinsonian syndrome

- Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)

- And at least one of the following:

    - Muscular rigidity
    - 4-6 Hz rest tremor
    - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Step 2 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- Presence of cerebral tumor or communicating hydrocephalus on CT scan
- Negative response to large doses of levodopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria for Parkinson's disease
(Three or more required for diagnosis of definite Parkinson's disease)

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

### *4.2 DSM-IV Criteria For Dementia Due To Parkinson's Disease*

294.1 Dementia Due To Parkinson's Disease

The essential feature of Dementia Due To Parkinson's Disease is the presence of dementia that is judged to be of direct pathophysiological consequence of Parkinson's disease. Parkinson's disease is a slowly progressive neurological condition, characterized by tremor, rigidity, bradykinesia, and postural instability. Dementia has been reported to occur in approximately 20%-60% of individuals with Parkinson's disease and is more likely to be present in older individuals or in those with more severe or advanced disease. The dementia associated with Parkinson's disease is characterized by cognitive and motor slowing, executive dysfunction and impairment in memory retrieval. Declining cognitive performance in individuals with Parkinson's disease is frequently exacerbated by depression. Findings on physical examination include the characteristic abnormal motor signs of resting tremor, evidence of slowness and poverty of movement (such as micrographia), or muscular rigidity and loss of associated movements. At autopsy, neuronal loss and Lewy bodies are evident in the substantia nigra. There are a number of syndromes that manifest with dementia, Parkinsonian movement disorders, and additional neurological features (e.g., progressive supranuclear palsy, olivopontocerebellar degeneration, and Vascular Dementia). Some individuals with Parkinson's disease and dementia are found at autopsy to have coexisting neuropathology indicative of Alzheimer's disease or of diffuse Lewy body disease.

## 5. Efficacy Outcome Measures And Selected Additional Instruments Used In Efficacy Study

These instruments are outlined below:

### *5.1 Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog)*

This is a validated instrument consisting of the following 11 items: Word Recall Task, Naming Fingers and Objects, Orientation Questions, Constructional Praxis Task, Following Commands, Ideational Praxis Task, Word Recognition Task, Rating of Spoken Language, Rating of Language Comprehension, Rating of Word Finding Difficulty and Rating of Ability to Recall Test Instructions. The total scores range from 0-70 with higher scores indicating greater cognitive impairment.

### *5.2 Alzheimer's Disease Cooperative Study – Clinician's Global Impression Of Change (ADCS-CGIC)*

This instrument provides for a rating of overall (global) change from baseline by an independent clinician experienced in the assessment of patients with dementia. The term "independent" implies that the rater is not to be involved in any additional manner in the evaluation and/or treatment of patients enrolled in this study

Assessments will be performed at baseline and at subsequent visits. It is recommended that the baseline interview be conducted by 2 independent raters, one designated as the primary rater and the other as a backup. Post-baseline ratings are to be conducted solely by the primary rater or, in his/her absence, by the back-up rater.

At baseline both raters will have access to all of the patients' available records and evaluations. At all subsequent visits, the rater is to rely (for baseline data) solely upon information obtained during the baseline assessment of the patient and caregiver by that rater (including written notes and, if available, the baseline interview audiotape or videotape). At post-baseline visits, data obtained directly from the patient may be supplemented by that obtained from the caregiver. The rater will not have access to other safety or efficacy data, including all previous post-baseline ADCS-CGIC ratings by either rater.

A standard 7-point categorical rating scale and its dichotomized version will both be used for rating and are further described below:

- The 7-point categorical scale is as follows:

| Change | Rating |
|---|---|
| Marked improvement | 1 |
| Moderate improvement | 2 |
| Minimal improvement | 3 |
| No change | 4 |
| Minimal worsening | 5 |
| Moderate worsening | 6 |
| Marked worsening | 7 |

- The dichotomized version of the 7-point categorical scale is derived as follows

| Rating On 7-Point Scale | Rating On Dichotomized Scale |
|---|---|
| 1, 2, or 3 | 1 |
| 4, 5, 6, or 7 | 2 |

The format for assessment is semi-structured with a guideline provided for assessing the global impression of change based on ratings of change for the following individual domains: cognition, behavior, and function.

A semi-structured format for assessing the severity of disease at baseline has also been used, again with a guideline provided for assessing the global impression of severity based on ratings of change for the following individual domains: cognition, behavior, and function.

### *5.3 Alzheimer's Disease Cooperative Study – Activities Of Daily Living Scale (ADCS-ADL)*

This is a rating scale used to assess basic and instrumental activities of daily living. 23 items are rated by the investigator using information supplied by the caregiver. The maximum total score is 78. Higher scores indicate better function.

### *5.4 Cognitive Drug Research Computerized Assessment System*

This is a computer-based system for assessing cognitive function. A series of tasks is used to assess each of several specific functions as indicated in the

table below. Only Level I (Attention) is assessed in the study contained in this submission.

| Level | Function Assessed | Tests |
|---|---|---|
| Level I | Attention | Simple Reaction Time<br>Choice Reaction Time<br>Digit Vigilance |
| Level II | Short-Term or Working Memory | Numeric Working Memory<br>Spatial Working Memory |
| Level III | Long-Term or Episodic Secondary Memory | Word Recall<br>Word Recognition<br>Picture Recognition<br>Face Recognition |
| Level IV | Motor Control | Tracking<br>Postural Stability |
| Other | Miscellaneous Functions | Rapid Visual Information Processing<br>Logical Reasoning<br>Tapping Rates<br>Critical Flicker Fusion Frequency<br>Digit Symbol Substitution Task<br>Pencil and Paper Procedures<br>Visual Analogue Scales |

A description of each of the tests at Level I is presented below

| Test | Description |
|---|---|
| Simple Reaction Time | The patient is asked to press the "YES" response button as quickly as possible every time the word "YES" is presented on the monitor |
| Digit Vigilance Task | A target digit is randomly selected and constantly displayed to the right of the monitor screen. A series of digits is presented in the center of the screen at the rate of 80 per minute and the patient is required to press the "YES" button every time the digit in the series matches the target digit |
| Choice Reaction Time | Either the word "NO" or the word "YES" is presented on the monitor and the patient is instructed to press the corresponding button as quickly as possible |

### *5.5 Delis-Kaplan Executive Functioning System (D-KEFS) Test Battery*

This test battery assesses verbal and non-verbal executive functions. 9 tests are included in this battery; each test is intended to be used as either a stand-alone instrument or in conjunction with other tests in the same battery. The tests are as follows: Trail Making Test, Verbal Fluency Test, Design Fluency Test, Color-Word Interference Test, Sorting Test (formerly called the California Card Sorting Test), Twenty Questions Test, Word Context Test, Tower Test, and Proverb Test (formerly called the California Proverb Test).

Only the Verbal Fluency Test from this battery was eventually used as a uniform outcome measure for this study; only one condition of this test, letter fluency, was used; here the patient was asked to generate as many words as possible for 3 different letters of the alphabet ("F," "A," and "S,") with 60 seconds being allowed for each alphabet tested. 2 other tests, the Sorting Test and the Color-Word

Interference Test were used at selected centers. The main outcome variable for each of these measures is listed below:

| Test | Main Outcome Variable |
|---|---|
| D-KEFS Verbal Fluency Test | Number of correct responses |
| D-KEFS Sorting Test | Sort recognition description score |
| D-KEFS Color-Word Interference Test | Completion time adjusted for errors |

### *5.6 Mini-Mental Status Examination*

This is a validated multi-item instrument that examines orientation, registration, attention, calculation, recall, visuospatial abilities and language. The maximum score is 30, with higher scores indicating better cognitive function.

### *5.7 Neuropsychiatry Inventory*

This is a validated instrument that assesses the following 12 domains (subscales): delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, sleep/night-time behavior, and appetite/eating changes . Each domain is rated according to its frequency (score ranging from 1 to 4) and severity (score ranging from 1 to 3); rating is based on interviewing a caregiver; if a symptom subsumed by a particular domain is absent, it will receive a rating of 0. For each domain, the score is the product of frequency and severity, with a maximum score of 12. The maximum total score for the 12 domains (the sum of the subscale scores) is 144 with a higher score indicating greater behavioral abnormality.

An earlier version of the Neuropsychiatry Inventory (Neuropsychiatry Inventory-10), consisting of the first 10 items above, and with a maximum total score of 100 has also been used.

#### *5.7.1 Neuropsychiatry Inventory – Distress*

For each of the 12 items on the Neuropsychiatry Inventory, caregiver distress is rated on a 5-point scale from 1 to 5, with higher scores indicating greater distress.

### *5.8 Ten-Point Clock Test*

This test is intended to measure executive functioning and visuospatial skills. The subject is asked to insert the numbers on the face of the clock and when that task is completed to insert the hands of the clock so as to indicate a time of ten minutes past eleven o'clock. The maximum score on this task is 10, with lower scores indicating greater degrees of impairment

### *5.9 Symbol-Digit Modalities Test*

This test is intended to measure information processing speed and attention. Subjects match numbers to symbols using a key; the symbols are printed and the numbers written in by the subject. 110 items are to be filled in a period of 90 seconds.

### *5.10 Health Economic Parameters*

These are to include the following

- Caregiver burden
- Caregiver productivity costs
- Caregiver and patient outpatient visits and hospitalizations
- Time to institutionalization

### *5.11 Unified Parkinson's Disease Rating Scale (UPDRS)*

This is a composite scale intended for rating patients with Parkinson's Disease. The scale is composed of 6 sections, each of which is rated categorically

| Part | Functions assessed | Number Of Items Rated |
|---|---|---|
| Part I | Cognition, behavior and mood | 4 |
| Part II | Activities of daily living | 13 |
| Part III | Motor examination | 14 |
| Part IV | Complications of therapy | 11 |
| Part V | Modified Hoehn and Yahr staging | Overall single rating |
| Part VI | Disability scale | Overall single rating |

Individual items are rated as follows

| | |
|---|---|
| Part I, II and III | 0-4 (0 = normal; 4 = maximal deficit, symptoms or impairment) |
| Part IV | 0-4 or 0-1 (0 = normal; 1,4 = maximal deficit, symptoms or impairment) |
| Part V | 8 stages from 0 to 5 (0 = no signs of disease; 5 = wheelchair bound or bedridden unless aided) |
| Part VI | 11 percentile points from 0% (loss of vegetative functions; bedridden) to 100% (completely independent) |

Part III of this scale (Motor Examination) will be used as an outcome measure in this study. The individual items in Part III are

- Speech
- Facial expression
- Tremor at rest
- Action or postural tremor of hands
- Rigidity
- Finger taps
- Hand movements
- Rapid alternating movements
- Leg agility
- Arising from chair
- Posture

- Gait
- Postural stability
- Body bradykinesia and hypokinesia

# 6. Summary Of Key Efficacy Study (EXPRESS Study; Study 2311)

The study protocol and main efficacy results for this study are summarized below.

## *6.1 Outline*

The study outline is below

| | | |
|---|---|---|
| Design | Randomized, double-blind, placebo-controlled, parallel-arm study | |
| Duration | 24 weeks | |
| Key Inclusion Criteria | Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria<br><br>Clinical diagnosis of Parkinson's Disease Dementia according to DSM-IV criteria (Code 294.1) with onset of symptoms of dementia within at least 2 years of the first diagnosis of idiopathic Parkinson's Disease<br><br>Mini-Mental Status Examination of 10 – 24 | |
| Primary Efficacy Measures | ADAS-Cog<br><br>ADCS-CGIC | |
| Population For Primary Efficacy Analysis | Intent-to-treat plus retrieved dropouts | |
| Secondary Efficacy Measures | Cognitive Drug Research Computerized Assessment System-Power Of Attention<br>D-KEFS* Verbal Fluency Test<br>Neuropsychiatry Inventory-10<br>Mini-Mental Status Examination<br>Ten-Point Clock Drawing Test<br><br>(*D-KEFS: Delis-Kaplan Executive Function System) | |
| Safety Measures | Adverse events, vital signs, safety laboratory tests, electrocardiograms, Unified Parkinson's Disease Rating Scale score | |
| Dose Arms | Rivastigmine (3 - 12 mg/day) | Placebo |
| Number randomized | 362 | 179 |
| Number completing | 263 | 147 |

## *6.2 Results Of Primary Efficacy Analysis*

The results of the primary efficacy analysis as performed on the intent-to-treat plus retrieved dropout population is summarized below

| Parameter | Rivastigmine | | Placebo | | Mean difference | p-value |
|---|---|---|---|---|---|---|
| | N | Mean ± SD | N | Mean ± SD | | |
| ADAS-Cog change from baseline to Week 24 | 329 | 2.1 ± 8.2 | 161 | - 0.7 ± 7.5 | 2.88* (LS means) | < 0.001** |
| ADCS-CGIC at Week 24 | 329 | 3.8 ± 1.4 | 165 | 4.3 ± 1.5 | 0.5 | 0.007*** |

*95% confidence interval: 1.44 to 4.31
**Based on two-way analysis of covariance model using treatment and country as factors and baseline ADAS-Cog as a covariate
***Based on van Elteren test blocking for country
Note that in the above table, negative ADAS-Cog change scores indicate a worsening and positive ADAS-Cog change scores an improvement

# 7. Description Of Efficacy Study 2311 (EXPRESS Study)

This study was conducted outside the purview of an IND application, and the protocol was not submitted to this Division for review prior to the study being conducted or at any time while the study was ongoing.

Note that the results of this study have also been published. The abstract of that publication has been provided later in this section

## *7.1 Protocol*

**The protocol described below is the final version**

### *7.1.1 Title*

A 24-Week, Prospective, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study Of the Efficacy, Tolerability, And Safety Of 3 – 12 Mg/Day Of Exelon® (Rivastigmine) Capsules In Patients With Parkinson's Disease Dementia

### *7.1.2 Objectives*

#### *7.1.2.1 Primary*

To evaluate the efficacy of Exelon® (3 to 12 mg/day) compared with placebo for a treatment period of 24 weeks in patients with Parkinson's Disease Dementia. Efficacy will be evaluated on the following:

- ADAS-Cog, a measure of cognition
- ADCS-ADL, a measure of global function

#### *7.1.2.2 Secondary*

- To evaluate the effects of Exelon® on attention, executive functioning, activities of daily living, behavior, caregiver distress, and health economic parameters

- To explore differences of efficacy of Exelon® depending on pre-existing attentional deficits
- To explore potential genetic factors related to Parkinson's Disease Dementia
- To explore potential biomarkers related to Parkinson's Disease Dementia
- To evaluate the safety and tolerability of Exelon®

### *7.1.3 Design, Duration, Sample Size, Dosage*

This was to be a 24-week randomized, double-blind, placebo-controlled, parallel-arm study.

About 540 patients were to be randomized 2:1 to Exelon® or placebo (i.e., about 360 patients to Exelon® and about 180 patients to placebo).

The overall study design is summarized in the following table:

| Phase | Pre-randomization | | Double-blind Treatment | | | | |
|---|---|---|---|---|---|---|---|
| Period | Screening | Baseline | Titration | | | | Maintenance |
| Week | -3 to-1 | 0 | 16 weeks | | | | 8 weeks |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 and 8 |
| Treatment | None | None | Exelon® 3-12 mg/d | | | | 12 mg/d or highest well-tolerated dose of Exelon® |
| | | | Placebo | | | | Placebo |

4 dose levels were to be used for Exelon® (and for matching placebo). The dose levels for Exelon® are shown in the following table

| Dose Level | Exelon® Dose |
|---|---|
| 1 | 1.5 mg BID |
| 2 | 3.0 mg BID |
| 3 | 4.5 mg BID |
| 4 | 6.0 mg BID |

The actual dosing regime was to be as follows:

- For the titration period
    - All patients were to begin at Dose Level 1
    - After 4 weeks, the dose was to be increased to Dose Level 2 unless tolerability was impaired
    - Subsequent increases to Dose Levels 3 and 4 were to be based on the tolerability of the preceding dose, and were to be considered only after 4 weeks of treatment at the previous dose
    - In the event of poor tolerability, an investigator could decide to reduce a dose to the preceding level, with increases to the next dose level being made as clinically indicated
    - All patients were expected to have found their highest tolerated dose by Week 16.

- For the maintenance period
    - The highest well-tolerated dose for each patient was to be maintained for the entire maintenance period
    - However, dose adjustments were permitted at any time

After completing the double-blind phase, patients were to have the option of receiving open-label treatment for up to 6 months.

Note that the Exelon® dose range proposed for use in this trial was identical to that used in clinical trials in Alzheimer's Disease.

### *7.1.4 Selection*

#### *7.1.4.1 Key Inclusion Criteria*

- Male or female
- Age ≥ 50 years
- Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank
- Diagnosis of Dementia Due To Parkinson's Disease according to DSM-IV criteria
- Mini-Mental Status Examination score of 12 to 24
- Sufficient education to read, write, and communicate effectively during the pre-morbid stage
- Cooperative
- Able to ingest oral medication
- Capable of completing the study either alone or with the assistance of a responsible caregiver
- Reliable caregiver
- Informed consent

#### *7.1.4.2 Key Exclusion Criteria*

- Any advanced, severe or unstable disease that could interfere with study evaluations

- Any disability that interferes with completion of study requirements
- Active uncontrolled peptic ulceration within the previous 3 months
- Women of child-bearing potential
- Bradycardia (< 50 beats per minute), sick sinus syndrome, conduction deficits (S-A block, second or third degree A-V block)
- Current diagnosis of any primary neurodegenerative disease other than Parkinson's Disease or any other causes of dementia
- A current diagnosis of probable or possible vascular dementia according to the NINDS-AIREN criteria
- Deep brain stimulation implants
- Current diagnosis of active, uncontrolled seizure disorder
- Current diagnosis of major depressive episode according to DSM-IV criteria or any other DSM-IV Axis I diagnosis that may interfere with the response of the patient to study medication, including bipolar disorder or schizophrenia as assessed by psychiatric examination
- A known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to Exelon® or other cholinergic compounds
- Participation in a previous study of cholinesterase inhibitor therapy during the 6 months prior to randomization
- Use of any of the following substances during the 4 weeks prior to randomization
    - Any investigational drug
    - A drug or treatment known to cause major organ toxicity
    - Other cholinesterase inhibitors or cholinergic drugs (except topical pilocarpine)
    - Centrally acting anticholinergic drugs, including tricyclic antidepressants
    - Neuroleptics other than clozapine, quetiapine, or olanzapine
    - Lithium
- Commencement of any of the following medications or change in medication dose during the 4 weeks prior to randomization

- Psychotropic medications (clozapine, quetiapine, olanzapine, antidepressants, anxiolytics or hynotics, including benzodiazepines and anticonvulsants)
- Anti-Parkinsonian medications

*7.1.4.3 Concomitant Medications*

7.1.4.3.1 Prohibited

- Any investigational drug
- A drug or treatment known to cause major organ toxicity
- Other cholinesterase inhibitors or cholinergic drugs (except topical pilocarpine)
- Centrally acting anticholinergic drugs, including tricyclic antidepressants
- Neuroleptics other than clozapine, quetiapine, or olanzapine
- Lithium
- New psychotropic medications (clozapine, quetiapine, olanzapine, antidepressants, anxiolytics or hynotics, including benzodiazepines and anticonvulsants)
- New anti-Parkinsonian medications
- Dose increases for dopaminomimetic medications
- Dose increases for anxiolytics or hypnotics, including benzodiazepines

7.1.4.3.2 Permitted (With Limitations)

- Psychosis should be treated according to the clinical standard. If persistent and if clinically indicated:

  - In patients already treated with atypical neuroleptics, a dose increase is permitted
  - In neuroleptic-naïve, atypical neuroleptics, such as clozapine, quetiapine, or olanzapine should be started at very low doses that are increased gradually

  While a decrease in dose or discontinuation of anti-Parkinsonian medication as a treatment for psychosis is permitted, elimination of all dopaminomimetic treatment is not recommended. However, changes in dose of amantadine and selegiline are not permitted during the trial, even during a psychotic episode.

- For isolated insomnia, the use of non-benzodiazepine hypnotics such as zopiclone, is permitted

- Patients on Vitamin E, estrogens, Ginkgo biloba, and nootropics, and in whom discontinuation of these drugs is not feasible, may continue with these agents, but the dose should remain unchanged throughout the trial

- Peripherally-acting anticholinergic drugs are permitted if patients have been on a stable dose for 4 weeks prior to randomization, and if doses are

kept stable during the study. In addition, if urinary urgency and incontinence develop newly during the trial, and cannot be overcome by non-pharmacological means, initiation of treatment with peripheral anticholinergics such as tolterodine and oxybutinin will be permitted

### *7.1.5 Schedule*

The study schedule is summarized in the following table, which I have copied from the submission.

| Phase | Pre-randomization | | Double-blind treatment | | | | | |
|---|---|---|---|---|---|---|---|---|
| Period | Screening | Baseline | Titration | | | | Maintenance | |
| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 / ED |
| Week | -3 to –1 | 0 | 4 | 8 | 12 | 16 | 20 | 24 |
| Eligibility | X | X | | | | | | |
| Demography and background information | X | | | | | | | |
| Informed Consent | X | | | | | | | |
| Relevant Medical History & Current Medical Conditions | X | X | | | | | | |
| Vital Signs | X | X | X | X | X | X | X | X |
| Physical and Neurological exams | X | | | | | | | |
| Electrocardiogram, Lab examinations | X | | | | | | | X |
| Pharmacogenetic and biomarker samples (only after PG informed consents have been signed) | X | | | | | | | |
| Unified Parkinson's Disease Rating Scale (UPDRS part III); ADAS-cog; ADCS-CGIC; ADCS-ADL; NPI (including NPI-D) | | X | | | | X | | X |
| UPDRS V | | X | | | | | | |
| CDR tests, Executive Function tests * | X | X | | | | X | | X |
| TPCT | | X | | | | | | X |
| MMSE | X | X | | | | | | X |
| Health economic parameters | | X | | | | | | X |

Adverse events and concomitant medications were recorded throughout the study. ED = Early Discontinuation; efficacy assessments were also required within 24 hours of last dose at ED.

* Symbol Digit Modalities test and D-KEFS verbal fluency test, color word interference and card sorting tests

**Note that brain imaging (i.e., computerized tomography or magnetic resonance scanning) was not required prior to entry into the study.**

Special diagnostic laboratory tests at screening included serum TSH, folic acid, Vitamin B12 and RPR.

Also note the following

- All primary and other cognitive outcome variables were to be assessed before lunch, beginning 1 hour after the intake of dopaminergic

medications, at the same time of day throughout the study for each patient, and using the same sequence of tests

- For patients with motor fluctuations and/or dyskinesias, efficacy assessments were to be performed during their "on" time (defined as intervals when parkinsonian symptoms were replaced by increased mobility)
- For patients with an acute psychosis, efficacy assessments were to be performed after remission of the psychosis
- Raters were advised to identify and discount if possible potential behavioral and functional changes due to the motor symptoms of Parkinson's Disease

### *7.1.6 Outcome Measures*

#### *7.1.6.1 Primary Efficacy Measures*

- ADAS-Cog
- ADCS-CGIC

#### *7.1.6.2 Secondary Efficacy Measures*

- Cognitive Drug Research Computerized Assessment System tests for the assessment of attention
- ADCS-ADL
- Neuropsychiatry Inventory
- Neuropsychiatry Inventory Caregiver Distress Scale
- Executive Function Battery
    - Ten-Point Clock Drawing Test
    - D-KEFS Verbal Fluency Test
    - D-KEFS Color Word Interference Test*
    - D-KEFS Card Sorting Test*
    - Symbol Digit Modalities Test*

    *These were designated as exploratory assessments and were considered optional for English and French speaking patients
- Health Economic Parameters, including caregiver burden, and patient and caregiver resource utilization
- Mini-Mental Status Examination

#### *7.1.6.3 Safety Measures*

Adverse events, safety laboratory tests, vital signs, body weight, electrocardiograms, and UPDRS Part III

### *7.1.7 Safety Monitoring*

Adverse events, safety laboratory tests, vital signs, body weight, electrocardiograms, and UPDRS Part III

### *7.1.8 Analysis Plan*

#### *7.1.8.1 General*

The data from each center were intended to be pooled with data from other centers so that an adequate number of patients would be available for analysis.

Unless otherwise specified, all statistical tests were to be conducted using a two-sided Type I error of 0.05.

#### *7.1.8.2 Study Populations*

##### 7.1.8.2.1 Intent-To-Treat With Retrieved Dropouts

This population was to include all randomized patients who received at least one dose of study medication and had at least a pre- and post-baseline assessment for one of the primary efficacy variables.

The imputation scheme that was to be used to create a score for every randomized subject is described as follows in the study protocol: If available, the endpoint assessment is used; if missing, the retrieved dropout assessment is used; if the retrieved dropout assessment is unavailable, the last observation available on the subject is used.

##### 7.1.8.2.2 Intent-To-Treat-Last-Observation-Carried-Forward

This population was to include all randomized patients who received at least one dose of study medication and had at least a pre- and post-baseline assessment for one of the primary efficacy variables.

The imputation scheme that was to be used to create a score for every randomized subject is described as follows in the study protocol: If available, the endpoint assessment is used; if missing, the immediate preceding observation available, scheduled or unscheduled, is utilized, provided that the assessment is made while the subject is still considered to be a participant in the study, i.e., at most 2 days after the last dose of study medication.

##### 7.1.8.2.3 Observed Cases

This population was to consist of all randomized patients 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 dose of study medication were not to be included. No imputation is involved with this population

7.1.8.2.4 Safety Population

This population was to consist of all patients who have received at least one dose of study medication and had at least one safety assessment after baseline.

*7.1.8.3 Demographic And Other Baseline Characteristics*

- These characteristics were to be presented by treatment group and country
- Continuous variables were to be summarized using descriptive statistics
- Discrete variables were to be summarized by frequencies and percentages
- Descriptive p-values were to be generated using appropriate test statistics

*7.1.8.4 Study Medications*

Descriptive statistics for study drug exposure by treatment and data listings for study drug doses administered were also to be provided

*7.1.8.5 Concomitant Therapy*

Descriptive statistics (frequency counts and percentages) for concomitant medication were to be presented by treatment group for patients in the safety population

*7.1.8.6 Primary Efficacy Parameters*

- The primary efficacy parameters were the following

    - Change from baseline to endpoint in ADAS-Cog score
    - ADCS-CGIC rating at endpoint (on the 7-point scale)

    [Note that the statistical analysis plan does not explicitly state that the endpoint used for the primary efficacy analysis was to be Week 24, rather than Week 16.]

- The population for the primary efficacy analysis was to be the intent-to-treat plus retrieved dropouts population as defined above. Analyses on other populations were to be considered supportive to the main efficacy analysis

- The main analysis for the change from baseline to endpoint in ADAS-Cog score was to be as follows

- The treatment groups were to be compared using least square means derived from an analysis of covariance model with the following explanatory variables: treatment, country, and baseline ADAS-Cog score
- 95% confidence intervals for the difference in treatment groups based on the analysis of covariance were to be reported
- In addition, summary statistics were to be presented by treatment group for baseline and post-baseline evaluations for the populations being analyzed

- The main analysis of the ADCS-CGIC was to be by comparing the treatment groups using a Cochran-Mantel-Haenszel test with modified ridit scores with country as stratification variable. In addition, a proportional odds regression analysis with the following explanatory variables was to be performed: treatment and country. A secondary analysis was also to be performed on the dichotomized ADCS-CGIC using logistic regression with the same explanatory variables as the proportional odds regression model

*7.1.8.7 Secondary Efficacy Parameters And Additional Analyses*

Secondary efficacy variables were to be analyzed using an analysis of covariance model with treatment, country, and the corresponding baseline measurement as the covariates.

Secondary efficacy analyses of the primary efficacy variables were to be performed on population subgroups defined by the presence of impaired attention and concentration on the baseline attentional task scores of the Cognitive Drug Research computerized battery.

*7.1.8.8 Safety Parameters*

- The safety parameters were to be adverse events, vital signs, electrocardiograms and safety laboratory tests.

- Adverse events will be coded using the MedDRA dictionary and presented (number and proportion) by treatment group, body system, and individual event, and also grouped according to severity, relationship to study medication, and outcome. The proportion of patients in each treatment group discontinuing prematurely for any reason and for adverse events was to be compared descriptively

- Laboratory data were to be summarized by presenting shift tables for change from baseline to most extreme post-baseline value, and descriptive statistics of raw data and change from baseline values, and by flagging notable values in data listings.

- Data from vital signs and electrocardiograms were to be listed, notable values were to be flagged, and any other information collected was to be

listed as appropriate. Any statistical tests performed were to be exploratory

- The change from baseline on the UPDRS score was to be analyzed using an analysis of covariance model

*7.1.8.9 Sample Size Rationale*

Sample size estimates were performed using the two primary efficacy parameters the ADAS-Cog and the ADCS-CGIC, and is further summarized below

7.1.8.9.1 Sample Size Estimate Based On ADAS-Cog

Estimates of standard deviation from the intent-to-treat analysis of 6-month change from baseline ADAS-Cog data in clinical trials of Exelon® in Alzheimer's Disease range from 6 to 7 points

To ensure adequate power in case of a higher variability in 6-month change from baseline ADAS-Cog scores in those with Parkinson's Disease as compared with those with Alzheimer's Disease, a standard deviation of 7.5 points was assumed for this sample size estimate

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) is required to detect a difference of at least 2.25 points in the ADAS-Cog change from baseline score between Exelon® and placebo with a power of 90%.

7.1.8.9.2 Sample Size Estimate Based On ADCS-CGIC

Assumptions regarding the variability and treatment differences for the ADCS-CGIC are based on data available for the CIBIC-Plus from completed Exelon® studies in Alzheimer's Disease; the ADCS-CGIC and CIBIC-Plus are very similar instruments.

To ensure adequate power in case of a higher variability in ADCS-CGIC scores in those with Parkinson's Disease as compared with those with Alzheimer's Disease, a standard deviation of 1.3 points was assumed for this sample size estimate

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) is required to detect a difference of at least 0.40 points on the intent-to-treat analysis in the ADCS-CGIC score at Month 6 between Exelon® and placebo with a power of 90%.

7.1.8.9.3 Overall Sample Size Estimate

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

## *7.2 Study Results*

The study was conducted in Austria, Belgium, Canada, France, Germany, Italy, the Netherlands, Norway, Portugal, Spain, Turkey, and the United Kingdom, between October 10, 2002, and January 20, 2004.

A total of 68 centers participated in the study.

### *7.2.1 Patient Disposition*

A total of 650 patients were screened, of whom 541 were randomized, 362 to the Exelon® group and 179 to the placebo.

| | 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) |
| Subject withdrew consent | 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) |

As the above sponsor table indicates, a total of 410 patients (263 [72.7%] who received Exelon®, and 147 [82.1%] who received placebo, completed the study).

As the table above also indicates, the majority of discontinuations were due to adverse events: 17.1% of patients in the Exelon® group and 7.8% of patients in the placebo group discontinued on account of adverse events.

### *7.2.2 Protocol Deviations*

Protocol violations are summarized in the following table, which I have copied from the submission.

| | Exelon | Placebo | Total |
|---|---|---|---|
| Total number of patients | 362 | 179 | 541 |
| **Number (%) of patients with:** | | | |
| At least one protocol violation | 82 (22.7) | 33 (18.4) | 115 (21.3) |
| MMSE score < 10 or > 24 | 6 ( 1.7) | 3 (1.7) | 9 (1.7) |
| Date diagnosis PD> Date of first symptoms of PDD -2 years | 13 ( 3.6) | 3 (1.7) | 16 (3.0) |
| Increased dose or newly introduced psychotropic/dopaminergic medication | 39 (10.8) | 18 (10.1) | 57 (10.5) |
| No valid assessment of both primary variables | 27 ( 7.5) | 13 (7.3) | 40 (7.4) |

MMSE scores at baseline visit are reported.

The table indicates that protocol violations were slightly more frequent in the Exelon® group than in the placebo group. The most common protocol violation was an increase in dose or the new introduction of a psychotropic or dopaminergic medication; this category of violation was about equal in incidence between the treatment groups.

### *7.2.3 Groupings For Analysis*

The groupings for analysis are summarized in the following sponsor table.

| | Exelon | Placebo | Total |
|---|---|---|---|
| **Analysis population** | n (%) | n (%) | n (%) |
| Safety population | 362 (100) | 179 (100) | 541 (100) |
| ITT + RDO population | 335 (92.5) | 166 (92.7) | 501 (92.6) |
| of which RDO (retrieved drop-outs) | 19 (5.2) | 4 (2.2) | 23 (4.3) |
| LOCF population | 290 (80.1) | 159 (88.8) | 449 (83.0) |
| OC (observed cases) population | 290 (80.1) | 159 (88.8) | 449 (83.0) |

ITT: Intent-to-treat
LOCF: Last-observation-carried-forward

Note that similar proportions of those in the Exelon® and placebo groups are in the intent-to-treat plus retrieved dropout groups used for the primary efficacy analysis.

### *7.2.4 Demographic And Other Baseline Characteristics*

As the sponsor table below indicates, baseline characteristics for age, gender, and race were comparable between treatment groups. The table pertains to the randomized/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) |

Baseline Parkinson's Disease and dementia characteristics were also broadly comparable between treatment groups, including entry Mini-Mental Status Examination scores; the table depicts the randomized/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** (UPDRS Part V) | 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 |

### *7.2.5 Study Medication*

The cumulative duration of patient exposure is summarized by treatment group in the next table, which I have copied from the submission. As might be expected from the discontinuation rates in each treatment group alluded to before, the mean duration of exposure was slightly lower in the Exelon® group than in the placebo group.

| | Exelon | Placebo |
|---|---|---|
| **Duration of exposure** | | |
| Any exposure | 362 (100) | 179 (100) |
| at least 1 week | 358 (98.9) | 177 (98.9) |
| at least 2 weeks | 354 (97.8) | 174 (97.2) |
| at least 3 weeks | 351 (97.0) | 173 (96.6) |
| at least 4 weeks | 347 (95.9) | 170 (95.0) |
| at least 8 weeks | 326 (90.1) | 165 (92.2) |
| at least 12 weeks | 306 (84.5) | 162 (90.5) |
| at least 16 weeks | 283 (78.2) | 159 (88.8) |
| at least 24 weeks | 191 (52.8) | 112 (62.6) |
| **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 |

The average daily Exelon® dose per treatment interval is in the next table, which I have copied from the submission. The average daily Exelon® dose for the entire study (± standard deviation) is 6.3 mg (± 2.3 mg).

| | 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 |
| | > 24 weeks | 158 | 8.1 ± 3.7 |

### *7.2.6 Concomitant (And Prior) Medication*

Non-central nervous system related concomitant medications, taken both prior to and after the start of the study, were used by 80.7% of patients in the Exelon® group and 79.3% of patients in the placebo group. The most frequently reported medication was aspirin (16.3% of Exelon®-treated patients and 19.6% of placebo-treated patients).

Central nervous system-related concomitant medication taken within 4 weeks prior to start of the study were used by 100% of those in the Exelon® group and 99.4% of those in the placebo group as might have been expected for a

population with Parkinson's Disease. Concomitant medications that were central nervous system-related were used by 100% of patients in both treatment groups. The most widely used central-nervous system related concomitant medications were those in the dopaminergic class. The pattern of dopaminergic agent use in various classes is summarized in the following table, taken from the submission.

| Dopaminergic agents (ATC class) | Exelon (N = 362) | Placebo (N = 179) |
|---|---|---|
| | n (%) | n (%) |
| **Prior to start of study drug** | 362 (100) | 178 (99.4) |
| 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) |
| Prolactin inhibitors | 43 (11.9) | 21 (11.7) |
| **Newly introduced after start of study drug** | 38 (10.5) | 17 (9.5) |
| Adamantane derivatives | 2 (0.6) | 0 |
| Dopa and dopa derivatives | 28 (7.7) | 12 (6.7) |
| Dopamine agonists | 9 (2.5) | 5 (2.8) |
| Monoamine oxidase B inhibitors | 0 | 1 (0.6) |
| Other dopaminergic agents | 4 (1.1) | 3 (1.7) |
| Prolactin inhibitors | 2 (0.6) | 0 |
| **Dose increase after start of study drug** | 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 |

### *7.2.7 Efficacy Results*

#### *7.2.7.1 Primary Efficacy Results*

##### 7.2.7.1.1 ADAS-Cog

In the protocol-specified primary efficacy analysis of the ADAS-Cog (intent-to-treat plus retrieved dropouts), the Exelon® treatment group improved by a mean of 2.1 points, whereas the placebo group deteriorated by a mean of 0.7 points, both at Week 24, with the difference being statistically significant as displayed in the following table

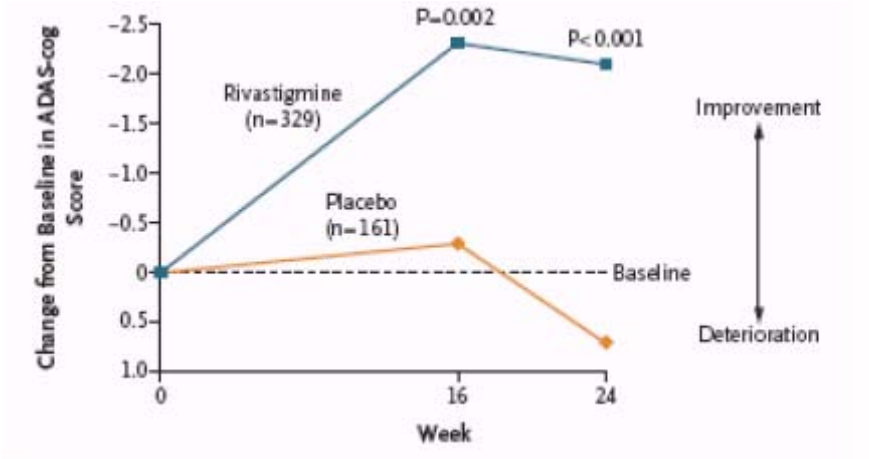
| | Exelon | | Placebo | | | | |
|---|---|---|---|---|---|---|---|
| | n | mean ± SD | n | mean ± SD | LS means difference | p-value | 95% CI (Exelon – placebo) |
| ITT+RDO baseline | 329 | 23.8 ± 10.2 | 161 | 24.3 ± 10.5 | | | |
| Change at week 16 | 329 | 2.3 ± 7.3 | 161 | 0.3 ± 6.8 | 2.06 | 0.002 * | 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 |
| OC baseline wk 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 |
| OC baseline wk 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 |

Higher change scores indicate greater improvement.

* p < 0.05. p-value based on two-way 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).

Somewhat greater treatment differences, which were again nominally statistically significant, were seen for both the intent-to-treat last-observation-carried-forward and observed cases populations.

The time-course of the change in ADAS-Cog score in the intent-to-treat plus retrieved dropouts population in this study is displayed in the next figure, which I have copied from the published report of this study.




A categorical analysis of the ADAS-Cog based on the proportion of patients improving (i.e., improving by at least 4 points) in each treatment group at Weeks 16 and 24 is summarized in the following sponsor table.

| | | 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.
p-values are based on CMH test blocking for country. * p < 0.05

For the categorical analysis above, nominally statistically significant treatment differences were seen, as indicated by the table for the both the intent-to-treat last-observation-carried-forward and observed cases populations.

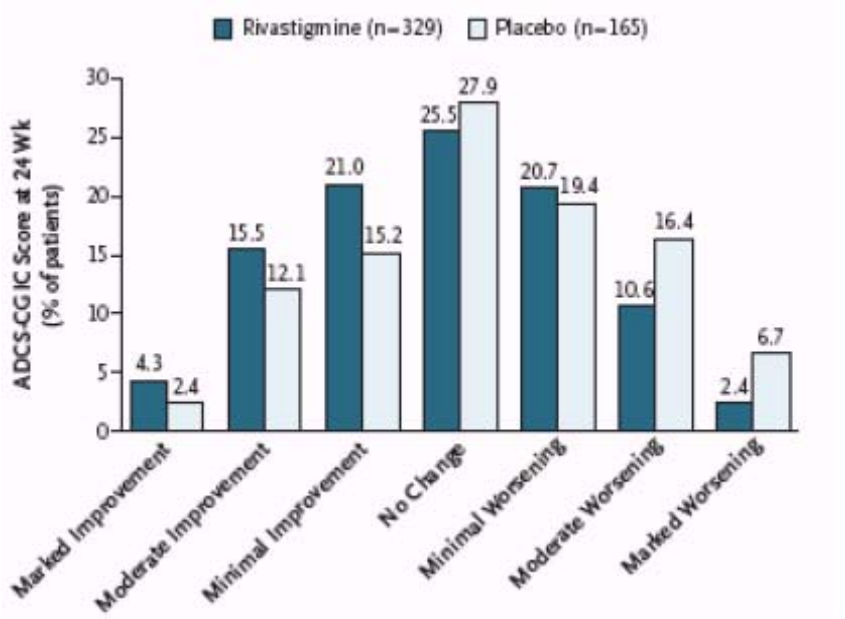
7.2.7.1.2 ADCS-CGIC

In the protocol-specified primary efficacy analysis of the ADCS-CGIC (intent-to-treat plus retrieved dropouts), the Exelon® treatment group showed a mean score of 3.8 at Week 24, whereas the placebo group showed a mean score of 4.3 at the same time timepoint, with the difference being statistically significant as displayed in the following sponsor table.

| | ITT+RDO | | LOCF | | OC | |
|---|---|---|---|---|---|---|
| | 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 | Exelon | Placebo | Exelon | Placebo | Exelon | Placebo |
| 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. *: p<0.05

The categorical data for the intent-to-treat plus retrieved dropouts population in the above table are also displayed in the following figure which I have copied from the published report of this study.




Similar treatment differences, which were nominally statistically significant, were seen for both the intent-to-treat last-observation-carried-forward and observed cases populations.

The categorical analysis of the ADCS-CGIC in the next sponsor table indicates that there were nominally statistically significantly higher proportions of patients improving in the Exelon® group relative to the placebo group in all populations analyzed.

| | Exelon | | Placebo | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Population/ Visit | N | % impr. | N | % impr. | p-value | Treatment effect | p-value | Odds ratio | 95% CI for odds ratio |
| ITT+RDO | | | | | | | | | |
| Week 16 | 318 | 42% | 159 | 31% | 0.028* | 0.23 ± 0.11 | 0.027* | 1.60 | 1.06 2.41 |
| Week 24 | 329 | 41% | 165 | 30% | 0.025* | 0.24 ± 0.11 | 0.023* | 1.61 | 1.07 2.44 |
| LOCF | | | | | | | | | |
| Week 16 | 282 | 46% | 153 | 31% | 0.007* | 0.30 ± 0.11 | 0.006* | 1.81 | 1.18 2.77 |
| Week 24 | 289 | 44% | 158 | 30% | 0.006* | 0.30 ± 0.11 | 0.006* | 1.83 | 1.19 2.82 |
| OC | | | | | | | | | |
| Week 16 | 282 | 46% | 153 | 31% | 0.007* | 0.30 ± 0.11 | 0.006* | 1.81 | 1.18 2.77 |
| Week 24 | 252 | 46% | 145 | 30% | 0.002* | 0.36 ± 0.12 | 0.002* | 2.07 | 1.31 3.26 |

Improving (impr.) is defined as markedly, moderately, or minimally improved.

p-values are based on a CMH test blocking for country. * $p < 0.05$

The odds ratio denotes the likelihood of an Exelon patient experiencing improvement relative to the likelihood of a placebo - treated patient experiencing improvement. An odds ratio > 1 represents an outcome in favor of Exelon.

### *7.2.7.2 Secondary Efficacy Results*

#### 7.2.7.2.1 ADCS-ADL

Nominal statistically significant treatment differences favoring Exelon® over placebo were seen at Week 24 for the mean change from baseline to endpoint in

the ADCS-ADL in all 3 populations analyzed, including the intent-to-treat retrieved dropout population. These results are in the sponsor table below.

| | Exelon | | Placebo | | | | |
|---|---|---|---|---|---|---|---|
| | N | mean ± SD | n | mean ± SD | LS means difference | p-value | 95% CI (Exelon – placebo) |
| ITT+RDO baseline | 333 | 41.6 ± 18.6 | 165 | 41.2 ± 17.7 | | | |
| Change at week 16 | 333 | -0.4 ± 11.2 | 165 | -1.5 ± 8.3 | 1.09 | 0.262 | -0.82 3.00 |
| Change at week 24 | 333 | -1.1 ± 12.6 | 165 | -3.6 ± 10.3 | 2.51 | 0.023* | 0.35 4.67 |
| LOCF baseline | 289 | 41.6 ± 18.5 | 158 | 40.9 ± 17.9 | | | |
| Change at week 16 | 289 | -0.2 ± 11.7 | 158 | -1.3 ± 8.4 | 1.17 | 0.263 | -0.88 3.22 |
| Change at week 24 | 289 | -0.8 ± 13.1 | 158 | -3.5 ± 10.4 | 2.72 | 0.021* | 0.41 5.04 |
| OC baseline wk 16 | 283 | 41.5 ± 18.4 | 157 | 41.1 ± 17.9 | | | |
| Change at week 16 | 283 | -0.2 ± 11.8 | 157 | -1.3 ± 8.4 | 1.19 | 0.261 | -0.89 3.26 |
| OC baseline wk 24 | 260 | 41.8 ± 18.5 | 142 | 42.4 ± 17.8 | | | |
| Change at week 24 | 260 | -0.3 ± 13.1 | 142 | -3.5 ± 10.7 | 3.20 | 0.010* | 0.77 5.62 |

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

Higher scores indicate better performance.

7.2.7.2.2 Neuropsychiatry Inventory

Nominal statistically significant treatment differences favoring Exelon® over placebo were seen at Week 24 for the mean change from baseline to endpoint in the 10-point Neuropsychiatry Inventory total score in the intent-to-treat retrieved dropout and intent-to-treat last-observation-carried-forward populations (these results are displayed in the table below).

| Population/ Visit | | Exelon | | Placebo | | Exelon vs. Placebo |
|---|---|---|---|---|---|---|
| | | N | Mean ± SD | N | Mean ± SD | p-value |
| ITT+RDO | Baseline | 334 | 12.7 ± 11.7 | 166 | 13.2 ± 13.0 | |
| Week 16 | Change | 334 | -1.6 ± 9.9 | 166 | 0.4 ± 10.7 | 0.018 * |
| Week 24 | Change | 334 | -2.0 ± 10.0 | 166 | 0.0 ± 10.4 | 0.015 * |
| LOCF | Baseline | 289 | 12.3 ± 11.7 | 159 | 13.0 ± 13.0 | |
| Week 16 | Change | 287 | -1.8 ± 10.3 | 157 | -0.0 ± 10.1 | 0.038* |
| Week 24 | Change | 288 | -2.1 ± 10.3 | 159 | -0.4 ± 9.7 | 0.032 * |
| OC | | | | | | |
| Week 16 | Baseline | 284 | 12.4 ± 11.8 | 157 | 12.8 ± 13.0 | |
| | Change | 284 | -1.9 ± 10.3 | 157 | -0.0 ± 10.1 | 0.038 * |
| Week 24 | Baseline | 262 | 12.4 ± 11.7 | 144 | 12.1 ± 11.8 | |
| | Change | 262 | -2.5 ± 10.5 | 144 | -1.1 ± 9.2 | 0.182 |

p-values are based on two-way analysis of covariance. * p < 0.05

Lower change scores indicate greater improvement

The proportion of patients with an improved 10-point Neuropsychiatry Inventory total score was also reported to show a nominally statistically significant superiority to placebo in all 3 analysis populations. Treatment group differences on the 12- point Neuropsychiatry Inventory were not even nominally statistically significant.

A nominally statistically significant treatment difference favoring Exelon® was seen for the Neuropsychiatry Inventory Caregiver Distress score for a single item: aberrant motor behavior.

7.2.7.2.3 Health Economic Parameters

The analysis of these measures is to be reported separately.

7.2.7.2.4 Cognitive Drug Research – Attention Battery

The combined Power of Attention mean change from baseline score at Week 24 showed a nominally statistically significant difference from placebo.

| Population/ Visit | | Exelon | | Placebo | | Exelon vs. Placebo |
|---|---|---|---|---|---|---|
| | | N | Mean ± SD | N | Mean ± SD | p-value |
| ITT+RDO | Baseline | 328 | 2197.0 ± 1170.2 | 158 | 2490.5 ± 2134.8 | |
| Week 16 | Change | 328 | -26.5 ± 892.2 | 158 | 33.0 ± 1432.4 | 0.110 |
| Week 24 | Change | 328 | -30.5 ± 989.7 | 158 | 142.7 ± 1780.2 | 0.009* |
| LOCF | Baseline | 283 | 2235.7 ± 1218.2 | 151 | 2519.2 ± 2362.3 | |
| Week 16 | Change | 283 | -26.9 ± 955.0 | 151 | -26.2 ± 1223.8 | 0.276 |
| Week 24 | Change | 283 | -34.6 ± 1059.0 | 151 | 82.5 ± 1636.9 | 0.028* |
| OC | | | | | | |
| Week 16 | Baseline | 261 | 2197.2 ± 1184.4 | 143 | 2469.4 ± 2369.4 | |
| | Change | 261 | -29.2 ± 994.6 | 143 | -27.7 ± 1257.8 | 0.287 |
| Week 24 | Baseline | 249 | 2218.4 ± 1200.9 | 134 | 2326.9 ± 2164.7 | |
| | Change | 249 | -63.9 ± 1106.0 | 134 | 139.7 ± 1709.5 | 0.025* |

Lower change scores indicate greater improvement. p-values are based on two-way analysis of covariance. * p < 0.05

7.2.7.2.5 Executive Functioning Tests

Since D-KEFS executive function tests were not performed at all centers, the analyses were performed only in the Observed Cases population.

On the D-KEFS Letter Fluency test change score, a nominally statistically significant treatment difference was seen at Week 24, with the Exelon® group improving and placebo group deteriorating on mean scores (see sponsor table below).

| Population/ Visit | | Exelon | | Placebo | | Exelon vs. Placebo |
|---|---|---|---|---|---|---|
| OC | | N | Mean ± SD | N | Mean ± SD | p-value |
| Baseline | | 290 | 13.9 ± 9.5 | 158 | 14.5 ± 9.4 | |
| Week 16 | Change | 280 | 0.6 ± 6.3 | 152 | -1.2 ± 5.6 | 0.006* |
| Week 24 | Change | 258 | 1.7 ± 6.8 | 144 | -1.1 ± 6.3 | <0.001* |

p-values are based on van Elteren test blocking for country. * p < 0.05

Higher change scores indicate greater improvement

In the D-KEFS Color Word Interference and Card Sorting Tests, a few sub-scores showed nominally statistically significant differences favoring Exelon®.

On the Symbol Digits Modality Test, the number of correct substitutions showed a nominally statistically significant improvement in favor of Exelon® at Week 24.

#### 7.2.7.2.6 Ten Point Clock Test

This test too was performed only on a subset of the study population and analyses were confined to the Observed Cases dataset. As the sponsor-supplied table below indicates, the mean change from baseline score for this small subset improved slightly in the Exelon® group and deteriorated slightly in the placebo group, with the difference being nominally statistically significant.

| Population/ Visit | Exelon | | Placebo | | Exelon vs. placebo |
|---|---|---|---|---|---|
| OC | N | Mean ± SD | N | Mean ± SD | p-value |
| Baseline | 62 | 3.5 ± 3.7 | 37 | 2.9 ± 3.8 | |
| Change from baseline at week 24 | 50 | 0.6 ± 2.5 | 30 | -0.6 ± 2.4 | 0.015* |

Lower scores indicate worse cognitive performance. *: p-value <0.05

#### 7.2.7.2.7 Mini-Mental Status Examination

In the intent-to-treat plus retrieved dropouts population, mean Mini-Mental Status Examination scores increased by 0.8 points in the Exelon® group and decreased by 0.2 points in the placebo, at Week 24, with the difference being nominally statistically significant. Similar results were seen with the other two analysis populations.

### *7.2.7.3 Overall Efficacy Response*

An overall responder was defined as a patient with a combination of the following

- An improvement in ADAS-Cog of at least 4 points
- ADCS-CGIC category of 1 to 4
- ADCS-ADL change ≥ 0 points

The categorical analysis of the percentage of overall responders showed a nominally statistically significant treatment difference favoring Exelon® over placebo at Week 24 for the intent-to-treat-last-observation-carried-forward population only (20% of patients in the Exelon® group and 13% of patients in the placebo group were considered responders in this dataset).

### *7.2.7.4 Pharmacogenetic Analyses*

302 out of 541 randomized patients consented to pharmacogenetic sampling. The results of these analyses are to be reported separately.

### *7.2.7.5 Biomarker Analyses*

356 and 324 patients consent to biomarker serum and urine sampling, respectively. The results of these analyses are to be reported separately.

### *7.2.8 Safety Results*

#### *7.2.8.1 Overall Adverse Event Experience*

The overall incidence of all adverse events (i.e., proportion of patients randomized who had any adverse event) was higher in the Exelon® group (83.7%) than in the placebo group (70.9%).

The following table, copied from the submission, summarizes the incidence of the most common adverse events (those with an incidence of at least 5% in either treatment group) in this study, in descending order of frequency.

| | Exelon | Placebo |
|---|---|---|
| No. (%) of patients studied | 362 | 179 |
| No. (%) of patients with AE(s) | 303 (83.7) | 127 (70.9) |
| **AE preferred term** | n (%) | n (%) |
| Nausea | 105 (29.0) | 20 (11.2) |
| Vomiting | 60 (16.6) | 3 ( 1.7) |
| Tremor | 37 ( 10.2) | 7 ( 3.9) |
| Diarrhea | 26 ( 7.2) | 8 ( 4.5) |
| Anorexia | 22 ( 6.1) | 5 ( 2.8) |
| Fall | 21 ( 5.8) | 11 ( 6.1) |
| Dizziness | 21 ( 5.8) | 2 ( 1.1) |
| Hypotension | 19 ( 5.2) | 14 ( 7.8) |
| Hallucination | 17 ( 4.7) | 17 ( 9.5) |
| Constipation | 16 ( 4.4) | 12 ( 6.7) |
| Confusion | 13 ( 3.6) | 10 ( 5.6) |
| Orthostatic hypotension | 6 ( 1.7) | 9 ( 5.0) |

AEs are listed by descending order of frequency in the Exelon group. Shown are all AEs with an incidence of at least 5% in either group.

As the table above indicates, the most common of the adverse events, all of which were more frequent in the Exelon® group than in the placebo group, were nausea, vomiting, tremor, diarrhea, and anorexia. The incidence of dizziness was also substantially greater in the Exelon® group than in the placebo group.

The next table, also copied from the submission, indicates the overall incidence of adverse events during each (4-week) treatment period.

| | Exelon | Placebo |
|---|---|---|
| No. (%) of patients studied | 362 | 179 |
| No. (%) of patients with AE(s) | 303 (83.7) | 127 (70.9) |
| **Study period** | n/N (%) | n/N (%) |
| Baseline to week 4 | 107/362 (29.6) | 56/179 (31.3) |
| Week 5 to week 8 | 150/343 (43.7) | 46/168 (27.4) |
| Week 9 to week 12 | 126/324 (38.9) | 46/165 (27.9) |
| Week 13 to week 16 | 99/301 (32.9) | 35/162 (21.6) |
| Week 17 to week 20 | 67/281 (23.8) | 26/158 (16.5) |
| Week 21 to week 24 | 48/271 (17.7) | 34/151 (22.5) |
| Week 25 to day of last dose + 2 days | 13/158 (8.2) | 4/96 (4.2) |

Percentages refer to the number of patients on treatment at the start of each study period interval.

As the table above indicates, these events appear to have been more frequent, in the Exelon® group, during the titration phase of this study than during the maintenance phase.

*7.2.8.2 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events*

The incidence of adverse events in each item in this grouping is summarized in the following table, which I have copied from the submission.

| | Exelon | Placebo |
|---|---|---|
| No. (%) of patients studied | 362 | 179 |
| No. (%) of patients with AE(s) | 303 (83.7) | 127 (70.9) |
| **Number (%) of patients with serious or other significant events** | n (%) | n (%) |
| Death | 4 (1.1) | 7 ( 3.9) |
| SAE(s) | 47 (13.0) | 26 (14.5) |
| Clinically significant AE(s) | | |
| Discontinued due to SAE(s) | 20 ( 5.5) | 14 (7.8) |
| Discontinued due to non-serious AE(s) | 46 (12.7) | 6 (3.4) |

Treatment-emergent deaths and SAE(s) are reported.

7.2.8.2.1 Deaths

4 patients (1.1% of those randomized) in the Exelon® group and 7 patients in the placebo group (3.9% of those randomized) died during the study. All deaths listed occurred while receiving study drug or within 15 days of study drug discontinuation (all deaths that occurred while on study drug or within 30 days of study drug discontinuation were to be captured).

Individual deaths in both the Exelon® and placebo groups are listed in the following table, which I have copied from the submission.

| Treatment group Patient number | Age/gender/ race | Study day of last dose | Study day of death | Principal cause of death (preferred term) |
|---|---|---|---|---|
| **Exelon** | | | | |
| BEL/0002/00003 | 77/M/Ca | 68 | 69 | Myocardial infarction |
| ESP/0074/00004 | 76/M/Ca | 88 | 88 | Sudden cardiac death |
| FRA/0012/00003 | 82/F/Ca | 141 | 142 | Dehydration |
| GBR/0087/00003 | 79/F/Ca | 121 | 127 | Pneumonia aspiration |
| **Placebo** | | | | |
| BEL/0003/00001 | 74/M/Ca | 74 | 82 | Cerebral hemorrhage |
| ESP/0073/00005 | 76/M/Ca | 19 | 34 | Neuroleptic malignant syndrome |
| ESP/0075/00002 | 82/M/Ca | 114 | 115 | Cardiac arrest |
| FRA/0016/00005 | 82/M/Ca | 11 | 19 | Cardiac failure |
| GBR/0085/00001 | 72/M/Ca | 49 | 50 | Pneumonia |
| GBR/0089/00007 | 63/M/Ca | 88 | 88 | Pulmonary embolism |
| GBR/0094/00002 | 76/M/Ca | 148 | 149 | Bronchopneumonia |

7.2.8.2.2 Non-Fatal Serious Adverse Events

13.0% of those in the Exelon® group and 14.5% of those in the placebo group experienced a non-fatal serious adverse event during this study. The incidence of such events by system organ class is in the following table.

| | Exelon | Placebo |
|---|---|---|
| No. (%) of patients studied | 362 | 179 |
| No. (%) of patients with SAE(s) | 47 (13.0) | 26 (14.5) |
| **System organ class** | n (%) | n (%) |
| **AE preferred term** | | |
| Cardiac disorders | 3 (0.8) | 3 (1.7) |
| Gastrointestinal disorders | 9 (2.5) | 4 (2.2) |
| Infections and infestations | 5 (1.4) | 7 (3.9) |
| Injury, poisoning and procedural complications | 10 (2.8) | 4 (2.2) |
| Investigations | 4 (1.1) | 0 |
| Metabolism and nutrition disorders | 7 (1.9) | 2 (1.1) |
| Dehydration | 5 (1.4) | 2 (1.1) |
| Nervous system disorders | 6 (1.7) | 8 (4.5) |
| Syncope | 0 | 2 (1.1) |
| Psychiatric disorders | 7 (1.9) | 6 (3.4) |
| Confusional state | 2 (0.6) | 2 (1.1) |
| Respiratory, thoracic and mediastinal disorders | 1 (0.3) | 2 (1.1) |
| Vascular disorders | 4 (1.1) | 1 (0.6) |

I have read the listings for all individual serious adverse events. It is hard to link the individual events that occurred in patients treated with Exelon® to the drug. All events appeared to be consistent with intercurrent illnesses common in the elderly, and their complications.

7.2.8.2.3 Discontinuations Due To Adverse Events

66 patients (18.2%) receiving Exelon® and 20 patients (11.2%) of those receiving placebo discontinued study drug prematurely on account of an adverse event.

Individual adverse events leading to discontinuation that occurred in at least 2 Exelon®-treated patients are in the following table which I have created from one supplied by the sponsor.

| Adverse Events | Exelon® (n = 362) | | Placebo (n = 179) | |
|---|---|---|---|---|
| | N | % | N | % |
| Nausea | 13 | 3.6 | 1 | 0.6 |
| Vomiting | 7 | 1.9 | 1 | 0.6 |
| Diarrhea | 4 | 1.1 | 2 | 1.1 |
| Asthenia | 2 | 0.6 | 0 | 0.0 |
| Abasia | 2 | 0.6 | 0 | 0.0 |
| Dehydration | 2 | 0.6 | 1 | 0.6 |
| Tremor | 6 | 1.7 | 0 | 0.0 |
| Parkinson's Disease | 3 | 0.8 | 0 | 0.0 |
| Dizziness | 2 | 0.6 | 0 | 0.0 |
| Headache | 2 | 0.6 | 0 | 0.0 |
| Parkinsonism | 2 | 0.6 | 0 | 0.0 |
| Balance disorder | 2 | 0.6 | 0 | 0.0 |
| Hallucination | 4 | 1.1 | 2 | 1.1 |
| Confusional state | 3 | 0.8 | 1 | 0.6 |
| Hypotension | 2 | 0.6 | 0 | 0.0 |

I have read the listings for all individual adverse events that led to treatment discontinuation. With the exception of events such as nausea, vomiting, and diarrhea, which could be a consequence of the cholinomimetic effects of Exelon®, it is hard to link the individual events that occurred in patients treated with Exelon® to the drug. All other events appeared to be consistent with intercurrent illnesses common in the elderly (and in the study population) and their complications.

*7.2.8.3 Other Significant Adverse Events*

Adverse event terms that might be considered to possibly represent a worsening of Parkinson's Disease were pre-specified in the study protocol. The incidence of all such events was higher in the Exelon® group (27.3%) than in the placebo group (15.6%). The incidence of individual adverse events is summarized in the following table. [A number of additional event terms did not occur at all].

| | Exelon | | | Placebo | | |
|---|---|---|---|---|---|---|
| No. (%) of patients studied | 362 (100) | | | 179 (100) | | |
| No. (%) of patients with AE(s) | 303 (83.7) | | | 127 (70.9) | | |
| No. (%) of patients with PD worsening AE(s) | 99 (27.3) | | | 28 (15.6) | | |
| Maximum severity | Mild | Moderate | Severe | Mild | Moderate | Severe |
| **PD AE preferred term** | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Tremor | 18 (5.0) | 18 (5.0) | 1 (0.3) | 5 (2.8) | 2 (1.1) | 0 |
| Fall | 14 (3.9) | 6 (1.7) | 1 (0.3) | 10 (5.6) | 1 (0.6) | 0 |
| (Worsening of) PD | 6 (1.7) | 5 (1.4) | 1 (0.3) | 1 (0.6) | 1 (0.6) | 0 |
| Bradykinesia | 4 (1.1) | 4 (1.1) | 1 (0.3) | 1 (0.6) | 1 (0.6) | 1 (0.6) |
| (Worsening of) Parkinsonism | 2 (0.6) | 5 (1.4) | 1 (0.3) | 0 | 1 (0.6) | 0 |
| Dyskinesia | 2 (0.6) | 3 (0.8) | 0 | 1 (0.6) | 0 | 0 |
| Gait abnormal | 2 (0.6) | 2 (0.6) | 1 (0.3) | 0 | 0 | 0 |
| Salivary hypersecretion | 1 (0.3) | 3 (0.8) | 1 (0.3) | 0 | 0 | 0 |
| Balance disorder | 2 (0.6) | 1 (0.3) | 0 | 1 (0.6) | 0 | 1 (0.6) |
| Dystonia | 2 (0.6) | 0 | 1 (0.3) | 0 | 0 | 1 (0.6) |
| Musculoskeletal stiffness | 2 (0.6) | 1 (0.3) | 0 | 0 | 0 | 0 |
| Drooling | 0 | 2 (0.6) | 0 | 0 | 2 (1.1) | 0 |
| Extrapyramidal disorder | 0 | 1 (0.3) | 0 | 0 | 0 | 0 |
| Hyperkinesia | 1 (0.3) | 0 | 0 | 0 | 0 | 0 |
| Hypokinesia | 0 | 0 | 1 (0.3) | 0 | 0 | 0 |
| Motor dysfunction | 1 (0.3) | 0 | 0 | 0 | 0 | 0 |
| Movement disorder | 0 | 1 (0.3) | 0 | 0 | 0 | 0 |
| Muscle rigidity | 0 | 1 (0.3) | 0 | 0 | 0 | 0 |
| On and off phenomenon | 0 | 1 (0.3) | 0 | 1 (0.6) | 0 | 0 |
| Rigors | 0 | 1 (0.3) | 0 | 0 | 0 | 0 |
| Dysarthria | 0 | 0 | 0 | 1 (0.6) | 0 | 0 |
| Freezing phenomenon | 0 | 0 | 0 | 0 | 1 (0.6) | 0 |
| Hypertonia | 0 | 0 | 0 | 1 (0.6) | 0 | 0 |

AE preferred terms are sorted by descending frequency in the Exelon group

A higher incidence of tremor, worsening of Parkinson's Disease, worsening of parkinsonism, bradykinesia, dyskinesia, abnormal gait, and salivary hypersecretion in the Exelon® group is noteworthy.

*7.2.8.4 Laboratory Tests*

The sponsor has highlighted changes from baseline in serum amylase, lipase, and prolactin, which were more apparent in the Exelon® group than in the placebo.

As the sponsor table below indicates, the mean change from baseline in these parameters was greater in the Exelon® group than in the placebo group. The table also shows the mean levels for each parameter at Week 24.

| | Mean ± SD baseline values | | Mean ± SD change from baseline | |
|---|---|---|---|---|
| | Exelon | Placebo | Exelon | Placebo |
| **Biochemistry** | | | | |
| Amylase (U/L) | 65.98 ± 31.72 | 66.94 ± 25.54 | 13.23 ± 30.50 | 3.97 ± 17.21 |
| Lipase (blood) (U/L) | 33.14 ± 18.38 | 33.59 ± 19.69 | 13.23 ± 58.75 | -0.34 ± 18.69 |
| Prolactin (blood) (µg/L) | 13.10 ± 27.49 | 12.71 ± 23.71 | 4.14 ± 30.80 | 1.96 ± 18.93 |

The proportions of patients in each treatment group who had normal serum amylase, lipase, and prolactin levels at baseline, but higher than normal values at Week 24 are in the following table. Again, the proportion of such elevations is higher in the Exelon® group than in the placebo group.

| Parameter | Proportion with normal values at baseline and elevations at Week 24* | |
|---|---|---|
| | Exelon® | Placebo |
| Serum amylase | 17.1% | 10.1% |
| Serum lipase | 9.0% | 3.6% |
| Serum prolactin | 9.5% | 7.9% |

*The data for serum prolactin are for values outside the reference range, not merely

Narratives have been provided for all patients with elevated serum amylase and/or lipase during the study.

The sponsor also points out the following:

- The maximum serum amylase at Week 24 was 196 U/L (reference range of 1 to 88 U/L); the maximum serum lipase at Week 24 was 342 U/L (reference range of 0 to 63 U/L)
- No patient was diagnosed to have pancreatitis (as an adverse event during the study)
- No patient discontinued treatment on account of elevated serum amylase or lipase

The incidence of other newly occurring notable laboratory abnormalities is in the following table which I have copied from the submission:

| | | Exelon | Placebo |
|---|---|---|---|
| No. of patients studied | | 362 | 179 |
| **Notable hematology abnormality** | | n (%) | n (%) |
| Lymphocytes | Low | 3 (1.3) | 2 (1.6) |
| Eosinophils | High | 1 (0.4) | 1 (0.8) |
| Platelets | Low | 2 (0.9) | 0 |
| **Notable serum chemistry abnormality** | | n (%) | n (%) |
| AST | High | 1 (0.4) | 0 |
| Bilirubin | High | 1 (0.4) | 0 |
| BUN | High | 9 (3.5) | 5 (3.6) |
| Creatinine | High | 1 (0.4) | 0 |
| Potassium | Low | 0 | 1 (0.7) |
| | High | 0 | 1 (0.7) |
| Phosphate | Low | 1 (0.4) | 0 |
| | High | 1 (0.4) | 0 |
| Glucose | Low | 1 (0.4) | 0 |
| | High | 5 (2.0) | 4 (3.0) |
| Cholesterol | High | 5 (1.9) | 1 (0.7) |
| Triglycerides | High | 7 (2.8) | 1 (0.7) |

Percentages are based on the number of evaluable patients (those having a baseline and a post-baseline result) for each parameter.

*7.2.8.5 Vital Signs*

The number of patients with newly occurring or worsening vital sign and weight abnormalities was comparable between treatment groups, as indicated in the following sponsor table.

| | | Exelon | Placebo |
|---|---|---|---|
| No. of patients studied | | 362 | 179 |
| **Notable abnormality** | | n (%) | n (%) |
| Pulse rate | High | 1 ( 0.3) | 1 ( 0.6) |
| | Low | 4 ( 1.1) | 1 ( 0.6) |
| Diastolic blood pressure | High | 3 ( 0.8) | 3 ( 1.7) |
| | Low | 12 ( 3.3) | 10 ( 5.6) |
| Systolic blood pressure | High | 7 ( 1.9) | 3 ( 1.7) |
| | Low | 26 ( 7.2) | 18 (10.1) |
| | High and Low | 0 | 1 ( 0.6) |
| Weight | High | 24 ( 6.6) | 7 ( 3.9) |
| | Low | 59 (16.3) | 25 (14.0) |
| | High and Low | 0 | 1 ( 0.6) |

Data on vital signs refer to data obtained after standing for 2 minutes.

The mean changes from baseline in these parameters were comparable in the 2 treatment groups.

*7.2.8.6 Electrocardiograms*

Summary statistics for electrocardiogram parameters have been reviewed fully. The sponsor has drawn attention to the following:

- The mean $QT_c$ interval remained unchanged in the placebo group over the course of the study, but decreased slightly in the Exelon® group at Week 24
- A slight increase in mean RR interval was seen in the Exelon® group, but the change was not felt to be statistically significant
- Newly occurring clinically significant electrocardiogram abnormalities were seen in 1.4% of patients in the Exelon® group and 1.1% of patients in the placebo group. The new abnormalities seen in the Exelon® group were artificial pacemaker rhythm, right bundle branch block, inferior myocardial infarction, and T wave inversion

*7.2.8.7 UPDRS Part III Scores*

The UPDRS motor scores were used as a means of assessing changes in the motor manifestations of Parkinson's Disease during the study. The mean change from baseline scores at Weeks 16 and 24 are summarized in the following table, which I have copied from the submission.

| Visit | | Exelon | | Placebo | | Difference in LS Means | Exelon vs. placebo |
|---|---|---|---|---|---|---|---|
| | | N | Mean ± SD | N | Mean ± SD | | p-value |
| Week 16 | Baseline | 286 | 33.5 ± 14.5 | 159 | 32.7 ± 13.0 | | |
| | Change | 286 | -0.6 ± 8.7 | 159 | -0.5 ± 7.8 | 0.09 | 0.914 |
| Week 24 | Baseline | 263 | 32.9 ± 14.2 | 146 | 32.5 ± 13.0 | | |
| | Change | 263 | -0.3 ± 9.5 | 146 | -0.4 ± 8.5 | 0.20 | 0.827 |

p-values are based on two-way analysis of covariance. *: $p < 0.05$

The changes in each treatment group at each timepoint were similar and were not considered clinically significant. The differences in change score were not even nominally statistically significant.

The sponsor also points out that statistically significant treatment differences were not seen for any of the individual UPDRS Part III item scores. The mean change from baseline for the tremor score at Week 24 was 0.1 ± 2.6 for the Exelon® group and 0.0 ± 2.1 in the placebo group.

### *7.3 Sponsor's Conclusions*

In this trial, which was conducted in dementia associated with Parkinson's Disease, the efficacy of Exelon® in a dose of 3 to 12 mg/day for 24 weeks was significantly superior to that of placebo on a measure of cognition (which was assessed by the ADAS-Cog) and on a measure of the clinical global rating of change (ADCS-CGIC). The primary objective of the study was therefore achieved

Secondary efficacy measures that assessed activities of daily living, behavior, attention and executive functioning also improved more significantly in those treated with Exelon® than in those treated with placebo.

The safety profile of Exelon® in this study was consistent with published data for Exelon® administered to patients with Alzheimer's Disease. While the incidence of adverse events associated with a worsening of Parkinson's Disease was higher in the Exelon® group than in the placebo group, the UPDRS Part III (motor) ratings did not reveal any clinically or statistically relevant difference between treatment groups for either the total score or any of the individual item scores. Changes in laboratory tests and electrocardiograms were considered clinically insignificant.

### *7.4 Study Abstract*

Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, Durif F, Kulisevsky J, van Laar T, Lees A, Poewe W, Robillard A, Rosa MM, Wolters E, Quarg P, Tekin S, Lane R. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med. 2004;351:2509-18

BACKGROUND: Cholinergic deficits are prominent in patients who have dementia associated with Parkinson's disease. We investigated the effects of the dual cholinesterase inhibitor rivastigmine in such patients.

METHODS: Patients in whom mild-to-moderate dementia developed at least 2 years after they received a clinical diagnosis of Parkinson's disease were randomly assigned to receive placebo or 3 to 12 mg of rivastigmine per day for 24 weeks. Primary efficacy variables were the scores for the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) and Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC). Secondary clinical outcomes were the scores for the Alzheimer's Disease Cooperative Study-Activities of Daily Living, the 10-item Neuropsychiatric Inventory, the Mini-Mental State Examination, Cognitive Drug Research power of attention tests, the Verbal Fluency test, and the Ten Point Clock-Drawing test.

RESULTS: A total of 541 patients were enrolled, and 410 completed the study. The outcomes were better among patients treated with rivastigmine than among those who received placebo; however, the differences between these two groups were moderate and similar to those reported in trials of rivastigmine for Alzheimer's disease. Rivastigmine-treated patients had a mean improvement of 2.1 points in the score for the 70-point ADAS-cog, from a baseline score of 23.8, as compared with a 0.7-point worsening in the placebo group, from a baseline score of 24.3 ($P<0.001$). Clinically meaningful improvements in the scores for the ADCS-CGIC were observed in 19.8 percent of patients in the rivastigmine group and 14.5 percent of those in the placebo group, and clinically meaningful worsening was observed in 13.0 percent and 23.1 percent, respectively (mean score at 24 weeks, 3.8 and 4.3, respectively; $P=0.007$). Significantly better outcomes were seen with rivastigmine with respect to all secondary efficacy variables. The most frequent adverse events were nausea (affecting 29.0 percent of patients in the rivastigmine group and 11.2 percent of those in the placebo group, $P<0.001$), vomiting (16.6 and 1.7 percent, $P<0.001$), and tremor (10.2 and 3.9 percent, $P=0.01$).

CONCLUSIONS: In this placebo-controlled study, rivastigmine was associated with moderate improvements in dementia associated with Parkinson's disease but also with higher rates of nausea, vomiting, and tremor.

## *7.5 Additional Observations And Comments By Agency Statistical Reviewer About Study 2311*

The Agency Biometrics Reviewer for this submission, Dr Joanne Zhang, has made the following main observations, and drawn the overall conclusions outlined below regarding the efficacy results of this study

### *7.5.1 Observations*

- Dr Zhang has independently performed the protocol-specified primary efficacy analyses and has obtained results that agree with those obtained by the sponsor. However she has the following concerns about these analyses

    - An assumption underlying the use of an analysis of covariance (used in this instance for the primary efficacy analysis of the ADAS-Cog) is that the data be normally distributed. Dr Zhang tested the residuals for the analysis of covariance model used for the ADAS-Cog analysis with the Wilk-Shapiro test; the hypothesis of normality of the residuals was rejected (p-values of 0.0072 for Week 16, and < 0.0072 for Week 24). Dr Zhang therefore used a non-parametric method, the Wilcoxon rank sum test, for the analysis of the ADAS-Cog and demonstrated statistically significant differences favoring Exelon® over placebo at both Weeks 16 and 24 ($p < 0.005$ at both timepoints)

    - Another assumption underlying the use of an analysis of covariance model to test for differences between the drug and placebo groups is that of a constant regression relationship between the 2 treatment groups; if that assumption is violated it is indicative of an interaction between the treatment groups and independent variable (i.e., the baseline value) and this interaction renders difficult the interpretation of the final treatment effect due to the drug. Dr Zhang tested the heterogeneity of the slopes for the 2 treatment groups for the ADAS-Cog at Weeks 16 and 24 in the intent-to-treat plus retrieved dropouts population; while the slopes at Week 16 were similar, those at Week 24 were statistically significantly different, as indicated by the table below. Therefore, if the analysis of covariance model is relied on to predict the treatment effect due to the drug, the drug will be underestimated at low baseline values and overestimated at high baseline values. The results of the sponsor's analysis of covariance applied to the ADAS-Cog change from baseline data at Week 24 therefore need to be interpreted with caution

| | Timepoint | Estimate | Standard Error | P-values for the heterogeneity of slopes |
|---|---|---|---|---|
| Slope for Exelon® | Week 16 | 0.216 | 0.037 | |
| Slope for placebo | Week 16 | 0.215 | 0.051 | 0.982 |
| Slope for Exelon® | Week 24 | 0.270 | 0.041 | |
| Slope for placebo | Week 24 | 0.120 | 0.057 | 0.034 |

- When the percentage of those improving on the ADCS-CGIC at Weeks 16 and 24 in the Exelon® and placebo groups was compared by country (Austria, Norway, and Portugal were combined as the sample size for each was very small), the Exelon® group performed better than the placebo group for most countries whereas the placebo group performed better than the Exelon® group for the remaining countries

- Dr Zhang also repeated the primary efficacy analyses on subgroups defined by gender. Some of her findings are reproduced below

  - The number of male and female patients in each treatment group was as follows

| Treatment Group | Exelon® N | Placebo N |
|---|---|---|
| Women | 128 | 62 |
| Men | 234 | 117 |

  - Her subgroup analyses for the intent-to-treat plus retrieved dropouts populations on the ADAS-Cog change from baseline score at Week 24 are below

| Subgroup | Exelon® Mean change (SD) | Placebo Mean change (SD) | p-value |
|---|---|---|---|
| Women | 1.9 (8.4) | -0.9 (8.0) | 0.027 |
| Men | 2.2 (8.1) | -0.7 (7.2) | 0.001 |

  - Her subgroup analyses for the intent-to-treat plus retrieved dropouts populations on the ADCS-CGIC score at Week 24 are below

| | Women | | Men | |
|---|---|---|---|---|
| | Exelon® | Placebo | Exelon® | Placebo |
| N | 116 | 57 | 213 | 108 |
| Mean ± SD | 3.9 ± 1.5 | 4.3 ± 1.4 | 3.8 ± 1.4 | 4.3 ± 1.5 |
| Markedly improved (%) | 2 | 2 | 6 | 3 |
| Moderately improved (%) | 19 | 14 | 14 | 11 |
| Minimally improved (%) | 19 | 11 | 22 | 18 |
| Unchanged (%) | 28 | 30 | 24 | 27 |
| Minimally worse (%) | 14 | 21 | 24 | 19 |
| Moderately worse (%) | 15 | 19 | 8 | 15 |
| Markedly worse (%) | 3 | 4 | 2 | 8 |
| p-value | 0.350 | | 0.045 | |

- She has noted that the sponsor has used the intent-to-treat plus retrieved dropouts population for the primary efficacy analysis, whereas the Agency usually recommends that the intent-to-treat last-observation-carried-forward population be used for that purpose. She does, however, also note that when the same analysis was repeated for the intent-to-treat last-observation-carried-forward population, the results were similar.

### *7.5.2 Conclusions*

Dr Zhang has concluded that the data provided support the efficacy of Exelon® in Parkinson's Disease Dementia, based on the prospectively-specified statistical analysis plan; several sensitivity analyses support this conclusion. She does, however, note that a gender-based subgroup analysis suggests that this benefit may not extend to women.

## *7.6 Reviewer's Comments*

### *7.6.1 Efficacy Of Exelon®*

This study does indicate that Exelon® in a dose of 3 to 12 mg/day did have efficacy in the entire study population, based on prospectively-specified criteria. Although a statistically significant treatment effect was not seen in women alone on the gender-based subgroup analysis for the ADCS-CGIC performed by the Agency Biometrics Reviewer, the effect sizes (and variance) in that subgroup for the mean change from baseline to Week 24 in ADAS-Cog score and mean ADCS-CGIC score were similar to those seen in men, while fewer women than men were enrolled in the study.

The implications of the results of this study in the context of the new claim (i.e., "treatment of mild to moderate dementia associated with Parkinson's Disease") sought by the sponsor in this Supplemental Application are discussed later in the review.

### *7.6.2 Safety Of Exelon®*

The safety data for this study indicate that the adverse event profile of Exelon® in the study population was largely similar to that seen in clinical trials with Alzheimer's Disease, in that there was a distinctly higher frequency of nausea, vomiting, diarrhea, and anorexia in those exposed to Exelon® than in those exposed to placebo.

Of special relevance to a population with Parkinson's Disease, was the observation that tremor (which was not further characterized) was recorded as a treatment-emergent adverse event in about 10% of those received Exelon® and 4% of those who received placebo in this study (in the controlled clinical trials of Exelon® that were conducted prior to its approval for Alzheimer's Disease, tremor was seen in about 4% of those who received Exelon® and 1% of those who received placebo). Several other adverse events that may conceivably have been linked to a worsening in Parkinson's Disease were also more frequent in those treated with Exelon® than in those treated with placebo, but their incidence in the Exelon®-treated group was lower than that of tremor. However, changes in UPDRS total motor scores, probably a more objective measure of change in the motor manifestations of Parkinson's Disease than the incidence of treatment-emergent adverse events, showed no meaningful difference between treatment groups.

# 8. Study 2311E1 (Open-Label Uncontrolled Extension To Study 2311)

The protocol and main safety results for this study will be summarized briefly below. Note that I have not summarized the efficacy data for this study at all, despite presentation of those data by the sponsor in the study report, as uncontrolled data are not used to determine efficacy for regulatory purposes.

## *8.1 Protocol 2311E1*

Only a brief outline of the protocol has been provided below.

### *8.1.1 Title*

An Open-Label 24-Week Extension To A 24-Week, Prospective, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study Of The Efficacy, Tolerability, And Safety Of Exelon® (Rivastigmine) Capsules In Patients With Parkinson's Disease Dementia

### *8.1.2 Objectives*

#### *8.1.2.1 Primary*

To evaluate the safety and tolerability of open-label Exelon® (3 to 12 mg/day) for up to 24 weeks in patients who previously completed Study 2311, and to provide continued access to Exelon®

#### *8.1.2.2 Secondary*

To evaluate the effects of Exelon® on cognition, including executive function, activities of daily living, behavioral symptoms and health economic parameters including caregiver distress and caregiver burden

### *8.1.3 Design, Duration, Sample Size, Dosage*

This was to be an open-label uncontrolled extension study.

540 patients were planned to be enrolled in the preceding double-blind study.

The design of this study and its predecessor are summarized in the following table, which I have copied from the submission.

| Double-blind treatment phase | | | | Open-label treatment phase | |
|---|---|---|---|---|---|
| Study CENA713B2311 | | | | Study CENA713B2311E1 | |
| Treatment: Exelon (3 – 12 mg/day) or placebo | | | | Treatment: Exelon (3 – 12 mg/day) | |
| Weeks 1 – 24 | | | | Weeks 25 – 48 | |
| Screening period | Baseline period | Titration period | Maintenance period | Titration period | Maintenance period |
| Week | Week | Weeks | Weeks | Weeks | Weeks |
| -3 to -1 | 0 | 1 to 16 | 17 to 24 | 25 to 40 | 41 to 48 |

Note: the last day of the double-blind treatment phase was the first day of the open-label extension phase.

4 dose levels were to be used for Exelon® (and for matching placebo). The dose levels for Exelon® are shown in the following table.

| Dose Level | Exelon® Dose |
|---|---|
| 1 | 1.5 mg BID |
| 2 | 3.0 mg BID |
| 3 | 4.5 mg BID |
| 4 | 6.0 mg BID |

The actual dosing regime was to be as follows:

- For the titration period
    - All patients were to begin at Dose Level 1 (regardless of their treatment assignment in Study 2311)
    - After 4 weeks the dose was to be increased to Dose Level 2 unless there tolerability was impaired
    - Subsequent increases to Dose Levels 3 and 4 were to be based on the tolerability of the preceding dose, and were to be considered only after 4 weeks of treatment at the previous dose
    - In the event of poor tolerability, an investigator could decide to reduce a dose to the preceding level, with increases to the next dose level being made as clinically indicated after a minimum of 2 weeks
    - The aim was to find the highest tolerated dose for each patient by Week 16.
- For the maintenance period
    - The highest well-tolerated dose for each patient was to be maintained for the entire maintenance period
    - However, dose adjustments were permitted at any time

*8.1.4 Key Inclusion Criteria*

- Fulfilled eligibility criteria for Study 2311
- Either completed double-blind treatment phase of Study 2311 or discontinued early during that study, but returned for all the remaining scheduled efficacy assessments without significant protocol violations

- Informed consent
- Not treated with other acetylcholinesterase inhibitors or cholinomimetic agents, and anticholinergic drugs (including tricyclic antidepressants) within 4 weeks prior to entry into the study

### *8.1.5 Study Schedule*

The study schedule is summarized in the following table, which I have copied from the submission.

| | Phase | **Open-label treatment phase** | | | | | |
|---|---|---|---|---|---|---|---|
| | Period | Titration period | | | | | Maintenance period |
| | Visit | 11 | 12 | 13 | 14 | 15 | 16 |
| | Week | 24 | 28 | 32 | 36 | 40 | 48 or ED |
| Eligibility | | X * | | | | | |
| Informed consent | | X * | | | | | |
| Relevant medical history and current medical conditions | | X ** | | | | | |
| Vital signs | | X ** | X | X | X | X | X |
| Unified Parkinson's Disease Rating Scale (UPDRS part III) | | | | | | | X |
| ADAS-Cog | | | | | | | X |
| Executive Function test(s) | | | | | | | X |
| MMSE | | | | | | | X |
| ADCS-ADL | | | | | | | X |
| NPI | | | | | | | X |
| Health economic parameters | | | | | | | X |

Adverse events and concomitant medications were recorded throughout the study. ED = Early Discontinuation; efficacy assessments were also required within 24 hours of last dose at ED.

* recorded as source documents only

** performed in retrieved dropout patients only

### *8.1.6 Safety Outcome Measures*

Adverse events, safety laboratory tests, vital signs, body weight, electrocardiograms, and UPDRS Part III (Motor Function).

## ***8.2 Safety Results Of Study 2311E1***

### *8.2.1 Patient Disposition*

433 patients enrolled in Study 2311 were eligible to be enrolled in Study 2311E1; 334 patients actually consented to participate in the latter study, which 273 patients completed.

Patient disposition is summarized in the following sponsor table, with patients grouped according to whether they took Exelon® ("Exe") or placebo ("Plc") in the preceding double-blind study. Note that all discontinuations as well as

discontinuations due to adverse events were more common in those earlier exposed to placebo than in those previously exposed to Exelon®.

| | Exe-Exelon | Plc-Exelon | Total |
|---|---|---|---|
| **Number (%) of patients** | | | |
| Eligible for open-label extension phase | 282 | 151 | 433 |
| Consented to participate in open-label extension phase | 211 (100) | 123 (100) | 334 (100) |
| of which completers in double-blind phase | 207 (98.1) | 122 (99.2) | 329 (98.5) |
| of which completed as RDOs in double-blind phase | 4 (1.9) | 1 (0.8) | 5 (1.5) |
| Took study drug in open-label extension | 211 (100) | 123 (100) | 334 (100) |
| Completed open-label extension | 177 (83.9) | 96 (78.0) | 273 (81.7) |
| Discontinued open-label extension | 34 (16.1) | 27 (22.0) | 61 (18.3) |
| **Main reason for discontinuation** | n (%) | n (%) | n (%) |
| Adverse event(s) | 15 (7.1) | 15 (12.2) | 30 (9.0) |
| Unsatisfactory therapeutic effect | 3 (1.4) | 0 | 3 (0.9) |
| Patient withdrew consent | 11 (5.2) | 6 (4.9) | 17 (5.1) |
| Lost to follow-up | 0 | 3 (2.4) | 3 (0.9) |
| Administrative problems | 0 | 1 (0.8) | 1 (0.3) |
| Death | 5 (2.4) | 2 (1.6) | 7 (2.1) |

For patients who withdrew consent, sites were queried to confirm that main reason for discontinuation was not related to AEs.

### *8.2.2 Exposure To Study Drug*

The mean duration of exposure to Exelon® in this study was 21.6 weeks, and was similar in those exposed to Exelon® earlier as compared with those exposed to placebo (see the sponsor table below).

| Descriptive statistics | Exe-Exelon | Plc-Exelon | Total |
|---|---|---|---|
| Mean duration (weeks) | 21.9 | 21.1 | 21.6 |
| SD | 5.1 | 6.1 | 5.5 |
| Median duration (weeks) | 24 | 24 | 24 |
| Minimum (weeks) | 0.6 | 0.9 | 0.6 |
| Maximum (weeks) | 27.9 | 27.1 | 27.9 |

### *8.2.3 Concomitant Medication*

A slightly larger proportion of those who previously received Exelon® (than those who earlier received placebo) initiated new dopaminergic therapy or increased their dose of dopaminergic medication during the open-label extension phase, as indicated by the table below, which I have copied from the submission.

| | Exe-Exelon N=211 | Plc-Exelon N=123 | Total N=334 |
|---|---|---|---|
| **Dopaminergic agents** ATC Class | n (%) | n (%) | n (%) |
| **Newly introduced after start of open-label phase** | | | |
| Any dopaminergic agent | 22 (10.4) | 10 (8.1) | 32 (9.6) |
| Adamantane derivatives | 1 (0.5) | 0 | 1 (0.3) |
| Dopa and dopa derivatives | 9 (4.3) | 8 (6.5) | 17 (5.1) |
| Dopamine agonists | 8 (3.8) | 3 (2.4) | 11 (3.3) |
| Other dopaminergic agents | 5 (2.4) | 2 (1.6) | 7 (2.1) |
| Prolactin inhibitors | 2 (0.9) | 1 (0.8) | 3 (0.9) |
| **Increased dose after start of open-label phase** | | | |
| Any dopaminergic agent | 25 (11.8) | 12 (9.8) | 37 (11.1) |
| Dopa and dopa derivatives | 22 (10.4) | 10 (8.1) | 32 (9.6) |
| Dopamine agonists | 4 (1.9) | 1 (0.8) | 5 (1.5) |
| Other dopaminergic agents | 3 (1.4) | 1 (0.8) | 4 (1.2) |
| Prolactin inhibitors | 1 (0.5) | 0 | 1 (0.3) |

A medication / therapy can appear with more than one ATC class.

### *8.2.4 Overall Adverse Event Experience*

75.4% of patients enrolled in this study experienced adverse events with the incidence being comparable across the 2 pre-treatment groups. However, gastrointestinal adverse events were more common in those previously exposed to placebo (38.2%) than in those previously exposed to Exelon® (27.5%).

Adverse events that occurred in ≥ 5% of patients in the entire study cohort are listed in the following sponsor table. Nausea, vomiting, and tremor were all more common in those previously exposed to placebo than in those previously exposed to Exelon®.

| | Exe-Exelon | Plc-Exelon | Total |
|---|---|---|---|
| No. (%) of patients studied (safety population) | 211 (100) | 123 (100) | 334 (100) |
| No. (%) of patients with AE(s) | 159 (75.4) | 93 (75.6) | 252 (75.4) |
| **AE preferred term** | n (%) | n (%) | n (%) |
| Nausea | 29 (13.7) | 33 (26.8) | 62 (18.6) |
| Vomiting | 17 (8.1) | 20 (16.3) | 37 (11.1) |
| Tremor | 8 (3.8) | 15 (12.2) | 23 (6.9) |
| Confusional state | 10 (4.7) | 7 (5.7) | 17 (5.1) |

Preferred terms are listed by decreasing overall frequency.

The incidence of adverse events potentially indicating a worsening in the symptoms of Parkinson's Disease was 18.0% overall, 26.0% in those previously exposed to placebo, and 13.3% in those previously exposed to Exelon®. The most common of these adverse events was tremor which had an incidence of 6.9% overall, 12.2% in those previously exposed to placebo, and 3.8% in those previously exposed to Exelon®. Worsening of Parkinson's Disease had an

incidence of 3.6% overall, 4.1% in those previously exposed to placebo, and 3.3% in those previously exposed to Exelon®.

### *8.2.5 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events*

The overall incidence of deaths, serious adverse events, and adverse event discontinuations in this study is summarized in the following table, which I have copied from the submission:

| | Exe-Exelon | Plc-Exelon | Total |
|---|---|---|---|
| No. (%) of patients studied (safety population) | 211 (100) | 123 (100) | 334 (100) |
| No. (%) of patients with AE(s) | 159 (75.4) | 93 (75.6) | 252 (75.4) |
| **Number (%) of patients with events** | n (%) | n (%) | n (%) |
| Death | 5 (2.4) | 2 (1.6) | 7 (2.1) |
| SAE(s) | 37 (17.5) | 20 (16.3) | 57 (17.1) |
| Discontinued due to SAE(s) | 15 (7.1) | 4 (3.3) | 19 (5.7) |
| Discontinued due to non-serious AE(s) | 6 (2.8) | 13 (10.6) | 19 (5.7) |

A full listing of deaths that occurred in this study is in the following table, which I have copied from the submission.

| **DB treatment group** Country/Center/Patient | **Age/Sex/ Race** | **Day of last dose** | **Day of death** | **Principal cause (preferred term)** |
|---|---|---|---|---|
| **Exe-Exelon** | | | | |
| ESP/0075/00001 | 86/M/Ca | 181 | 188 | Pneumonia |
| ESP/0075/00007 | 70/M/Ca | 291 | 291 | Acute myocardial infarction |
| FRA/0017/00003 | 81/M/Ca | 335 | 336 | Cardiac failure |
| ITA/0043/00004 | 67/F/Ca | 315 | 316 | Myocardial infarction |
| TUR/0123/00001 | 74/M/Ca | 288 | 295 | Pneumonia |
| **Plc-Exelon** | | | | |
| NLD/0061/00005 | 72/F/Ca | 285 | 325 | Cerebrovascular accident |
| TUR/0122/00024 | 87/M/Ca | 222 | 224 | Cardio-respiratory arrest |

Note: Day is relative to the first day of treatment (day 1 of the double-blind period)

I have read the narratives for each death. None can be clearly linked to study drug; all appear to be due to intercurrent illnesses common in the study population.

As noted above, 17.1% of patients enrolled in this study experienced a serious adverse event, and 15.1% of patients enrolled experienced an adverse event that warranted treatment discontinuation.

The most frequent adverse events leading to treatment discontinuation were as follows, based on treatment assignment in the earlier double-blind study.

| Adverse Event Leading To Discontinuation | Exe-Exelon® | Plc-Exelon® |
|---|---|---|
| Nausea | 0.5% | 4.0% |
| Hallucination | 1.4% | 1.6% |
| Tremor | 0.5% | 1.6% |
| Vomiting | 0.0% | 2.4% |

I have read the listings and narratives for serious adverse events and discontinuations due to adverse events. With the exception of those events that could be attributed to the cholinomimetic effects of Exelon®, the adverse events describe are all consistent with intercurrent illnesses that are common in this population.

### *8.2.6 Laboratory Data*

No laboratory testing was performed during the open-label extension phase of this study.

### *8.2.7 Vital Signs And Weight*

Mean changes from baseline in vital sign parameters and weight, and the proportion of patients with notable vital sign or weight abnormalities have been summarized in tabular form by the sponsor. These changes were small.

### *8.2.8 Electrocardiograms*

No electrocardiograms were performed during this study.

### *8.2.9 UPDRS Part III Scores*

Patients enrolled in the open-label extension study worsened by a mean (± standard deviation) of 1.8 points (± 9.6 points) on the total UPDRS Part III score. Individual tremor score worsened by a mean (± standard deviation) of 0.1 points (± 2.3 points).

## ***8.3 Sponsor's Conclusions Regarding Safety***

In patients treated with Exelon® or placebo in Study 2311, the safety and tolerability of Exelon® in a dose of 3 to 12 mg/day in Study 2311E1 remained favorable, with no new unexpected adverse events reported and no clinically significant worsening of the motor symptoms of Parkinson's Disease. The tolerability profile of profile of Exelon® did not change over the 24-week open-label extension study.

## ***8.4 Reviewer's Comments***

I agree with the sponsor's conclusions

# 9. Study 2314 (Non-Interventional Validation Study)

Note that the study report contained in this submission is an interim report which is confined to the validation of various study instruments in Parkinson's Disease Dementia alone, whereas the original study protocol planned to validate these instruments in vascular dementia as well. The description of the study protocol and results below is, therefore, also confined to the validation of these study instruments in Parkinson's Disease Dementia alone.

## *9.1 Protocol*

### *9.1.1 Title*

A 4-Week, Non-Interventional, Cross-Sectional, Multicenter Study To Assess The Validity Of Various Assessment Scales Measuring Cognition, Executive Function, Behavior And Activities Of Daily Living In Patients With Mild To Moderate Parkinson's Disease Dementia

### *9.1.2 Objectives*

#### *9.1.2.1 Primary*

- To assess the criterion-related validity through determination of the ability of the ADAS-Cog to differentiate between mild and moderate severities of Parkinson's Disease Dementia

- To assess the test-retest reliability of the ADAS-Cog in Parkinson's Disease Dementia

#### *9.1.2.2 Secondary*

- To assess the criterion-related validity through determination of the ability of other dementia rating scales to differentiate between mild and moderate severities of Parkinson's Disease Dementia
- To assess the test-retest reliability of other dementia rating scales/tests
- To assess the convergent and divergent construct validity of the ADAS-Cog in patients with Parkinson's Disease Dementia
- To compare scores on dementia rating scales and tests in patients with Alzheimer's Disease with those who have Parkinson's Disease Dementia

### *9.1.3 Design*

Non-interventional cross-section study

### *9.1.4 Duration*

4 weeks

### *9.1.5 Sample Size*

The planned sample size was 100 patients, comprising 50 patients with Parkinson's Disease Dementia and 50 patients with Alzheimer's Disease.

### *9.1.6 Main Inclusion Criteria*

- Age: 50 to 85 years
- For patients with Alzheimer's Disease
    - Clinical diagnosis of Alzheimer's Disease according to DSM-IV criteria
    - Probable Alzheimer's Disease according to the NINCDS-ADRDA criteria
- For patients with Parkinson's Disease Dementia
    - Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank
    - Diagnosis of Dementia Due To Parkinson's Disease according to DSM-IV criteria
- Mini-Mental Status Examination score at entry between 10 and 24, further divided into mild dementia (Mini-Mental Status Examination score of 18 to 24) or moderate dementia (Mini-Mental Status Examination score of 10 to 17)
- Stable dose of existing therapy for at least 6 weeks prior to baseline and not expected to change medication doses during the study

### *9.1.7 Study Schedule*

The study schedule is summarized in the following table, which I have copied from the submission.

| Period | Screening | Baseline | Test-Retest (or early discontinuation) |
|---|---|---|---|
| Visit | 1 | 2* | 3* |
| **Procedures** | Weeks -6 to -1 | Week 0 | Weeks 4 |
| Informed consent | X | | |
| Inclusion/exclusion criteria[a] | X | X | |
| Background Information | X | X | |
| Demography | X | | |
| Physical /Neurological Exam [a] | X | X[b] | |
| CT (PDD and AD patients) [c] | X | | |
| Relevant medical history/Current Medical Conditions | X | X | |
| Previous Medications or Therapies | X | X | |
| Concomitant Medications or Therapies | | X | X |
| Mini Mental State Examination (MMSE) | X[a] | X | |
| Global Deterioration Scale (GDS) | X[a] | X | |
| Ten-Point Clock Test (TPCT) | X[a] | X | X |
| D-KEFS Verbal Fluency | X[a] | X | X |
| CDR computerized assessment system tests for attention | X[a] | X | X |
| Trail Making Test Part A (TMT-A) | X[a] | X | X |
| Cognitive Measures (ADAS-cog*, VaDAS**) | X[a] | X | X |
| Neuropsychiatric Inventory (NPI) (including NPI-D) | | X | X |
| Activities of Daily Living Scale (ADCS-ADL) | | X | X |
| AEs (including SAEs) | | As needed | |
| Study Completion Form | | | X |

[a] to be recorded as source documents only
[b] repeated only if assessment at screening revealed significant abnormality
[c] only needed if unavailable or available but CT or MRI imaging is over 6 months old for PDD and AD patients
[d] only needed if unavailable or if imaging according to standardized MRI protocol is over 6 months old for VaD patients
* conducted in all PDD patients
** conducted in all AD patients
* all assessments must be performed within a 3-day visit window

### *9.1.8 Assessment Scales To Be Validated*

- ADAS-Cog
- D-KEFS Verbal Fluency Test
- Ten-Point Clock Test
- Trailmaking Tests A and B
- Neuropsychiatry Inventory, including Neuropsychiatry Inventory-Distress
- ADCS-ADL
- Cognitive Drug Research Computerized Assessment System tests for the assessment of attention

### *9.1.9 Assessments Used For Staging*

- Mini-Mental Status Examination
- Global Deterioration Scale

## *9.2 Main Results*

### *9.2.1 Patient Disposition*

Patient disposition by dementia type and Mini-Mental Status Examination stratum is summarized in the following table, which I have copied from the submission.

| | PDD | | AD | | |
|---|---|---|---|---|---|
| | **mild** | **moderate** | **mild** | **moderate** | **Total** |
| **Number (%) of patients** | | | | | |
| Enrolled | 32 (100) | 23 (100) | 35 (100) | 23 (100) | 113 (100) |
| Completed | 31 (96.9) | 22 (95.7) | 35 (100.0) | 23 (100.0) | 111 (98.2) |
| Discontinued† | 1 (3.1) | 1 (4.3) | 0 | 0 | 2 (1.8) |

† For both patients who discontinued, reason was 'subject withdrew consent'

### *9.2.2 Demographic And Other Baseline Characteristics*

These are summarized in the next table, which I have copied from the submission.

| | PDD (N=55) | | AD N=(58) | | Total (N=113) |
|---|---|---|---|---|---|
| | Mild (N=32) | Moderate (N=23) | Mild (N=35) | Moderate (N=23) | |
| **Age (yr)** | | | | | |
| Mean (SD) | 74.3 (5.7) | 74.9 (5.1) | 74.3 (9.1) | 75.4 (6.2) | 74.6 (6.9) |
| Median | 74.5 | 73.0 | 75.0 | 76.0 | 75.0 |
| Range | 58-87 | 67-82 | 47-85 | 60-86 | 47-87 |
| **Age (yrs) – n(%)** | | | | | |
| < 65 | 1 (3.1) | 0 | 5 (14.3) | 1 (4.3) | 7 (6.2) |
| ≥ 65 | 31 (96.9) | 23 (100) | 30 (85.7) | 22 (95.7) | 106(93.8) |
| **Sex - n(%)** | | | | | |
| Male | 17 (53.1) | 10 (43.5) | 11 (31.4) | 3 (13.0) | 41 (36.3) |
| Female | 15 (46.9) | 13 (56.5) | 24 (68.6) | 20 (87.0) | 72 (63.7) |
| **Race - n(%)** | | | | | |
| Caucasian | 32 (100) | 23 (100) | 33 (94.3) | 22 (95.7) | 110(97.3) |
| Black | 0 | 0 | 2 (5.7) | 0 | 2 (1.8) |
| Oriental | 0 | 0 | 0 | 1 (4.3) | 1 (0.9) |
| Number (%) of patients taking anti-dementia medications | 12 (37.5) | 9 (39.1) | 32 (91.4) | 23 (100) | 76 (67.3) |
| **Total MMSE score** | | | | | |
| Mean (SD) | 21.2 (2.1) | 15.8 (1.8) | 21.2 (2.2) | 14.3 (2.3) | 18.7 (3.7) |
| Median | 21 | 17 | 21 | 14 | 19 |
| Range | 18 - 24 | 10 - 17 | 18 - 24 | 10 - 17 | 10 - 24 |
| **GDS score** | | | | | |
| Mean (SD) | 3.5 (0.7) | 4.4 (0.7) | 3.7 (0.8) | 4.5 (0.9) | 4.0 (0.9) |
| Median | 4 | 4 | 4 | 5 | 4 |
| Range | 2 - 5 | 3 - 6 | 2 - 5 | 2 - 6 | 2 - 6 |
| **Total ADAS-cog score** | | | | | |
| Mean (SD) | 18.9 (6.0) | 26.6 (7.6) | 17.8 (6.7) | 29.2 (7.8) | 22.1 (8.3) |
| Median | 18 | 25.8 | 17.7 | 28 | 21 |
| Range | 9.3 - 37 | 17 - 50 | 5 - 36 | 17.7 - 45.7 | 5 - 50 |

### *9.2.3 Primary Analysis Results*

The sponsor table below is intended to illustrate the ability of the mean ADAS-Cog score at baseline to differentiate between mild and moderate Parkinson's Disease Dementia (and Alzheimer's Disease), based on a t-test and supported by an analysis of variance with severity group and center as fixed effects.

| | MMSE stratum | | |
|---|---|---|---|
| | **Mild** | **Moderate** | **p-value** |
| **PDD patients** | | | |
| n | 32 | 22 | |
| Mean (SD) | 18.9 (6.0) | 26.6 (7.6) | <0.001 * |
| Median | 18.0 | 25.8 | |
| Range (min, max) | 9.3 - 37.0 | 17.0 - 50.0 | |
| **AD patients** | | | |
| n | 35 | 21 | |
| Mean (SD) | 17.8 (6.7) | 29.2 (7.8) | <0.001 * |
| Median | 17.7 | 28.0 | |
| Range (min, max) | 5.0 - 36.0 | 17.7 - 45.7 | |

Mild and Moderate groups are defined as MMSE total score 18 – 24 and 10 – 17, respectively
P-value was calculated using t-test

The sponsor points out that the mean ADAS-Cog score at baseline shows a distinct separation between mild and moderate patients in both the Parkinson's Disease Dementia and Alzheimer's Disease groups, with a similar variance associated with the mean in each dementia type and severity. The difference in mean ADAS-Cog score between the mild and moderate groups was statistically significant for each dementia type.

The size of the mean difference between Mini-Mental Status Examination strata was also examined using a Cohen's effect size computation. Using that computation, effect sizes of 0.2, 0.5, and 0.8 are generally considered small, medium, and large, respectively. Cohen's effect size for the mean difference between disease severities by dementia type, as determined by the sponsor, is in the following table; while this effect size was larger for the Alzheimer's Disease group, it remained large for the group with Parkinson's Disease Dementia as well. These results also suggest that the ADAS-Cog is a scale that can produce a good separation between Mini-Mental Status Examination strata in the patients studied.

| Scale | PDD patients N=55 | AD Patients N=58 |
|---|---|---|
| ADAS-cog | 1.107 | 1.566 |

Cohen's effect size was computed as (difference between the MMSE stratum mean scores)/(pooled standard deviation).

The test-retest reliability of the ADAS-Cog in this population was evaluated by determining the correlation coefficient between the ADAS-Cog value at baseline and that at Week 4 for each dementia type and severity; the results are in the following table contained in the submission, which indicates, according to the sponsor, that the correlation coefficients for the ADAS-Cog at baseline and Week 4 were strongly positive regardless of dementia type and severity; the sponsor further states that although the confidence intervals for each correlation coefficient were wide, even their lower limits showed a positive correlation.

| | PDD type, MMSE stratum | | | AD type, MMSE stratum | | |
|---|---|---|---|---|---|---|
| | Mild (N=32) | Moderate (N=23) | All (N=55) | Mild (N=35) | Moderate (N=23) | All (N=58) |
| ADAS-cog | | | | | | |
| Baseline | 18.9 (6.0) | 26.6 (7.6) | -- | 17.8 (6.7) | 29.2 (7.8) | -- |
| Week 4 (re-test) | 17.9 (6.6) | 27.5 (10.2) | -- | 17.8 (6.8) | 28.2 (7.6) | -- |
| Corr. coefficient | 0.652 | 0.714 | 0.775 | 0.690 | 0.747 | 0.808 |
| [95% CI] | [0.377, 0.926] | [0.430, 0.997] | [0.631, 0.920] | [0.510, 0.871] | [0.511, 0.983] | [0.706, 0.910] |

Spearman correlation coefficient was calculated based on the score of Week 0 and Week 4, and the 95% confidence interval was calculated using asymptotic standard error of the correlation coefficient.

### *9.2.4 Secondary Analyses*

#### *9.2.4.1 Ability Of Dementia-Rating Scales And Tests Other Than The ADAS-Cog To Differentiate Between Alzheimer's Disease Of Mild And Moderate Severity (Assessment Of Criterion-Related Validity)*

The ability of dementia rating scales and tests other than the ADAS-Cog to differentiate between mild and moderate severity Parkinson's Disease Dementia and Alzheimer's Disease were evaluated as with the ADAS-Cog by comparing the mean values obtained for each severity category at baseline and at Week 4, using a t-test. The results are in the following table, which indicate that for both types of dementia, the separation between mild and moderate severities was nominally statistically significant for the ADCS-ADL, Ten-Point Clock Test, Trailmaking Test A, and D-KEFS Verbal Fluency Test.

| Dementia type scale/test used | Mean baseline rating for MMSE stratum† and statistical comparison between severities | | |
|---|---|---|---|
| | Mild | Moderate | P-value* |
| **PDD patients** | **mean (SD)** | **mean (SD)** | |
| ADCS-ADL | 45.8 (13.7) | 36.8 (12.8) | 0.017 |
| NPI-12 | 14.6 (14.0) | 13.5 (13.0) | 0.766 |
| NPI-10 | 10.7 (12.1) | 11.3 (10.3) | 0.844 |
| NPI-D-12 | 8.5 (7.6) | 6.6 (5.3) | 0.291 |
| NPI-D-10 | 7.2 (6.8) | 5.8 (4.4) | 0.356 |
| TPCT‡ | 8.0 | 1.0 | <0.001‡ |
| CDR - Power of attention | 1695.1 (375.6) | 2050.1 (830.1) | 0.079 |
| TMT-A | 133.9 (74.0) | 205.3 (123.5) | 0.019 |
| D-KEFS verbal fluency – total correct responses | 17.3 (10.2) | 9.1 (6.1) | <0.001 |
| **AD patients** | **mean (SD)** | **mean (SD)** | |
| ADCS-ADL | 51.6 (11.4) | 44.6 (14.1) | 0.043 |
| NPI-12 | 12.0 (12.3) | 15.2 (19.0) | 0.482 |
| NPI-10 | 11.2 (11.3) | 13.4 (16.9) | 0.588 |
| NPI-D-12 | 5.9 (6.4) | 7.7 (10.6) | 0.455 |
| NPI-D-10 | 5.5 (5.7) | 7.2 (9.6) | 0.442 |
| TPCT‡ | 8.0 | 1.0 | 0.003‡ |
| CDR - Power of attention | 1688.9 (491.7) | 2266.5 (875.9) | 0.014 |
| TMT-A | 122.2 (67.7) | 193.4 (107.2) | 0.014 |
| D-KEFS verbal fluency – total correct responses | 18.8 (7.8) | 10.5 (7.4) | <0.001 |

† Mild and Moderate groups are defined as MMSE total score 18 – 24 and 10 – 17, respectively
* P-value was calculated using t-test
‡ median was presented and p-value was calculated using Wilcoxon rank-sum test
Higher scores in ADCS-ADL, TPCT, and D-KEFS verbal fluency and lower scores in CDR – Power of attention, NPI, and TMT-A indicate better functioning.

The differences for other measures are in the above table.

Test-retest reliability by dementia type and Mini-Mental Status Examination stratum is summarized in the following table, taken from the submission; reliability was determined, as with the ADAS-Cog by calculating correlation coefficients based on the baseline and Week 4 scores . The correlations were best for the ADCS-ADL and Neuropsychiatry Inventory-10 for both populations.

| Scale | Mild<br>Corr. Coeff.<br>[95% CI] | Moderate<br>Corr. Coeff.<br>[95% CI] | All<br>Corr. Coeff.<br>[95% CI] |
|---|---|---|---|
| PDD | (N=32) | (N=23) | (N=55) |
| ADAS-cog | 0.652<br>(0.377, 0.926) | 0.714<br>(0.430, 0.997) | 0.775<br>(0.631, 0.920) |
| ADCS-ADL | 0.936<br>(0.865, 1.000) | 0.916<br>(0.796, 1.000) | 0.939<br>(0.896, 0.982) |
| NPI-10 | 0.660<br>(0.406, 0.914) | 0.729<br>(0.522, 0.936) | 0.719<br>(0.560, 0.877) |
| TPCT | 0.788<br>(0.612, 0.964) | 0.452<br>(0.074, 0.830) | 0.755<br>(0.627, 0.883) |
| CDR – Power of attention | 0.631<br>(0.296, 0.967) | 0.463<br>(-0.057, 0.983) | 0.606<br>(0.331, 0.881) |
| TMT-A | 0.864<br>(0.748, 0.980) | 0.195<br>(-0.319, 0.709) | 0.657<br>(0.426, 0.888) |
| D-KEFS verbal fluency - Total correct responses | 0.786<br>(0.606, 0.966) | 0.546<br>(0.165, 0.928) | 0.799<br>(0.667, 0.930) |
| AD | (N=35) | (N=23) | (N=58) |
| ADAS-cog | 0.690<br>(0.510, 0.871) | 0.747<br>(0.511, 0.983) | 0.808<br>(0.706, 0.910) |
| ADCS-ADL | 0.915<br>(0.839, 0.992) | 0.883<br>(0.803, 0.963) | 0.916<br>(0.863, 0.969) |
| NPI-10 | 0.891<br>(0.794, 0.988) | 0.927<br>(0.860, 0.994) | 0.899<br>(0.834, 0.964) |
| TPCT | 0.618<br>(0.355, 0.881) | 0.880<br>(0.784, 0.975) | 0.727<br>(0.543, 0.910) |
| CDR – Power of attention | 0.692<br>(0.478, 0.905) | 0.546<br>(0.183, 0.908) | 0.722<br>(0.561, 0.884) |
| TMT-A | 0.782<br>(0.626, 0.938) | 0.392<br>(-0.135, 0.919) | 0.686<br>(0.467, 0.904) |
| D-KEFS verbal fluency - Total correct responses | 0.672<br>(0.469, 0.874) | 0.661<br>(0.326, 0.995) | 0.756<br>(0.604, 0.907) |

Spearman correlation coefficient was calculated based on the score of Week 0 and Week 4, and the 95% confidence interval was calculated using asymptotic standard error of the correlation coefficient.

### *9.2.4.2 Comparison Of Scores On Dementia Rating Scales In Patients With Alzheimer's Disease Versus Parkinson's Disease Dementia*

The total scores at baseline in the 2 populations were compared as indicated in the following table. The sponsor points out that statistically significant differences between the 2 populations were not apparent except for the ADCS-ADL score.

| Assessment parameters (total scores) | | PDD patients (N=55) | AD patients (N=58) | p-value† |
|---|---|---|---|---|
| ADAS-cog | n | 54 | 56 | |
| | mean (SD) | 22.1 (7.7) | 22.1 (9.0) | 0.980 |
| ADCS-ADL | n | 54 | 58 | |
| | mean (SD) | 42.0 (14.0) | 48.8 (12.9) | 0.008 |
| NPI-10 | n | 55 | 58 | |
| | mean (SD) | 10.9 (11.3) | 12.1 (13.7) | 0.636 |
| NPI-D-10 | n | 55 | 58 | |
| | mean (SD) | 6.6 (5.9) | 6.2 (7.5) | 0.737 |
| TPCT | n | 55 | 58 | |
| | mean (SD) | 4.9 (3.9) | 4.3 (3.7) | 0.395 |
| CDR – Power of attention | n | 50 | 51 | |
| | mean (SD) | 1844.2 (627.1) | 1904.1 (711.1) | 0.655 |
| TMT-A | n | 54 | 53 | |
| | mean (SD) | 164.3 (103.4) | 147.7 (89.8) | 0.379 |
| D-KEFS verbal fluency - Total correct responses | n | 55 | 58 | |
| | mean (SD) | 13.9 (9.6) | 15.5 (8.6) | 0.333 |

† P-value based on a t-test except for TPCT where p-value is based on a Wilcoxon rank-sum test

Higher scores in ADAS-cog, ADCS-ADL, TPCT, and D-KEFS verbal fluency and lower scores in CDR – Power of attention, NPI, and TMT-A indicate better functioning.

The sponsor has performed a factor analysis of the ADAS-Cog sub-item scores at baseline for the Parkinson's Disease Dementia and Alzheimer's Disease populations, as indicated in the following table, taken from the submission. The sponsor has observed that the sub-items group differently in each population, which may indicate a different profile of cognitive impairment. The sponsor does acknowledge that the sample sizes were small for these analyses.

| | PDD patients (N=55) | AD patients (N=58) |
|---|---|---|
| ADAS-cog sub-items | Factor | Factor |
| Item 4- Naming objects/ fingers | 1 | 1 |
| Item 8- Remembering test instructions | 1 | 1 |
| Item 9- Spoken language ability | 1 | 1 |
| Item 11- Comprehension | 1 | 1 |
| Item 1- Word Recall | 2 | 2 |
| Item 3- Constructional praxis | 2 | 3 |
| Item 5- Ideational praxis | 2 | 3 |
| Item 10- Word finding difficulty | 2 | 1 |
| Item 2- Commands | 3 | 3 |
| Item 6- Orientation | 3 | 3 |
| Item 7- Word recognition | 3 | 2 |

### *9.2.4.3 Convergent And Divergent Construct Validity Of The ADAS-Cog In Patients With Alzheimer's Disease And With Parkinson's Disease Dementia*

The degree of association between the ADAS-Cog and other scales was explored by performing a correlation test between the ADAS-Cog scores and those of each of the other scales at baseline. The sponsor considers the results, summarized in the table below, to indicate at least a moderate correlation of the ADAS-Cog with all assessments other than the Neuropsychiatry Inventory and

Neuropsychiatry Inventory-Distress. Correlation was best between the ADAS-Cog and Mini-Mental Status Examination, in both populations.

| | PDD patients<br>Corr. coeff. (95% CI) | AD patients<br>Corr. coeff. (95% CI) |
|---|---|---|
| ADCS-ADL | -0.470<br>( -0.701, -0.239) | -0.424<br>( -0.643, -0.205) |
| MMSE | -0.601<br>( -0.759, -0.442) | -0.820<br>( -0.923, -0.717) |
| NPI-10 | 0.099<br>( -0.165, 0.363) | -0.040<br>( -0.290, 0.211) |
| NPI-D-10 | -0.061<br>( -0.328, 0.206) | -0.029<br>( -0.272, 0.214) |
| TPCT | -0.459<br>( -0.704, -0.215) | -0.494<br>( -0.687, -0.301) |
| CDR - Power of attention | 0.351<br>( 0.080, 0.623) | 0.341<br>( 0.066, 0.616) |
| TMT-A | 0.297<br>( 0.029, 0.565) | 0.337<br>( 0.110, 0.565) |
| D-KEFS verbal fluency - Total correct responses | -0.467<br>( -0.710, -0.225) | -0.458<br>( -0.678, -0.239) |

Spearman correlation coefficient was calculated for the assessments at baseline, and the 95% confidence interval was calculated by asymptotic standard error of the estimate

### *9.3 Sponsor's Conclusions*

The following is a summary of the sponsor's conclusions:

- In patients with Parkinson's Disease Dementia, grouped into "mild" and "moderate" categories by baseline Mini-Mental Status Examination score, the ADAS-Cog score at baseline showed a statistically significant difference between these categories, thus demonstrating criterion-related validity for the ADAS-Cog, based on severity as the criterion. In the same population, a similar criterion-related validity was also demonstrated for the ADCS-ADL, Ten-Point Clock Test, Trailmaking Test A, and D-KEFS Verbal Fluency Test

- The ADAS-Cog and several other scales demonstrated test-retest reliability when used in patients with Parkinson's Disease Dementia.

- When the ADAS-Cog was correlated with scales that measured similar and different symptom domains, convergent and divergent construct validity was demonstrated for the ADAS-Cog in patients with Parkinson's Disease Dementia.

- For patients with a similar severity of dementia, as determined by Mini-Mental Status Examination score, total scores achieved on specific dementia rating scales in patients with Parkinson's Disease Dementia were similar to those in patients with Alzheimer's Disease. However, a factor analysis that compared the 2 populations on ADAS-Cog sub-item scores has indicated that the sub-items group differently in each

population suggesting that cognitive and behavioral symptom profiles in these populations may differ.

## 10. Summary Of Earlier Meeting Between Division And Sponsor Regarding This Application.

A meeting was held with the sponsor on May 18, 2005, at which the results of Study 2311 (EXPRESS Study) were discussed in outline and on a preliminary basis, in the context of a sponsor proposal to expand the current indication for Exelon® to include "the treatment of mild to moderate dementia associated with Parkinson's Disease."

The following is a summary of the salient views conveyed by the sponsor's team at that meeting.

- The entity of dementia associated with Parkinson's Disease (as exemplified by the patients enrolled in the EXPRESS Study) is linked to distinctive neuropathological findings (i.e., widespread Lewy bodies and Lewy neurites), with more recent publications strongly suggesting that the contribution of co-existing Alzheimer's-type neuropathological changes (e.g., senile plaques and neurofibrillary tangles) to the dementia are minor

- A cholinergic deficiency state is the basis for dementia associated with Parkinson's Disease, just as with Alzheimer's Disease

- The population enrolled in the EXPRESS trial was distinct from that enrolled in the pre-approval clinical trials of rivastigmine in Alzheimer's Disease (and was actually excluded from those trials)

- Although patients enrolled in the EXPRESS trial were not selected based on those neuropsychological deficits that, according to the DSM IV definition of "Dementia Due To Parkinson's Disease," (294.1) are distinctive for that disorder (i.e., "cognitive and motor slowing, executive dysfunction, and impairment in memory retrieval"), selecting patients based on the extent of such deficits is unlikely to help differentiate them from patients with Alzheimer's Disease

- The results of the EXPRESS Study are sufficiently robust for that study alone to be the basis for the expansion of the current claim to include dementia associated with Parkinson's Disease, especially since the mechanism by which rivastigmine may have its effect in that condition and in Alzheimer's Disease may be the same.

The Division's key concerns about an expansion of the current claim for rivastigmine to include dementia associated with Parkinson's Disease, especially on the basis of the results of the EXPRESS study alone, were as follows

- The criteria used to diagnose dementia when including patients in the EXPRESS Study were no different from those used to enroll patients in the pre-approval

efficacy studies of rivastigmine in Alzheimer's Disease; i.e., these patients were not identified on the basis of any purportedly distinctive features of dementia associated with Parkinson's Disease. In addition, the clinical course of the placebo arm and the size of the effect seen with rivastigmine in the EXPRESS trial were no different from similar observations in pre-approval efficacy trials of rivastigmine in Alzheimer's Disease. These observations call into question how distinct the patients in the EXPRESS trial were from those enrolled in the pre-approval Alzheimer's Disease trials, and whether any effect of rivastigmine on performance that was seen in the former study was mediated through its effects on co-existing Alzheimer's Disease.

- DSM-IV is a standard reference manual containing diagnostic criteria for the entire spectrum of psychiatric and neuropsychiatric disorders, including "Dementia Due To Parkinson's Disease" (294.1). In the EXPRESS Study, patients with dementia associated with Parkinson's Disease were enrolled based on their having dementia, but without the more distinctive cognitive deficits described in DSM-IV, thus raising the possibility that the appropriate diagnostic criteria for that entity may not have been applied in that study.

- The sponsor is currently seeking a claim for the use of rivastigmine in dementia associated with Parkinson's Disease based on a single study (i.e., EXPRESS). While the sponsor considers the results of that study to be robust, the Division has generally required that evidence for the efficacy of a drug in a distinct clinical entity be replicated, and a second study would, therefore, ordinarily be required to address the claim that the sponsor is currently pursuing

The Division was of the view that the entity of dementia associated with Parkinson's Disease should be discussed at a meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee. The sponsor proposed submitting a Supplemental NDA based on efficacy data from the EXPRESS Study only, with a request for a standard review and the possibility of holding a meeting of the Advisory Committee during the course of that review was discussed.

The Division was, very shortly after the meeting, to discuss internally whether it would be prepared to file a Supplemental NDA for rivastigmine in the treatment of dementia associated with Parkinson's Disease, based on efficacy data derived from the EXPRESS Study alone, given the proposed common mechanism of action of rivastigmine in both dementia associated with Parkinson's Disease and Alzheimer's Disease, and was to inform the sponsor of its view shortly.

On May 24, 2005, the Division informed the sponsor that it would accept the filing of a Supplemental NDA for Exelon® in the treatment of dementia associated with Parkinson's Disease based on the results of the EXPRESS Study alone and that review of that application would include a discussion with the Peripheral and Central Nervous Systems Drugs Advisory Committee during the 10-month review period.

# 11. Sponsor's Current View Of Dementia Associated With Parkinson's Disease, And Appropriateness Of ADAS-Cog And ADCS-ADL In Evaluating Treatment Effects In Dementia Associated With Parkinson's Disease

Separate independent expert reports have been commissioned by the sponsor to address each of these 2 subjects. The contents of these reports, with which the sponsor appears to concur, are summarized below. Note that the sponsor has supplemented the results of the second of the reports below with the conclusions drawn from Study 2314.

## *11.1 Dementia Associated With Parkinson's Disease (Expert Report: Diagnosing Dementia Associated With Parkinson's Disease And Distinguishing It From Alzheimer's Disease)*

The report has been prepared by 3 academics at the request of the sponsor. These individuals are Professors J. Cummings, M. Emre, and C. W. Olanow.

In the report they have provided their opinion in 2 areas

- Whether the dementia associated with Parkinson's Disease is a different disease entity from the dementia associated with Alzheimer's Disease
- Whether practitioners can differentiate the 2 conditions

They have concluded that

- There is a distinction between dementia associated with Parkinson's Disease and Alzheimer's Disease
- Operational criteria permit the 2 conditions to be readily distinguished
- The same operational criteria can be applied by community practitioners to easily differentiate between the 2 conditions

The basis for their conclusions, as stated in the report, is provided under the headings below, which are the same as those used by the authors of the report; Please see the text of the report for full details. Note that although many publications are cited in the report, full citations are provided for only some of those publications; also note that some publications cited are untraceable through standard search engines.

### *11.1.1 Prevalence And Incidence Of Dementia Associated With Parkinson's Disease*

- Based on a published meta-analysis, the prevalence of dementia in patients with Parkinson's Disease is about 40%. However, since dementia in Parkinson's Disease is associated with increased mortality, it is likely to be under-represented in cross-sectional studies or in longitudinal studies that do not account for differential mortality

- Incidence studies, which are relatively free of survival bias indicate a 4-6 times higher incidence of dementia in patients with Parkinson's Disease as compared with age-matched controls; since the incidence of dementia in the control population probably represents the occurrence of Alzheimer's Disease and other degenerative and symptomatic dementias in the population, the increased incidence of dementia in populations with Parkinson's Disease in all likelihood represents an excess of dementia that is directly attributable to Parkinson's Disease

*11.1.2 Risk Factors For Dementia Associated With Parkinson's Disease*

- The most significant risk factors for dementia in patients with Parkinson's Disease are old age, duration of Parkinson's Disease, age at onset of Parkinson's Disease, akinetic-rigid form of the disease, and the severity of motor symptoms

- The presence of subtle involvement of executive functions in non-demented Parkinson's Disease patients predicts the emergence of dementia later

- Dementia becomes more common with advancing Parkinson's Disease

- Risk factors for dementia associated with Parkinson's Disease differ from those for Alzheimer's Disease, with the principal risk factor for the former being the presence of Parkinson's Disease itself

- The diagnostic entities of dementia associated with Parkinson's Disease and probable Alzheimer's Disease are mutually exclusive by definition, since the diagnosis of probable Alzheimer's Disease (NINCDS-ADRDA criteria)/dementia of the Alzheimer's type (American Psychiatric Association criteria) requires the exclusion of other brain disorders capable of causing a dementia syndrome

*11.1.3 Genetic Distinctions Between Alzheimer's Disease And Parkinson's Disease*

- The majority of cases of both Parkinson's Disease and Alzheimer's Disease occur sporadically. However, genetic mutations have been identified in some Alzheimer's Disease and Parkinson's Disease patients; the genetic mutations associated with Parkinson's Disease differ from those associated with Alzheimer's Disease, and no gene mutation has been identified which causes both. Such genetic defects as have been associated with Alzheimer's Disease tend to be associated with disorders of amyloid production and metabolism, while some genetic forms of Parkinson's Disease are associated with mutations and increased deposition of alpha-synuclein

- There is no excess of Alzheimer's Disease among probands with Parkinson's Disease as might be anticipated if the major genetic factors contributing to their etiologies are shared

- Specific APOE alleles tend to be associated with Alzheimer's Disease and Parkinson's Disease, respectively.

- The genetic distinctions between Alzheimer's Disease and Parkinson's Disease are summarized in the table below

| 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 |

AD: Alzheimer's Disease
PDD: dementia associated with Parkinson's Disease

### *11.1.4 Neuropathological Distinctions Between Alzheimer's Disease And Parkinson's Disease*

- Stains that are specific and sensitive for detecting Lewy body and neurite pathology in Parkinson's Disease have been helpful in understanding the basis for dementia associated with Parkinson's Disease

- Cortical Lewy bodies and the extent of Lewy neurites in the CA2 region of the hippocampus show a strong correlation with the extent of cognitive impairment

- Marked nigrostriatal dopaminergic neuronal degeneration is a unique pathological feature of dementia associated with Parkinson's Disease. Pathological abnormalities in the locus ceruleus may also contribute to dementia associated with Parkinson's Disease

- In Parkinson's Disease, there is also a loss of cholinergic neurons in the nucleus basalis of Meynert and a marked cholinergic deficiency, both of which may occur early in the course of that disorder. These changes are most pronounced in patients with dementia associated with Parkinson's Disease. The severity of the cholinergic deficiency in dementia associated with Parkinson's Disease is greater than that occurring in Alzheimer's Disease.

- While the pathological abnormalities characteristic of Alzheimer's Disease (i.e., neurofibrillary tangles and senile plaques) are commonly present in patients with dementia associated with Parkinson's Disease, they are more commonly present when dementia is advanced, and they do not account for all or even a majority of cases of dementia associated with Parkinson's Disease

- Differences in the neuropathology of dementia associated with Parkinson's Disease and Alzheimer's Disease are summarized in the following table, which I have copied from the submission

| **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 |

*11.1.5 Neuroimaging In Dementia Associated With Parkinson's Disease*

Only limited neuroimaging studies have been done in dementia associated with Parkinson's Disease.

Preliminary MRI observations suggest that while atrophy of the temporal lobes, including the hippocampus and parahippocampal gyrus, is more severe in patients with Alzheimer's Disease, severe atrophy of the thalamus and occipital lobes is more characteristic of Parkinson's Disease.

Functional imaging studies (single-photon emission computerized tomography; positron emission tomography) using radiolabeled ligands which provide a measure of pre-synaptic dopaminergic neurons and terminals have revealed significant reductions in striatal uptake or binding of these ligands, as compared with patients who have Alzheimer's Disease or controls.

*11.1.6 Neuropsychological Differences Between Dementia Associated With Parkinson's Disease And Alzheimer's Disease*

These differences are summarized in the following table, which I have modified slightly, for the sake of clarity, from one contained in the submission.

| Neuropsychological Domain | Dementia Associated with Parkinson's Disease | Alzheimer's Disease |
|---|---|---|
| Memory | Retrieval deficit syndrome | Amnestic type of memory disturbance |
| Executive function deficit | Prominent | Moderate |
| Language deficit | Limited | Prominent |
| Visuospatial deficits | Prominent, may be attributable to executive abnormalities | Milder, independent of executive dysfunction |
| Bradyphrenia | Present | Absent |
| Fluctuation in attention | Characteristic | Uncommon |

### *11.1.7 Distinction Between Dementia Associated With Parkinson's Disease And Alzheimer's Disease Based On Non-Cognitive Clinical Features*

These differences are summarized in the following table, which I have modified, for the sake of clarity, from one contained in the submission.

| Non-Cognitive Feature | Dementia Associated with Parkinson's Disease | Alzheimer's Disease |
|---|---|---|
| Motor signs of Parkinson's Disease | Present | Absent (parkinsonism may emerge late) |
| Neuroleptic sensitivity | Present | Absent |
| Autonomic dysfunction | Common | Uncommon |
| REM sleep behavior disorder | Common | Absent |

### *11.1.8 Parkinson's Disease Can Be Distinguished From Alzheimer's Disease By A Practitioner*

The currently available diagnostic criteria for dementia associated with Parkinson's Disease are those contained in DSM-IV. According to the authors of the report, all major criteria, which are listed below, should be present for a diagnosis to be made.

- Parkinson's disease
- Dementia comprising the following
    - 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

Reviewer's Note: What is actually stated in DSM-IV (see below) is not quite the same as the above

294.1 Dementia Due To Parkinson's Disease

The essential feature of Dementia Due To Parkinson's Disease is the presence of dementia that is judged to be of direct pathophysiological consequence of Parkinson's disease. Parkinson's disease is a slowly progressive neurological condition, characterized by tremor, rigidity, bradykinesia, and postural instability. Dementia has been reported to occur in approximately 20%-60% of individuals with Parkinson's disease and is more likely to be present in older individuals or in those with more severe or advanced disease. The dementia associated with Parkinson's disease is characterized by cognitive and motor slowing, executive dysfunction and impairment in memory retrieval. Declining cognitive performance in individuals with Parkinson's disease is frequently exacerbated by depression. Findings on physical examination include the characteristic abnormal motor signs of resting tremor, evidence of slowness and poverty of movement (such as micrographia), or muscular rigidity and loss of associated movements. At autopsy, neuronal loss and Lewy bodies are evident in the substantia nigra. There are a number of syndromes that manifest with dementia, Parkinsonian movement disorders, and additional neurological features (e.g., progressive supranuclear palsy, olivopontocerebellar degeneration, and Vascular Dementia). Some individuals with Parkinson's disease and dementia are found at autopsy to have coexisting neuropathology indicative of Alzheimer's disease or of diffuse Lewy body disease.

A medical practitioner can apply these criteria easily.

### *11.2 Appropriateness Of Using The ADAS-Cog And ADCS-ADL As Outcome Measures In Dementia Associated With Parkinson's Disease*

An expert report prepared by Philip D. Harvey, PhD, has been provided in this submission. Although this report addresses both the use of the ADAS-Cog and ADCS-ADL in this condition, it is entitled: *"Reliability and Validity of the Alzheimer's Disease Assessment Scale – Cognitive Subscale in Clinical Trials for Dementia Associated with Parkinson's Disease."*

The report was created partly in response to comments made by the European Agency for the Evaluation of Medicinal Products/Committee for Proprietary Medicinal Products after review of an earlier version of the protocol for the non-interventional study 2314.

Note that this report, which was completed on October 28, 2004, does not cite the results of either Study 2311 or Study 2314, and appears to have been completed without taking these data into consideration. It is based on a review of the medical literature (but that review does not include the published results of Study 2311).

The contents of this report are briefly summarized below under the following headings.

### *11.2.1 ADAS-Cog*

#### *11.2.1.1 ADAS-Cog In Alzheimer's Disease*

The author of the report states that the ADAS-Cog has the following properties when used in Alzheimer's Disease.

- Reliability
- Face validity and sensitivity to impairment
- Sensitivity to change (criterion validity)

The author also points out that in efficacy studies in this population, the benefits of active treatment are evaluated in relation to placebo groups which experience a decline in cognition over the study; in some of these studies, the active treatment group experienced no improvement relative to baseline. In other words, a net benefit relative to placebo is assessed rather than an absolute improvement with active treatment relative to baseline.

#### *11.2.1.2 ADAS-Cog In Parkinson's Disease Dementia*

The following is a summary of what is stated by the author of this report.

##### 11.2.1.2.1 Face Validity Of ADAS-Cog

Parkinson's Disease Dementia is characterized by the following

- Impaired memory, but of less severity than that seen in Alzheimer's Disease. (The memory deficit seen in Parkinson's Disease Dementia is of the subcortical variety with impaired rate of learning and free recall, but with preserved delayed recognition memory [the impairments of memory are related to changes in cortical cholinergic function])
- Executive function deficits along with deficits in motor speed and working memory, which in themselves are unlikely to fully account for the memory deficits seen in this condition. (The author also indicates that cognitive test performance may be influenced by depression, motor symptoms, bradykinesia, and bradyphrenia)

While executive dysfunction is not well assessed by the ADAS-Cog, it is a feature of both Alzheimer's Disease and Parkinson's Disease Dementia.

The ADAS-Cog is sufficient to evaluate episodic memory impairment in Parkinson's Disease Dementia and therefore captures critical features of that condition.

##### 11.2.1.2.2 Temporal Change In ADAS-Cog

The course of cognitive decline in Parkinson's Disease Dementia has not been adequately studied; existing published studies have a number of limitations. The

few treatment studies in this condition prior to Study 2311 suggest that the cognitive change that occurs in Parkinson's Disease Dementia over time is not as rapid or extensive as that seen over a similar period in patients with Alzheimer's Disease.

11.2.1.2.3 Sensitivity To Impairment And To Effects Of Treatment

The very limited literature covering the use of the ADAS-Cog in Parkinson's Disease Dementia suggests that scores on that instrument correlate with those on the Mini-Mental Status Examination, suggesting that the ADAS-Cog is sensitive to impairment in that condition. The limited literature available also suggests that the ADAS-Cog is as sensitive to treatment effects in Parkinson's Disease Dementia as in Alzheimer's Disease.

11.2.1.2.4 Criterion Validity: Clinically Relevant Differences

Based on the small number of published studies, treatment effects in Parkinson's Disease Dementia, as measured by the ADAS-Cog, are at least as large as those in Alzheimer's Disease and, therefore, at least as clinically meaningful.

### *11.2.2 ADCS-ADL*

#### *11.2.2.1 ADCS-ADL In Alzheimer's Disease*

The author highlights the following properties of the ADCS-ADL in Alzheimer's Disease, based on the published literature:

- Good test-retest reliability
- Convergent validity
    - Good correlation of individual items on the scale with the level of dementia severity as measured by the Mini-Mental Status Examination
    - Ability to detect a decline in activities of daily living across levels of dementia severity
    - Significant correlation with scores on various cognitive measures such as the ADAS-Cog and Mini-Mental Status Examination
- Sensitivity to treatment effects in clinical drug trials in Alzheimer's Disease

#### *11.2.2.2 ADCS-ADL In Parkinson's Disease Dementia*

While there are no published studies of the use of the ADCS-ADL in Parkinson's Disease Dementia, the experience in Alzheimer's Disease supports its use as a "secondary" outcome measure in Parkinson's Disease Dementia.

However, clinical changes in domains in Parkinson's Disease other than cognition can result in changes in performance on activities of daily living.

# 12. Financial Disclosure Certification

Financial disclosure information has been collected for the following studies: 2311, 2311E1, and 2314.

## *12.1 Components Of Certification*

This certification provided by the sponsor has 2 components.

### *12.1.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests*

The sponsor has supplied a list of all such investigators and sub-investigators who were involved in these studies. In regard to this list the sponsor has

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

This certification has been provided on FDA Form 3454.

### *12.1.2 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests*

The sponsor has provided the name of a single investigator participating in Study 2311 who had a disclosable financial interest. This investigator had received a grant from the sponsor to conduct a study of rivastigmine in nursing home patients with severe dementia.

This certification has been provided on FDA Form 3455.

## *12.2 Reviewer's Comments*

It appears unlikely that the financial arrangements disclosed above introduced significant bias into the results of trials submitted with this application.

# 13. Site Inspection Report

Pending

# 14. Review Of Proposed Labeling

Deferred

# 15. Comments

## *15.1 General*

In this supplemental New Drug Application, the sponsor is seeking the approval of Exelon® (rivastigmine tartrate) capsules for the treatment of "mild to moderate dementia associated with Parkinson's Disease." The putative entity of "mild to moderate dementia associated with Parkinson's Disease" has also been referred to, interchangeably, as "Parkinson's Disease Dementia" in this application.

Exelon® is currently approved for marketing in this country, as both capsule and oral solution formulations, for the treatment of mild to moderate dementia of the Alzheimer's type.

The sponsor has provided evidence from two completed clinical studies in support of the efficacy and safety of Exelon® for the proposed new indication. These are:

- Study 2311, which was randomized, double-blind, placebo-controlled, and parallel-arm in design
- Study 2311E1, the open-label uncontrolled extension to Study 2311

In addition, the sponsor has performed a non-interventional study (Study 2314) of the validity of a number of assessment scales in the Parkinson's Disease Dementia (and vascular dementia); partial results for this study have been submitted in this application.

## *15.2 Efficacy*

### *15.2.1 Summary Of Study 2311*

The results of a single randomized, double-blind, placebo-controlled study (also referred to as the EXPRESS Study) of the efficacy of rivastigmine in the proposed entity of Parkinson's Disease Dementia or dementia associated with Parkinson's Disease has been submitted in this application. The main features of this study were as follows

- This was a randomized (2:1 [Exelon®:Placebo]), double-blind, placebo-controlled, parallel-arm study

- The key inclusion criteria for the study were as follows

  - Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria
  - Clinical diagnosis of Parkinson's Disease Dementia according to DSM-IV criteria (Code 294.1) with onset of symptoms of dementia within at least 2 years of the first diagnosis of idiopathic Parkinson's Disease
  - Mini-Mental Status Examination score of 10 – 24 at entry

- The study was of 24 weeks' duration

- The 2 parallel treatment arms were

  - Rivastigmine 3 to 12 mg/day (flexible dose; BID administration)
  - Placebo

- The primary efficacy measures were the ADAS-Cog and ADCS-CGIC. The primary efficacy analysis was performed on the intent-to-treat plus retrieved dropouts population. In the sponsor's primary efficacy analysis, the 2 treatment groups were compared on the ADAS-Cog using an analysis of covariance, and on the ADCS-CGIC using the Cochran-Mantel-Haenszel test

- The secondary efficacy measures were the following: ADCS-ADL; Neuropsychiatry Inventory-10; Mini-Mental Status Examination; Cognitive Drug Research Computerized Assessment System; D-KEFS Verbal Fluency Test; and Ten Point Clock-Drawing Test

- Safety was assessed through adverse events, vital signs, safety laboratory tests, electrocardiograms, and Unified Parkinson's Disease Rating Scale score

- The sponsor's primary efficacy analysis was performed on the intent-to-treat plus retrieved dropouts dataset using the following statistical models

  - The change from baseline to endpoint in the ADAS-Cog score was to be compared between the treatment groups using an analysis of covariance with treatment, country, and baseline ADAS-Cog score as explanatory variables
  - The ADCS-CGIC score at endpoint was to be analyzed using a Cochran-Mantel-Haenszel test with modified ridits scores and with country as a stratification variable

- Note that the study procedures included a number of precautions to minimize the effects of the motor manifestations of Parkinson's Disease on the efficacy assessments

  - All primary and other cognitive outcome variables were to be assessed before lunch, beginning 1 hour after the intake of dopaminergic medications, at the same time of day throughout the study for each patient, and using the same sequence of tests
  - For patients with motor fluctuations and/or dyskinesias, efficacy assessments were to be performed during their "on" time (defined as intervals when parkinsonian symptoms were replaced by increased mobility)
  - For patients with an acute psychosis, efficacy assessments were to be performed after remission of the psychosis
  - Raters were advised to identify and discount, if possible, potential behavioral and functional changes due to the motor symptoms of Parkinson's Disease

Key efficacy results for this study were as follows

- 541 patients were randomized, of whom 442 patients completed the study. Their distribution by treatment group was as follows:

| Treatment Group | Exelon® | Placebo |
|---|---|---|
| Number randomized | 362 | 179 |
| Number completed | 263 | 147 |

- The primary efficacy analysis, using Study Week 24 as the endpoint, revealed statistically significant differences between the treatment groups on the ADAS-Cog (difference in mean change from baseline score at endpoint: 2.90; $p < 0.001$) and ADCS-CGIC (difference in mean score between treatment groups at endpoint: 0.5; $p = 0.007$). Note that an Agency statistical reviewer has judged the distribution of ADAS-Cog data not to be normal and therefore in violation of the assumptions of the analysis of covariance model proposed; however, even with the use of a non-parametric model, the Wilcoxon rank sum test, the Exelon® group showed a statistically significant superiority over placebo on this measure

- Nominally statistically significant differences were seen between the treatment groups on all secondary efficacy variables at Week 24 in the same dataset as that used for the primary efficacy analysis

- Analyses of the primary efficacy parameters using other datasets (intent-to-treat last-observation-carried-forward, and observed cases) yielded similar results.

### *15.2.2 Sponsor's View Of The Entity Of Parkinson's Disease Dementia (Dementia Associated With Parkinson's Disease)*

The sponsor's view of the entity of dementia associated with Parkinson's Disease appears to be consistent with an expert report included in this submission. The main conclusions of the expert report may be summarized as follows:

- Based on epidemiologic, genetic, neuropathological, neuroimaging, and cognitive and non-cognitive clinical data, dementia associated with Parkinson's Disease is an entity distinct from Alzheimer's Disease.

- The severity of dementia associated with Parkinson's Disease is better correlated with pathological changes that are distinctive for Parkinson's Disease such as the presence of cortical Lewy bodies. Although neurofibrillary tangles and senile plaques are frequently present in the brains of patients with dementia associated with Parkinson's Disease, the extent of these changes is less pronounced than those that are distinctive for Parkinson's Disease and less well-correlated with the severity of dementia. The neuropathological changes in the brains of patients with dementia associated with Parkinson's Disease include lesions of cholinergic pathways distinct from those seen in Alzheimer's Disease.

  Marked nigrostriatal neuronal degeneration is a unique feature of dementia associated with Parkinson's Disease; cell loss in the medial substantia nigra is

associated with the presence of dementia. Pathological abnormalities in the locus ceruleus may also contribute to the dementia of Alzheimer's Disease.

- The diagnostic entities of dementia associated with Parkinson's Disease and Alzheimer's Disease are mutually exclusive by definition. The diagnosis of dementia associated with Parkinson's Disease should be based on the presence of all of the following criteria [which the sponsor believes are stipulated in DSM-IV (294.1)]

    - Presence of Parkinson's Disease
    - Presence of dementia syndrome
    - Evidence of Parkinson's Disease prior to the onset of dementia
    - Exclusion of other causes of dementia

- Dementia associated with Parkinson's Disease is an entity that be diagnosed by a community medical practitioner

### *15.2.3 Implications Of Efficacy Results Of Study 2311 (EXPRESS Study)*

Study 2311 may be considered "positive" in that it demonstrates the efficacy of Exelon® in the study population based on prospectively-specified criteria for success. The dual efficacy outcome measure paradigm used for demonstrating the efficacy of Exelon® in this study is the same as used to demonstrate the efficacy of drugs approved for the treatment of Alzheimer's Disease (dementia of the Alzheimer's type).

However, **the key regulatory question that needs to be addressed in the context of this application is whether the results of Study 2311 establish that Exelon® is effective in the treatment of an entity (dementia associated with Parkinson's Disease [Parkinson's Disease Dementia]) that is sufficiently distinct from mild to moderate dementia of the Alzheimer's type [for the treatment of which Exelon® is already approved] to justify a separate regulatory claim**.

Note that for a drug to be approved for a specific condition the following must generally be true

- The condition can be defined without ambiguity using criteria that have wide acceptance, and are both valid and reliable
- Appropriate instruments be used for measurement of the clinical effect of the drug on that condition; such instruments must measure what they are intended to under the conditions under which they are actively employed
- Clinical trials should be appropriately designed to measure that effect
- The effect measured should be clinically meaningful

I will address the question (in bolded text) above, and several additional questions under the following headings

*15.2.3.1 Is Parkinson's Disease Dementia (dementia associated with Parkinson's Disease) a distinct entity (i.e., distinct from Alzheimer's Disease) and do widely accepted, valid, and reliable criteria exist for its clinical diagnosis?*

- While it is widely accepted that there is an increased prevalence of dementia in Parkinson's Disease, the pathological basis for that dementia has been a matter of controversy, in regard to both the specific histopathological abnormalities seen and their location. The medical literature indicates that in patients with Parkinson's Disease who develop dementia, the neuropathological findings are varied; while a number of the pathological abnormalities seen are considered distinctive for that entity (e.g., cortical Lewy bodies and degeneration of the medial substantia nigra) and may correlate best with the severity of dementia, Alzheimer's-type pathology (such as neurofibrillary tangles and amyloid plaques) frequently co-exists, albeit often not to a sufficient degree for a separate pathological diagnosis of Alzheimer's Disease to be made; pathological lesions attributed to cerebrovascular disease may also co-exist. The variability in pathological abnormalities described in those studies may, in part, reflect differences in the methods used in each instance.

  More recently published studies are considered by some to indicate that earlier histopathological data may have underestimated the extent to which Lewy bodies were present in the brain (and especially in the neocortex and limbic cortex) of patients with Parkinson's Disease and dementia; these studies were done prior to the availability of modern immunohistochemical techniques such as stains for ubiquitin and alpha-synuclein. The earlier studies may, therefore, according to the sponsor and others, have attributed a greater-than-justified role for Alzheimer's type pathology in the pathogenesis of dementia in these patients, while more recent studies suggest that cortical Lewy bodies may have a greater role in the pathogenesis of dementia, although their extent may not correlate with the severity of dementia (see Braak H et al below).

  Thus, recently published data suggest that the pathological substrate underlying the dementia that occurs in Parkinson's Disease may be more distinctive for that disease than previously believed. Note that a recent consensus report (McKeith et al [2005]) for a closely-linked disorder, dementia with Lewy bodies (see below), states that "the relative contributions of Lewy body formation and synuclein pathology, Alzheimer's Disease-type pathology, neuron loss, or neurochemical deficits as determinants of dementia in Parkinson's Disease remain unresolved although recent studies suggest that Lewy-related pathology is more strongly associated than Alzheimer's Disease-type changes.

  The cholinergic deficit seen in patients with Parkinson's Disease dementia has been linked to the loss of neurons in the nucleus basalis of Meynert

and to a more marked brain cholinergic deficiency than in Alzheimer's Disease.

- A further question is whether the dementia that occurs in Parkinson's Disease is clinically distinct or dissimilar from that which occurs in Alzheimer's Disease, and in other types of primary degenerative dementia, and whether validated criteria exist for the diagnosis of the former.

  Many publications, including relatively recent articles, state that the cognitive deficits that are seen in the dementia that occurs in Parkinson's Disease are distinctive to at least some degree, with the following higher cortical process being impaired to a greater degree, and, in some instances, qualitatively, as compared with patients with Alzheimer's Disease:

  - Attention (fluctuations in attention are also seen)
  - Executive functions
  - Free recall memory (with preserved recognition memory)
  - Visuospatial function
  - Verbal fluency (with other aspects of language function, as well as praxis, being preserved)
  - Speed of mental processing

  Behavioral and personality changes are also stated to be more common in Parkinson's Disease than in Alzheimer's Disease

- Criteria for diagnosing "Dementia Due To Parkinson's Disease" exist under DSM-IV (294.1). These criteria state that *"the essential feature of Dementia Due To Parkinson's Disease is the presence of dementia that is **judged** to be of direct pathophysiological consequence of Parkinson's disease"* but do not provide a further indication of how that judgment is to be made beyond stating that "dementia associated with Parkinson's Disease" is "characterized by cognitive and motor slowing, executive dysfunction, and impairment in memory retrieval." The criteria are primarily descriptive, and, importantly, do not clearly state how this entity is to be distinguished from other dementias such as Alzheimer's Disease; they have never been validated against the histopathological abnormalities that have recently been described as being more distinctive for dementia in Parkinson's Disease; in fact, these criteria are deficient enough in their specifications, or lack thereof, that they are likely to be difficult to apply in a validation study. Note that a just-issued American Academy of Neurology Practice Parameter (see Miyasaki et al, below) suggests that given the pattern of deficits reported to seen in patients with dementia associated with Parkinson's Disease, the DSM-IV criteria for establishing dementia per se may not be appropriate to use.

A recently published relatively large study (see Braak H et al below) that correlated cognitive status with neuropathological stage in Parkinson's Disease, and concluded that the burden of Alzheimer -type pathological changes was relatively low in such patients, did not require that patients with dementia who were included in that study needed to have a specific pattern of cognitive deficits such as that considered by some authors to be distinctive for Parkinson's Disease (see above). The criteria used were as follows

- Clinical diagnosis of Parkinson's Disease
- Presence of dementia, without that dementia syndrome needing to have any distinctive features
- Evidence of Parkinson's Disease more than a year prior to the onset of dementia

A number of other published studies that have reported clinicopathological correlations in demented patients with Parkinson's Disease have also not required such patients to have a specific qualitative pattern of cognitive deficits

Thus, there do not appear to be validated diagnostic criteria for Parkinson's Disease Dementia, let alone criteria that stipulate that a specific pattern of cognitive deficits must be present. The remaining question is whether the clinical diagnosis of Parkinson's Disease together with the presence of dementia (but without a specific pattern of cognitive deficits), with the onset of Parkinson's Disease preceding the onset of dementia by not more than two years and the exclusion of other causes of dementia to the extent clinically possible, are together sufficient to define a clinical syndrome that is sufficiently distinct from Alzheimer's Disease to justify a separate treatment claim.

- Note that the recently-issued American Academy of Neurology Practice Parameter (see Miyasaki et al, below) contains the following statements, among others, in regard to dementia in Parkinson's Disease (PD)

  - *"The etiology of dementia in PD is unclear"*

  - *Cognitive decline in PD is characterized by impaired executive function, visuospatial abnormalities, impaired memory, and language deficits. An appropriate scale that reliably incorporates executive function (e.g., frontal assessment battery and other practical tests of executive function) should be incorporated into a screening test for PD dementia. When evaluating new screening tools, the DSM-IV criteria for dementia may not be the most appropriate gold standard for patients with PD. DSM-IV criteria for dementia have not been validated in PD. In PD patients, it may be difficult to assess impairments in domains other than memory.*

*15.2.3.2 What are the implications of the diagnostic criteria for dementia with Lewy bodies for the entity of Parkinson's Disease Dementia?*

Another entity that combines dementia with features of Parkinson's Disease is dementia with Lewy bodies for which revised diagnostic criteria have recently been proposed (see McKeith et al [2005] below). In the more recent medical literature, this entity has generally been distinguished from Parkinson's Disease Dementia by the (arbitrary) "one-year rule" criterion where the onset of dementia within 12 months of the onset of parkinsonism is stated to be consistent with dementia with Lewy bodies whereas if parkinsonism has been present for more than 12 months prior to the onset of dementia, the condition is considered to represent Parkinson's Disease Dementia. The neuropathological abnormalities that underlie both conditions are considered to be similar with changes considered distinctive for Parkinson's Disease being combined with other pathology, notably Alzheimer-type changes. Whether these entities are the same disease or separate distinct entities is still a matter of some controversy, although the consensus view appears to be that they are the same neurobiological entity with clinical phenotypes that differ, based solely on the arbitrary "one-year rule."

Note that the revised criteria for the diagnosis of dementia with Lewy bodies include the following "central" (required) feature: *"Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages, but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent."* The publication that describes these revised diagnostic criteria (McKeith et al [2005]) further states the following: *"The cognitive profile of dementia with Lewy bodies (DLB) comprises both cortical and subcortical impairments with substantial attentional deficits and prominent executive and visuospatial dysfunction. A "double discrimination" can help differentiate DLB from Alzheimer disease (AD), with relative preservation of confrontation naming and short and medium term recall as well as recognition, and greater impairment on verbal fluency, visual perception and performance tasks."* These cognitive abnormalities are similar to those described by a number of authors as being distinctive for Parkinson's Disease Dementia

Thus the same (reportedly) distinctive clinical features may be common to both dementia with Lewy bodies and Parkinson's Disease Dementia, while both entities may also have the same neuropathological basis.

*15.2.3.3 Was the population enrolled in Study 2311 selected appropriately in the context of the proposed new indication, such that the effects of Exelon® in that population could be considered distinct from those already established as occurring in patients with Alzheimer's Disease?*

- The key inclusion criteria used to identify patients as having Parkinson's Disease Dementia were prospectively specified as being as follows

    - Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria
    - Clinical diagnosis of Parkinson's Disease Dementia according to DSM-IV criteria (Code 294.1) with onset of symptoms of dementia within at least 2 years of the first diagnosis of idiopathic Parkinson's Disease

  As noted earlier, there are serious limitations to the practical application of the DSM-IV criteria for "Dementia due to Parkinson's Disease." In addition, no evidence has been supplied in this submission that dementia associated with Parkinson's Disease was diagnosed at study entry based on the features that are stated to distinctive for that condition such as deficits of attention, executive function, and memory retrieval (which in any case have never been validated). In fact, the criteria used to diagnose dementia itself in these patients may have been no different than those used for patients enrolled in the key pre-approval efficacy trials of Exelon® in Alzheimer's Disease. Admittedly, the NINCDS-ADRDA criteria for the diagnosis of probable Alzheimer's Disease, which were used to enroll patients in the pre-approval efficacy trials of Exelon®, if strictly applied, required the exclusion of patients with Parkinson's Disease.

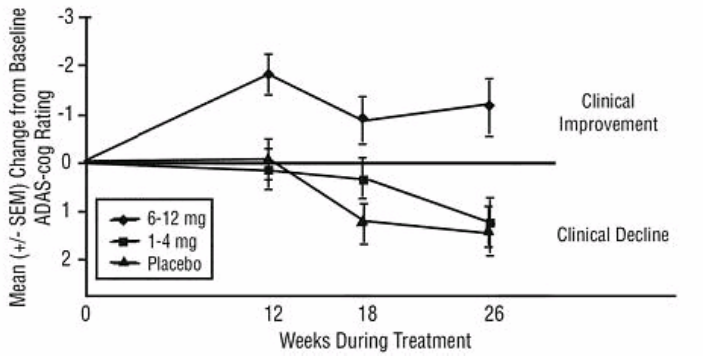
  In their essence, the criteria used to diagnose dementia associated with Parkinson's Disease in Study 2311 consisted of the following

    - Presence of Parkinson's Disease
    - Presence of dementia syndrome, without that dementia syndrome needing to have any distinctive features specific to Parkinson's Disease Dementia
    - Evidence of Parkinson's Disease prior to, but within 2 years of, the onset of dementia
    - Exclusion of other causes of dementia

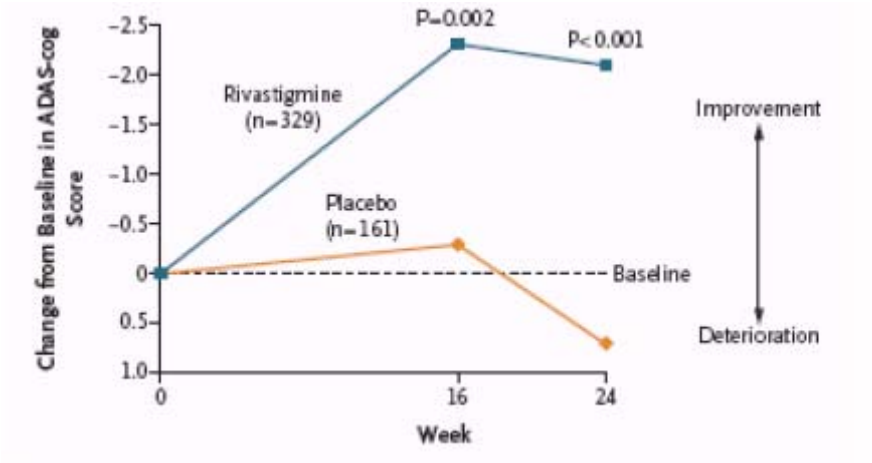
  While the latter criteria do have face validity for diagnosing dementia in patients with Parkinson's Disease, they themselves do not appear to have been correlated with neuropathological findings in a formal study (especially one that was prospective) of sufficient size (the recently-published study by Braak et al [see below] might, however, address that objective to some extent)

- It is noteworthy that the effects or rivastigmine on the primary efficacy measures in Study 2311 are not very different from those observed for rivastigmine, and, indeed other acetylcholinesterase inhibitors, on the same measures in the key pre-approval efficacy trials of those drugs in mild to moderate probable Alzheimer's Disease: in addition, the clinical course of the placebo group in Study 2311 and the placebo groups in the pre-approval efficacy trials of Exelon® in Alzheimer's Disease were similar, also suggesting that the study populations in each instance may have been similar too (see below):

  The following were the changes seen in the Exelon® and placebo groups on the ADAS-Cog in a key pre-approval efficacy trial in Alzheimer's Disease (the figure is taken from the approved product labeling




  The following were the corresponding changes seen in Study 2311




As noted earlier, in patients with Parkinson's Disease who develop dementia, Alzheimer's-type pathology (neurofibrillary tangles, amyloid plaques) frequently co-exists, albeit often not to a sufficient degree for a separate pathological diagnosis of Alzheimer's Disease to be made. If a similar mixed pathology underlay the dementia in patients enrolled in the Study 2311, it is possible (and no evidence to the contrary has been supplied) that the

apparent benefit of rivastigmine in that study was mediated through its effects on co-existing Alzheimer's-type pathology. It is unlikely that the criteria used to diagnose dementia associated with Parkinson's Disease in Study 2311, could have excluded those with co-existing Alzheimer's-type pathology, despite a stipulation in those criteria that other causes of dementia should be excluded.

These observations raise the question of whether the efficacy of rivastigmine in dementia associated with Parkinson's Disease, as seen in the population enrolled in Study 2311, is really distinct from its already-established effects in mild to moderate probable Alzheimer's Disease, and for which rivastigmine is already approved.

As explained further below, the overall design of this trial was otherwise similar in many ways to the now-standard study design used to demonstrate the efficacy of drugs intended for the treatment of Alzheimer's Disease, again raising the question of how distinct the effects of Exelon® in this study were from those already established in Alzheimer's Disease.

Unless the efficacy of rivastigmine as demonstrated in Study 2311 is judged to be mechanistically distinct from its established effects in Alzheimer's Disease, the grant of a separate claim for the treatment of mild to moderate dementia associated with Parkinson's Disease may not be justified.

*15.2.3.4 Was the population enrolled in Study 2311 otherwise selected appropriately?*

- Among the exclusion criteria for this study were the following (I have emphasized elements of these criteria in bold underlined font)

    - Current diagnosis of any primary neurodegenerative disease other than Parkinson's Disease or **any other causes of dementia** (e.g., Alzheimer's Disease, frontotemporal dementia, Huntington's Disease, dementia with Lewy bodies, Parkinson-plus syndromes such as progressive supranuclear palsy or olivopontocerebellar degeneration, Vitamin B12 or folate deficiency, hypothyroidism or syphilis)
    - A current diagnosis of probable or possible vascular dementia according to the NINDS-AIREN criteria, i.e., clinical and brain imaging evidence of cerebrovascular disease and a relationship between dementia and cerebrovascular disease (Reviewer's note: these are criteria for the diagnosis of probable vascular dementia only; the diagnosis of possible vascular dementia does not require the demonstration of a clear relationship between dementia and stroke)

- Special diagnostic laboratory tests that were performed at screening and which were intended to help exclude other causes of dementia were serum TSH, folic acid, Vitamin B12 and RPR.

- **However, under the protocol for Study 2311, brain imaging (i.e., computerized tomography or magnetic resonance scanning) was not required prior to entry into the study.** Study Case Report Forms do not document which patients may have had brain imaging prior to entry into the study, and at the time that this review was completed, data as to the proportion of study patients who had undergone brain imaging had not yet been made available by the sponsor in response to a request from us. The following observations may be pertinent in this context:

    - The American Academy of Neurology Practice Parameter for Dementia (see Knopman et al below) recommends the use of a neuroimaging examination (either a non-contrast CT scan or MRI scan) "under most circumstances" at the time of the initial dementia assessment to identify pathology such as brain neoplasms or subdural hematomas, although it is also stated that a third condition, normal pressure hydrocephalus, which might be detected by CT or MRI is very rare

    - The UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for Parkinson's Disease list as an exclusion criterion (Step 2) "the presence of cerebral tumor or communicating hydrocephalus on CT scan." [However, it can hardly be considered standard clinical practice for brain imaging to be performed routinely for the diagnosis of Parkinson's Disease]

    - In key efficacy trials of drugs in Alzheimer's Disease, it is standard practice to perform either a CT scan of the head or MRI at screening, if not performed within the preceding 12 months

    - A standard neurological examination directed at detecting focal neurological deficits is more difficult to perform in patients with Parkinson's Disease, and often considerably more difficult

- **The question may therefore be raised as to how adequately patients enrolled in Study 2311 were evaluated for "non-degenerative" causes of dementia such as cerebrovascular lesions, brain tumors, subdural hematomas, and communicating hydrocephalus in the absence of brain imaging. Admittedly, those conditions are often associated with additional symptoms and signs on neurological evaluation, but a standard neurological evaluation can be more difficult than usual to perform in patients with co-existing Parkinson's Disease so that subtle physical signs may not be detected.**

*15.2.3.5 Was the overall design of Study 2311 appropriate and were the primary efficacy measures used suitable for evaluating the efficacy and safety of rivastigmine in mild to moderate dementia associated with Parkinson's Disease?*

- The paradigm used for designing this study is very similar to that used in standard efficacy trials in Alzheimer's Disease. More specifically:

- This was a randomized, double-blind, placebo-controlled, parallel-arm trial of 6 months' duration
- The stipulated entry Mini-Mental Status Examination score range was consistent with that used to define the "mild to moderate" range for Alzheimer's Disease
- For the study to be considered to have demonstrated the efficacy of Exelon® in treating mild to moderate Parkinson's Disease Dementia, it was required that a statistically significant superiority of Exelon® be demonstrated on both cognitive and global primary efficacy measures
- The cognitive and global primary efficacy measures used in this study, the ADAS-Cog and ADCS-CGIC were identical to those used in the efficacy studies in Alzheimer's Disease

- Whether this design is an appropriate one for trials in Parkinson's Disease Dementia is a matter for further discussion. Assuming that the condition itself is a distinct entity justifying a separate claim, the following might need consideration in deciding whether the design for that study was appropriate for the proposed indication:

    - The natural clinical course of Parkinson's Disease Dementia, for which information is lacking
    - The nature of the cognitive deficits seen in that entity
    - Whether the outcome measures, and especially, the ADAS-Cog were appropriate to use in Parkinson's Disease Dementia. The ADAS-Cog is not, for example, particularly appropriate for evaluating executive function (also note that the just-issued American Academy of Neurology Practice Parameter [see Miyasaki et al, below] also states that in patients with Parkinson's Disease, it may be difficult to assess impairments in domains other than memory).

- The results of non-interventional study (Study 2314) that was intended to validate several assessment scales used in Study 2311 have been interpreted by the sponsor to demonstrate the following:

    - That the ADAS-Cog score can differentiate between dementia associated with Parkinson's Disease of mild and moderate severities, as can the scores several of the secondary efficacy assessment instruments used in this study
    - That the ADAS-Cog and several secondary efficacy measures had test-retest reliability in this population
    - That the ADAS-Cog scores correlated with those of several other efficacy instruments, whether those measures assessed cognition or other domains
    - A factor analysis that compared populations with Parkinson's Disease Dementia and Alzheimer's Disease on ADAS-Cog sub-item scores had indicated that the sub-items grouped differently in each population, suggesting that the cognitive and behavioral profiles in these populations might differ

- This study does not address whether the efficacy measures used in Study 2311, and especially the ADAS-Cog, had "content" validity; i.e., did the components of the ADAS-Cog evaluate the main cognitive domains believed to be impaired in that condition. It is currently unclear as to whether it is currently possible for a conclusion to be reached that the ADAS-Cog has content validity in this population. The factor analysis referred to above suggested that the cognitive profiles in Alzheimer's Disease and Parkinson's Disease differ.

*15.2.3.6 Could the apparent beneficial effects of Exelon® on cognition and/or global function in Study 2311 have been due to a beneficial effect on the motor manifestations of Parkinson's Disease rather than on the dementia itself?*

If there was a beneficial effect of Exelon® on specific motor manifestations of Parkinson's Disease such as bradykinesia or dysarthria, it is possible that such a benefit may have been reflected in a beneficial effect on the ADAS-Cog and/or ADCS-CGIC, in the absence of a true effect on the dementia itself

Such a possibility is unlikely for the following reasons

- There was no overall difference between treatment groups in the mean change from baseline to endpoint in total UPDRS motor scores. Notable differences between treatment groups were not seen for important individual UPDRS item scores
- Adverse events that might be considered to represent a worsening in the motor manifestations of Parkinson's Disease were, in aggregate, more common in those assigned to Exelon® than in those assigned to placebo

[Also note that the study procedures included a number of precautions to minimize the effects of the motor manifestations of Parkinson's Disease on the efficacy assessments].

*15.2.3.7 Do the results of Study 2311 warrant replication for a claim for the treatment of dementia associated with Parkinson's Disease to be granted?*

All drugs approved by this Agency so far for the treatment of dementia of the Alzheimer's type (Alzheimer's Disease) have been approved based on the demonstration of the desired treatment effect in at least 2 adequate and well-controlled trials; the same has applied to the approval of drugs for other discrete clinical entities. This Division's view so far is that the same principle must apply to other types of dementia, unless they are variants or grades of severity of Alzheimer's Disease not subsumed under the current claim.

Therefore, if dementia associated with Parkinson's Disease is indeed a form of dementia that is distinct from Alzheimer's Disease, it would be appropriate to require that the results of Study 2311 be replicated.

### *15.2.3.8 References*

The references, based upon which a number of the above comments have been made are listed

**Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA**. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 2005;64:1404-10

**Aarsland D, Perry R, Brown A, Larsen JP, Ballard C**. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Ann Neurol 2005;58:663-5.

**Emre M**. Dementia associated with Parkinson's disease. Lancet Neurol 2003;2:229-37

**Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP**. 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 2003;74:1215-20

**McKeith IG, Dickson DW, et al**. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863-72

**McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, Dickson D, Dubois B, Duda JE, Feldman H, Gauthier S, Halliday G, Lawlor B, Lippa C, Lopez OL, Carlos Machado J, O'Brien J, Playfer J, Reid W; International Psychogeriatric Association Expert Meeting on DLB**. Dementia with Lewy bodies. Lancet Neurol 2004; 3:19-28

**Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, Shulman LM, Gronseth G, Weiner WJ; Quality Standards Subcommittee of the American Academy of Neurology**. Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2006;66:996-1002

**Knopman DS, DeKosky ST, Cummings JL, Chui H, Corey-Bloom J, Relkin N, Small GW, Miller B, Stevens JC**. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1143-53 [Guideline reaffirmed: February 13, 2004]

## ***15.3 Safety***

Evidence for the safety of Exelon® in dementia associated with Parkinson's Disease is derived from 2 sources

### *15.3.1 Study 2311*

This study has already been summarized above. Salient safety findings for this study were as follows.

- The incidence of nausea, vomiting, and tremor was appreciably higher in the rivastigmine group than in the placebo group; a similar adverse event profile was seen in the key controlled clinical trials of Exelon® in Alzheimer's Disease
- Several treatment-emergent adverse events that may have represented a worsening in the motor manifestations of Parkinson's Disease, tremor in particular, were more frequent in those treated with Exelon® than in those treated with placebo. However, changes in UPDRS total motor scores, probably a more objective measure of change in the motor manifestations of Parkinson's Disease than the incidence of treatment-emergent adverse events, showed no meaningful difference between treatment groups.

### *15.3.2 Study 2311E1*

This was an 24-week open-label uncontrolled extension to Study 2311 intended primarily to evaluate the safety and tolerability of Exelon® in the study

population. Patients given the option of enrolling in this study had either completed the double-blind treatment phase of Study 2311 or discontinued early during that study, but returned for all the remaining scheduled efficacy assessments without significant protocol violations. Regardless of their previous treatment assignment, patients enrolled in the extension study were all re-titrated to a flexible dose of Exelon® that ranged from 1.5 mg BID to 6.0 mg BID, based on tolerability.

433 patients enrolled in Study 2311 were eligible to enroll in Study 2311E1 of whom 334 actually consented to participate and 273 completed the study. The adverse event profile of Exelon® in Study 2311 was broadly similar to that seen in Study 2311E1

## 16. Conclusions

Deferred, pending discussion of this application at a scheduled meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee

## 17. Recommendation

Deferred, pending discussion of this application at a scheduled meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee

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Medical Reviewer

rbm 4/18/06
cc:
HFD-120
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