CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-823 / S-016
21-025 / S-008

Trade Name: Exelon

Generic Name: rivastigmine tartrate

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: Junio 27, 2006

Indications: For the treatment of mild to moderate dementia associated with Parkinson's Disease.

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APPLICATION NUMBER:

20-823 / S-016

21-025 / S-008

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APPLICATION NUMBER:

20-823 / S-016

21-025 / S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-823/S-016
NDA 21-025/S-008

Novartis Pharmaceuticals Corporation
Attention: Martina Struck, Ph.D.
One Health Plaza
East Hanover, New Jersey 07936-1080

Dear Dr. Struck:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exelon (rivastigmine) Capsules and Liquid.

We acknowledge receipt of your submissions dated January 19, 2006 and April 14, 2006.

These supplemental new drug applications provide for the use of Exelon in the treatment of mild to moderate dementia associated with Parkinson's Disease.

We completed our review of these applications. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for package insert).

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Neurology and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Melina Griffis, R.Ph, Sr. Regulatory Project Manager, at (301) 796-1078.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
6/27/2006 04:25:32 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-823 / S-016

21-025 / S-008

LABELING

NOVARTIS

T2005-55

Exelon®

(rivastigmine tartrate)

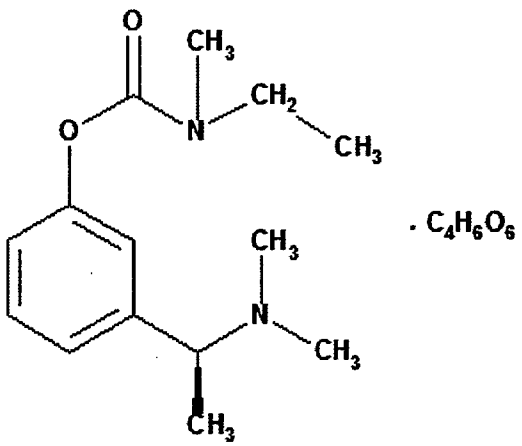
Capsules and Oral Solution

Rx only

Prescribing Information

DESCRIPTION

Exelon® (rivastigmine tartrate) is a reversible cholinesterase inhibitor and is known chemically as (S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate. Rivastigmine tartrate is commonly referred to in the pharmacological literature as SDZ ENA 713 or ENA 713. It has an empirical formula of $C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6$ (**hydrogen tartrate salt** – hta salt) and a molecular weight of 400.43 (hta salt). Rivastigmine tartrate is a white to off-white, fine crystalline powder that is very soluble in water, soluble in ethanol and acetonitrile, slightly soluble in n-octanol and very slightly soluble in ethyl acetate. The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 3.0.



Exelon Capsules contain rivastigmine tartrate, equivalent to 1.5, 3, 4.5 and 6 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Each hard-gelatin capsule contains gelatin, titanium dioxide and red and/or yellow iron oxides.

Exelon Oral Solution is supplied as a solution containing rivastigmine tartrate, equivalent to 2 mg/mL of rivastigmine base for oral administration. Inactive ingredients are citric acid, D&C yellow #10, purified water, sodium benzoate and sodium citrate.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pathological changes in Dementia of the Alzheimer type and Dementia **associated with Parkinson's disease** involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, Exelon's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process. After a 6-mg dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% 5 hours after dosing.

In vitro and *in vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

Clinical Trial Data

Dementia of the Alzheimer's type

The effectiveness of Exelon® (rivastigmine tartrate) as a treatment for Alzheimer's Disease is demonstrated by the results of 2 randomized, double-blind, placebo-controlled clinical investigations in patients with Alzheimer's Disease [diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental State Examination (MMSE) ≥10 and ≤26, and the Global Deterioration Scale (GDS)]. The mean age of patients participating in Exelon trials was 73 years with a range of 41-95. Approximately 59% of patients were women and 41% were men. The racial distribution was Caucasian 87%, Black 4% and Other races 9%.

Study Outcome Measures: In each study, the effectiveness of Exelon was evaluated using a dual outcome assessment strategy.

The ability of Exelon to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on ADAS-cog of approximately 23 units, with a range from 1 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggest that they gain 6-12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in Exelon trials was approximately 3-8 units per year.

The ability of Exelon to produce an overall clinical effect was assessed using a Clinician's Interview-Based Impression of Change (CIBIC) that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-Plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-Plus evaluations from other clinical trials. The CIBIC-Plus used in the Exelon trials was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of three domains: patient cognition, behavior and functioning, including assessment of activities of daily living. It represents the assessment of a skilled clinician using validated scales based on his/her observation at interviews conducted separately with the patient and the caregiver familiar with the behavior of the patient over the interval rated. The CIBIC-Plus is scored as a 7-point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening." The CIBIC-Plus has not been systematically compared directly to assessments not using information from caregivers or other global methods.

U.S. 26-Week Study

In a study of 26 weeks duration, 699 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week

forced-dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo were 1.9 and 4.9 units for the 1-4 mg and 6-12 mg treatments, respectively. Both treatments were statistically significantly superior to placebo and the 6-12 mg/day range was significantly superior to the 1-4 mg/day range.

Figure 1: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

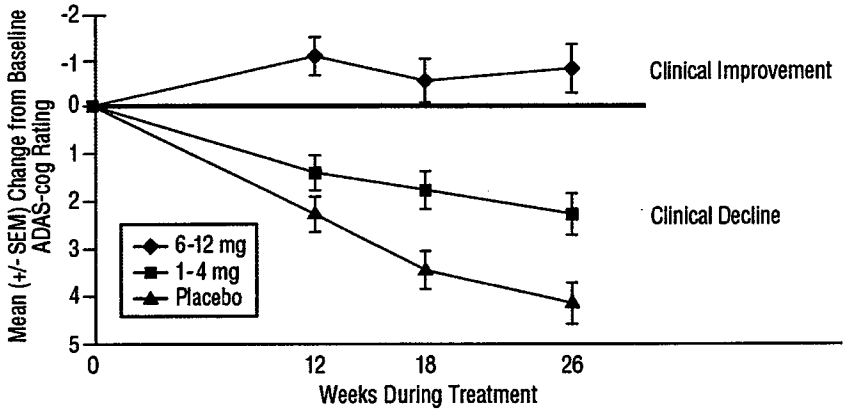
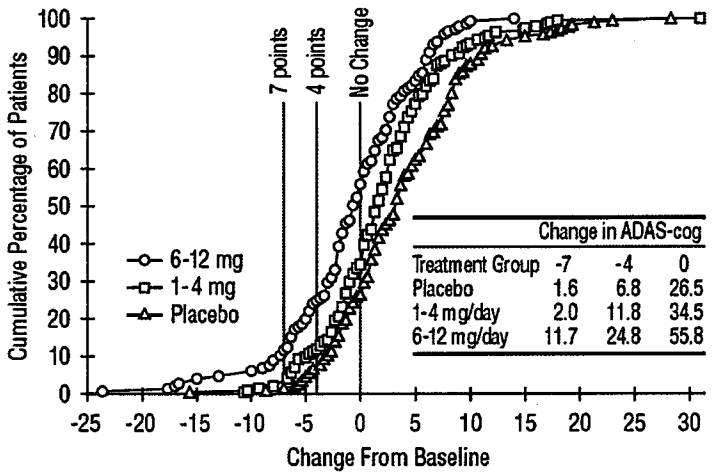


Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

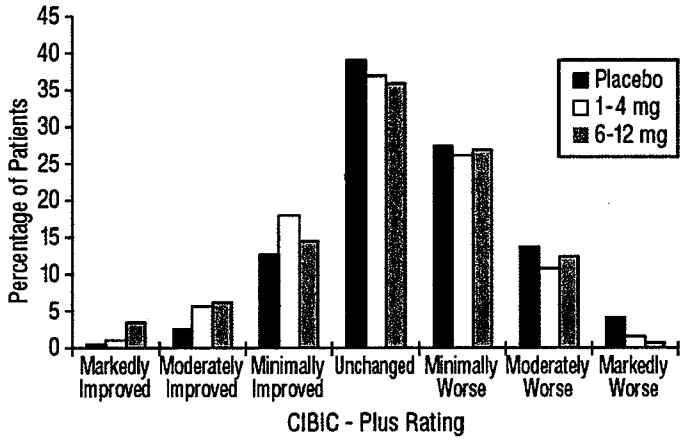
The curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the Exelon groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

Figure 2: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 84%, 1-4 mg 85%, and 6-12 mg 65%.



Effects on the CIBIC-Plus: Figure 3 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients in the mean rating of change from baseline were 0.32 units and 0.35 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day and 1-4 mg/day groups were statistically significantly superior to placebo. The differences between the 6-12 mg/day and the 1-4 mg/day groups were statistically significant.

Figure 3: Frequency Distribution of CIBIC-Plus Scores at Week 26



Global 26-Week Study

In a second study of 26 weeks duration, 725 patients were randomized to either a dose range of 1-4 mg or 6-12 mg of Exelon per day or to placebo, each given in divided doses. The 26-week study was divided into a 12-week forced-dose titration phase and a 14-week maintenance phase. The patients in the active treatment arms of the study were maintained at their highest tolerated dose within the respective range.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo were 0.2 and 2.6 units for the 1-4 mg and 6-12 mg treatments, respectively. The 6-12 mg/day group was statistically significantly superior to placebo, as well as to the 1-4 mg/day group. The difference between the 1-4 mg/day group and placebo was not statistically significant.

Figure 4: Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 26 Weeks of Treatment

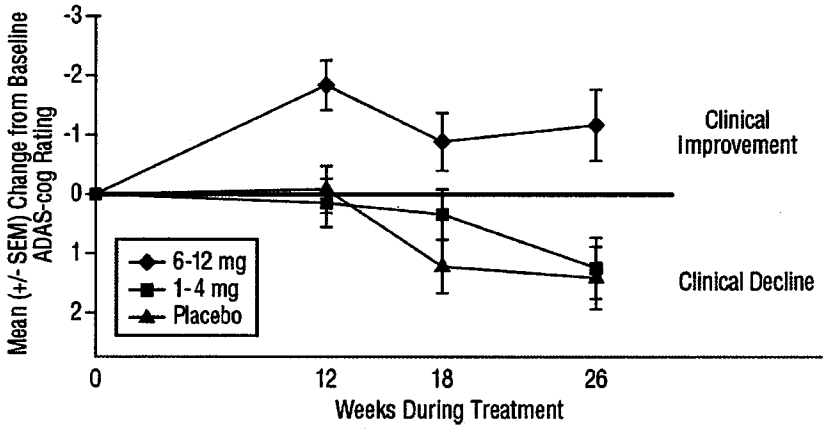
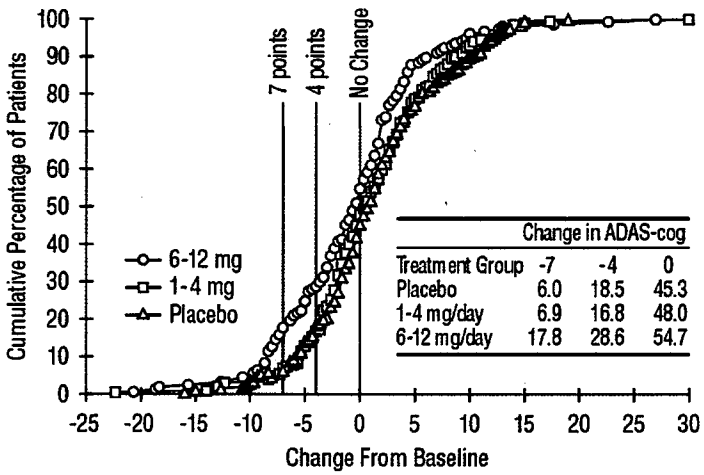


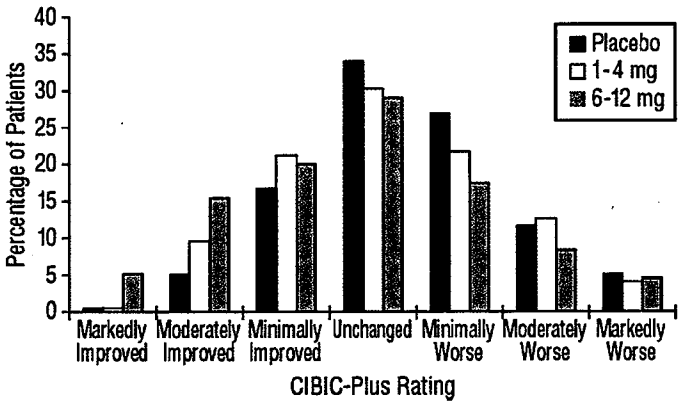
Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X axis. Similar to the U.S. 26-week study, the curves demonstrate that both patients assigned to Exelon and placebo have a wide range of responses, but that the 6-12 mg/day Exelon group is more likely to show the greater improvements.

Figure 5: Cumulative Percentage of Patients Completing 26 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 87%, 1-4 mg 86%, and 6-12 mg 67%.



Effects on the CIBIC-Plus: Figure 6 is a histogram of the frequency distribution of CIBIC-Plus scores attained by patients assigned to each of the three treatment groups who completed 26 weeks of treatment. The mean Exelon-placebo differences for these groups of patients for the mean rating of change from baseline were 0.14 units and 0.41 units for 1-4 mg and 6-12 mg of Exelon, respectively. The mean ratings for the 6-12 mg/day group was statistically significantly superior to placebo. The comparison of the mean ratings for the 1-4 mg/day group and placebo group was not statistically significant.

Figure 6: Frequency Distribution of CIBIC-Plus Scores at Week 26



U.S. Fixed-Dose Study

In a study of 26 weeks duration, 702 patients were randomized to doses of 3, 6, or 9 mg/day of Exelon or to placebo, each given in divided doses. The fixed-dose study design, which included a 12-week forced titration phase and a 14-week maintenance phase, led to a high dropout rate in the 9 mg/day group because of poor tolerability. At 26 weeks of treatment, significant differences were observed for the ADAS-cog mean change from baseline for the 9 mg/day and 6 mg/day groups, compared to placebo. No significant differences were observed between any of the Exelon-dose groups and placebo for the analysis of the CIBIC-Plus mean rating of

change. Although no significant differences were observed between Exelon treatment groups, there was a trend toward numerical superiority with higher doses.

Dementia Associated with Parkinson's disease (PDD)

International Twenty-Four-Week Study

The effectiveness of Exelon® as a treatment for dementia associated with Parkinson's disease is demonstrated by the results of one randomized, double-blind, placebo-controlled clinical investigation in patients with mild to moderate dementia, with onset at least 2 years after the initial diagnosis of idiopathic Parkinson's disease. The diagnosis of idiopathic Parkinson's Disease was based on the United Kingdom Parkinson's Disease Society Brain Bank clinical criteria. The diagnosis of dementia was based on the criteria stipulated under the DSM-IV category "Dementia Due To Other General Medical Condition" (code 294.1x), but patients were not required to have a distinctive pattern of cognitive deficits as part of the dementia. Alternate causes of dementia were excluded by clinical history, physical and neurological examination, brain imaging, and relevant blood tests. Patients enrolled in the study had a MMSE score ≥ 10 and ≤ 24 at entry. The mean age of patients participating in this trial was 72.7 years with a range of 50 – 91. Approximately, 35.1% of patients were women and 64.9% of patients were men. The racial distribution was 99.6% Caucasian and Other races 0.4%.

Study Outcome Measures: This study used a dual outcome assessment strategy to evaluate the effectiveness of Exelon.

The ability of Exelon to improve cognitive performance was assessed with the ADAS-cog.

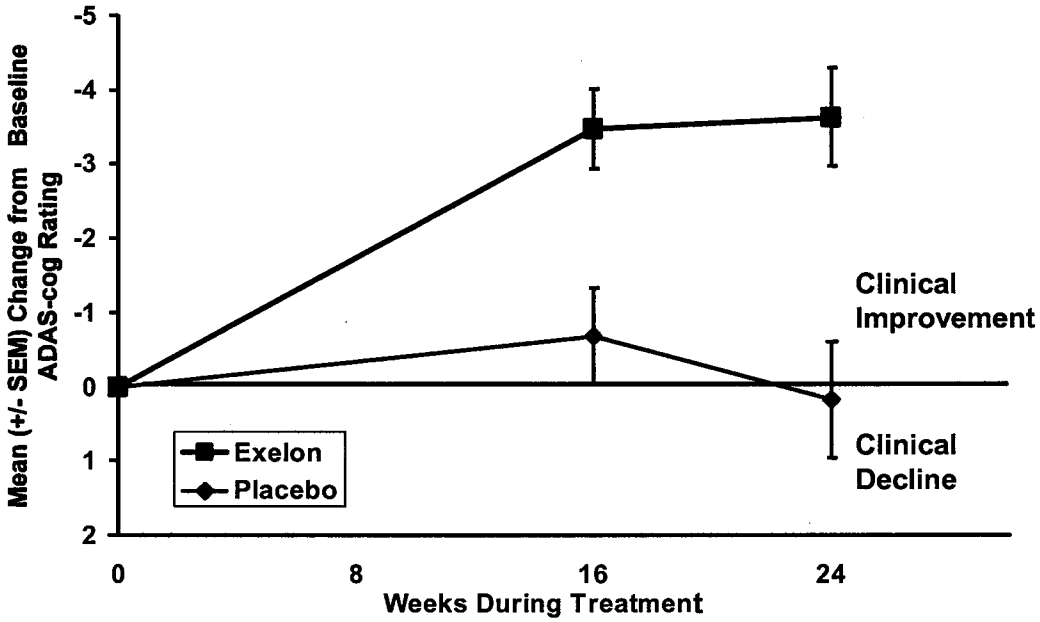
The ability of Exelon to produce an overall clinical effect was assessed using the Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change (ADCS-CGIC). The ADCS-CGIC is a more standardized form of CIBIC-Plus and is also scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved," to a score of 4, indicating "no change" to a score of 7, indicating "marked worsening."

Study Results: In this study, 541 patients were randomized to a dose range of 3 – 12 mg of Exelon per day or to placebo in a ratio of 2:1, given in divided doses. The 24-week study was divided into a 16-week titration phase and an 8-week maintenance phase. The patients in the active treatment arm of the study were maintained at their highest tolerated dose within the specified dose range.

Effects on the ADAS-cog: Figure 7 illustrates the time course for the change from baseline in ADAS-cog scores for both treatment groups over the 24 week study. At 24 weeks of treatment, the mean difference in the

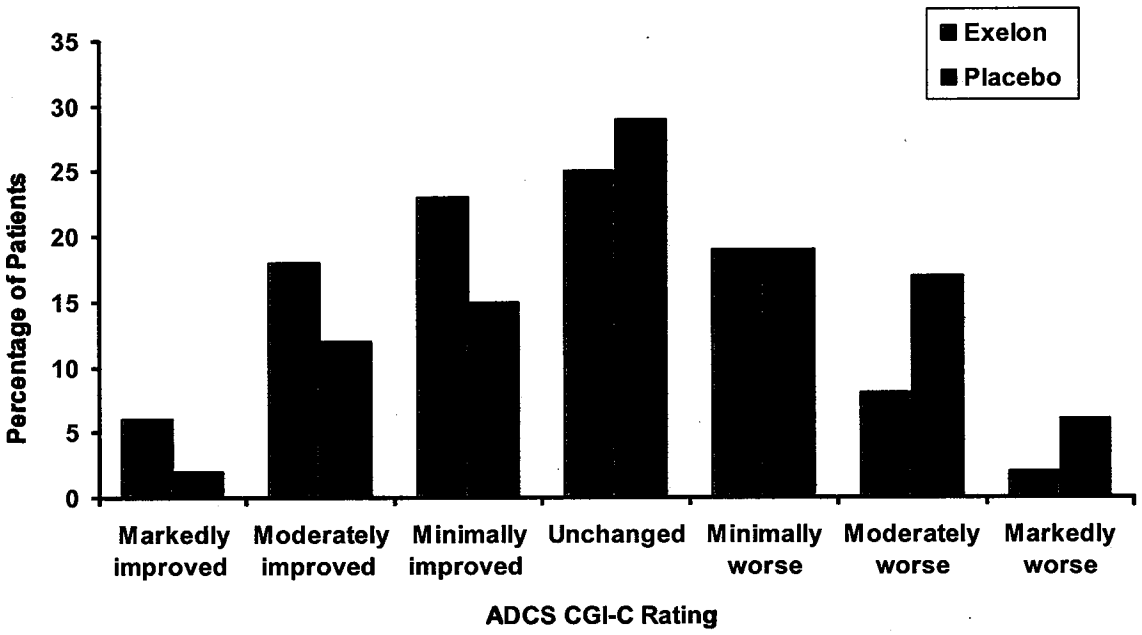
ADAS-cog change scores for the Exelon-treated patients compared to the patients on placebo was 3.8 points. This treatment difference was statistically significant in favor of Exelon when compared to placebo.

Figure 7: Time course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks Of Treatment



Effects on the ADCS-CGIC: Figure 8 is a histogram of the distribution of patients' scores on the ADCS-CGIC (Alzheimer's Disease Cooperative Study—Clinicians Global Impression of Change) at 24 weeks. The mean difference in change scores between the Exelon and placebo groups from baseline was 0.5 points. This difference was statistically significant in favor of Exelon treatment.

Figure 8: Distribution of ADCS-CGIC Scores for Patients Completing 24 Weeks Of Treatment



Age, Gender and Race: Patients' age, gender, or race did not predict clinical outcome of Exelon treatment.

Pharmacokinetics

Rivastigmine is well absorbed with absolute bioavailability of about 40% (3-mg dose). It shows linear pharmacokinetics up to 3 mg BID but is non-linear at higher doses. Doubling the dose from 3 to 6 mg BID results in a 3-fold increase in AUC. The elimination half-life is about 1.5 hours, with most elimination as metabolites via the urine.

Absorption: Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. Absolute bioavailability after a 3-mg dose is about 36%. Administration of Exelon with food delays absorption (t_{max}) by 90 minutes, lowers C_{max} by approximately 30% and increases AUC by approximately 30%.

Distribution: Rivastigmine is widely distributed throughout the body with a volume of distribution in the range of 1.8-2.7 L/kg. Rivastigmine penetrates the blood brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. Mean $AUC_{1\text{-}12hr}$ ratio of CSF/plasma averaged 40 ± 0.5% following 1-6 mg BID doses.

Rivastigmine is about 40% bound to plasma proteins at concentrations of 1-400 ng/mL, which cover the therapeutic concentration range. Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1-400 ng/mL.

Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Based on evidence from in vitro and animal studies, the major cytochrome P450 isozymes are minimally involved in rivastigmine metabolism. Consistent with these observations is the finding that no drug interactions related to cytochrome P450 have been observed in humans (see Drug-Drug Interactions).

Elimination: The major pathway of elimination is via the kidneys. Following administration of ^{14}C-rivastigmine to 6 healthy volunteers, total recovery of radioactivity over 120 hours was 97% in urine and 0.4% in feces. No parent drug was detected in urine. The sulfate conjugate of the decarbamylated metabolite is the major component excreted in urine and represents 40% of the dose. Mean oral clearance of rivastigmine is 1.8 ± 0.6 L/min after 6 mg BID.

Special Populations

Hepatic Disease: Following a single 3-mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). After multiple 6-mg BID oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10). Dosage adjustment is not necessary in hepatically impaired patients as the dose of drug is individually titrated to tolerability.

Renal Disease: Following a single 3-mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients (n=8, GFR=10-50 mL/min) than in healthy subjects (n=10, GFR ≥60 mL/min); Cl/F=1.7 L/min (cv=45%) and 4.8 L/min (cv=80%), respectively. In severely impaired renal patients (n=8, GFR <10 mL/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects (n=10, GFR ≥60 mL/min); Cl/F=6.9 L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired patients. However, dosage adjustment may not be necessary in renally impaired patients as the dose of the drug is individually titrated to tolerability.

Age: Following a single 2.5-mg oral dose to elderly volunteers (>60 years of age, n=24) and younger volunteers (n=24), mean oral clearance of rivastigmine was 30% lower in elderly (7 L/min) than in younger subjects (10 L/min).

Gender and Race: No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Exelon, but a population pharmacokinetic analysis indicates that gender (n=277 males and 348 females) and race (n=575 White, 34 Black, 4 Asian, and 12 Other) did not affect the clearance of Exelon.

Nicotine Use: Population PK analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% (n=75 Smokers and 549 Nonsmokers).

Drug-Drug Interactions

Effect of Exelon on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on in vitro studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single-dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), ß-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal antiinflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15). In addition, in clinical trials, no increased risk of clinically relevant untoward effects was observed in patients treated concomitantly with Exelon and these agents.

INDICATIONS AND USAGE

Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to **moderate dementia associated with Parkinson's disease.**

The dementia of Parkinson's disease is purportedly characterized by impairments in executive function, memory retrieval, and attention, in **patients with an established diagnosis of Parkinson's disease. The**

diagnosis of the dementia of Parkinson's disease, however, can reliably be made in patients in whom a progressive dementia syndrome occurs (without the necessity to document the specific deficits described above) at least 2 years after a diagnosis of Parkinson's disease has been made, and in whom other causes of dementia have been ruled out (see CLINICAL PHARMACOLOGY, Clinical Trial Data).

CONTRAINDICATIONS

Exelon® (rivastigmine tartrate) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation (see DESCRIPTION).

WARNINGS

Gastrointestinal Adverse Reactions

Exelon® (rivastigmine tartrate) use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. For this reason, patients should always be started at a dose of 1.5 mg BID and titrated to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose (see DOSAGE AND ADMINISTRATION) to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5-mg dose after 8 weeks of treatment interruption).

Nausea and Vomiting: **In the controlled clinical trials, 47% of the patients treated with an Exelon dose in the therapeutic range of 6-12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of Exelon-treated patients developed at least one episode of vomiting (compared with 6% for placebo). The rate of vomiting was higher during the titration phase (24% vs. 3% for placebo) than in the maintenance phase (14% vs. 3% for placebo). The rates were higher in women than men. Five percent of patients discontinued for vomiting, compared to less than 1% for patients on placebo. Vomiting was severe in 2% of Exelon-treated patients and was rated as mild or moderate each in 14% of patients. The rate of nausea was higher during the titration phase (43% vs. 9% for placebo) than in the maintenance phase (17% vs. 4% for placebo).**

Weight Loss: **In the controlled trials, approximately 26% of women on high doses of Exelon (greater than 9 mg/day) had weight loss equal to or greater than 7% of their baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high-dose group experienced a similar degree of weight loss compared to 4% in**

placebo-treated patients. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

Anorexia: In the controlled clinical trials, of the patients treated with an Exelon dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course or the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding: Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal antiinflammatory drugs (NSAIDs). Clinical studies of Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia

Exelon as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions

Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6-12 mg/day of Exelon, compared to 2% of placebo patients.

Genitourinary

Although this was not observed in clinical trials of Exelon, drugs that increase cholinergic activity may cause urinary obstruction.

Neurological Conditions

Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's Disease.

Pulmonary Conditions

Like other drugs that increase cholinergic activity, Exelon should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS

Information for Patients and Caregivers

Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Caregivers should be instructed in the correct procedure for administering Exelon® (rivastigmine tartrate) Oral Solution. In addition, they should be informed of the existence of an Instruction Sheet (included with the product) describing how the solution is to be administered. They should be urged to read this sheet prior to administering Exelon Oral Solution. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist.

Caregivers and patients should be advised that, like other cholinomimetics, Exelon® may exacerbate or induce extrapyramidal symptoms. Worsening in **patients with Parkinson's disease,** including an increased incidence or intensity of tremor, has been observed.

Drug-Drug Interactions

Effect of Exelon on the Metabolism of Other Drugs: Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on in vitro studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72),

ß-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal antiinflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15).

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In carcinogenicity studies conducted at dose levels up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg/day on a mg/m^2 basis.

Rivastigmine was clastogenic in two in vitro assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three in vitro assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the in vivo mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg-base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/day on a mg/m^2 basis.

Pregnancy

Pregnancy Category B: Reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day (approximately 2 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 2.3 mg-base/kg/day (approximately 4 times the maximum recommended human dose on a mg/m^2 basis) revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity; decreased weights were seen at doses which were several fold lower than the maximum recommended human dose on a mg/m^2 basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Exelon should be used

during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether rivastigmine is excreted in human breast milk. Exelon has no indication for use in nursing mothers.

Pediatric Use

There are no adequate and well-controlled trials documenting the safety and efficacy of Exelon in any illness occurring in children.

ADVERSE REACTIONS

Dementia of the Alzheimer's type

Adverse Events Leading to Discontinuation

The rate of discontinuation due to adverse events in controlled clinical trials of Exelon® (rivastigmine tartrate) was 15% for patients receiving 6-12 mg/day compared to 5% for patients on placebo during forced weekly dose titration. While on a maintenance dose, the rates were 6% for patients on Exelon compared to 4% for those on placebo.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6-12 mg/day Exelon® Using a Forced Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1,189)	Placebo (n=788)	Exelon ≥6-12 mg/day (n=987)	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1,189)
Event/% Discontinuing						
Nausea	<1	8	<1	1	1	8
Vomiting	<1	4	<1	1	<1	5
Anorexia	0	2	<1	1	<1	3
Dizziness	<1	2	<1	1	<1	2

Most Frequent Adverse Clinical Events Seen in Association with the Use of Exelon

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Exelon's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions

Exelon use is associated with significant nausea, vomiting, and weight loss (see WARNINGS).

Adverse Events Reported in Controlled Trials

Table 2 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon doses of 6-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

No systematic effect of race or age could be determined from the incidence of adverse events in the controlled studies. Nausea, vomiting and weight loss were more frequent in women than men.

Table 2. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Exelon® (6-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=868)	Exelon® (6-12 mg/day) (n=1,189)
Percent of Patients with any Adverse Event	79	92
Autonomic Nervous System		
Sweating increased	1	4
Syncope	2	3
Body as a Whole		
Accidental Trauma	9	10
Fatigue	5	9

Asthenia	2	6
Malaise	2	5
Influenza-like Symptoms	2	3
Weight Decrease	<1	3
Cardiovascular Disorders, General		
Hypertension	2	3
Central and Peripheral Nervous System		
Dizziness	11	21
Headache	12	17
Somnolence	3	5
Tremor	1	4
Gastrointestinal System		
Nausea	12	47
Vomiting	6	31
Diarrhea	11	19
Anorexia	3	17
Abdominal Pain	6	13
Dyspepsia	4	9
Constipation	4	5
Flatulence	2	4
Eructation	1	2
Psychiatric Disorders		
Insomnia	7	9
Confusion	7	8
Depression	4	6
Anxiety	3	5
Hallucination	3	4
Aggressive Reaction	2	3
Resistance Mechanism Disorders		
Urinary Tract Infection	6	7
Respiratory System		
Rhinitis	3	4

Other adverse events observed at a rate of 2% or more on Exelon 6-12 mg/day but at a greater or equal rate on placebo were chest pain, peripheral edema, vertigo, back pain, arthralgia, pain, bone fracture, agitation, nervousness, delusion, paranoid reaction, upper respiratory tract infection, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

Dementia Associated with Parkinson's disease

Adverse Events leading to discontinuation

The rate of discontinuation due to adverse events in the single controlled trial of Exelon® (rivastigmine tartrate) was 18.2% for patients receiving 3-12 mg/day compared to 11.2% for patients on placebo during the 24 week study.

The most frequent adverse events that led to discontinuation from this study, defined as those occurring in at least 1% of patients receiving Exelon and more frequent than those receiving placebo, were nausea (3.6% Exelon vs. 0.6% placebo), vomiting (1.9% Exelon vs 0.6% placebo), and tremor (1.7% Exelon vs. 0.0% placebo).

Most Frequent Adverse Clinical Events Seen in Association with the Use of Exelon

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Exelon's cholinergic effects. These include nausea, vomiting, tremor, anorexia, and dizziness.

Adverse Events Reported in Controlled Trials

Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon doses of 3-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

Table 3. Adverse Events Reported in the Single Controlled Clinical Trial in at Least 2% of Patients Receiving Exelon® (3-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=179)	Exelon® (3-12 mg/day) (n=362)
Percent of Patients with any Adverse Event	71	84
Gastrointestinal disorders		
Nausea	11	29
Vomiting	2	17
Diarrhea	4	7
Upper abdominal pain	1	4
General Disorders and administrative site conditions		
Fatigue	3	4
Asthenia	1	2
Metabolism and nutritional disorders		
Anorexia	3	6
Dehydration	1	2
Nervous system Disorders		
tremor	4	10
dizziness	1	6
headache	3	4
somnolence	3	4
Parkinson's disease (worsening)	1	3
Parkinsonism	1	2

Psychiatric Disorders		
Anxiety	1	4
Insomnia	2	3

Other Adverse Events Observed During Clinical Trials

Dementia of the Alzheimer's Type

Exelon has been administered to over 5,297 individuals during clinical trials worldwide. Of these, 4,326 patients have been treated for at least 3 months, 3,407 patients have been treated for at least 6 months, 2,150 patients have been treated for 1 year, 1,250 have been treated for 2 years, and 168 have been treated for over 3 years. With regard to exposure to the highest dose, 2,809 patients were exposed to doses of 10-12 mg, 2,615 patients treated for 3 months, 2,328 patients treated for 6 months, 1,378 patients treated for 1 year, 917 patients treated for 2 years, and 129 treated for over 3 years.

Treatment-emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-label trials in North America, Western Europe, Australia, South Africa, and Japan were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5,297 patients from these trials who experienced that event while receiving Exelon. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug-caused. Events are classified by body system and listed using the following **definitions: frequent adverse events** – those occurring in at least 1/100 **patients; infrequent adverse events** – those occurring in 1/100 to 1/1,000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent:* Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paresthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia,

hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goiter, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. */nfrequent:* Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. */nfrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. */nfrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. */nfrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. I*nfrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. */nfrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. */nfrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). */nfrequent:* Alopecia, skin ulceration, urticaria, contact dermatitis.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, deep thrombophlebitis, aneurysm, intracranial

hemorrhage .

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage,

blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.

Dementia Associated with Parkinson's Disease

Exelon has been administered to 485 individuals during clinical trials worldwide. Of these, 413 patients have been treated for at least 3 months, 253 patients have been treated for at least 6 months, and 113 patients have been treated for 1 year.

Additional treatment emergent adverse events in patients with Parkinson's disease dementia occurring in at least 1 patient (approximately 0.3%) are listed below, excluding events that are already listed above for the dementia of the Alzheimer's type or elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug-caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1,000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Cardiovascular System: *Frequent:* Chest pain. *Infrequent:* Sudden cardiac death.

Central and Peripheral Nervous System: *Frequent:* Dyskinesia, bradykinesia, restlessness, transient ischemic attack . *Infrequent:* Dystonia, hemiparesis, epilepsy, restless leg syndrome.

Endocrine System: *Infrequent:* Elevated prolactin level.

Gastrointestinal System: *Frequent:* Dyspepsia. *Infrequent:* Faecaloma, dysphagia, diverticulitis, peritonitis.

Hearing and Vestibular Disorders: *Frequent:* Vertigo. *Infrequent:* Meniere's disease.

Heart Rate and Rhythm Disorders: *Infrequent:* Adam-Stokes syndrome.

Liver and Biliary System Disorders: *Infrequent:* Elevated alkaline phosphatase level, elevated gamma-glutamyltransferase level.

Musculoskeletal Disorders: *Frequent: Back pain. Infrequent:* Muscle stiffness, myoclonus, freezing phenomenon.

Psychiatric Disorders: *Frequent:* Agitation, depression. *Infrequent:* Delusion, insomnia.

Reproductive Disorders (Female & Male): *Infrequent:* endometrial hypertrophy, mastitis, prostatic adenoma.

Respiratory System: *Frequent:* Dyspnoea. *Infrequent:* Cough

Urinary System Disorders: *Infrequent:* Urinary incontinence, neurogenic bladder.

Vascular (extracardiac) Disorders: *Infrequent:* Vasovagal syncope, vasculitis.

Vision Disorders: *Infrequent:* Blurred vision, blepharospasm, conjunctivitis, retinopathy.

Post-Introduction Reports

Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

As Exelon® (rivastigmine tartrate) has a short plasma half-life of about one hour and a moderate duration of acetylcholinesterase inhibition of 8-10 hours, it is recommended that in cases of asymptomatic overdoses, no further dose of Exelon should be administered for the next 24 hours.

As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions.

Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when co-administered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of Exelon, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46-mg overdose with Exelon, the patient experienced vomiting, incontinence, hypertension, psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

DOSAGE AND ADMINISTRATION

Dementia of the Alzheimer's type

The dosage of Exelon® (rivastigmine tartrate) shown to be effective in controlled clinical trials in Alzheimer's Disease is 6-12 mg/day, given as twice-a-day dosing (daily doses of 3 to 6 mg BID). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.

The starting dose of Exelon is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of 2 weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above (see WARNINGS). The maximum dose is 6 mg BID (12 mg/day).

Dementia associated with Parkinson's Disease

The dosage of Exelon® shown to be effective in the single controlled clinical trial conducted in dementia associated with Parkinson's Disease is 3 to 12 mg/day, given as twice-a-day dosing (daily doses of 1.5 to 6 mg BID). In that medical condition, the starting dose of Exelon® is 1.5 mg BID; subsequently, the dose may be increased to 3 mg BID and further to 4.5 mg BID and 6 mg BID, based on tolerability, with a minimum of 4 weeks at each dose.

Exelon should be taken with meals in divided doses in the morning and evening.

Recommendations for Administration: Caregivers should be instructed in the correct procedure for administering Exelon Oral Solution. In addition, they should be directed to the Instruction Sheet (included with the product) describing how the

solution is to be administered. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist (see PRECAUTIONS: Information for Patients and Caregivers).

Patients should be instructed to remove the oral dosing syringe provided in its protective case, and using the provided syringe, withdraw the prescribed amount of Exelon Oral Solution from the container. Each dose of Exelon Oral Solution may be swallowed directly from the syringe or first mixed with a small glass of water, cold fruit juice or soda. Patients should be instructed to stir and drink the mixture.

Exelon Oral Solution and Exelon Capsules may be interchanged at equal doses.

HOW SUPPLIED

Exelon® (rivastigmine tartrate) Capsules equivalent to 1.5 mg, 3 mg, 4.5 mg, or 6 mg of rivastigmine base are available as follows:

1.5 mg Capsule – yellow, "Exelon 1,5 mg" is printed in red on the body of the capsule.

Bottles of 60.....**NDC 0078-0323-44**

Bottles of 500.....**NDC 0078-0323-08**

Unit Dose (blister pack) Box of 100 (strips of 10).....**NDC 0078-0323-06**

Unit Dose Blister Card of 30.....**NDC 0078-0323-15**

3 mg Capsule – orange, "Exelon 3 mg" is printed in red on the body of the capsule.

Bottles of 60.....**NDC 0078-0324-44**

Bottles of 500.....**NDC 0078-0324-08**

Unit Dose (blister pack) Box of 100 (strips of 10).....**NDC 0078-0324-06**

Unit Dose Blister Card of 30.....**NDC 0078-0324-15**

4.5 mg Capsule – red, "Exelon 4,5 mg" is printed in white on the body of the capsule.

Bottles of 60.....NDC 0078-0325-44

Bottles of 500.....NDC 0078-0325-08

Unit Dose (blister pack) Box of 100 (strips of 10).....NDC 0078-0325-06

Unit Dose Blister Card of 30.....NDC 0078-0325-15

6 mg Capsule – orange and red, "Exelon 6 mg" is printed in red on the body of the capsule.

Bottles of 60.....NDC 0078-0326-44

Bottles of 500.....NDC 0078-0326-08

Unit Dose (blister pack) Box of 100 (strips of 10).....NDC 0078-0326-06

Unit Dose Blister Card of 30.....NDC 0078-0326-15

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in a tight container.

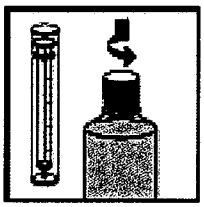
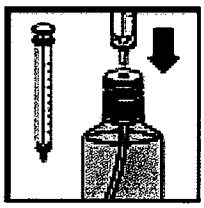
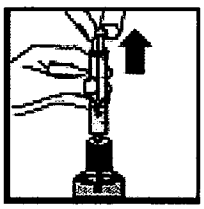
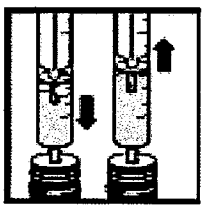
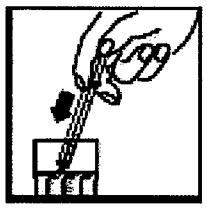
Exelon® (rivastigmine tartrate) Oral Solution is supplied as 120 mL of a clear, yellow solution (2 mg/mL base) in a 4-ounce USP Type III amber glass bottle with a child-resistant 28-mm cap, 0.5-mm foam liner, dip tube and self-aligning plug. The oral solution is packaged with a dispenser set which consists of an assembled oral dosing syringe that allows dispensing a maximum volume of 3 mL corresponding to a 6-mg dose, with a plastic tube container.

Bottles of 120 mL.....NDC 0078-0339-31

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Store in an upright position and protect from freezing.

When Exelon Oral Solution is combined with cold fruit juice or soda, the mixture is stable at room temperature for up to 4 hours.

Exelon® (rivastigmine tartrate) Oral Solution
Instructions for Use

	1. Remove oral dosing syringe from its protective case. Push down and twist child resistant closure to open bottle.
	2. Insert tip of syringe into opening of white stopper.
	3. While holding the syringe, pull the plunger up to the level (see markings on side of syringe) that equals the dose prescribed by your doctor.
	4. Before removing syringe containing prescribed dose from bottle, push out **large** bubbles by moving plunger up and down a few times. After the large bubbles are gone, pull the plunger again to the level that equals the dose prescribed by your doctor. Do not worry about a few tiny bubbles. This will not affect your dose in any way. Remove the syringe from the bottle.
	5. You may swallow Exelon Oral Solution directly from the syringe or mix with a small glass of water, cold fruit juice or soda. If mixing with water, juice or soda, be sure to stir completely and to drink the entire mixture. DO NOT MIX WITH OTHER LIQUIDS.

	6. After use, wipe outside of syringe with a clean tissue and put it back into its case. Close bottle using child resistant closure.

Store Exelon Oral Solution at room temperature below 25°C (77°F) in an upright position. Do not place in freezer.

NOVARTIS

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-823 / S-016

21-025 / S-008

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data

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	**6/9/06**
Reviewer:	**Ranjit B. Mani, M.D.**

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Executive Summary

Recommendation

I recommend that this application not be approved. The sponsor should be asked to conduct a second adequate and well-controlled trial of rivastigmine in dementia associated with Parkinson's Disease, to confirm its efficacy in the treatment of that condition, prior to approval.

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 selection 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 dementia according to DSM-IV criteria for Dementia Due To Other General Medical Conditions (Code 294.1x), with onset of symptoms of dementia at least 2 years after the first diagnosis of idiopathic Parkinson's Disease
    - The exclusion of alternate causes of dementia
    - 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 Of Peripheral And Central Nervous Systems Drugs Advisory Committee

This application was discussed at a meeting of the Peripheral and Central Nervous Systems Drugs Advisory Committee held on May 17, 2006. The following were the conclusions reached by the Committee:

- A neuropathologically-distinct entity is the basis for most instances of dementia associated with Parkinson's Disease. This entity is, in particular, pathologically distinct from Alzheimer's Disease, and is characterized by the occurrence of neocortical and limbic Lewy bodies

- The clinical diagnosis of the neuropathologically distinct entity of dementia associated with Parkinson's Disease does not entail the identification of a distinctive pattern of cognitive deficits. What is required for its diagnosis are merely the following criteria which may be easily applied by the non-specialist neurologist:

    - The presence of idiopathic Parkinson's Disease
    - The presence of a dementia in itself
    - The onset of Parkinson's disease preceding the onset of dementia
    - The exclusion of alternate causes of dementia

- In Study 2311, the above criteria were appropriately applied and alternate causes of dementia, including Alzheimer's Disease, excluded to a clinically reasonable degree from the clinical history, and physical examination, and through brain imaging, and blood tests

- The design of Study 2311, including the outcome measures used, was appropriate for evaluating the efficacy and safety of rivastigmine in Parkinson's Disease.

- Based on the effects seen on the 2 primary efficacy measures, Study 2311 provided evidence for the efficacy of rivastigmine (in a dose of 3 to 12 mg/day) in mild to moderate dementia associated with Parkinson's Disease.

- The results of Study 2311 do <u>not</u> need replication to confirm that rivastigmine has efficacy in the treatment of dementia associated with Parkinson's Disease.

  The following were the reasons for that view

    - The very clear evidence for efficacy in Study 2311
    - The common pathophysiology (i.e., a cholinergic deficiency state) underlying dementia associated with Parkinson's Disease and Alzheimer's Disease, and the common mechanism of action (i.e., acetylcholinesterase inhibition) of rivastigmine in both disorders

- The contents of this application provided evidence that rivastigmine (in a dose of 3 to 12 mg/day) was safe in the treatment of mild to moderate dementia associated with Parkinson's Disease

Conclusions

This reviewer's conclusions are in two categories:

- The following conclusions are in agreement with those of the Advisory Committee
    - A neuropathologically-distinct entity is the basis for most instances of dementia associated with Parkinson's Disease. This entity is, in particular, pathologically distinct from Alzheimer's Disease.
    - The clinical diagnosis of the neuropathologically distinct entity of dementia associated with Parkinson's Disease can be based on criteria that are easily applied by the non-specialist neurologist, and does not entail the identification of a distinctive pattern of cognitive deficits.
    - In Study 2311, the above criteria were appropriately applied and alternate causes of dementia, including Alzheimer's Disease, excluded to a clinically reasonable degree.
    - The design of Study 2311, including the outcome measures used, was appropriate for evaluating the efficacy and safety of rivastigmine in Parkinson's Disease.
    - Based on the effects seen on the 2 primary efficacy measures, Study 2311 provided evidence for the efficacy of rivastigmine (in a dose of 3 to 12 mg/day) in mild to moderate dementia associated with Parkinson's Disease.
    - The contents of this application provided evidence that rivastigmine (in a dose of 3 to 12 mg/day) was safe in the treatment of mild to moderate dementia associated with Parkinson's Disease
- However, the results of Study 2311 do warrant replication to confirm that rivastigmine has efficacy in the treatment of dementia associated with Parkinson's Disease. The following are the reasons for that view
    - A cholinergic deficiency state may not be the main pathophysiological mechanism underlying the dementia in patients with relatively early Alzheimer's Disease, or the only pathophysiological mechanism in dementia associated with Parkinson's Disease

- Acetylcholinesterase inhibitor drugs may have mechanisms of action in Alzheimer's Disease that extend beyond merely enhancing cholinergic function by increasing the availability of acetylcholine at synapses

- The seemingly unequivocal evidence for the efficacy of rivastigmine in a single adequately-designed study may not be sufficient to make the assumption that similar efficacy will in all likelihood be seen in additional studies

Note

The contents of this submission are also cross-referenced by a submission (SE1-008; letter date February 10, 2006) under NDA 210125 which seeks the approval of Exelon® Oral Solution for the same indication. My conclusions and recommendations are the same for both submissions.

1. Background

This submission, a Supplemental New Drug Application, seeks the approval of Exelon® (rivastigmine tartrate capsules) 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 contents of this submission are also cross-referenced by a submission (SE1-008; letter date February 10, 2006) under NDA 210125 which seeks the approval of Exelon® Oral Solution for the same indication.

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
- Further sponsor clarifications regarding selection criteria for Study 2311

- Peripheral and Central Nervous Systems Drugs Advisory Committee Meeting: May 17, 2006
- Additional summary comments by reviewer
- 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 Choice Reaction Time Digit Vigilance
Level II	Short-Term or Working Memory	Numeric Working Memory Spatial Working Memory
Level III	Long-Term or Episodic Secondary Memory	Word Recall Word Recognition Picture Recognition Face Recognition
Level IV	Motor Control	Tracking Postural Stability
Other	Miscellaneous Functions	Rapid Visual Information Processing Logical Reasoning Tapping Rates Critical Flicker Fusion Frequency Digit Symbol Substitution Task Pencil and Paper Procedures 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 Clinical diagnosis of Parkinson's Disease Dementia according to DSM-IV criteria (Code 294.1) with onset of symptoms of dementia at least 2 years after the first diagnosis of idiopathic Parkinson's Disease Mini-Mental Status Examination of 10 – 24	
Primary Efficacy Measures	ADAS-Cog 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 D-KEFS* Verbal Fluency Test Neuropsychiatry Inventory-10 Mini-Mental Status Examination Ten-Point Clock Drawing Test (*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)

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, with onset of symptoms of dementia at least 2 years after the first diagnosis of idiopathic Parkinson's Disease (for further details of how DSM-IV criteria were actually used to diagnose dementia for entry into this study, see Section 16.1)
- 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 – 9.8)	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 – 5.0)	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

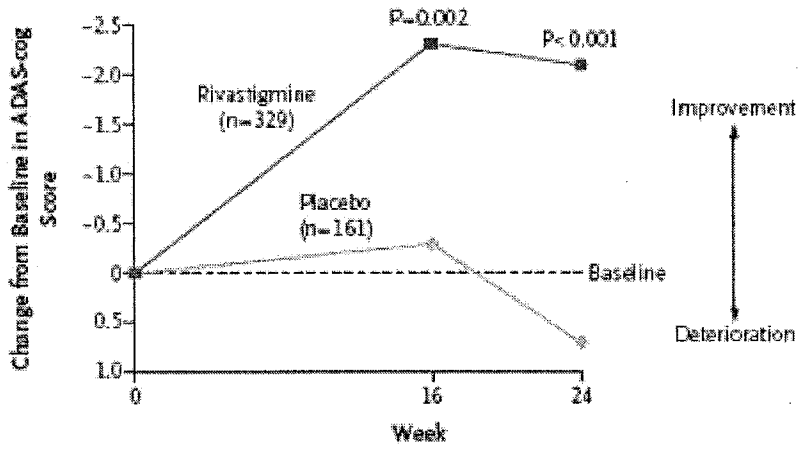
	Exelon		Placebo				
	n	mean ± SD	n	mean ± SD	LS means difference	p-value	95% CI (Exelon – placebo)
ITT+RDO baseline	329	23.8 ± 10.2	161	24.3 ± 10.5			
Change at week 16	329	2.3 ± 7.3	161	0.3 ± 8.8	2.06	0.002 *	0.78 3.34
Change at week 24	329	2.1 ± 8.2	161	-0.7± 7.5	2.88	<0.001 *	1.44 4.31
LOCF baseline	287	24.0 ± 10.3	154	24.5 ± 10.6			
Change at week 16	287	2.8 ± 7.4	154	0.3 ± 8.7	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 ± 8.8	2.78	<0.001 *	1.43 4.12
OC baseline wk 24	258	23.7 ± 10.4	139	23.4 ± 9.8			
Change at week 24	258	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	38%	161	25%	0.022*
	week 24	329	37%	161	28%	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.

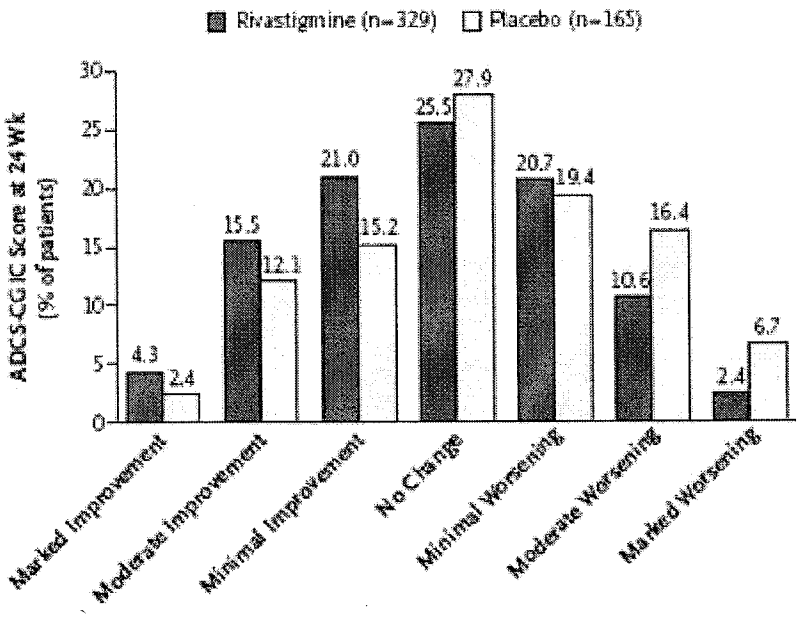
7.2.7.1.2 ADCS-CGIC

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%	18%	12%	18%	12%
Minimally improved (3)	21%	15%	23%	16%	23%	15%
Unchanged (4)	28%	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	316	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 3.28

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	41.6 ± 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	2219.4 ± 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 ± 6.6	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	0.8 ± 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 Corr. Coeff. [95% CI]	Moderate Corr. Coeff. [95% CI]	All Corr. Coeff. [95% CI]
PDD	(N=32)	(N=23)	(N=55)
ADAS-cog	0.652 (0.377, 0.926)	0.714 (0.430, 0.997)	0.775 (0.631, 0.920)
ADCS-ADL	0.938 (0.865, 1.000)	0.916 (0.796, 1.000)	0.939 (0.896, 0.982)
NPI-10	0.660 (0.406, 0.914)	0.729 (0.522, 0.936)	0.719 (0.560, 0.877)
TPCT	0.788 (0.612, 0.964)	0.452 (0.074, 0.830)	0.755 (0.627, 0.883)
CDR – Power of attention	0.631 (0.296, 0.967)	0.463 (-0.057, 0.983)	0.606 (0.331, 0.881)
TMT-A	0.864 (0.748, 0.980)	0.195 (-0.319, 0.709)	0.657 (0.426, 0.888)
D-KEFS verbal fluency - Total correct responses	0.786 (0.606, 0.966)	0.546 (0.165, 0.928)	0.799 (0.667, 0.930)
AD	(N=35)	(N=23)	(N=58)
ADAS-cog	0.690 (0.510, 0.871)	0.747 (0.511, 0.983)	0.808 (0.706, 0.910)
ADCS-ADL	0.915 (0.839, 0.992)	0.883 (0.803, 0.963)	0.916 (0.863, 0.969)
NPI-10	0.891 (0.794, 0.988)	0.927 (0.860, 0.994)	0.899 (0.834, 0.964)
TPCT	0.618 (0.355, 0.881)	0.860 (0.784, 0.975)	0.727 (0.543, 0.910)
CDR – Power of attention	0.692 (0.478, 0.905)	0.546 (0.183, 0.908)	0.722 (0.561, 0.884)
TMT-A	0.762 (0.626, 0.938)	0.392 (-0.135, 0.919)	0.686 (0.467, 0.904)
D-KEFS verbal fluency - Total correct responses	0.672 (0.469, 0.874)	0.661 (0.326, 0.995)	0.756 (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	56	
	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 (827.1)	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 Corr. coeff. (95% CI)	AD patients Corr. coeff. (95% CI)
ADCS-ADL	-0.470 (-0.701, -0.239)	-0.424 (-0.643, -0.205)
MMSE	-0.601 (-0.759, -0.442)	-0.820 (-0.923, -0.717)
NPI-10	0.099 (-0.165, 0.363)	-0.040 (-0.290, 0.211)
NPI-D-10	-0.061 (-0.328, 0.206)	-0.029 (-0.272, 0.214)
TPCT	-0.459 (-0.704, -0.215)	-0.494 (-0.687, -0.301)
CDR - Power of attention	0.351 (0.080, 0.623)	0.341 (0.066, 0.616)
TMT-A	0.297 (0.029, 0.565)	0.337 (0.110, 0.565)
D-KEFS verbal fluency - Total correct responses	-0.467 (-0.710, -0.225)	-0.458 (-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 dysfunctior
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

A Clinical Inspection Summary has been completed by Mark Seaton, PhD, of the Division of Scientific Investigations. Please see that summary for full details.

The study sites inspected are summarized in the table below:

Center #	Location	Principal Investigator	Number of Patients Randomized
0122	Istanbul, Turkey	F. Sibel Ozekmekci, MD	30
0049	Pescara, Italy	Marco Onofrj, MD	31

The overall assessment of the Division of Scientific Investigations is that while there were deficiencies in record keeping and protocol compliance at each site inspected, the data from these sites was acceptable for use in support of the pending application.

14. Proposed Labeling

Changes (additions) have been to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of labeling. These changes are highlighted below. The labeling has been edited by me in a separate document.

14.1 CLINICAL PHARMACOLOGY/Clinical Trial Data

14.1.1 New Sub-Heading

Clinical Trial Data

b(4)

5 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__√__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical-__1__

Exelon should be taken with meals in divided doses in the morning and evening.

Recommendations for Administration: Caregivers should be instructed in the correct procedure for administering Exelon Oral Solution. In addition, they should be directed to the Instruction Sheet (included with the product) describing how the solution is to be administered. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist (see PRECAUTIONS: Information for Patients and Caregivers).

Patients should be instructed to remove the oral dosing syringe provided in its protective case, and using the provided syringe, withdraw the prescribed amount of Exelon Oral Solution from the container. Each dose of Exelon Oral Solution may be swallowed directly from the syringe or first mixed with a small glass of water, cold fruit juice or soda. Patients should be instructed to stir and drink the mixture.

Exelon Oral Solution and Exelon Capsules may be interchanged at equal doses.

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 at least 2 years after 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.

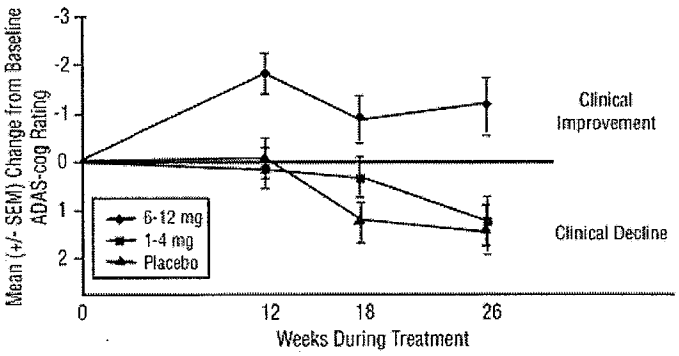
  In their essence, the criteria used to diagnose dementia associated with Parkinson's Disease in Study 2311 consisted of the following

    - 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 dementia a minimum of 2 years following the first diagnosis of Parkinson's Disease
    - Exclusion of other causes of dementia

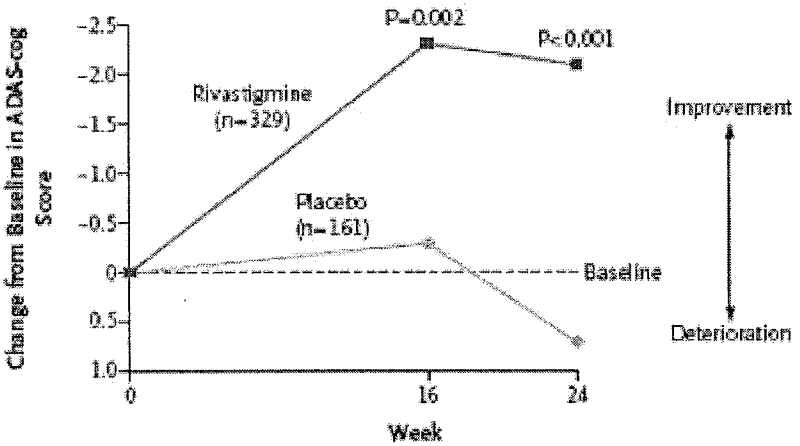
  While the latter criteria do have face validity for diagnosing dementia in patients with Parkinson's Disease, they themselves do not appear to have been correlated with neuropathological findings in a formal study (especially one that was prospective) of sufficient size (the recently-published study 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

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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

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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. Further Sponsor Clarifications Regarding Selection Criteria For Study 2311

In communications shortly prior to, and during, the Peripheral and Central Nervous Systems Drugs Advisory Committee Meeting of May 17, 2006 (see Section 17), the sponsor provided the following clarifications regarding two items:

- The criteria for diagnosing dementia associated with Parkinson's Disease for inclusion in Study 2311
- The extent of brain imaging in Study 2311

16.1 Diagnosis Of Dementia Associated With Parkinson's Disease For Inclusion In Study 2311

The sponsor now stated that the DSM-IV criteria for Dementia Due To Parkinson's Disease (294.1) should be considered as being subsumed under the criteria for Dementia Due To Other General Medical Conditions (294.1x) which are listed below; the sponsor now considers the latter, rather than the former, to be the main criteria used to diagnose dementia associated with Parkinson's Disease for enrollment in this study (note that the study protocol only refers to the DSM-IV criteria for Dementia Due To Parkinson's Disease [294.1] as the basis for making that diagnosis).

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information or to recall previously learned information)

(2) one (or more) of the following cognitive disturbances:

(a) aphasia (language disturbance)
(b) apraxia (impaired ability to carry out motor activities despite intact motor function)
(c) agnosia (failure to recognize or identify objects despite intact sensory function)
(d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct physiological consequence of a general medical condition other than Alzheimer's disease or cerebrovascular disease (e.g., HIV infection, traumatic brain injury, *Parkinson's disease*, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, normal-pressure hydrocephalus, hypothyroidism, brain tumor, or vitamin B_{12} deficiency).

D. The deficits do not occur exclusively during the course of a delirium.

Code based on presence or absence of a clinically significant behavioral disturbance:

294.10 Without Behavioral Disturbance: if the cognitive disturbance is not accompanied by any clinically significant behavioral disturbance.
294.11 With Behavioral Disturbance: if the cognitive disturbance is accompanied by a clinically significant behavioral disturbance (e.g., wandering, agitation).

Coding note: Also code the general medical condition on Axis III (e.g., 042 HIV infection, 854.00 head injury, 332.0 Parkinson's disease, 333.4 Huntington's disease, 331.1 Pick's disease, 046.1 Creutzfeldt-Jakob disease; see Appendix G for additional codes).

16.2 Extent Of Brain Imaging In Study 2311

The sponsor states that brain imaging was required as a screening tool for all patients to determine eligibility for enrollment in the proposed study, based on the following:

- Patients with a current diagnosis of probable or possible vascular dementia, according to the NINDS-AIREN criteria, were to be excluded from the study. Among the NINDS-AIREN criteria cited by the sponsor was evidence of relevant cerebrovascular disease by brain imaging; for that purpose CT or MRI scans performed within 6 months prior to study entry (or the radiologist report thereof) must have been available for source document verification
- Step 2 of the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (which were used to diagnose idiopathic Parkinson's Disease in this

study) required the exclusion of patients with the presence of cerebral tumor or communicating hydrocephalus on CT scan

Note that brain imaging was not stipulated as a study procedure in the protocol nor listed in any study Case Report Form.

The following table, taken from the sponsor's presentation at the Advisory Committee meeting indicates the extent to which brain imaging was performed and its timing

Timing of Imaging (MRI or CT Scans)
Core Study—All Randomized Patients

	N = 541 n (%)
Occurred between screening and baseline visits	178 (33)
< 90 days before screening visit	209 (39)
90 - < 182 days before screening visit	50 (9)
183 - < 365 days before screening visit	14 (3)
> 365 days before screening visit	6 (1)
After baseline visit	21 (4)
Missing	11 (2)
Unable to retrieve charts off site	9 (2)
Confirmed that no imaging was performed	0
No response received to date	43 (8)

Source data verification is ongoing, 92% received as of 5/12/06.

The information summarized in the above table was collected in response to the following request from the Division to the sponsor on April 4, 2006: *"Please indicate what proportion of patients enrolled in Study 2311 underwent imaging of the brain (i.e., CT or MRI) during the screening period for that study."*

At the Advisory Committee meeting, the sponsor indicated that the information that was being collected pertained only to the extent to which brain imaging was performed during the study. The sponsor did not have information currently available as to the details of what the imaging studies revealed in each instance; that information was contained only in the source documents at each study center. However, the sponsor did assume that the respective investigators

considered the results of brain imaging in each subject enrolled in the study to be consistent with the diagnosis of dementia associated with Parkinson's Disease, based on the selection criteria stipulated in the study protocol.

16.3 Reviewer Comments

The additional information provided above appears to indicate the following:

- Patients were enrolled in Study 2311, based on their having a dementia per se; they were not required to have a dementia with the features described in the medical literature as being purportedly distinctive for those with Parkinson's Disease

- 437/541 (80.8%) of those enrolled in the study underwent brain imaging either between screening and baseline, or within 6 months prior to the screening visit. 472/541 (87.2%) of those enrolled in the study underwent brain imaging either between the screening visit and end of study or within 1 year prior to the screening visit.

  The extent to which brain imaging was apparently performed in Study 2311 is acceptable. It is not customary for us when reviewing the results of clinical trials in dementia to review individual CT or MRI reports; we merely confirm that imaging was performed and that the investigator considered their results consistent with the clinical entity being studied.

17. Peripheral And Central Nervous Systems Drugs Advisory Committee Meeting: May 17, 2006

The meeting was held to discuss the current application.

The conclusions reached at this meeting are summarized under 2 separate headings.

17.1 Response To Questions From Agency

The following is the response of the Advisory Committee to each of the Agency's specific questions (in italics). All votes were unanimous.

1. *Is there a distinct form of dementia associated with Parkinson's Disease (and, in particular, a dementia that is distinct from Alzheimer's Disease) and do operational criteria exist for its clinical diagnosis?*

   Yes

2. *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?

Yes

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

   Yes

4. *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?*

   Yes

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

   No

6. *Do the data presented in this application indicate that Exelon® is safe for use in this population at a dose range of 3 to 12 mg/day?*

   Yes

17.2 Related And Additional Key Conclusions

The following is a summary of related and additional key conclusions reached by the Advisory Committee during their deliberations at the meeting :

- The dementia that occurs in Parkinson's Disease has a distinctive underlying neuropathology in the majority of instances, comprising neocortical and limbic Lewy bodies.

- Although the neuropathology of dementia in Parkinson's Disease may be distinctive, the clinical diagnosis of dementia associated with Parkinson's Disease does not require the identification of a distinctive pattern of cognitive deficits in patients suspected of having that condition. Instead, the requirements for a clinical diagnosis of dementia associated with Parkinson's Disease are limited to the following

- A diagnosis of idiopathic Parkinson's Disease
- A diagnosis of dementia
- Onset of Parkinson's disease preceding the onset of dementia
- The exclusion of alternate causes of dementia

These diagnostic criteria can easily be applied in the clinical setting, even by a non-specialist neurologist.

- Although the neuropathology of dementia associated with Parkinson's Disease is distinct from that associated with Alzheimer's Disease, the presence of reduced cortical cholinergic activity in dementia associated with Parkinson's Disease indicates a pathophysiology that is similar to that in Alzheimer's Disease, and, therefore, a common mechanism of action for cholinesterase inhibitor drugs, such as rivastigmine, in both disorders.

- The analysis of secondary efficacy measures for Study 2311 suggests that while the ADAS-Cog and ADCS-CGIC may have been suitable for use in that study, they might not have been the best measures to use.

- A combination of the following observations was cited in support of the Committee's view that there was no need for the results of Study 2311 to be replicated:

  - The very clear evidence for efficacy in that study
  - The common pathophysiology (i.e., a cholinergic deficiency state) underlying dementia associated with Parkinson's Disease and Alzheimer's Disease, and the common mechanism of action (cholinesterase inhibition) of rivastigmine in both disorders

18. Additional Summary Comments By Reviewer

Based on the information summarized in Sections 16 and 17, a number of additional summary comments have been made regarding Study 2311 and the entity of dementia associated with Parkinson's Disease. The majority, but not all, of these comments are in agreement with the conclusions of the Advisory Committee already summarized in Section 17.

The issue of whether the results of Study 2311 warrant replication merits further, and separate discussion.

18.1 Summary Comments In Agreement With Conclusions Of Advisory Committee

The following comments are in general agreement with the views expressed by members of the Advisory Committee:

- A neuropathological disorder, that is distinct from Alzheimer's Disease, appears to underlie the majority of instances of dementia associated with Parkinson's Disease. Although some neuropathological changes of Alzheimer's Disease may co-exist with those considered distinct for Parkinson's Disease in such patients, the former are generally minor and insufficient to account for the dementia.

- The clinical diagnosis of the neuropathologically distinct entity of dementia associated with Parkinson's Disease does not entail the identification of a distinctive pattern of cognitive deficits. What is required for its diagnosis is merely the following:

    - The presence of idiopathic Parkinson's Disease
    - The presence of a dementia per se
    - The onset of Parkinson's disease preceding the onset of dementia
    - The exclusion of alternate causes of dementia

- In Study 2311, the above criteria may be considered to have been appropriately applied and alternate causes of dementia, including Alzheimer's Disease, excluded to a clinically reasonable degree from the clinical history, and physical examination, and through brain imaging, and blood tests.

- The design of Study 2311, including the outcome measures used, was appropriate for evaluating the efficacy and safety of rivastigmine in Parkinson's Disease.

- The results of Study 2311 indicate that rivastigmine (in a dose of 3 to 12 mg/day) has efficacy in the treatment of dementia associated with Parkinson's Disease, as evidenced by its effects on the primary efficacy measures in that study.

- The safety profile of rivastigmine in dementia associated with Parkinson's Disease was broadly similar to that seen in Alzheimer's Disease, and revealed no new areas of concern.

18.2 Need For Replication Of Results Of Study 2311

The Agency has thus far required that for a drug to be approved for the treatment of dementia of the Alzheimer's type (Alzheimer's Disease), the desired treatment effect should have been approved in at least 2 adequate and well-controlled trials. 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.

While concluding that dementia associated with Parkinson's Disease is an entity pathologically distinct from Alzheimer's Disease, the Advisory Committee also

reached a consensus, at its meeting on May 17, 2006, that the results of Study 2311 did not warrant replication, based on the following:

- The clear evidence for efficacy in that study
- The common pathophysiology (i.e., a cholinergic deficiency state) underlying dementia associated with Parkinson's Disease and Alzheimer's Disease, and the common mechanism of action (i.e., acetylcholinesterase inhibition) of rivastigmine in both disorders.

I will address, in turn, each of the above-cited reasons for why the Advisory Committee believed that the results of Study 2311 did not warrant replication, and then provide my own summary view.

18.2.1 Critique Of Individual Reasons Why Advisory Committee Felt That Results Of Study 2311 Did Not Need Replication

18.2.1.1 Clear Evidence For Efficacy Of Rivastigmine In Dementia Associated With Parkinson's Disease In Study 2311

There is little doubt that the results of Study 2311 demonstrated that rivastigmine had efficacy in the treatment of the study population, based on prospectively-specified criteria. At the Advisory Committee meeting, it was stated by the discussants that the results of the study were robust, and that it was, therefore, unlikely that the results of a second similar study would, in any way, be different. (In this regard, it may be noted that while the p-values derived from the primary efficacy analysis were very low, rendering also very low the possibility that these results were observed merely by chance, the effect sizes seen on these analyses were at best modest and comparable with the effect sizes seen with rivastigmine and with other acetylcholinesterase inhibitor drugs [and with memantine] in Alzheimer's Disease).

Unfortunately, the outcome of at least two other clinical development programs in dementia does not support the presumption that a single set of results as convincingly "positive" as that seen in Study 2311 consistently predicts efficacy in additional clinical trials of the same drug for the same indication. These 2 examples are as follows:

- Unequivocal evidence for efficacy on both a cognitive and a global measure in a Phase III trial of donepezil in vascular dementia of adequate design was not demonstrated on a global measure in a second similar trial

- Clear evidence for efficacy on both a cognitive and global measure in a Phase III trial of memantine in mild to moderate Alzheimer's Disease, was not seen in two further adequately-designed Phase III trials of memantine in similar populations on either type of measure

In the "positive" trials of donepezil and memantine cited above, the evidence for efficacy could be considered as having been as substantial as that seen in Study 2311.

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 efficacy in at least 2 adequate and well-controlled trials. This Division's view so far has been that the same principle should apply to other types of dementia, unless they are variants or grades of severity of Alzheimer's Disease not subsumed under the current claim.

18.2.1.2 Evidence For A Cholinergic Deficiency State Underlying Both Dementia Associated With Parkinson's Disease And Alzheimer's Disease

Another reason cited by the members of the Advisory Committee for their consensus view that the results of Study 2311 did not need replication is the purported similarity in pathophysiology between both disorders: in both disorders, there is reported to be a cholinergic deficiency state secondary to pathological abnormalities that are mainly in the nucleus basalis of Meynert and, to a lesser extent, in the pedunculopontine nucleus (the pathological abnormalities in these two locations consist of neuronal loss in both conditions and Lewy bodies and neurofibrillary tangles in Parkinson's Disease Dementia and Alzheimer's Disease, respectively), and it has been hypothesized that the cholinergic deficiency state is the basis for the cognitive deficits in both disorders.

On reviewing the pathophysiology of dementia associated with Parkinson's Disease and Alzheimer's Disease in more detail:

- In patients with Parkinson's Disease and dementia, the severity of dementia appears to generally correlate with the extent of neocortical Lewy bodies (although, as stated by Braak et al [*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*]: "In some individuals, however, cognitive decline can develop in the presence of mild Parkinson disease-related cortical pathology, and, conversely, widespread cortical lesions do not lead to cognitive decline.").

  Reductions in choline acetyltransferase and acetylcholinesterase activity in the cerebral cortex have also been demonstrated in dementia associated with Parkinson's Disease, and to a greater extent than in Alzheimer's Disease; these reductions have been correlated with impaired performance on tests of attention and executive function. However, these observations do not establish that reduced cortical cholinergic activity is the sole or main pathophysiological basis for dementia associated with Parkinson's Disease Dementia; it has been suggested for example, that abnormalities of dopaminergic, noradrenergic, and serotoninergic pathways may also contribute to the cognitive deficits seen in that disorder

(see *Pillon B, Czernecki V, Dubois B. Dopamine and cognitive function. Curr Opin Neurol 2003;16 Suppl 2:S17-22*)

- A number of publications, some relatively recent, have called into question whether the cholinergic hypothesis can explain the cognitive deficits seen early in Alzheimer's Disease; these publications suggest that cholinergic markers (such as choline acetyltransferase or acetylcholinesterase activity) do not show deficits at those stages of the disease.

1. Davis KL, Mohs RC, Marin D, Purohit DP, Perl DP, Lantz M, Austin G, Haroutunian V. Cholinergic markers in elderly patients with early signs of Alzheimer disease. JAMA 1999;281:1401-6.

2. Tiraboschi P, Hansen LA, Alford M, Masliah E, Thal LJ, Corey-Bloom J. The decline in synapses and cholinergic activity is asynchronous in Alzheimer's disease. Neurology. 2000 Nov 14;55(9):1278-83.

3. DeKosky ST, Ikonomovic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, Cochran EJ, Kordower JH, Mufson EJ. Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. Ann Neurol. 2002 Feb;51(2):145-55.

4. Rinne JO, Kaasinen V, Jarvenpaa T, Nagren K, Roivainen A, Yu M, Oikonen V, Kurki T. Brain acetylcholinesterase activity in mild cognitive impairment and early Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2003 Jan;74(1):113-5.

The abstract for the first of the above papers (that by Davis et al), possibly the most persuasive of the four, is below:

CONTEXT: A central tenet of Alzheimer disease (AD) is the loss of cortical cholinergic function and cholinergic markers in postmortem brain specimens. Whether these profound deficits in cholinergic markers found in end-stage patients are also found in patients with much earlier disease is not known.

OBJECTIVE: To determine whether cholinergic deficits in AD precede, follow, or occur in synchrony with the earliest signs of cognitive deterioration.

DESIGN, SETTING, AND PATIENTS: Postmortem study of nursing home residents with Clinical Dementia Rating (CDR) Scale scores of 0.0 to 2.0 and 4.0 to 5.0 who underwent autopsy between 1986 and 1997, comparing the activity of the cholinergic marker enzymes in the cortices of 66 elderly subjects with no (CDR score = 0.0; n = 18), questionable (CDR score = 0.5; n = 11), mild (CDR score = 1.0; n = 22), or moderate (CDR score = 2.0; n = 15) dementia vs subjects with severe dementia (CDR score = 4.0-5.0; n = 15).

MAIN OUTCOME MEASURES: Activity of the cholinergic marker enzymes choline acetyltransferase and acetylcholinesterase in 9 neocortical brain regions. RESULTS: The activity of choline acetyltransferase and acetylcholinesterase in 9 neocortical brain regions did not differ significantly in subjects with CDR scores of 0.0 to 2.0, but was significantly lower in subjects with severe dementia (CDR score = 4.0-5.0). Choline acetyltransferase levels were significantly correlated with severity of neuropathological lesions of AD, as measured by density of neuritic plaques and neurofibrillary tangles.

CONCLUSIONS: Although neocortical cholinergic deficits are characteristic of severely demented AD patients, in this study, cholinergic deficits were not apparent in individuals with mild AD and were not present until relatively late in the course of the disease. These results suggest that patients with more severe disease should be a target for cholinergic treatment.

- An older study indicated that the earliest pathological abnormalities seen in Alzheimer's Disease are in the entorhinal cortex and hippocampus, rather than in the basal forebrain cholinergic neurons (Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol [Berl] 1991;82:239-59)

  Note that in the 3 key efficacy studies of rivastigmine in Alzheimer's Disease that are described in the approved product labeling, the mean Mini-Mental Status Examination score at entry ranged from 19.7 to 20, indicating that these subjects did not have advanced Alzheimer's Disease.

18.2.1.3 Evidence For A Common Mechanism Of Action of Rivastigmine In Both Dementia Associated With Parkinson's Disease And Alzheimer's Disease

The Advisory Committee had concluded that given the presence of a cholinergic deficit in both Alzheimer's Disease and dementia associated with Parkinson's Disease, and given that rivastigmine is a cholinesterase inhibitor, its mechanism of action in each condition was likely to be the same.

Acetylcholinesterase inhibitors may have mechanisms of action in Alzheimer's Disease beyond merely enhancing cholinergic function via an increase in the availability of acetylcholine at synapses. It has been suggested, for example, that their beneficial effects in Alzheimer's Disease may include non-amyloidogenic amyloid precursor protein processing, and reduced tau phosphorylation; it has also been suggested that these effects may explain the apparent benefit of such drugs in the earlier stages of Alzheimer's Disease where a cholinergic deficiency may not be present (see *Lane RM, Kivipelto M, Greig NH. Acetylcholinesterase and its inhibition in Alzheimer disease. Clin Neuropharmacol 2004;27:141-9*). The latter mechanisms cannot be considered to explain the apparent beneficial effects of drugs such as rivastigmine in dementia associated with Parkinson's Disease as well.

18.2.2 Summary

The Advisory Committee was of the view that the results of Study 2311 did not warrant replication, based on a combination of the following:

- The unequivocal evidence for efficacy in that study
- The common pathophysiology (i.e., a cholinergic deficiency state) underlying dementia associated with Parkinson's Disease and Alzheimer's Disease
- The common mechanism of action (i.e., acetylcholinesterase inhibition) of rivastigmine in both dementia associated with Parkinson's Disease and Alzheimer's Disease.

However, as discussed above:

- A cholinergic deficiency state may not be the main pathophysiological mechanism underlying the dementia in patients with relatively early Alzheimer's

Disease, or the only pathophysiological mechanism in dementia associated with Parkinson's Disease

- Acetylcholinesterase inhibitor drugs may have mechanisms of action in Alzheimer's Disease that extend beyond merely enhancing cholinergic function via an increase in the availability of acetylcholine at synapses
- The seemingly unequivocal evidence for the efficacy of rivastigmine in a single adequately-designed study may not be sufficient for assuming that similar efficacy will in all likelihood be seen in additional studies

Given the above uncertainties about the validity of the Advisory Committee's assumptions, it would be much preferred that the efficacy of rivastigmine in dementia associated with Parkinson's Disease be established by empirical means alone. Since dementia associated with Parkinson's Disease appears to be a disorder that is neuropathologically distinct from Alzheimer's Disease, the efficacy of rivastigmine for the former should be established by two adequately-designed and conducted studies. Thus, for rivastigmine to be approved for the treatment of mild to moderate dementia associated with Parkinson's Disease, its efficacy should be established in a second study.

19. Conclusions

The final conclusions that this reviewer has reached are divided into two categories

- The following conclusions are in agreement with those of the Peripheral Nervous Systems Drugs Advisory Committee, as reached at their meeting held on May 17, 2006:

    - A neuropathologically-distinct entity is the basis for most instances of dementia associated with Parkinson's Disease. This entity is, in particular, pathologically distinct from Alzheimer's Disease.

    - The clinical diagnosis of the neuropathologically distinct entity of dementia associated with Parkinson's Disease can be based on criteria that are easily applied by the non-specialist neurologist, and does not entail the identification of a distinctive pattern of cognitive deficits.

    - In Study 2311, the above criteria were appropriately applied and alternate causes of dementia, including Alzheimer's Disease, excluded to a clinically reasonable degree.

    - The design of Study 2311, including the outcome measures used, was appropriate for evaluating the efficacy and safety of rivastigmine in Parkinson's Disease.

    - Based on the effects seen on the 2 primary efficacy measures, Study 2311 provided evidence for the efficacy of rivastigmine (in a dose of 3 to 12 mg/day) in mild to moderate dementia associated with Parkinson's Disease.

- The contents of this application provided evidence that rivastigmine (in a dose of 3 to 12 mg/day) was safe in the treatment of mild to moderate dementia associated with Parkinson's Disease

- However, the results of Study 2311 do warrant replication to confirm that rivastigmine has efficacy in the treatment of dementia associated with Parkinson's Disease. The following are the reasons for that view

  - A cholinergic deficiency state may not be the main pathophysiological mechanism underlying the dementia in patients with relatively early Alzheimer's Disease, or the only pathophysiological mechanism in dementia associated with Parkinson's Disease

  - Acetylcholinesterase inhibitor drugs may have mechanisms of action in Alzheimer's Disease that extend beyond merely enhancing cholinergic function by increasing the availability of acetylcholine at synapses

  - The seemingly unequivocal evidence for the efficacy of rivastigmine in a single adequately-designed study may not be sufficient to make the assumption that similar efficacy will in all likelihood be seen in additional studies

20. Recommendation

I recommend that this application not be approved. The sponsor should be asked to conduct a second adequate and well-controlled trial of rivastigmine in dementia associated with Parkinson's Disease, to confirm its efficacy in the treatment of that condition.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 6/9/06
cc:
HFD-120
NDA 20823 (SE1-016)

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/s/

Ranjit Mani
6/13/2006 07:43:57 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-823 / S-016

21-025 / S-008

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-823
DRUG NAME:	Exelon ® (rivastigmine tartrate)
INDICATION:	Mild to moderate dementia associated with Parkinson's disease
APPLICANT:	Novartis
DATE OF RECEIPT:	Date of Document: 08/31/2005
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics I & VI
STATISTICAL REVIEWER:	Joanne Zhang, Ph.D. (HFD-705)
CONCURRENT REVIEWERS:	Kun Jin, Ph.D., team Leader Kooros Mahjoob, Ph.D., Deputy Director of Division of Biometrics I (HFD-710)
MEDICAL DIVISION:	Division of Neuropharm
CLINICAL TEAM:	Ranjit Mani, M.D., Clinical Reviewer
PROJECT MANAGER:	Melina Griffis, P.Ph.

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Exelon ® (rivastigmine) was approved by the US Food and Drug Administration (FDA) on April 21, 2000 for the treatment of mild to moderate dementia of Alzheimer's type. The indication of this supplement NDA (the core study 2311 and its extension study 2311 E1) is the use of Exelon (3-12 mg/day) for the treatment of mild to moderate dementia associated with Parkinson's disease (PDD), for which no approved pharmacologic treatment is currently available. It is not totally unexpected a drug that is effective for Alzheimer's disease should work for PD related dementia as well. The core efficacy trial, study 2311, supported the efficacy of Exelon (3-12 mg/day) in the treatment of PDD. The extension of the core efficacy trial, 2311 E1 continuously demonstrated long-term effectiveness of Exelon in PDD patients.

1.2 Brief Overview of Clinical Studies

The submission of this sNDA consisted of one randomized controlled efficacy study 2311, one uncontrolled extension study 2311 E1 and one non-interventional study 2314.

Study 2311 was a 24-week, prospective, randomized, multi-center, double-blind, placebo-controlled study in patients with a clinical diagnosis of Parkinson's disease according to DSM-IV criteria. The study was designed to evaluate the efficacy, safety, and tolerability of Exelon at doses of 3 to 12 mg/day in this patient population. There were 68 centers in Europe and Canada from 12 countries. The 12 countries are Austria (1 center), Belgium (4 centers), France (9 centers), Germany (12 centers), Italy (11 centers), Netherlands (2 centers), Norway (1 center), Portugal (1 center), Spain (8 centers), Turkey (3 centers), United Kingdom (9 centers) and Canada (7 centers). A total of 541 patients with PDD were to be randomly assigned to treatment with either Exelon 3-12 mg/day or placebo in a 2:1 ratio of the drug and placebo.

There were 4 dose levels for Exelon, dose level 1 – Exelon 1.5 mg; dose level 2 – Exelon 3.0 mg; dose level 3 – Exelon 4.5 mg and dose level 4 - Exelon 6.0 mg. Exelon and placebo capsules were identical appearance. All patients were started on dose 1.5 mg or placebo, with increases to the next dose level after a minimum of 4 weeks. Dosage could be reduced to the next lower dose in case of tolerability problems and then increased again by one dose level. After finding the highest well-tolerated dose for each individual patient within the 16 week titration period, the highest well-tolerated dose for each individual patient was then to be maintained for the remaining 8 weeks, although dose adjustments were allowed at any time during this maintenance period. Throughout this report, Exelon 3-12mg/day refers to the above described flexible titration dosing scheme.

The primary endpoints were the "Alzheimer's Disease Assessment Scale-cognitive Subscale" (ADAS-cog) and the "Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change" (ADCS-CGIC). The primary analysis for ADAS-cog was ANCOVA and the primary analysis for ADCS-CGIC was the nonparametric categorical analysis using country as blocking – Van Elteren test. The primary population proposed by the sponsor for comparing the treatment groups was the ITT+RDO population. This population was the intent to treat including patients

who discontinued study treatment early but continued to attend scheduled visits for efficacy evaluations (Retrieved Drop Out patients).

Following the completion of study 2311, all patients who participated in the core efficacy study 2311 were elected to continue in the extension study 2311 E1 for up to 24 weeks. Study 2311 E1 was an uncontrolled open-label study, where all patients received Exelon for up to 24 weeks. Regardless of whether they had been receiving placebo or Exelon in the core study, all patients who continued in the extension study, started a dose of 1.5 mg b.i.d. and were titrated to their maximum tolerated dose. No inferential statistics on efficacy evaluations were planned in this open-label study.

An additional uncontrolled study, study 2314, designed to show that the assessment scales used in study 2311 were valid and reliable in patients with PDD. In this study, patients did not receive study medication and efficacy was, therefore, not evaluated.

This reviewer will focus only on the efficacy core study 2311.

1.3 Statistical Issues and Findings

The core efficacy study 2311 was a prospective, randomized, multi-center, double-blind, placebo-controlled, parallel group study in patients with PDD. Five hundred and forty one (541) patients from 12 countries, 68 centers were randomized to receive the drug Exelon or placebo (ratio 2:1). The objective of the study is to test if the drug, Exelon statistically performs better in terms of specified clinical endpoints. Two primary efficacy endpoints, the change from baseline of the total ADAS-Cog score and ADCS-CGIC at Week 16 and Week 24 were considered. The sponsor proposed to use least square means derived by ANCOVA model with the following explanatory variables, country, baseline and treatment to analyze ADAS-Cog. The main analysis for ADCS-CGIC was the nonparametric categorical analysis.

Statistical Issues

- The primary population for the analysis is recommended by the agency is normally the ITT+LOCF, the intent to treat population using LOCF methodology to impute the missing values. In this study, the primary population for comparing the treatment groups proposed by the sponsor was the ITT+RDO population. This population included patients who discontinued study treatment early but continued to attend scheduled visits for efficacy evaluations (RDO patients). There were 23 RDO patients and among them 19 from Exelon groups and 4 from placebo group. In the ITT+LOCF population, values more than 2 days after the last dose of study drug were not carried forward; therefore, sample size in the ITT+LOCF population is smaller than that in the ITT+RDO population. However, it has been noticed that patients excluded from the Exelon group in the LOCF population (41 patients) is almost 6 fold of the patients in the placebo group (7 patients). The sponsor should explain why more patients' assessments were performed two days after the last dose in the Exelon group than in the placebo group.

  In this review, ITT+LOCF and ITT+RDO mean ITT population using LOCF or RDO to impute missing values.

- It has been noticed that the standard deviations of the placebo group for Austria were substantially smaller than the rest of the groups, consistently for baseline, Week 16 and Week 24. The standard deviations for Austria and the average standard deviations for other counties (Austria was excluded) at each treatment group are listed in Table 1. For example, at Week 24, the standard deviation for the placebo group (4 patients) was only 2.1 compared with 16.8 in the Exelon group (5 patients) in Austria and 10.24 for the rest of Exelon group and 12.04 for the rest of placebo group. Figures 1, 2 and 3, the grouped bar with error plots, show the average total ADAS scores and the corresponding standard deviations for both Exelon and placebo against the 12 countries at baseline, Week 16 and Week 24. The numbers in parentheses are the sample sizes in each country for the placebo and Exelon, respectively. It can be seen clearly that the standard deviation of the placebo group in Austria is much smaller than the rest.

- In this study, the center specific sample sizes were quite variable, ranged from 1 to 32. The sponsor showed significant improvement of the patients in the Exelon group for the two primary endpoints at both Week 16 and Week 24 when combining all the centers together. Like any multi-center study, the evaluation of the consistency of a treatment effect across the centers should be considered. In this multi-center study, since some centers had no patient assigned to one of the treatment arms, this reviewer examined the treatment effect by countries instead of centers for the cognitive function scale. Figure 4 and Figure 5 display the total change of ADAS-Cog scale from baseline at both weeks 16 and 24 across all countries. As can be seen from these graphs, the magnitude of the treatment effects differs among countries and the direction of the treatment effects are not consistent as well. Austria and Portugal show the wrong trend of the direction.

  Four different models were considered. Two models with only the main effect with/without combining the small centers together and the two models with both the main effect and the interaction term of the treatment and country with/without combining the small centers together. Table 2 displays the two-tailed P values for the least mean square results with ADAS-Cog endpoint for the above mentioned four different models. Scenario 1 is what was reported by the sponsor. The explanatory variables considered in the model were the country and treatment. In scenario 2, another term, the interaction of country and treatment was added based on the model in scenario 1. In scenario 3, after combining 3 small countries, Austria (5 subjects in Exelon, 3 subjects in placebo), Norway (4 subjects in Exelon, 1 subject in placebo) and Portugal (6 subjects in Exelon, 3 subject in placebo), the same model as in scenario 1 was considered. In scenario 4, the interaction term was added based on the model considered in scenario 3.

  If allowing sample sizes vary across all the countries (without pooling the small countries together), the results for the treatment effect can be very different depending on if the country-by-treatment interaction term was included in the ANCOVA model (comparing scenarios 1 and 2). There is no consensus whether the interaction term should be included in the model. If the interaction term was left out from the model, each country receives the weight according to the sample size of the patients enrolled in that country; whereas for the interaction model, each country receives an equal weight. Therefore, it is

not a surprise to observe a totally different result for the treatment effect based on the two different models if sample sizes are very different across countries. Even though only 9 patients enrolled in Portugal, since this center is treated as same important as others in the interaction model, due to the large reversed treatment effect, this center can change the final result. It needs to be noted that though in the original protocol, the sponsor only proposed to use the main effect model.

After combining the small countries together, the final conclusions for both the main effect model and interaction model are very similar (comparing scenarios 3 and 4) since the sample sizes in each country are relatively compatible now.

Table 1 Standard deviations of Austria and the average of other 11 countries (Source: Reviewer's Analysis for study 2311)

	Country	Exelon (SD)	Placebo (SD)
Baseline	Austria	13.1	5.0
	Mean of others	10.12	10.2
Week 16	Austria	16.8	2.3
	Mean of others	10.61	11.69
Week 24	Austria	16.8	2.1
	Mean of others	10.24	12.04

Figure 1 Raw average total ADAS-Cog scores in each country and the corresponding standard errors at baseline (Source: Reviewer's Analysis for study 2311)

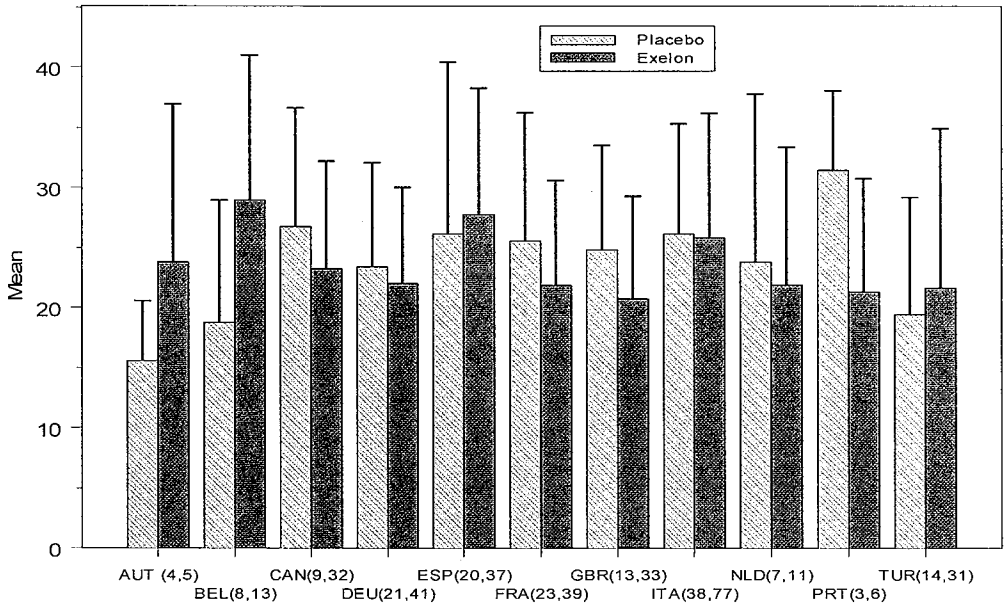

Figure 2 Raw average total ADAS-Cog scores in each country and the corresponding standard errors at Week 16 (Source: Reviewer's Analysis for study 2311)

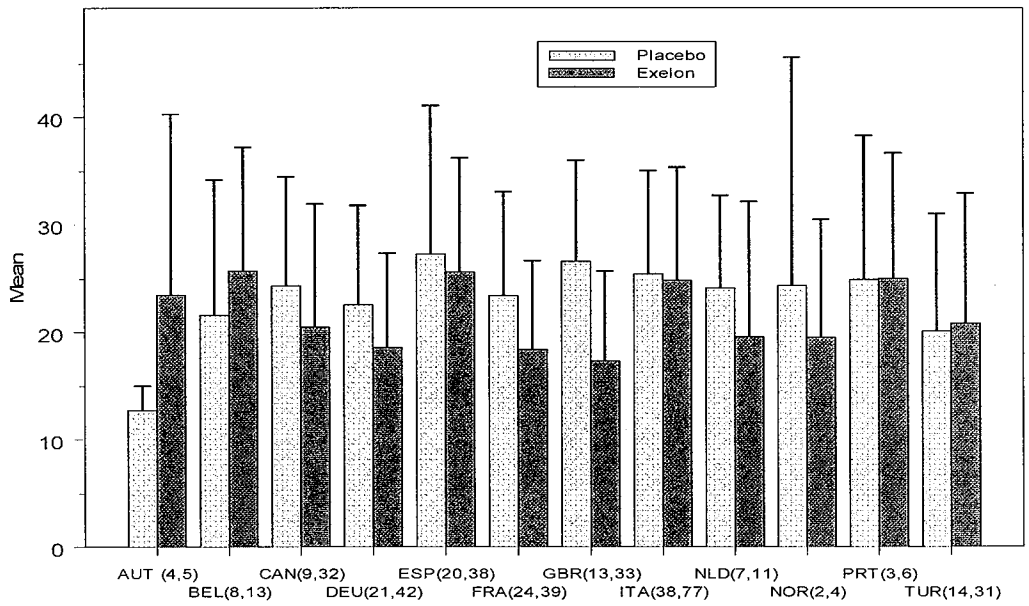

Figure 3 Raw average total ADAS-Cog scores in each country and the corresponding standard errors at Week 24 (Source: Reviewer's Analysis for study 2311)

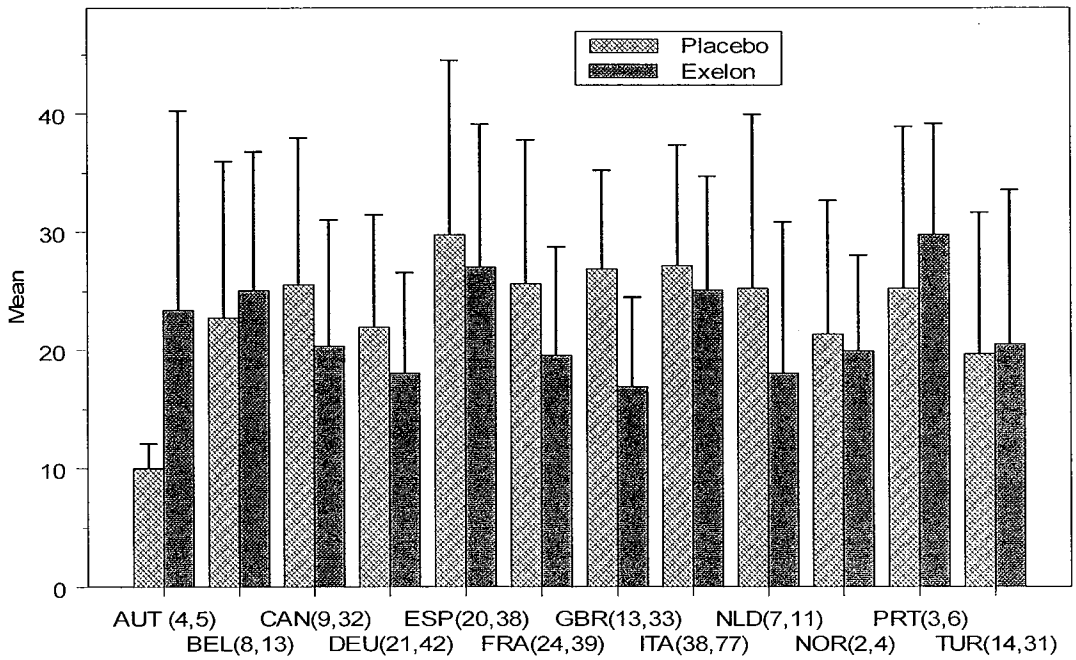

Figure 4 Total change from baseline for ADAS-Cog at Week 16 (Source: Reviewer's Analysis for study 2311)

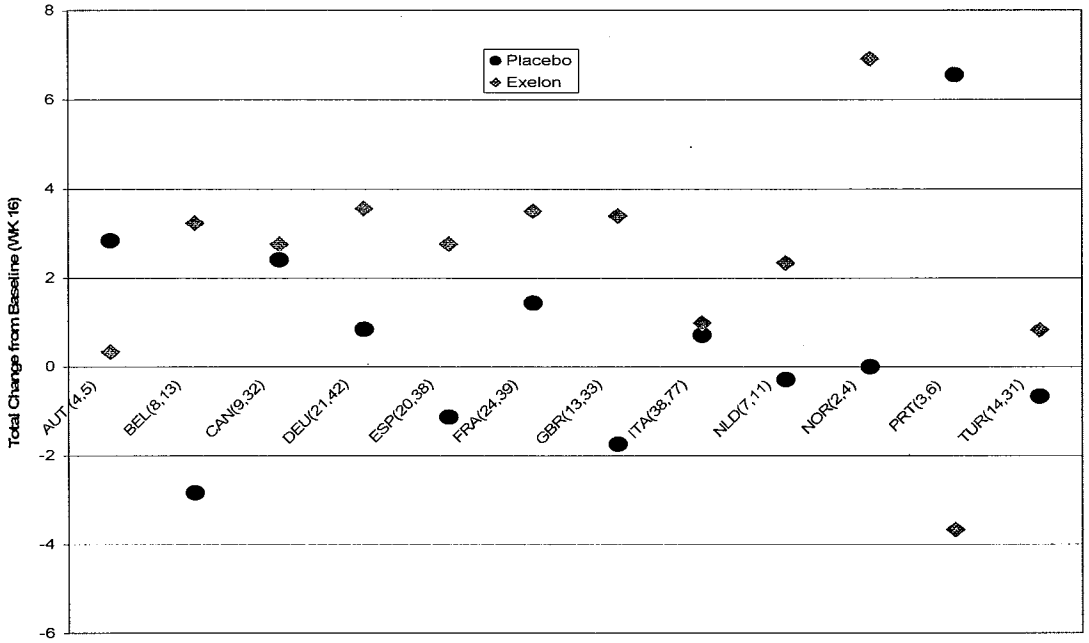

Figure 5 Total change from baseline for ADAS-Cog at Week 24 (Source: Reviewer's Analysis for study 2311)

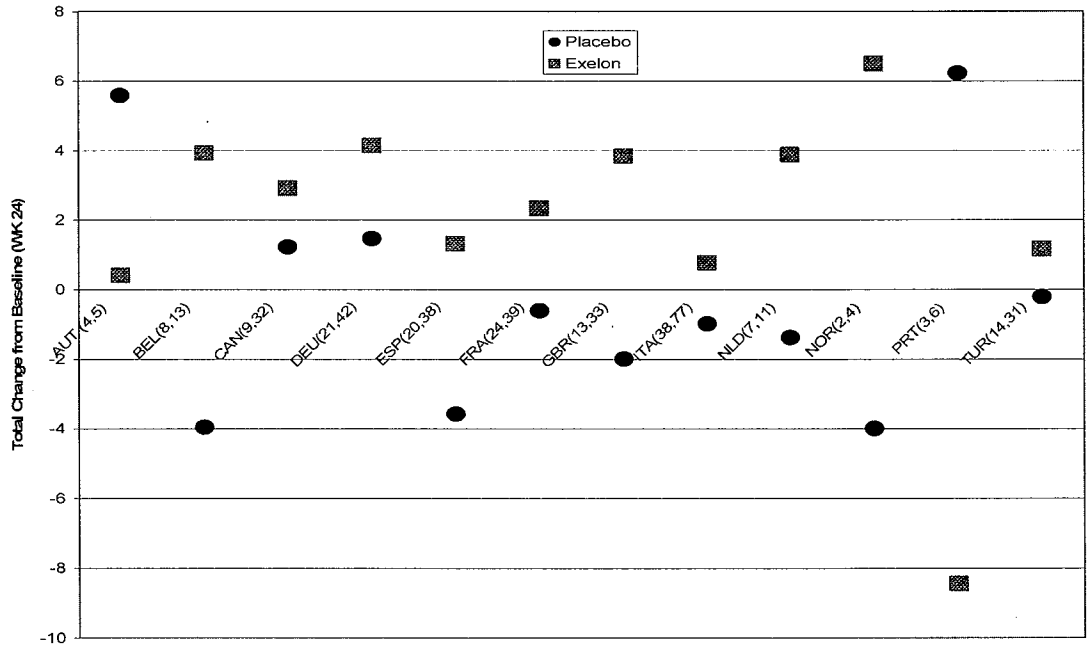

Table 2 P values for testing Exelon and placebo effect in a multi-center trial with/without interaction and combining small centers (Source: Reviewer's Analysis for study 2311)

	P values
Main effects [1]	
Week 16	0.0016
Week 24	<.0001
Interaction [2]	
Week 16	0.2019
Week 24	0.1121
Main effects (combining) [3]	
Week 16	0.0015
Week 24	<.0001
Interaction (combining) [4]	
Week 16	0.0058
Week 24	0.001

1: Scenario 1; 2: Scenario 2; 3: Scenario 3; 4: Scenario 4.

2 INTRODUCTION

Exelon ® (rivastigmine) was approved for treatment of mild to moderately severe Alzheimer's disease (AD) in 2000. The current core efficacy study 2311 aimed to evaluate the safety and efficacy of Exelon (3-12 mg/day) for 24 weeks in patients with Parkinson's Disease Dementia (PDD). The sponsor also conducted an uncontrolled open-label extension study, where all the PDD patients received Exelon for up to 24 weeks. In addition, another uncontrolled study, where all patients diagnosed with PDD dementia did not receive Exelon, was designed to validate various assessment scales used in the core efficacy study for the PDD patients. In this review, only the core efficacy study 2311 is relevant to the efficacy evaluation.

2.1 Overview

According to the sponsor's report, dementia occurs in approximately 20-60% of individuals with Parkinson's disease (PD), and is more likely to be present in elderly patients or those with more severe or advanced disease. Dementia in patients with PD is characterized by a clinical syndrome of mental slowing, executive dysfunction, retrieval type memory deficit and attentional impairment that may lead to a pronounced decline in the level of cognitive functioning, activities of daily living and behavior. Deficits in similar symptom domains of dementia are also observed in patients with AD. Exelon ® (rivastigmine) is a brain-selective, dual inhibitor of both acetylcholinesterase and butyrylcholinesterase that has been approved for the treatment of mild to moderately severe Alzheimer's disease. The present study aimed to study the efficacy and safety of Exelon (3-12 mg/day) in patients with PDD. It is a clinical judgment though how different AD and PDD are and whether practitioners can differentiate these differences.

The efficacy of Exelon in the treatment of PDD was evaluated in study 2311. This study was a 24-week prospective, randomized, multi-center, double-blind, placebo-controlled, two treatment

arm parallel group study. Patients enrolled were of either sex aged 50 years or older with the onset of dementia symptoms according to DSM IV criteria, occurring at least 2 years after the first diagnosis of idiopathic PD according to UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria, with an MMSE score of 10 to 24. The dose of the drug was 3-12 mg/day. The overall duration of treatment was 24 weeks and consisted of a 16 week titration phase with titration steps at 4 week intervals and an 8-week maintenance phase. The primary efficacy endpoints included the change from baseline in ADAS-Cog total scores and ADCS-CGIC scale. The evaluation was performed at Week 16 and Week 24.

2.2 Data Sources

All documents reviewed for this NDA submission are in electronic form. The path to CDER Electronic Document Room for documents of this NDA is listed below:
\\CDSESUB1\N20823\S_016\2005-08-31

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Objectives

The primary objective of Study 2311 was to evaluate the efficacy of Exelon (3-12 mg/day for 24 weeks) compared with placebo in patients with PDD based on ADAS-Cog (Alzheimer's Disease Assessment Scale-cognitive subscale) and the clinical global rating of change, ADCS-CGIC (Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change).

The secondary objectives included

- To evaluate the effects of Exelon on attention, executive functioning, activities of daily living, behavior and health economic parameters.
- To explore potential differences in efficacy of Exelon depending on preexisting attentional deficits.
- To explore the potential genetic factors related to PDD.
- To explore the potential biomarkers related to PDD.
- To evaluate the safety and tolerability of Exelon.

3.1.2 Study Design

The core study 2311 was a 24-week, prospective, randomized, multi-center, double-blind, placebo-controlled, parallel group study in patients with a diagnosis of Parkinson's disease dementia according to the DSM-IV criteria (Code 294.1). The study was to be conducted in 68 centers in Europe and Canada. A total of 541 patients with PDD were to be randomly assigned to treatment with either Exelon 3-12 mg/day, or placebo in an assignment ratio of 2:1, i.e. 362 patients on Exelon and 179 patients on placebo.

After completion of the double-blind treatment phase, patients had the option to receive open-label treatment with Exelon for up to 6 months. This open-label extension study were to evaluate the safety and tolerability of Exelon for up to 24 weeks of exposure to the treatment in patients with PDD who completed a 24 week double-blind placebo-controlled core study, and to provide access or continued access to Exelon.

This reviewer will focus on the core study 2311 only.

3.1.3 EFFICACY MEASURES

3.1.3.1 Primary Efficacy Endpoints

There were two primary efficacy variables, a cognitive measure (Alzheimer's disease Assessment Scale-cognitive subscale, ADAS-cog) and a global measure (The Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change, ADCS-CGIC).

3.1.3.2 Secondary Efficacy Endpoints

Secondary efficacy parameters included:

- Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) for the assessment of activities of daily living
- Cognitive Drug Research (CDR) Computerized Assessment System tests for the assessment of attention
- D-KEFS Verbal Fluency Test, D-KEFS Color-Word Interference Test, D-KEFS Card Sorting Test and Symbol Digit Modalities Test for the assessment of executive functioning.
- Mini Mental State Examination (MMSE) score.
- NPI Caregiver Distress Scale (NPI-D) for the assessment of caregiver distress.
- Health Economic parameters, including caregiver burden, patient and caregiver resource utilization.

3.1.4 STATISTICAL ANALYSIS METHODS

The statistical efficacy tests were performed on several analysis data sets including Intent to Treat with Retrieved Dropouts (ITT+RDO), Last Observation Carried Forward (LOCF) and Observed Cases (OC). The proposed primary population for comparing the treatment groups was the ITT+RDO population. Analysis of covariance, ANCOVA, on the mean change from baseline was performed for the primary endpoint, ADAS-cog. A nonparametric categorical analysis, Van Elteren test was performed for the second primary endpoint, ADCS-CGIC in the presence of country as the blocking. All statistical tests were two-sided at the 5% significance level.

Primary Efficacy Analysis

Change from Baseline to Weeks 16 and 24 in Total ADAS-cog Score

The primary efficacy analysis of the change in total ADAS-cog score from baseline was based on a general linear model for analysis of covariance (ANCOVA) with factors for treatment group, countries and with baseline score of ADAS-cog as a covariate.

Global Clinical Rating of Change (ADCS-CGIC) at Week 24

The primary efficacy analysis of ADCS-CGIC was the treatment comparison based on a nonparametric test (Van Elteren test) with country as stratification variable.

3.1.5 STUDY RESULTS

3.1.5.1 Analysis Populations

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

Additional analyses based on populations ITT-Last observation carried forward (LOCF) and Observed Cases (OC) are considered supportive to the main analysis.

3.1.5.2 Analysis Populations

Patient disposition and main reasons for discontinuation are summarized in Table 3. Of the 541 patients randomized, 362 were in the Exelon group and 179 were in the placebo group. A total of 410 patients (76%) completed the study. The percentage of patients who discontinued was higher in the Exelon group (27.3%) compared to placebo (17.9%). This difference was mainly because of the adverse events (17.1% on Exelon and 7.8 % on placebo) and withdrawals of consent by the patients (5.8 % on Exelon and 1.1 % on placebo).

Table 3 Summary of Patient Disposition - All Patients Randomized (Source: Table 7-1 from 2311 study report)

	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)

3.1.5.3 Demographic Characteristics and Baseline Comparability

The patient demographic values at baseline are summarized in Table 4. Baseline demographic characteristics for age, gender and race were comparable in both treatment groups. The majority of patients were Caucasians.

Duration of PD, duration of PDD, and time interval between diagnosis of PD and initial symptoms of PDD were reported in Table 5. In the total population, the durations of PD reported by patients/caregivers and diagnosed by physicians were about 10 and 9 years, respectively. The durations of PDD reported by patients/caregivers and diagnosed by physicians were about 2.2 and 1.2 years. The mean duration between diagnosis of PD and first symptoms of PDD was 6.8 years. The distribution of PD severity as measured by Hoehn and Yahr as well as the average MMSE scores in both treatment groups were also reported in the table.

Table 4 Demographic Summary by Treatment Group (Source: Table 7-4 from 2311 study report)

		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)

Table 5 Background Characteristics by Treatment Group (Source: Table 7-5 from 2311 study report)

		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

3.1.5.4 Protocol Violations

The type of protocol violations is listed in Table 6. Nine patients had MMSE scores outside the range of 10-24 permitted by the protocol. The duration between date of diagnosis of PD and initial symptoms of PDD was less than 2 years in 16 patients. The most frequent type of protocol violation in all patients was either new introduction or increase in dose of ongoing dopaminergic or psychotropic medication. Forty patients discontinued the trial prematurely

because of no primary assessment scales after the baseline evaluation. The percentage of patients with protocol violations was slightly higher in the Exelon group.

Table 6 Protocol Violations (Source: Table 7-4 from 2311 study report)

	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.

3.1.5.5 Efficacy Results Reported by Sponsor

Primary Efficacy Results

ADAS-Cog

The results for the primary efficacy endpoint ADAS-Cog at week 16 and week 24 in both the primary analysis population (ITT+RDO) and the additional analysis populations (LOCF and OC) are listed in Table 7. The treatment groups were compared using least square means derived by ANCOVA with the following explanatory variables: treatment, country, and baseline total ADAS-Cog score. The treatment group difference for the change from baseline was statistically significantly in favor of Exelon in all three analysis populations, both at week 16 and at week 24.

Table 7 ADAS-Cog Change from Baseline (Source: Table 9-1 from 2311 study report)

	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).

ADCS-CGIC

The endpoint ADCS-CGIC ratings were grouped into seven categories: (1) Markedly improved, scored as 1; (2) Moderately improved, scored as 2; (3) Minimally improved, scored as 3; (4) Unchanged, scored as 4; (5) Minimally worse, scored as 5; (6) Moderately worse, scored as 6 and (7) Markedly worse, scored as 7. The results for this primary efficacy endpoint at Week 24 are listed in Table 8. The treatment comparison for the mean scores in the two treatment groups was based on categorical analysis with country as a stratification variable. The difference of the ADCS-CGIC ratings at Week 24 was statistically significant different between two groups in favor of Exelon. This reviewer also performed the same analysis for Week 16. The improvement of ADCS-CGIC ratings due to Exelon at Week 16 was also statistically significant.

Table 8 ADCS-CGIC Ratings at Week 24 (Source: Table 9-3 from 2311 study report)

	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

3.1.5.6 Review's Analysis

According to the protocol, the primary objective of the study requires demonstration of a statistically significant difference at the two-sided 5% level of significance between the Exelon group and the placebo group for each of the two primary endpoints, ADAS-Cog and ADCS-CGIC. This reviewer performed primary efficacy analyses independently following the methods specified in the protocol, and the results agree with those reported by the sponsor, treatment differences are statistically significant different in favor of the investigated drug. It needs to be pointed out though some issues have to be considered.

One requirement for the ANCOVA is the normality of the data. This reviewer tested the residuals using Shapiro-Wilk's test. The hypothesis of normality of the residual was rejected (P values = 0.0072 for Week 16 and < 0.0072 for Week 24) so that a nonparametric method (Wilcoxon rank test) was also performed. The results using the nonparametric method agree with those reported by the sponsors. For both weeks, the p-values are less than 0.05 in favor of Exelon.

For the ADAS-Cog endpoint, the sponsor proposed ANCOVA method using baseline total ADAS-Cog score, treatment and country as independent variables. The interpretation of the treatment effect is meaningful only if the regression relationships among two treatment groups are the same. Regression relationships that differ among two groups indicate an interaction between the treatment groups and the independent variable, the baseline measurement, and this interaction makes it hard to interpret the final treatment effect due to the drug. This reviewer performed an analysis to test for the heterogeneity of the slopes. Table 9 displays the results of the test for ADAS-Cog endpoint at both Week 16 and Week 24 among ITT+RDO population. It turns out that the two slopes at Week 16 are very similar; however, the slopes among two treatment groups at Week 24 are statistically significant

different. Therefore, if relying on the ANCOVA model to predict the treatment effect due to the drug, at low baseline values, the drug effect turns to be underestimated; whereas at the high baseline values, the drug effect will be overestimated.

Table 9 Estimates of the slopes in each treatment group and the P values for testing the heterogeneity of the slopes (Source: Reviewer's Analysis for study 2311)

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

For another primary endpoint, ADCS-CGIC, the sponsor proposed to use Van Elteren nonparametric method to test for the treatment effect using country as the blocking variable. At both Week 16 and Week 24, the results across all the countries are not consistent in terms of percentage of improvement after treatment. The total percentage changes from baseline after each treatment for each country are listed in Tables 10 & 11. Because of small sample sizes, three countries, Austria, Norway and Portugal were combined. As can be seen from both tables, in most countries, Exelon is better than placebo; however, in some countries, placebo performs better than Exelon. Since the results per country were not consistent, the final results should be interpreted with caution.

Table 10 ADCS CGIC – patients improving by treatment and country (Week 16) (Source: Reviewer's Analysis for study 2311)

		Exelon		Placebo	
	N	# Impr. (% Impr.)	N	# Impr. (% Impr.)	P values
Belgium	13	4 (30.77)	8	2 (25)	0.369
Canada	29	14 (48.28)	9	5 (55.56)	0.277
Austria, Norway, Portugal	13	8 (61.54)	8	1 (12.50)	0.035
Germany	42	16 (38.10)	21	3 (14.29)	0.036
Spain	37	13 (15.14)	20	5 (25)	0.178
France	35	17 (48.57)	20	6 (30)	0.094
United Kingdom	33	13 (39.39)	14	3 (21.43)	0.139
Italy	77	28 (36.36)	39	13 (33.33)	0.156
Netherlands	10	5 (50.0)	7	1 (14.29)	0.143
Turkey	29	17 (58.62)	13	11 (84.62)	0.077

Table 11 ADCS CGIC – patients improving by treatment and country (Week 24) (Source: Reviewer's Analysis for study 2311)

Week 24		Exelon		Placebo	
	N	# Impr. (% Impr.)	N	# Impr. (% Impr.)	P values
Belgium	13	3 (23.08)	8	2 (25)	0.394
Canada	31	15 (48.39)	9	5 (55.56)	0.275
Austria, Norway, Portugal	14	5 (35.71)	9	5 (55.56)	0.221
Germany	42	18 (42.86)	21	3 (14.29)	0.017
Spain	38	9 (23.68)	20	3 (15.00)	0.208
France	38	20 (52.63)	23	6 (26.09)	0.028
United Kingdom	34	15 (44.12)	14	4 (28.57)	0.161
Italy	77	23 (29.87)	40	12 (30.00)	0.168
Netherlands	11	5 (45.45)	7	1 (14.29)	0.174
Turkey	31	21 (67.74)	14	8 (57.14)	0.206

3.2 Evaluation of Safety

Please refer to Clinical Review by Dr. Ranjit Mani for Evaluation of Safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The primary efficacy measures were analyzed in subgroups with regard to gender. There were a total of 190 female patients (128 females in the Exelon group and 117 females in the placebo group) and 351 male patients (234 males in the Exelon group and 117 males in the placebo group) in the study.

The subgroup efficacy results for ADAS-Cog are listed in Table 12. The results were consistent with overall findings even though some results for female do not meet the 0.05 nominal level.

The results for ADCS-CGIC are listed in Tables 13 & 14. When the subgroup analysis was performed by gender, the p-values for testing the difference of ADCS-CGIC ratings for both male and female PDD patients at Week 16 and for female patients at Week 24 for the primary analysis population are greater than 0.05.

It needs to be noted that the subgroup analysis was a post hoc analysis, without power and sample size properly adjusted for the significant testing.

Since all the patients were 50 years or older and 539 out of 541 enrolled patients were Caucasians, the subgroup analyses by age and by race are not performed.

Table 12 ADAS-Cog - Change from Baseline (Source: Reviewer's Analysis for study 2311)

	Exelon Mean (SD)	Placebo	p-value
Female			
ITT+RDO			
Week 16	2.2 (7.7)	0.6 (6.5)	0.166
Week 24	1.9 (8.4)	-0.9 (8.0)	0.027
ITT+LOCF			
Week 16	2.7 (7.9)	0.6 (6.2)	0.075
Week 24	2.6 (8.6)	-1.0 (8.0)	0.010
OC			
Week 16	2.8 (8.0)	0.6 (6.2)	0.066
Week 24	3.3 (8.5)	-1.7 (7.9)	0.004
Male			
ITT+RDO			
Week 16	2.4 (7.1)	0.1 (6.9)	0.005
Week 24	2.2 (8.1)	-0.6 (7.2)	0.001
ITT+LOCF			
Week 16	2.8 (7.1)	0.1 (7.0)	<0.001
Week 24	2.5 (8.3)	-0.7 (7.3)	<0.001
OC			
Week 16	2.8 (7.1)	0.1 (7.2)	<0.001
Week 24	2.6 (8.3)	-0.7 (7.4)	0.001

Table 13 ADCS-CGIC at Week 16 and Week 24 for Female (Source: Reviewer's Analysis for study 2311)

	ITT+RDO		ITT+LOCF		OC	
Female, Week 16	Exelon	Placebo	Exelon	Placebo	Exelon	Placebo
N	116	57	96	52	96	52
Mean ± SD	3.9 ± 1.4	4.2 ± 1.4	3.7 ± 1.4	4.2 ± 1.3	3.7 ± 1.4	4.2 ± 1.3
Markedly Improved (1)	4	4	4	4	4	4
Moderately improved (2)	13	11	15	10	15	10
Minimally improved (3)	28	9	30	10	30	10
Unchanged (4)	27	31	27	31	27	31
Minimally worse (5)	13	31	11	33	11	33
Moderately worse (6)	14	13	11	12	11	12
Markedly worse (7)	3	2	1	2	1	2
p-value	0.245		0.049		0.049	
Female, Week 24						
N	116	57	99	54	81	50
Mean ± SD	3.9 ± 1.5	4.3 ± 1.4	3.7 ± 1.4	4.4 ± 1.4	3.6 ± 1.4	4.2 ± 1.3
Markedly Improved (1)	2	2	2	0	2	0
Moderately improved (2)	19	14	20	13	25	14
Minimally improved (3)	19	11	23	11	21	12
Unchanged (4)	28	30	30	30	30	32
Minimally worse (5)	14	21	11	22	12	24
Moderately worse (6)	15	19	11	20	9	16
Markedly worse (7)	3	4	2	4	1	2
p-value	0.350		0.035		0.012	

Table 14 ADCS-CGIC at Week 16 and Week 24 for Male (Source: Reviewer's Analysis for study 2311)

	ITT+RDO		ITT+LOCF		OC	
Male, Week 16	Exelon	Placebo	Exelon	Placebo	Exelon	Placebo
N	206	104	186	101	186	101
Mean ± SD	3.7 ± 1.3	4.0 ± 1.4	3.6 ± 1.3	4.0 ± 1.4	3.6 ± 1.3	4.0 ± 1.4
Markedly Improved (1)	4	2	4	2	4	2
Moderately improved (2)	15	13	16	13	16	13
Minimally improved (3)	23	21	24	21	24	21
Unchanged (4)	29	30	28	30	28	30
Minimally worse (5)	23	19	23	20	23	20
Moderately worse (6)	4	12	3	12	3	12
Markedly worse (7)	2	4	1	3	1	3
p-value	0.167		0.06		0.06	
Male, Week 24						
N	213	108	190	104	171	95
Mean ± SD	3.8 ± 1.4	4.3 ± 1.5	3.8 ± 1.4	4.2 ± 1.5	3.7 ± 1.4	4.2 ± 1.5
Markedly Improved (1)	6	3	6	3	7	3
Moderately improved (2)	14	11	14	12	15	12
Minimally improved (3)	22	18	23	18	23	17
Unchanged (4)	24	27	23	27	23	27
Minimally worse (5)	24	19	24	17	23	17
Moderately worse (6)	8	15	8	15	8	17
Markedly worse (7)	2	8	2	8	2	7
p-value	0.045		0.055		0.025	

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor proposed to use the ITT+RDO as their primary analysis population. Normally it is recommended by the agency to use the ITT+LOCF as the primary analysis population. RDO patients discontinued study treatment early but came back for the efficacy evaluations. The ITT+LOCF population only carried forward the results if their assessment were done within 2 days after the last dose of study drug. In study 2311, values of 41 patients in Exelon group and 7 patients in Placebo group were not carried forward since the assessment were done 2 days after the last dose of the study drug (the ratio is almost 6 between the two treatment groups). The sponsor did perform the same analyses for ITT+LOCF population and the results were consistent with the findings based on the analysis from ITT+RDO population. This reviewer's analysis agrees with the reported findings.

The results based on the subgroup analyses (by gender) show that in some situations, the magnitude of the treatment difference between male and female is different. For instance, for the primary endpoint ADAS-Cog, the data did not show a difference between the two groups for female at Week 16 at a nominal level 0.05. For another primary endpoint ADCS-CGIC, among the female patients, at both week 16 and 24, the data did not show a difference between the two treatments at a nominal level 0.05 based on ITT+RDO population. Among the male patients, no differences between Exelon and Placebo were detected at Week 16 based on all the three analysis populations and at Week 24 based on ITT+LOCF population at a nominal level 0.05. As mentioned above, the subgroup analysis is a post hoc analysis.

5.2 Conclusions and Recommendations

The data based on Study 2311 support the efficacy of 3-12 mg/day of Exelon® (rivastigmine) in patients with Parkinson's disease dementia based on the statistical methods proposed in the original protocol. Some sensitivity analyses still support the efficacy of Exelon.

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APPLICATION NUMBER:

20-823 / S-016

21-025 / S-008

OTHER REVIEW(S)

Review and Evaluation of Clinical Data

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: Labeling Review**
Correspondence Date:	**8/31/05**
Date Received / Agency:	**9/1/05**
Date Review Completed	**6/9/06**
Reviewer:	**Ranjit B. Mani, M.D.**

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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."

This review addresses only the proposed labeling in the submission. The rest of the submission has been reviewed in detail separately.

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 contents of this submission are also cross-referenced by a submission (SE1-008; letter date February 10, 2006) under NDA 210125 which seeks the approval of Exelon® Oral Solution for the same indication.

2. Proposed And Edited Labeling

Changes (additions) have been to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of labeling. These changes are outlined below, as are the changes to the current product labeling proposed by me.

2.1 Changes Proposed By Sponsor

2.1.1 CLINICAL PHARMACOLOGY/Clinical Trial Data

2.1.1.1 New Sub-Heading

Clinical Trial Data

Dementia of the Alzheimer's type

11 Page(s) Withheld

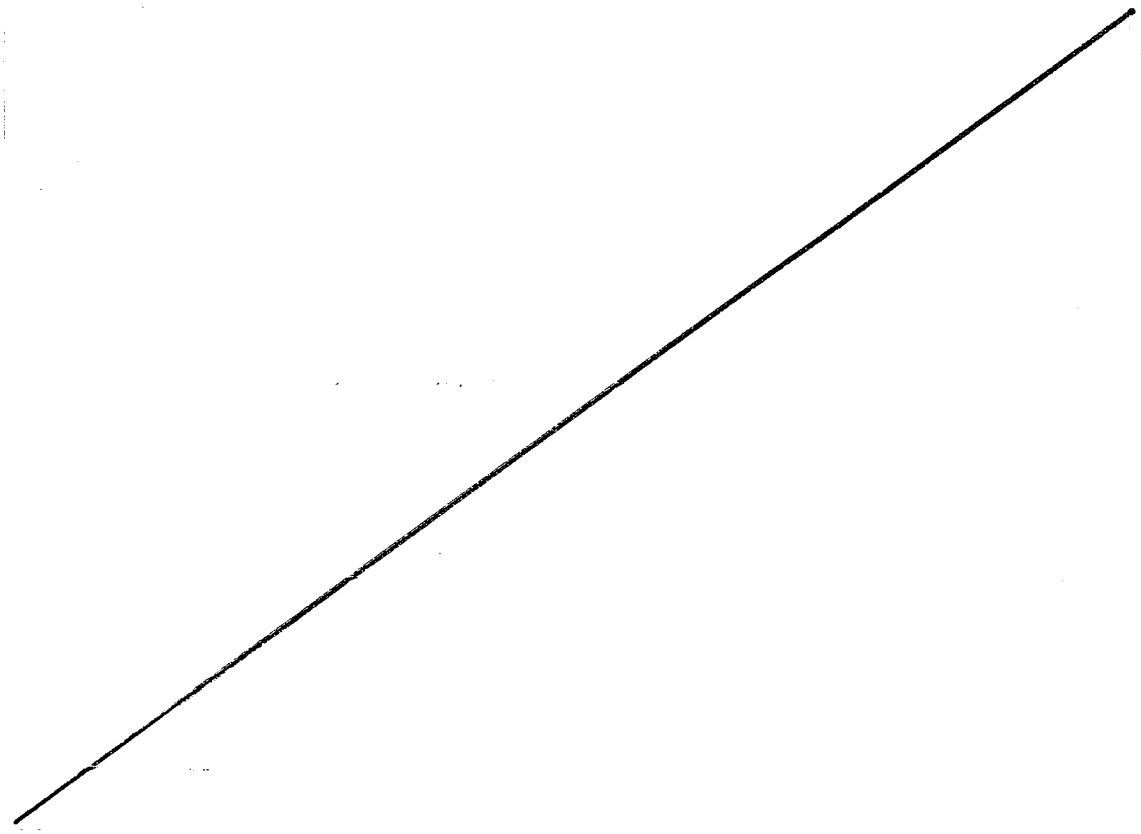
_____ Trade Secret / Confidential (b4)

√ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Other Reviews- 1



b(4)

3. Comments

Each of the sections of the product labeling for which changes have been proposed by the sponsor, as well as changes that I have made to a further section are addressed separately below.

3.1 Sections For Which Changes Have Been Proposed By The Sponsor

3.1.1 CLINICAL PHARMACOLOGY/Clinical Trial Data

I have modified the sponsor's description of the study conducted in Dementia associated with Parkinson's Disease to include the following:

- A more detailed description of the entry criteria, including a clarification that patients enrolled in the study were not required to have a distinctive pattern of cognitive deficits
- A description of the primary efficacy measures, in particular, the ADCS-CGIC
- A description of the effects of rivastigmine on the ADAS-Cog and ADCS-CGIC using the Observed Cases dataset, rather than the intent-to-treat-plus-retrieved dropout dataset used by the sponsor. The Observed Cases dataset has been used to describe the effects of rivastigmine in Alzheimer's Disease in the same section of the product label

3.1.2 INDICATIONS AND USAGE

The changes proposed by the sponsor are acceptable.

3.1.3 PRECAUTIONS/Information For Patients And Caregivers

The changes proposed by the sponsor are acceptable.

3.1.4 ADVERSE REACTIONS

A description of esophageal rupture in a patient who received Exelon® in the Post-Introductory reports subsection has been eliminated as it is already described in the WARNINGS section.

The sponsor's proposed changes to this section are otherwise acceptable.

3.1.5 DOSAGE AND ADMINISTRATION

The dosing regimen for patients with dementia associated with Parkinson's Disease has been clearly separated from that in patients with dementia of the Alzheimer's type and outlined in greater detail.

3.2 Other Sections

3.2.1 CLINICAL PHARMACOLOGY/Mechanism Of Action

I have altered the current approved labeling to indicate that, as in Alzheimer's Disease, the pathological changes in Dementia associated with Parkinson's Disease also involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus

4. Conclusion

I have modified the current approved product labeling for Exelon® so as to incorporate information included in this supplemental New Drug Application. The modifications that I have made are somewhat different from those proposed by the sponsor.

The full text of the product labeling for Exelon®, as modified by me is in a separate Microsoft Word document.

Although the modifications to the current approved product labeling for Exelon® that I have proposed are intended for use in the event that the drug is approved for the treatment of dementia associated with Parkinson's Disease, I have recommended against approval of this application; please see my review of the main body of this application for further details as to the basis for that recommendation.

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 6/9/06
cc:
HFD-120
NDA 20823 (SE1-016)

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/s/

Ranjit Mani
6/13/2006 07:49:22 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-823 / S-016

21-025 / S-008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-823
NDA 21-025

Novartis Pharmaceuticals Corporation
Attn: Michelle Campbell
One Health Plaza
East Hanover, NJ 07936-1080

Dear Ms. Campbell:

Please refer to the following Supplemental New Drug Applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exelon (Rivastigmine Tartrate).

NDA #	Supp. #	Dosage Form	Approval Date
20-823	S-016	Capsules	June 27, 2006
21-025	S-008	Liquid	June 27, 2006

Since 2000, FDA has conducted several comprehensive inspections of bioequivalence studies in which the bioanalytical analysis was conducted by [redacted]. The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing. Our findings from these inspections include, but are not limited to, the following: b(4)

- Failure to conduct a systematic and thorough evaluation to identify and correct sources of contamination.
- Failure to investigate anomalous results.
- Lack of assay reproducibility between original and repeat results.
- Assay accuracy not assured under the conditions of sample processing.
- Biased exclusion of study data resulting in the acceptance of failed runs.
- Failure to demonstrate the accuracy of analytical methods with appropriate validation experiments and documentation.

As a result of these findings, [redacted] agreed to conduct an audit of data from all its bioequivalence studies generated from January 2000 to December 2004. However, FDA identified significant deficiencies with the [redacted] audit during its most recent inspection. Thus, serious questions remain b(4)

about the validity of any data generated by —— in studies during this time period that have not been inspected by FDA. In view of these findings, FDA is informing holders of approved NDAs of these issues. b(4)

The impact of the data from these studies (which may include bioequivalence, pharmacokinetic, drug-drug interaction and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us within 30 days of receipt of this letter if you have submitted any studies conducted by —— during the time period of concern (January 2000 through December 2004). Please submit information on each of the studies submitted, including supplement number (if appropriate), study name/protocol number, and date of submission. This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to: b(4)

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

Once we have made an assessment regarding the potential impact of these data, we will contact you regarding the steps that need to be taken, if any, to assure the accuracy of the data submitted to your application.

If you have any questions, call CDR Melina Griffis, Regulatory Project Manager, at 301-796-1078.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Robbin Nighswander
1/19/2007 02:07:13 PM
For Division Director

DSI CONSULT: Request for Clinical Inspections

Date: October 17, 2005

To: Ni Aye Khin, HFD-47

Through: Joanne L. Rhoads, M.D., Director, DSI, HFD-45
Russell Katz, MD, Director, HFD-120

From: Melina Griffis, R. Ph, Senior Regulatory Project Manager, HFD-120

Subject: **Request for Clinical Inspections**
NDA 20-823/S-016
Novartis Pharmaceuticals
Exelon (rivastigmine) Capsules

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication: To evaluate the efficacy of Exelon compared to placebo for a treatment period of 24 weeks in patients with Parkinson's Disease Dementia.

Protocol #: CENA713B2311

1. Center 0122- 30 Patients
   Sibel Ozekmekci
   Istanbul University, Cerrahpasa Medical School
   Neurology Department
   Cerrahpasa
   Istanbul, Turkey 34098

2. Center 0049- 31 Patients
   Marco Onofrj
   Ospedale Civile dello Spirito
   Santo, Università G. D'Annunzio
   Servizio di Neurofisiopatologia
   Dip. di Oncologia e Neuroscienze
   Via Fonte Romana, 8
   Pescara, Italy 65100

International Inspections:

We have requested inspections because (please check appropriate statements):

___ There are insufficient domestic data

__X__ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) May 1, 2005. We intend to issue an action letter on this application by (action goal date) June 31, 2005.

Should you require any additional information, please contact Melina Griffis.

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/s/

Russell Katz
10/19/2005 07:50:37 AM