CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-083

MEDICAL REVIEW

Review and Evaluation of Clinical Data

NDA	**22083**
Sponsor:	**Novartis**
Drug:	**Exelon® Patch***
Proposed Indication:	**Alzheimer's Disease****
Material Submitted:	**New Drug Application/Proposed Labeling**
Correspondence Date:	**9/8/06**
Date Received / Agency:	**9/8/06**
Date Review Completed	**7/2/07**
Reviewer:	**Ranjit B. Mani, M.D.**

*The full title of the drug product is Exelon® Patch (rivastigmine) transdermal system
The sponsor is seeking the approval of this product for the treatment of mild to moderate **Alzheimer's Disease and the treatment of mild to moderate Parkinson's Disease

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1. Background

This New Drug Application seeks the approval of a new transdermal formulation of Exelon® (rivastigmine tartrate) for the following two indications:

- **The treatment of mild to moderate dementia of the Alzheimer's type**
- **The treatment of mild to moderate dementia associated with Parkinson's** Disease.

In this application, the sponsor has sought the approval ——— dosage strengths of the proposed transdermal formulation of Exelon. These dosage strengths are summarized by patch size, nominal dose of rivastigmine delivered per 24 hours and rivastigmine content per patch, in the following table.

Exelon® Patch Size	**Rivastigmine Nominal Dose**	**Rivastigmine Content Per Patch**
5 cm^2	4.6 mg/24 hours	9 mg
10 cm^2	9.5 mg/24 hours	18 mg
[redacted]	[redacted]	[redacted]

b(4)

This document reviews only the proposed labeling contained in this application. The main contents of the application have been reviewed in a separate document; please refer to that review for further details.

Exelon® (rivastigmine tartrate) is a cholinesterase inhibitor drug initially approved by this Agency on March 21, 2000, as immediate-release capsule and oral solution formulations, for the treatment of mild to **moderate dementia of the Alzheimer's type.** Please refer to the primary reviews of NDA 20823 (for the immediate-release capsule formulation) and NDA 21025 (for the oral solution formulation), and to the current product labeling for both formulations, for full details of those applications.

The immediate-release capsule and oral solution formulations of Exelon® were also approved by this Agency for the treatment of mild to moderate dementia associated with **Parkinson's Disease (under NDA 20823 [SE1-016] and NDA 21025 [SE1-008],** respectively) on June 27, 2006.

The Exelon® Patch (rivastigmine) transdermal system is referred to –interchangeably - as the "Exelon® patch" or the "rivastigmine patch" in this review.

In this submission, the sponsor has proposed product labeling for the transdermal formulation of rivastigmine that is entirely separate from that for the oral formulations.

The actual product labeling, as further edited by me, is in a separate document.

Note that during this labeling review, **I have closely compared the sponsor's** proposed labeling with the currently approved labeling for the oral formulations of Exelon®.

2. Contents Of Review

The proposed labeling has been reviewed under the following headings and in the same order as below:

- **Sponsor's proposed labeling with reviewer comments**
- Overall comments
- Recommendation

3. Sponsor's Proposed Labeling With Reviewer Comments

3.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

3.1.1 Sponsor's Proposed Labeling

b(4)

3.1.2 Reviewer's Comments

I have edited this section of the labeling as follows.

- The treatment of mild to moderate Parkinson's Disease Dementia has been deleted as an approved indication as I have recommended (for reasons stated in

my main review) against approving the transdermal formulation of Exelon® for that indication.

- Other sections have been made consistent with the full labeling text.
- Information that I have considered not particularly informative or helpful has been deleted.
- Other minor changes have been made.

3.2 FULL PRESCRIBING INFORMATION

3.2.1 INDICATIONS AND USAGE

3.2.1.1 Sponsor's Proposed Labeling

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3.2.1.2 Reviewer's Comments

I have deleted the section headed '[redacted]' as I have recommended (for reasons stated in my main review) against approving the transdermal formulation of Exelon® for that indication. **The heading '[redacted] has also been deleted as I am recommending that this drug be** approved for a single indication (the treatment of mild to moderate dementia of **the Alzheimer's type) only.**

b(4)

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

3.2.2.2 Reviewer's Comments

I have referred to the dose strengths of Exelon® Patch primarily as the nominal dose delivered per 24 hours as that is more informative, consistent with the product label for other approved transdermal formulations (such as rotigotine [Neupro®]), and recommended by the staff of the Division of Medical Errors and Technical Support (DMETS) in a consultation. DMETS has recommended against the use of the terms "Exelon Patch 5," "Exelon Patch 10," [redacted] b(4)

The language used to describe dose titration has been made consistent with that already approved as labeling for the oral formulations of Exelon®.

I have included text recommending that the Exelon® Patch be applied to only to the upper and lower back since the upper back was the site of patch application in most clinical trials, and since a patch applied to the back is likely to be less easily removed by patients with Alzheimer's Disease.

The text of this section has been altered in several other areas to improve its clarity.

I have deleted the section headed [redacted] as I have recommended (for reasons stated in my main review) against approving the transdermal formulation of Exelon® for that indication. The heading [redacted] has also been deleted as I am recommending that this drug be approved for a single indication (the treatment of mild to moderate dementia of the Alzheimer's type) only. b(4)

The following statements have been deleted from under the [redacted] heading as no evidence has been supplied in their support:

[redacted] b(4)

Note that in my main review, I have not recommended the use of Exelon® Patch dosage strengths [redacted] 10 cm^2 (delivery rate of 9.5 mg/24 hours). This recommendation is based on the lack of evidence of additional efficacy and the evidence of poorer safety and tolerability at a dosage strength of [redacted], as compared with 10 cm^2. [redacted] b(4)

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

3.2.3.2 Reviewer's Comments

I have inserted the table that I created for the DOSAGE AND ADMINISTRATION which compares patch size, nominal rivastigmine delivery per 24 hours, and rivastigmine base contents into this section as well.

Note that in my main review, I have not recommended the use of Exelon® Patch dosage strengths [redacted] 10 cm^2 (delivery rate of 9.5 mg/24 hours) [redacted]

b(4)

This section of the proposed label is to also be reviewed by the Chemistry staff of the Agency, and I will defer to their recommendations in case they differ from the changes I have made. Modifications to this section will also need to be made based on recent discussions with the sponsor that included Clinical, Chemistry, and DMETS staff from the Agency.

3.2.4 CONTRAINDICATIONS

3.2.4.1 Sponsor's Proposed Labeling

[redacted]

b(4)

3.2.4.2 Reviewer's Comments

I have added the phrase "see DESCRIPTION" in parentheses to the proposed text (a similar phrase is in the text of the current approved labeling for the oral formulations of Exelon®) and directs the reader to the section that describes the components that are specific to the transdermal formulation.

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

3.2.5.2 Reviewer's Comments

I have extensively revised (and **"strengthened) the sub-section headed "Gastrointestinal Adverse Events" so as to** make that sub-section consistent with the current approved labeling for the oral formulations of Exelon®:

b(4)

I recommend that the text I have proposed be retained even if only the 10 cm^2 Exelon® Patch is approved for marketing; given the minimal efficacy of this drug, it is then likely that doses higher than 10 cm^2 will be prescribed not infrequently in clinical practice (and especially since that dose has been evaluated in clinical trials).

Minor additional revisions have been made to sections other than Special Populations; these revisions include transpositions of text.

The text of the Special Populations sub-section has been deleted with the **exception of that under the heading "Low Body Weight." The deleted items are** adequately addressed in either Section 2 (Dosage and Administration) or in Section 8 (Use in Special Populations) and they are not of such concern as to be included in this section.

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_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

3.2.6.2 Reviewer's Comments

The sponsor's proposed labeling for this section has been extensively revised.

The main revisions that I have made include the following.

- The inclusion of a section describing adverse events that led to treatment **discontinuation in the controlled clinical trial of the Exelon® patch in Alzheimer's** Disease

- A request to the sponsor to include a single table in this section which compares the incidence of the more common adverse events in the aforementioned controlled clinical (i.e., those with a frequency of ≥ 2% in any Exelon® Patch-

treated group and with a greater frequency in the placebo-treated group) and shows their incidence in each treatment group

- An expansion of the section describing application site reactions in the controlled clinical trial
- **The exclusion of several elements of the sponsor's labeling that I considered** redundant and/or uninformative

3.2.7 DRUG INTERACTIONS

3.2.7.1 Sponsor's Proposed Labeling

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b(4)

3.2.7.2 Reviewer's Comments

This section of the product label has been edited by me largely on the basis of comments received from the Clinical Pharmacology reviewer of this application, Dr Veneeta Tandon.

The following sentence has been deleted as it appears redundant and is not contained in the current approved product label for the oral formulations of **rivastigmine**:

b(4)

The following sentence has been deleted, as no supporting evidence for that statement has been cited in the annotated proposed labeling and as it is not contained in the approved product label for the oral formulations of rivastigmine:

b(4)

The following sentence has been deleted as it conveys the same meaning as the next sentence and is not contained in the current approved product label for the **oral formulations of rivastigmine**:

b(4)

b(4)

3.2.8 USE IN SPECIFIC POPULATIONS

3.2.8.1 Sponsor's Proposed Labeling

b(4)

3.2.8.2 Reviewer's Comments

The sponsor's text is taken from the current approved labeling for the oral formulations of Exelon® and is acceptable to this reviewer.

At the recommendation of the Clinical Pharmacology reviewer, I have added text pertaining to the use of rivastigmine in individuals with hepatic and renal impairment (the text matches that contained in the current approved label for rivastigmine) and for individuals with low body weight (which is new text).

I have also added text (taken verbatim from the current approved label) pertaining to the effects of gender and race (modified slightly using data from the current submission) and nicotine use on the disposition of Exelon®.

The recommendations of the Pharmacology-Toxicology Team may also be sought as to whether any changes are warranted to the Pregnancy subsection.

3.2.9 OVERDOSAGE

3.2.9.1 Sponsor's Proposed Labeling

b(4)

b(4)

3.2.9.2 Reviewer's Comments

I have revised the sponsor's text proposed text to make this section of the product labeling consistent with the same text in the current approved labeling for the oral formulations of Exelon®; however, I have substituted relevant pharmacokinetic data for the Exelon® patch (in place of pharmacokinetic data for the oral formulation), and in**cluded the sponsor's statement** that there is currently

no data on overdose with the Exelon® Patch (rivastigmine) transdermal system per se.

The sponsor has not cited any data to support other elements of the proposed new text above [redacted] b(4)

[redacted] in the annotated proposed labeling.

3.2.10 DESCRIPTION

3.2.10.1 Sponsor's Proposed Labeling

[redacted] b(4)

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

3.2.11.2 Reviewer's Comments

The review of the above Mechanism of Action and Pharmacodynamics subsections of the proposed labeling has been deferred to the Agency Pharmacology-Toxicology Team. However, I would recommend that the text for those sections be identical to what is in the current approved labeling for the oral formulations of Exelon®. The sponsor has not cited any data to support other elements of the proposed new text above in the annotated proposed labeling.

I have made a number of changes to the Pharmacokinetics sub-section based largely on the recommendations of the Clinical Pharmacology reviewer.

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

3.2.13.2 Reviewer's Comments

The dose strengths of Exelon® Patch have been expressed as milligrams released per 24 hours, rather than as patch size for reasons stated earlier in this review.

I have eliminated the sub-section headed '[redacted] as I have recommended against approving this formulation of Exelon® for that indication. b(4)

I have also eliminated all references to the ADCS-ADL from this section. Although the ADCS-ADL was technically a designated primary efficacy measure for this study, it was not utilized as a primary efficacy measure in the analysis that was agreed upon with this Agency a priori, and was therefore not a basis for deciding whether the efficacy study described in this section was positive or not or to the evaluation of this application. There was no prior agreement with this Division that the ADCS-ADL was a measure, the effects of the Exelon® patch on which could be described in labeling if the results of the study were considered positive; neither was a plan of analysis for this measure agreed upon a priori with this Division. Moreover, there is considerable overlap between the functions evaluated by the ADCS-ADL and the ADCS-CGIC, making a description of the former redundant.

The text for this section has been made consistent with the text used in the currently approved labeling for the oral formulations of Exelon®.

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

I have made minor further changes to the labeling that Ms Best has proposed in a separate document (a document that is separate from the rest of the edited labeling).

These include the following:

- The addition of vomiting to the possible list of serious side-effects
- The restriction of potential sites of patch application to the upper and lower back since the upper back was the site of patch application in most clinical trials and since a patch applied to the back is likely to be less easily removed by patients **with Alzheimer's Disease**
- A request to the sponsor to include a phone number and website that patients/caregivers can access for more information, as well as the phonetic spelling of the proprietary name of the drug

4. Overall Comments

Comments appropriate to each section of the product labeling have been made in those sections.

5. Recommendation

I recommend that the Exelon® Patch (rivastigmine) transdermal system be approved for the treatment of mild to moderate dementia of the Alzheimer's type in strengths of 5 cm^2 (delivering 4.6 mg of rivastigmine per 24 hours) and 10 cm^2 (delivering 9.5 mg of rivastigmine per 24 hours) only.

Proposed labeling is provided in a separate document.

(Please see my main review for full details of the basis of this recommendation).

Ranjit B. Mani, M.D.
Medical Reviewer

rbm 7/2/07
cc:
HFD-120
NDA 22083

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Ranjit Mani
7/2/2007 03:25:03 PM
MEDICAL OFFICER

Review and Evaluation of Clinical Data

NDA	**22083**
Sponsor:	**Novartis**
Drug Product:	**Exelon® Patch***
Proposed Indication:	**Alzheimer's Disease****
Material Submitted:	**New Drug Application**
Correspondence Date:	**9/8/06**
Date Received / Agency:	**9/8/07**
Date Review Completed	**7/2/07**
Reviewer:	**Ranjit B. Mani, M.D.**

*The full title of the drug product is Exelon® Patch (rivastigmine) transdermal system
The sponsor is seeking the approval of this product for the treatment of mild to moderate **Alzheimer's Disease and the treatment of mild to moderate Parkinson's Disease

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EXECUTIVE SUMMARY

Recommendation

I recommend that the Exelon® Patch (rivastigmine) transdermal system be approved for the treatment of mild to moderate dementia of the Alzheimer's type in strengths of 5 cm^2 (delivering 4.6 mg of rivastigmine per 24 hours) and 10 cm^2 (delivering 9.5 mg of rivastigmine per 24 hours) only.

Proposed Indication

This New Drug Application seeks the approval of a new transdermal formulation of Exelon® (rivastigmine tartrate) for the following two indications:

- **The treatment of mild to moderate dementia of the Alzheimer's type**
- **The treatment of mild to moderate dementia associated with Parkinson's** Disease.

In this application, the sponsor has sought the approval [redacted] dosage strengths of the proposed transdermal formulation of Exelon. These dosage strengths are summarized by patch size, nominal dose of rivastigmine delivered per 24 hours and rivastigmine content per patch, in the following table.

Exelon® Patch Size	**Rivastigmine Nominal Dose**	**Rivastigmine Content Per Patch**
5 cm^2	4.6 mg/24 hours	9 mg
10 cm^2	9.5 mg/24 hours	18 mg
[redacted]	[redacted]	[redacted]

b(4)

Currently, immediate-release capsule and oral solution formulations of Exelon® are approved, under NDA 20823, for the treatment of both mild to moderate **dementia of the Alzheimer's type and mild** to moderate dementia associated with **Parkinson's Disease.**

Summary Of Clinical Findings

The main efficacy, safety, and pharmacokinetic data that the sponsor has submitted in support of this application are summarized below.

Efficacy

The sponsor has submitted the results of a single efficacy study , [redacted]713D2320, of the proposed new transdermal formulation of Exelon®. This study has been conducted in patients with mild to moderate dementia of the **Alzheimer's type.**

b(4)

The sponsor has not conducted a study of the proposed new transdermal formulation of **Exelon® in patients with mild to moderate dementia associated with Parkinson's**

Disease, but has presented an argument in support of that proposed indication; that argument is outlined in a later section of this summary.

The design and efficacy data for Study ——— /13D2320 are described further below. b(4)

This study was conducted at a total of 100 centers in 21 countries.

Design

This was a randomized, double-blind, placebo-controlled, parallel-arm study of 24 weeks duration.

The two key criteria used for enrolling patients in this study were a diagnosis of **Probable Alzheimer's Disease, using the National Institute for Neurological and Communicative Diseases and Stroke – Alzheimer's Disease and Related** Disorders Association (NINCDS-ADRDA) criteria, and a baseline Mini-Mental Status Examination score of 10-20.

Patients enrolled in this study were randomized to treatment with one of the following regimes for the 24-week period of double-blind, parallel-arm treatment, divided into a 16-week titration phase and an 8-week maintenance phase.

- Placebo
- Exelon® 10 cm^2 patch QD (nominal rivastigmine release rate of 9.5 mg/24 hours)
- Exelon® 20 cm^2 patch QD (nominal rivastigmine release rate of 17.4 mg/24 hours)
- Exelon® capsules 6 mg BID

The assigned doses of Exelon® (patch or capsules) were to be achieved by titration, as already noted, but doses below the target dose were permitted during the maintenance period in the event of poor tolerability.

The primary efficacy measures for the study were:

- **A measure of cognition, the Alzheimer's Disease Assessment Scale – Cognitive** Subscale (ADAS-Cog)
- A measure of global function, the **Alzheimer's Disease Cooperative Study –** Clinical Global Impression Of Change (ADCS-CGIC)
- **A measure of activities of daily, the Alzheimer's Disease Cooperative Study – Activities of Daily Living – Severe scale (ADCS-ADL-Severe).**

Secondary efficacy measures included the Neuropsychiatry Inventory, Mini-Mental Status Examination, Ten-Point Clock Test, and Trailmaking Tests A and B. Safety measures included adverse events, vital signs, and electrocardiograms. Pharmacokinetic outcome measures included plasma levels of rivastigmine and NAP 226-90 (the principal metabolite of rivastigmine). Study

outcome measures also included assessments of patch adhesion and skin irritation at the site of patch application.

Two separate types of primary efficacy analysis were stipulated a priori by the sponsor, as agreed upon at a Pre-NDA Meeting with this Division that was held on November 8, 2005.

- The first of these types of analysis addressed 4 originally-specified study hypotheses in sequence and was planned to meet the requirements of the European Agency for the Evaluation of Medicinal Products (EMEA).

- **The second type of primary efficacy analysis was designed to meet this Agency's** requirements for approval and addressed only two of the 4 original study hypotheses in sequence (agreement was reached with the Agency prior to breaking the study blind that this type of primary efficacy analysis would be the basis for evaluating the efficacy of the transdermal formulation of Exelon®).

The second type of primary efficacy analysis involved evaluating the following two hypotheses in the same order as below.

- The first hypothesis involved the comparison of the 20 cm^2 Exelon® patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 20 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.
- The second hypothesis involved the comparison of the 10 cm^2 Exelon® patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 10 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.

Since the study hypotheses were arranged in order a priori, and as both primary efficacy parameters were be tested simultaneously, no correction of Type I error was considered required for testing each hypothesis (i.e., a Type I error of 0.05 [2-sided] could be used to test each hypothesis).

The steps to be taken in the testing process were to be as follows:

Step 1. The superiority of the 20 cm^2 Exelon® patch over placebo was to be demonstrated simultaneously for both primary efficacy variables, the ADAS-Cog and ADCS-CGIC. If for both treatment comparisons, the corresponding two-sided p-values were less than 0.05, then the superiority of the 20 cm^2 Exelon® patch over placebo was to be regarded as confirmed and it would then be possible to proceed to Step 2. Otherwise the testing procedure was to be stopped, and neither of the confirmatory hypotheses considered established

Step 2. The superiority of the 10 cm^2 Exelon® patch over placebo was to be demonstrated simultaneously for both primary efficacy variables, the ADAS-Cog and ADCS-CGIC. If for both treatment comparisons, the corresponding two-sided p-values were less than 0.05, then the superiority of the 10 cm^2 Exelon® patch

over placebo was to be regarded as confirmed. Otherwise the superiority of the 10 cm^2 Exelon® patch over placebo would not be regarded as having been established.

Both types of primary efficacy analysis was carried out on an intent-to-treat (ITT) basis, using the last-observation-carried-forward (LOCF) method for imputing data. The intent-to-treat population was defined as consisting of 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 primary analysis of cognitive function was based on the change from baseline score for the ADAS-Cog; the treatment groups were compared using least square means derived from an analysis of covariance model with the following explanatory variables: treatment, country, and the baseline total ADAS-Cog score. The primary analysis for the ADCS-CGIC was to be a treatment comparison using a Cochran-Mantel-Haenszel test with modified ridit scores with country as stratification variable.

Results

1195 patients were randomized of whom 1190 patients received study drug. The number of patients randomized to, and completing the study in each treatment group is summarized in the following table

Category	Treatment Group			
	Exelon® 20 cm^2 N (%)	Exelon® 10 cm^2 N (%)	Exelon® Capsule N (%)	Placebo N (%)
Randomized	303 (100.0)	293 (100.0)	297 (100.0)	302 (100.0)
Completing Study	241 (79.5)	229 (78.2)	234 (78.8)	266 (88.1)

Patients actually enrolled in this study had a mean (± standard deviation) baseline Mini-Mental Status Examination score in each treatment group as follows.

Treatment Group	Mini-Mental Status Examination score at baseline Mean (SD)
Exelon® 20 cm^2	16.6 (2.9)
Exelon® 10 cm^2	16.6 (3.1)
Exelon® Capsule	16.4 (3.1)
Placebo	16.4 (3.0)

The number and proportion of patients in each of the three Exelon® groups in whom the mode dose during the maintenance period was the target dose was as follows.

Treatment Group	Number and proportion of patients in each group in whom mode Exelon® dose was target dose
Exelon® 20 cm²	165 (62.7)
Exelon® 10 cm²	206 (85.5)
Exelon® Capsule	163 (65.2)

The mean change from baseline to Week 24 in the ADAS-Cog was -1.6, -0.6, and 1.0 in the Exelon® 20 cm^2, Exelon® 10 cm^2, and placebo groups, respectively.

The mean ADCS-CGIC score at Week 24 was 4.0, 3.9, and 4.2, in the Exelon® 20 cm^2, Exelon® 10 cm^2, and placebo groups, respectively. The results of the categorical analysis are described in full in the submission.

At Step 1 of the FDA-required primary efficacy analysis (the comparison of the 20 cm^2 Exelon® patch with placebo), the p-values were < 0.001 and 0.054 for the ADAS-Cog change from baseline score at Week 24 and the ADCS-CGIC rating at Week 24, respectively. As noted earlier, the primary efficacy analysis was performed on the ITT-LOCF dataset; the sponsor pointed out that although the analysis of the ADCS-CGIC at Week 24 at Step 1 using that dataset yielded a p-value that was marginally exceeded the pre-specified alpha of 0.05, supportive analyses of this measure at Week 24 using two other pre-specified datasets - ITT **plus retrieved dropouts with LOCF as the means of imputation; observed cases –** yielded p-values that were < 0.05. These results were considered to provide substantial evidence of the superiority of the 20 cm^2 patch over placebo and sufficient for the sponsor to proceed to Step 2.

At Step 2 of the FDA-required primary efficacy analysis (the comparison of the 10 cm^2 Exelon® patch with placebo), the p-values were 0.005 and 0.010 for the ADAS-Cog change from baseline score at Week 24 and the ADCS-CGIC rating at Week 24, respectively. These results were considered to demonstrate the superiority of the 10 cm^2 patch over placebo.

The analysis of the intent-to-treat plus retrieved dropouts, and intent-to-treat observed cases datasets were judged to be consistent with those of the primary efficacy analysis above for the ADAS-Cog change from baseline score, and, as already mentioned, for the ADCS-CGIC, both at Week 24.

No treatment differences that were even nominally statistically significant were seen when the 20 cm^2 and 10 cm^2 Exelon® patches were compared with placebo on the change from baseline to Week 24 in the Neuropsychiatry Inventory and Ten-Point Clock Test scores; such differences were however seen on the Mini-Mental Status Examination and Trailmaking Test A change scores.

Reviewer's Conclusion

The results of this study do provide evidence of the efficacy of both the 10 cm^2 Exelon® patches in comparison with placebo, b(4

b(4

Safety

The safety data contained in this application were derived from the following sources:

- The single randomized, double-blind, placebo-controlled, parallel-arm study /13D2320, also referred to as Study 2320 b(4
- The completed uncontrolled open-label extension to Study 2320, also referred to as 2320E1
- **Smaller, open-label, uncontrolled Phase II trials in patients with Alzheimer's** Disease
- Clinical pharmacology studies in healthy subjects

Safety assessments in these trials including the following: adverse events, vital signs, electrocardiograms, and formal assessments of skin irritation at the site of patch application.

In Study 2320, the qualitative spectrum of adverse events in patients administered the transdermal formulation of Exelon® was no different from that seen with the capsule formulation (with the exception of application site reactions). The incidence of specific, common, mainly gastrointestinal, adverse events was higher in those assigned to the 20 cm^2 patch than in those assigned to the 10 cm^2 patch (for example, the incidence of nausea and vomiting were about 21% and 19%, respectively, in those assigned to the 20 cm^2 patch, as compared with 7% and 6%, respectively, in those assigned to the 10 cm^2 patch); at the same time, the incidence of such adverse events seen in patients receiving the 20 cm^2 patch was similar to that seen in those receiving the capsule formulation in a dose of 6 mg BID. The transdermal formulation of Exelon® was tolerated well at the site of skin application and its adhesiveness was satisfactory.

The spectrum of adverse events in the uncontrolled, open-label extension trial 2320E1 and in other trials conducted with the transdermal formulation of Exelon® **in Alzheimer's Disease was also similar to** those seen with similar trials of the capsule formulation of Exelon® (again, with the exception of application site reactions): many of the events seen appeared to be incidental illnesses common in this population.

Adverse events and other safety abnormalities seen in clinical pharmacology trials of transdermal Exelon® conducted in healthy subjects were largely minor and/or consistent with the cholinomimetic effects of rivastigmine.

The extent of exposure (during this development program) to transdermal formulations of Exelon® at the doses proposed for marketing, in patients with **Alzheimer's Disease, appears to be adequate for a new drug formulation of a** molecular entity that is already marketed.

Pharmacokinetics

The patch sizes for the transdermal Exelon® formulation proposed for marketing and their rivastigmine content are in the table below

Rivastigmine patch size	Rivastigmine content
5 cm^2	9 mg
10 cm^2	18 mg

b(4)

Key pharmacokinetic data for the Exelon® patch formulation proposed for marketing are as follows, according to the sponsor.

- A T_{max} of about 8 hours at steady state
- Lower C_{max} and higher $_{AUC0-24}$, and less peak-to-trough fluctuations than the oral formulation at comparable doses
- Estimated rivastigmine release rates as follows over a 24 hour period

Rivastigmine patch size	Estimated rivastigmine release rates over 24 hours
5 cm^2	4.6 mg
10 cm^2	9.5

b(4)

- Less metabolism of rivastigmine to its principal metabolite NAP226-90 with the patch formulation than at comparable doses of the oral formulation
- Elimination half-life for rivastigmine ranging from 2.2 to 3.9 hours after patch application versus 1.4 hours after oral or intravenous administration
- Highest exposure with patch application to the upper back, chest, or upper arm.

[Please also refer to the Agency Clinical Pharmacology review of this application].

Efficacy And Safety Of Transdermal Formulation Of Exelon® In Dementia Associated With Parkinson's Disease

Evidence In Favor Of The Efficacy And Safety Of Transdermal Formulation Of Exelon® In Dementia Associated With Parkinson's Disease

The sponsor has not provided or cited data from any clinical trials of the proposed transdermal formulation of Exelon® in dementia associated with Parkinson's Disease but has presented an argument in favor of the approval of the same formulation for that indication that may be summarized as follows.

- A transdermal formulation of Exelon® will serve an unmet medical need for patients with dementia associated with Parkinson's Disease, such as patients with impaired swallowing.

- The efficacy and safety of Exelon® immediate-release capsules in the treatment of dementia associated with Parkinson's Disease has been demonstrated previously.

- The current submission indicates that the 10 cm^2 ——— Exelon® patches have efficacy and safety in the treatment of mild to moderate Alzheimer's Disease, as demonstrated by the results of Studies 2320 and 2320E1. b(4)

- A pharmacokinetic study in patients with mild to moderate Alzheimer's Disease has indicated that the range of exposure to rivastigmine, based on AUC_{0-24}, with the Exelon® patch sizes ranging from 5 cm^2 to 20 cm^2 encompassed that for the dose range of 6 to 12 mg/day (for Exelon® immediate-release capsules) used in Study 2311 in dementia associated with Parkinson's Disease, that was the basis for the approval of Exelon® for the treatment of that condition.

- A common cholinergic deficit underlies the cognitive, behavioral, and functional deficits seen in both Alzheimer's Disease and dementia associated with Parkinson's Disease, and the mechanism of action of rivastigmine in both conditions appears to be similar.

Reviewer's Conclusion

The sponsor has failed to provide evidence of the efficacy of Exelon® in dementia associated with Parkinson's Disease. The reasons for that conclusion may be summarized as follows.

- Dementia associated with Parkinson's Disease is pathologically distinct from Alzheimer's Disease
- It cannot be considered established that a common cholinergic deficiency state is the main pathophysiological mechanism underlying both dementia associated with Parkinson's Disease and Alzheimer's Disease; nor can it be considered established that the mechanism of action of rivastigmine in both conditions is clearly known or similar

The sponsor should be required to establish the efficacy of the transdermal formulation of rivastigmine in dementia **associated with Parkinson's Disease in a** separate randomized, double-blind controlled clinical trial prior to approval of the transdermal formulation for that indication.

Overall Conclusions

Efficacy

The efficacy of the Exelon® Patch (rivastigmine) transdermal system as a treatment for mild to moderate **dementia of the Alzheimer's** type, in patch sizes of 10 cm^2 [redacted] that nominally deliver 9.5 mg/24 hours [redacted] of rivastigmine, respectively, has been established to a sufficient degree through the submission of this application [redacted] b(4)

The efficacy of Exelon® Patch (rivastigmine) transdermal system, in any dose, as a treatment for mild to **moderate dementia associated with Parkinson's Disease** has not been established.

Safety

The safety and tolerability of Exelon® Patch (rivastigmine) transdermal system in a patch size of 20 cm^2 (nominally delivering 17.4 mg of rivastigmine every 24 hours) is comparable to that of the capsule formulation of Exelon® administered in the approved maximum dose of 6 mg BID, with a fairly high incidence of nausea and vomiting (see above). The safety and tolerability of the 10 cm^2 Exelon® patch is considerably better than the 20 cm^2 patch.

Dosage Strengths Of Exelon® Patch To Be Approved

[redacted] b(4)

only the 5 cm^2 and 10 cm^2 patches should be approved for marketing

1. Background

This New Drug Application (NDA) seeks the approval of a new transdermal formulation of Exelon® (rivastigmine tartrate) for the following two indications:

- **The treatment of mild to moderate dementia of the Alzheimer's type**
- **The treatment of mild to moderate dementia associated with Parkinson's** Disease.

In this NDA, the sponsor has sought the approval [redacted] dosage strengths of the new transdermal formulation of Exelon. These dosage strengths are summarized by patch size, nominal dose of rivastigmine delivered per 24 hours and rivastigmine content per patch, in the following table. b(4)

Exelon® Patch Size	**Rivastigmine Nominal Dose**	**Rivastigmine Content Per Patch**
5 cm^2	4.6 mg/24 hours	9 mg
10 cm^2	9.5 mg/24 hours	18 mg
[redacted]		

b(4)

Exelon® (rivastigmine tartrate) is a cholinesterase inhibitor drug initially approved by this Agency on March 21, 2000, as immediate-release capsule and oral solution formulations, for the treatment of mild to moderate dementia of the **Alzheimer's type. Please refer to the** primary reviews of NDA 20823 (for the immediate-release capsule formulation) and NDA 21025 (for the oral solution formulation), and to the current product labeling for both formulations, for full details of those applications.

The immediate-release capsule and oral solution formulations of Exelon® were also approved by this Agency for the treatment of mild to moderate dementia **associated with Parkinson's Disease** (under NDA 20823 [SE1-016] and NDA 21025 [SE1-008], respectively) on June 27, 2006.

Whereas the capsule and oral solution formulations of Exelon® have been developed under IND 35774, the transdermal formulation of Exelon® has been developed under IND 54051.

The Exelon® Patch (rivastigmine) **transdermal system is referred to – interchangeably - as the "Exelon® patch" or the "rivastigmine patch" in this** review.

2. Contents Of Submission

This New Drug Application has been submitted entirely in electronic format and is comprised of the following main elements:

- The original submission of this application (sponsor letter dated September 8, 2006) containing the following:

    - Clinical and statistical data (with Case Report Forms and Case Report Tabulations)
    - Chemistry, manufacturing, and controls data
    - Clinical pharmacology data
    - Pharmacology-toxicology data
    - Financial disclosure certification
    - Labeling
    - Other items

- The 120-Day Safety Update for this application, dated January 8, 2007

- Proposed patch, container, and carton labeling submitted on February 21, 2007

- Additional Chemistry, Manufacturing, and Controls data submitted on March 2, 2007

- Responses to requests for information from the Agency

    - Clinical pharmacology data submitted on January 22, 2007
    - Chemistry, manufacturing, and controls data submitted on May 25, 2007

3. Contents Of Review

The contents of this application will be reviewed under the following headings and in the same order as below

- History of development of current formulation of Exelon®
- Summary tables for all clinical studies conducted with transdermal Exelon®
- Efficacy outcome measures used in main controlled clinical trial of Exelon® patch **transdermal system in Alzheimer's Disease**
- Description of main controlled clinical trial of Exelon® patch transdermal system **in mild to moderate Alzheimer's Disease**
- Efficacy of Exelon® patch transdermal system in mild to moderate dementia **associated with Parkinson's Disease**
- Integrated Summary of Safety
- 120-Day Safety Update
- Summary of clinical pharmacokinetics of Exelon® patch transdermal system
- Overall summary of clinical data
- Review of labeling
- Financial disclosure certification
- Site inspection report
- Conclusions
- Recommendation

4. History Of Development of Current Formulation Of Exelon®

The IND application (#54051) for the transdermal formulation of Exelon® was originally submitted on September 8, 1997, and allowed to proceed.

An End-of-Phase II meeting to discuss the further development of this formulation was held on October 22, 2002.

A pre-NDA meeting was then held with the sponsor on November 8, 2005.

Please see the minutes of the above meetings, as well as Agency reviews of submissions under this IND for further details.

Among the agreements reached at End-of-Phase II meeting was that the Agency was prepared to accept the results of a single appropriately-designed trial of the Exelon® Transdermal System as evidence for its efficacy.

5. Summary Tables For All Clinical Studies Conducted With Transdermal Exelon

This section summarizes all clinical studies of the transdermal formulation of Exelon® that are included in this application under 2 headings.

5.1 Clinical Pharmacology Studies

These are summarized in the table below

Trial Number	N	Study Design	Treatment	Treatment Duration	Locale
Alzheimer's Disease patients					
2331	40	Open-label, 2 parallel arms	Exelon patch 5-20 cm^2 or Exelon capsule 3-12 mg/day	8 weeks	US
Healthy volunteers (HV)					
W155	20	Open-label, crossover in young HV	10 cm^2 patch	Single applications	D
W159	20	Open-label, crossover in young HV	10 cm^2 patch	Single applications	D
W160	138	Open-label, HV age 23-81 (allergic sensitization study)	10 cm^2 patch	Multiple applications	US
2332	30	Open-label, crossover in HV age 60-85	3 mg oral solution, 10 cm^2 patch	Single applications	US
2333	36	Double-blind w/placebo in HV age 18-75 (phototoxicity study)	5 cm^2 or 7.5 cm^2 patch	Single applications	US
2334	56	Double-blind w/placebo in HV age 18-75 (photoallergy study)	7.5 cm^2 patch or one-half of a 7.5 cm^2 patch	Multiple applications	US
2335	39	Open-label in young HV	5 cm^2, 7.5 cm^2, 10 cm^2, 15 cm^2 patch	Single applications	UK
2338	40	Open-label, crossover in HV age 40-80	7.5 cm^2 patch	Single applications	US
1101	24	Open-label in young HV	5 cm^2, 7,5 cm^2 and 10 cm^2 patch	Multiple applications	Japan

HV: Healthy volunteers

5.2 Phase II And III Studies In Alzheimer's Disease

These are summarized in the table below, with additional details of the protocol for the main efficacy study 2320 being outlined in a second table.

Trial Number	N	Phase	Study Design	Treatments	Treatment Duration	Locale
2320	1195	III	Double blind, randomized, placebo- and active-controlled	Target dose of Exelon 20 cm^2patch, Exelon 10 cm^2patch, Exelon 12 mg capsule, Placebo	24 weeks	Global
2320E1 (ongoing)*	871	III	Open label extension for Study 2320	Starting dose 10cm^2, Maintenance: flexible dose 5-20 cm^2	28 weeks	Global
C152	40	IIa	Open-label	Exelon patch prototype patches 2.5-30 cm^2	Up to 6 weeks	US
401	64	IIa	Open-label	Exelon patch 5-20 cm^2	6 weeks	Global
1201	64	IIa	Open-label, 2 titration schemes	Exelon patch 5-20 cm^2	24 weeks	Japan

5.2.1 Main Efficacy Study: Study [redacted]13D2320

b(4)

The protocol for the main efficacy study (also referred to as Study 2320) is further summarized in tabular form below.

Protocol #	[redacted]**13D2320**
Objective	Efficacy and safety of transdermal Exelon® in the treatment of mild-to-moderate **Alzheimer's Disease**
Design	Randomized, double-blind, placebo-controlled, parallel-arm study
Key Inclusion Criteria	Dementia of the **Alzheimer's Type by DSM IV criteria** **Probable Alzheimer's Disease** by NINCDS-ADRDA criteria Mini-Mental Status Examination score of 10-20
Dose Groups/Doses	Placebo Exelon® patch 10 cm^2 once daily Exelon® patch 20 cm^2 once daily Exelon® oral capsule 6 mg twice daily
Duration	24 weeks
Sample Size	1040 patients (260 per group)
Primary Efficacy Measures	ADAS-Cog ADCS-CGIC ADCS-ADL
Secondary Efficacy Measures	NPI MMSE Ten-Point Clock Test Trailmaking Test Part A
Safety Measures	Adverse events, vital signs, skin irritation (and adhesion) index

b(4)

Protocol #	— 13D2320
Pharmacokinetic Measures	Plasma levels of rivastigmine and NAP 226-90
Other Outcome Measures	Pharmacogenetic measures (optional) Other unspecified biomarkers
Primary Efficacy Parameters	Change from baseline to endpoint in ADAS-Cog score Change from baseline to endpoint in ADCS-ADL score ADCS-CGIC score at endpoint
Primary Efficacy Analysis	Intent-to-treat population Last-observation-carried-forward method of imputation Analysis of covariance for ADAS-Cog and ADCS-ADL Cochran-Mantel-Haenszel test for ADCS-CGIC

6. Efficacy Outcome Measures Used In Main Controlled Clinical Trial Of Exelon® Patch Transdermal System In Alzheimer's Disease

6.1 Alzheimer's Disease Assessment Scale-Cog (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.

6.2 Alzheimer's Disease Cooperative Study-Clinical Global Impression Of Change (ADCS-CGIC)

The format for this instrument consists of the assessment of a independent clinician-rater based on observation of the patient at an interview, and information provided by the caregiver. The following areas of patient functioning may have been considered: global, cognitive, behavioral and activities of daily living. A 7-point categorical rating scale is used, ranging from a score of 1 **indicating "markedly improved", to a score of 7 indicating "markedly worse", and with a score of 4 indicating "no change". This is not a standardized instrument.**

6.3 Alzheimer's Disease Cooperative Study-Activities of Daily Living (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. Each item has a score range varying from 0-3 to 0-7. Higher scores indicate better function.

6.4 Mini-Mental Status Examination (MMSE)

This is a 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.

6.5 Neuropsychiatry Inventory (NPI)

This is a validated instrument that assesses the following 10 domains (subscales), plus 2 additional newer items listed in the next paragraph: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability and aberrant motor behavior. Each domain is rated according to its frequency and severity; rating is based on interviewing a caregiver. For each domain, the score is the product of frequency and severity. The maximum total score for the 10 domains (the sum of the subscale scores) is 100 with a higher score indicating greater behavioral abnormality.

A more recent version of this measure contains 2 additional items: night-time behavior disturbances and changes in appetite and eating behaviors. Using this most recent version, the maximum total score (the sum of the subscale scores) is 144 with a higher score indicating greater behavioral abnormality

The NPI Caregiver Distress Scale (NPI-D) will also be measured. This will provide a measure of distress experienced by caregivers in relation to individual symptom domains assessed by the NPI. Each domain is rated on a scale from 0 to 5 with a higher score being indicative of a greater degree of distress.

6.6 Trailmaking Test Part A

This test is intended to assess psychomotor speed and function, as well as attention, concentration, sequencing and mental flexibility. Part A requires the connection in proper order using pencil lines between 25 encircled numbers randomly arranged on a page. Scores are determined by the time in seconds taken to complete the task; the maximum time allowed for the task is 300 seconds.

6.7 Ten-Point Clock Test

This test measures executive functioning and visuospatial skills. The patient is asked to insert, in writing, numbers in the face of a clock and then insert the hands of the clock so as to indicate a time of ten minutes after 11.

7. Description Of Main Controlled Clinical Trial (CSR /13D2320) Of Exelon® Patch Transdermal System In Mild To Moderate Alzheimer's Disease

b(4)

7.1 Study Protocol

The study protocol below is the final version, as last amended on December 2, 2005.

7.1.1 Title

A 24-Week, Multi-Center, Randomized, Double-Blind, Placebo- And Active-Controlled, Parallel-Arm Evaluation Of The Efficacy, Safety, And Tolerability Of The Once-Daily Exelon® Patch Formulation In Patients With Probable **Alzheimer's Disease (Mini-Mental Status Examination 10 – 20)**

7.1.2 Objective

7.1.2.1 Primary

To confirm the efficacy of the Exelon® patch in patients with probable **Alzheimer's Disease (Mini-Mental Status** Examination 10 to 20) by testing the following hypotheses:

- Exelon® target patch size of 20 cm^2 is superior to placebo on change from baseline at Week 24, simultaneously on the ADAS-Cog and ADCS-CGI-C.
- Exelon® target patch size of 20 cm^2 is non-inferior to Exelon® capsule target dose of 12 mg on the change from baseline at Week 24 on the ADAS-Cog
- Exelon® target patch size of 10 cm^2 is superior to placebo on change from baseline at Week 24, simultaneously on the ADAS-Cog and ADCS-CGIC
- Exelon® target patch size of 20 cm^2 is superior to placebo on change from baseline at Week 24 on the ADCS-ADL

7.1.2.2 Secondary

To explore the efficacy, safety, and tolerability of Exelon® patch and capsules in **patients with probable Alzheimer's Disease** (Mini-Mental Status Examination 10 to 20) by testing the following hypotheses:

- Exelon® target patch size (10 cm^2 and 20 cm^2) and Exelon® capsules are superior to placebo on change from baseline at Week 24 on
  - Caregiver-based activities of daily living (ADCS-ADL)

- Behavioral symptoms (Neuropsychiatry Inventory)
- Brief, global cognitive testing (Mini-Mental Status Examination)
- Executive function (Ten-point clock test)
- Attention (Trailmaking Test Part A)
- Caregiver satisfaction/preferences

- Exelon® target patch size of 20 cm^2 is superior to Exelon® capsule target dose of 12 mg on change from baseline at Week 24 on the ADAS-Cog, if non-inferiority has been demonstrated on the second primary objective.

- Exelon® patch and Exelon® capsule have comparable safety over 24 weeks of planned exposure, as measured by the incidence of adverse events, serious adverse events, and changes in vital signs. The Exelon® 10 cm^2 patch/day has superior tolerability to Exelon® capsules (12 mg/day) over 24 weeks of planned exposure, as measured by the incidence of gastrointestinal adverse events (particularly nausea and vomiting), the degree of burden (severity x incidence) of gastrointestinal adverse events (nausea and vomiting) and discontinuations due to gastrointestinal adverse events.

- A[redacted]sizes of Exelon® patches (5, 10 [redacted] cm^2) have acceptable adhesion and skin irritation over 24 weeks of planned exposure. b(4)

- To collect pharmacokinetic information in Alzheimer's Disease patients receiving various patch sizes, using sparse sampling

- Pharmacogenetics: To explore whether individual genetic variation at the DNA level confers differential response to Exelon®. These include genetic factors that may relate to Alzheimer's Disease itself, predict response to treatment, predict susceptibility to drug-drug interactions, and predict genetic predisposition to clinically relevant or significant side effects

- Biomarkers: To conduct exploratory assays for novel proteins and other non-genetic elements of blood and urine that are associated with treatment response, or are possible correlates of disease severity or disease progression.

- To evaluate the safety and tolerability of Exelon® patch for up to 28 weeks of open-label treatment in patients with probable Alzheimer's Disease (Mini-Mental Status Examination score 10 to 20) who have completed the double-blind treatment phase of the study.

7.1.3 Design And Dosage

This was to be a randomized, double-blind, placebo- and active-controlled, parallel- and four-arm, fixed-dose study.

The study was to have 4 treatment arms, as follows:

- Placebo
- Exelon® patch 10 cm^2 once daily
- Exelon® patch 20 cm^2 once daily
- Exelon® oral capsule 6 mg twice daily

Patients were to be titrated to their target (or maximum-tolerated) dose of Exelon® patch or oral capsule as follows:

- There were four consecutive ascending dose levels as indicated in the following table

Dose Level (DL)	Exelon® Patch	Exelon® Capsule
1	5 cm^2 QD	1.5 mg BID
2	10 cm^2 QD	3.0 mg BID
3	15 cm^2 QD	4.5 mg BID
4	20 cm^2 QD	6.0 mg BID

- Increases in dose were to be made every 4 weeks until the target dose or maximum-tolerated dose was reached.

Additional items of information are below.

The quantity of rivastigmine loaded in a single patch of each size was depicted in the table below.

Patch Size	Quantity of rivastigmine per patch
5 cm^2	9 mg
10 cm^2	18 mg
[redacted]	[redacted]

b(4)

According to the sponsor, modeling data that included information from studies conducted with the same transdermal formulation of Exelon® and from studies with the capsule formulation suggested that:

- Exposure (AUC_{0-24}) with the 10 cm^2 patch is approximately equivalent to the capsule formulation administered in a daily dose of 7 to 8 mg

- Exposure (AUC_{0-24}) with the 20 cm^2 patch is approximately equivalent to the capsule formulation administered in a daily dose of 12 mg

Dose level adjustments were permitted during the maintenance period, in the event of poor tolerability in an effort to keep the patient on study drug. These were as follows (after the investigator had ensured that the patient is taking the capsule form of the study drug with meals)

- If tolerability was poor, the patch was to be removed and all doses of study drug avoided on the same and succeeding day(s), as recommended by the investigator

- Tolerability was to be re-evaluated after the recommended doses had been avoided. If the patient was better, and doses had been missed for ≤ 3 days, treatment could be restarted at the same dose level. If there remained concerns about the tolerability of the same dose level, treatment could be recommenced at the next lower dose level

- Titration could then be resumed using the same schedule, and doses could then be withheld if the drug was again poorly tolerated; if after the recommended period of dosage interruption, **the patient's ability to tolerate** the same dose was in question, study drug could be recommenced at the next lower dose level.

- Further attempts to titrate the dose upward could be made at the **investigator's discretion** (it was not necessary to achieve the target dose if that dose could not be tolerated)

- If a patient had not reached the target dose during the titration period, and if tolerability permitted, the investigator could resume titration during the maintenance period. However, if attempts to increase the dose were poorly tolerated, the previous highest well-tolerated dose level was to be resumed, and further dose increases avoided.

- Dose level decreases on account of poor tolerability are permitted at any time during the maintenance period.

Steps to be taken if dose interruption occurs on consecutive days were highlighted in the following sponsor table.

Consecutive Days Missed	Reason	Action
≤ 3	Any	Continue at the same DL, or restart at the next lower DL.
> 3	Tolerability problems	Retitrate starting at DL 1. Depending on past tolerability, dose increases may be performed at a minimum of 2-week interval
> 3	Other problem (e.g., medication not taken during a trip or patient illness)	Retitrate starting at DL 1 or restart at the next lower DL, depending on previous tolerability. Dose increases may be performed at a minimum of 2-week interval

The overall study design is also summarized in the following figure which I have copied from the submission

Phase	**Pre-Randomization**		**Double-blind Treatment**				
			Exelon® Patch, Capsule or Placebo				
Period	Screening	Baseline*	Titration Period				Maintenance**
Week	Wk -4 to -1	Wk 0	1-4	5 - 8	9 - 12	13 -16	17-24
Visit	V1	V2	V3	V4	V5	V6	V7 or PD
Treatment	None		**Group A:** Exelon® patch titrated from 5 to 10 cm^2 patch size				10 cm^2 Exelon® patch size
			Group B: Exelon® patch titrated from 5 to 10, 15, and 20 cm^2 patch size				20 cm^2 Exelon® patch size
			Group C: Exelon® capsule titrated from 3 to 6, 9 and 12 mg/d				12 mg/d Exelon® capsule
			Group D: Placebo				Placebo

* Study medication will be started on the day after the baseline visit

** The maintenance dose is defined as the target patch size for the treatment group or the highest well-tolerated dose for each individual patient.

PD: Premature discontinuation

The period of double-blind treatment was to be followed by a 28-week period of open-label treatment (extension protocol) in all patients who had previously completed the double-blind phase. The extension protocol would involve 12 weeks of dose titration and 16 weeks of maintenance treatment. All patients entering the extension study were to receive the patch only and were to be titrated to their maximum tolerated dose using the same titration schedule used for the double-blind phase.

7.1.3.1 Blinding

Study blinding was to be maintained to the extent possible by the scheme outlined in the following table

Phase	Pre-Randomization		Double-blind Treatment				
Period	SCR	BL	Titration				Maintenance
Week	-4 to -1	0	1-4	5-8	9-12	13-16	17-24
Visit	V1	V2	V3	V4	V5	V6	V7 or PD
Dose level (DL)*			DL1	DL2	DL3	DL4	DL4
Group A Exelon® 10 cm^2 patch			5 cm^2 Patch and PC	10 cm^2 Patch and PC	10 cm^2 Patch and PC	10 cm^2 Patch and PC	10 cm^2 Patch and PC
Group B Exelon® 20 cm^2 patch			5 cm^2 Patch and PC	10 cm^2 Patch and PC	15 cm^2 Patch and PC	20 cm^2 Patch and PC	20cm^2 Patch and PC
Group C Exelon® 12 mg/day capsules			1.5 mg BID Capsules and 5 cm^2 PP	3 mg BID Capsules and 10 cm^2 PP	4.5 mg BID Capsules and 10 cm^2 PP	6 mg BID Capsules and 10 cm^2 PP	6 mg BID Capsules and 10 cm^2 PP
					OR		
					4.5 mg BID Capsules and 15 cm^2 PP	6 mg BID Capsules and 20 cm^2 PP	6 mg BID Capsules and 20 cm^2 PP
Group D Placebo			PC and 5 cm^2 PP	PC and 10 cm^2 PP	PC and 10 cm^2 PP	PC and 10 cm^2 PP	PC and 10 cm^2 PP
					OR		
					PC and 15 cm^2 PP	PC and 20 cm^2 PP	PC and 20 cm^2 PP

PP: Placebo Patch PC: Placebo capsules

As the sponsor acknowledged, patients assigned to the 10 cm^2 Exelon® or placebo patch would still be distinguishable from those wearing the 20 cm^2 Exelon® or placebo patch. However, the sponsor believed that blinding would have been enhanced by equal distribution of the target patch sizes within Groups C and D, i.e., 50% of those in each of these groups would have been randomized to the 20 cm^2 (placebo) patch and 50% to the 10 cm^2 (placebo) patch.

[The sponsor had pointed out earlier that perfectly double-blind treatment will require each patient to wear 2 patches daily, an inconvenience that would, it was believed, interfere with compliance].

7.1.3.2 Site Of Patch Application

The patch was to be applied to the scapular area.

7.1.4 Duration

24 weeks of double-blind parallel-arm treatment

7.1.5 Sample Size

1040 patients randomized equally to the 4 treatment groups (260 patients per group).

7.1.6 Selection

7.1.6.1 Key Inclusion Criteria

- Male or female
- Age: 50-85 years
- **Dementia of the Alzheimer's Type by DSM IV criteria**
- **Probable Alzheimer's Disease by** NINCDS-ADRDA criteria. The brain imaging procedure (CT scan or MRI) used to establish that these criteria have been met must have been done within 1 year prior to randomization.
- Mini-Mental Status Examination score of 10-20
- If female, must be surgically sterile or at least one year post-menopausal
- Sufficient education to read, write, and communicate effectively during the pre-morbid state
- Reliable caregiver
- Written informed consent from patient, legal representative (if applicable), and witness (if applicable)
- Capable of complying with the requirements of the study

7.1.6.2 Key Exclusion Criteria

- Any advanced, severe or unstable disease that could interfere with study evaluations or put patient at special risk
- Any disability that interferes with completion of study requirements
- Any medical or neurological condition, other **than Alzheimer's Disease,** that could explain **the patient's dementia**
- Current diagnosis of possible or probable vascular dementia (NINDS-AIREN criteria)
- Score of > 4 on the modified Hachinski Ischemic Scale
- Active uncontrolled peptic ulceration, or gastrointestinal bleeding, within the previous 3 months

- Bradycardia (< 50 beats per minute), sick sinus syndrome, conduction deficits (S-A block, second or third degree A-V block)
- Clinically significant urinary tract obstruction
- Severe or unstable cardiovascular disease
- Current diagnosis of acute, severe, or unstable obstructive lung disease
- A history within the past year or current diagnosis of cerebrovascular disease
- Score of > 4 on the modified Hachinski Ischemic Scale
- Current diagnosis of active, uncontrolled seizure disorder
- Current DSM-IV diagnosis of major depression; patients may be included if currently on antidepressant therapy that does not have anticholinergic effects, have improved and are stable for at least 4 weeks.
- Any other DSM-IV Axis I **diagnosis that may interfere with the patient's** response to study medication, including other primary degenerative dementia, schizophrenia or bipolar disorder
- A known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to rivastigmine or other cholinergic compounds
- History of allergy to topical compounds containing Vitamin E
- Current diagnosis of an active skin disorder or lesion that would prevent accurate assessment of the adhesion and skin irritation potential of the patch
- Previous lack of efficacy with cholinesterase inhibitors
- Use of any of the following substances prior to randomization:
    - Any investigational drug during the 4 weeks prior to screening
    - A drug or treatment known to cause major organ toxicity during the previous 4 weeks
    - Hypnotics including zolpidem or zopiclone within the previous 24 hours, unless chronic stable doses of these medications were to be used.

- **Approved or unapproved cholinesterase inhibitors, "other approved treatments for Alzheimer's Disease," or memantine during the previous 4** weeks.
- Succinylcholine-type muscle relaxants during the two weeks prior to randomization
- Centrally-acting anticholinergic drugs during the preceding 4 weeks
- Selegiline during the previous 4 weeks
- Peripherally-acting anticholinergics, not taken at a stable dose, within the previous 4 weeks
- Any new psychotropic medication, or dopaminergic agent or any psychotropic medication or dopaminergic agent not taken at a stable dose during the previous 4 weeks
- Lithium during the past 2 weeks

7.1.6.3 Concomitant Medications

See Section 7.1.6.2.

7.1.7 Schedule

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

Phase		Pre-Randomization		Double- Blind Treatment				
Period	C[a]	SCR	BL	Titration				Maintenance
Visit Week		-4 to -1	0	1-4	5-8	9-12	13-16	17-24
Visit		V1	V2	V3	V4	V5	V6	7* or PD
Screening Information								
Screening Log / Informed Consent	S	X						
Inclusion/exclusion Criteria	S	X	X					
DSM-IV / Criteria for dementia of the Alzheimer's type	S	X	X					
NINCDS/ADRDA Criteria for Probable AD	S	X	X					
MRI / CT Scan	S	X						
MHIS	S	X						
Lab. Diagnostic Screening Tests	D	X						
ECG	~~S~~ D	X						X
Physical and Neurological Exam	S[b]	X	X[d]					
Demographic/Baseline Charac.								
Demography and Background Info.	D	X						
Medical History/Current Conditions	D	X	X					
Treatment Assessments								
Drug Dispensing Label	S		X	X	X	X	X	
Dosage Administration Record	D			X	X	X	X	X
Prior/conc. Medications/CNS Related	D	X	X	X	X	X	X	X
Treatment compliance	S			X	X	X	X	X
Efficacy Assessments								
ADAS-Cog	D[c]	X	X				X	X
ADCS-CGIC	D		X				X	X
ADCS-ADL	D		X				X	X
NPI (including NPI-D)	D		X				X	X
MMSE	D[c]	X	X				X	X
Ten Points Clock Test	D		X				X	X
Trail Making Test (Part A)	D		X				X	X
Safety Assessment								
Adverse Events	D			As needed				
Serious AE's	D	As needed						
Vital Signs	D	X	X	X	X	X	X	X
Laboratory Tests	D	X	X[d]					
Skin Irritation and Adhesion								
Patch Adhesion Assessment	D			X	X	X	X	X
Skin Irritation Assessment	D			X	X	X	X	X
Other								
ADCPQ Satisfaction/Preference	D		X		X			X
Pharmacokinetic Sample	D							X
Pharmacogenetic Sample	D	X[e]						
Biomarker Samples	D	X[e]						X[e]
Study Completion Form	D							X

* C: Category. This indicates whether the data are entered into the database (D) or remain in source documents only (S).
[b] Clinically significant abnormalities should be captured in the database on the Current Medical Conditions eCRF.
[c] These assessments are performed at screening for eligibility and /or to familiarize the patient with the assessments; the result at screening is not recorded in the database.
[d] Reported only if clinical abnormalities are present at the screening period.
[e] Pharmacogenetic and Biomarker sampling will only be performed once a separate informed consent for each sampling has been signed.

7.1.8 Outcome Measures

7.1.8.1 Primary Efficacy Measures

- ADAS-Cog
- ADCS-CGIC
- ADCS-ADL

7.1.8.2 Secondary Efficacy Measures

- NPI
- MMSE
- Ten-Point Clock Test
- Trailmaking Test Part A

7.1.8.3 Safety Measures

Adverse events, vital signs, electrocardiograms

7.1.9 Skin Irritation And Adhesion

- Skin irritation assessment (see below)

Investigator's rating

With the following scale in hand, please select the most appropriate overall description of the skin irritation on the side last used for the patch application.

Select the most appropriate rating for each sign of irritation

Erythema	0 = No erythema 1 = Very slight erythema (diffuse, barely visible) 2 = Mild erythema (well defined, locally restricted) 3 = Moderate erythema (red) 4 = Severe erythema (strong fiery-red)
Edema	0 = No edema 1 = Very slight edema (barely visible) 2 = Mild edema (skin elevated <1 mm) 3 = Moderate edema (skin elevated ~1 mm) 4 = Severe edema (skin raised >1 mm)
Scaling	0 = No scaling 1 = Dryness, glossy effect 2 = Mild fine scaling 3 = Moderate scaling 4 = Severe scaling
Fissures	0 = No fissures 1 = Very superficial, epidermal small fissures 2 = Single or some deep wide fissures 3 = Deep fissures with bleeding
Pruritus	0 = Negative 1 = Very slight reaction 2 = Mild reaction 3 = Moderate reaction 4 = Severe reaction
Pain, stinging and/or burning	0 = There was No pain, stinging and/or burning 1 = There was Very slight reaction 2 = There was Mild reaction 3 = There was Moderate reaction 4 = There was Severe reaction

Caregiver's rating

With the following scale in hand, please select the most appropriate description of the skin irritation of the patch since the last visit.

Redness	0 = Not present 1 = Mild 2 = Moderate 3 = Severe
Swelling	0 = Not present 1 = Mild 2 = Moderate 3 = Severe
Itching	0 = Not present 1 = Mild 2 = Moderate 3 = Severe
Pain, stinging and/or burning	0 = Not present 1 = Mild 2 = Moderate 3 = Severe

- Skin adhesion: caregiver-rated patch adhesion scale (see below)

With the following scale in hand, please select the most appropriate response describing how most of the patches looked immediately before you removed them in the morning: On most mornings: 0= The patch remained completely on 1= The edges of the patch were lifting off 2= The patch was mostly half off 3= The patch was just hanging on 4= The patch was completely detached

7.1.9.1 Pharmacokinetic Measures

Plasma levels of rivastigmine and NAP 226-90 (the principal metabolite of rivastigmine)

7.1.9.2 Pharmacogenetic Measures (Optional)

Genetic markers (or polymorphisms) to be studied included those for the **following: etiology of Alzheimer's** Disease; mechanism of action of the rivastigmine patch; possible adverse events associated with the rivastigmine patch; and absorption, distribution, metabolism, and excretion of the rivastigmine patch.

7.1.9.3 Other Biomarkers (Optional)

- Profile of proteins and peptides in serum and urine (not further specified)
- Profile of metabolites (including carbohydrates and lipids) in serum and urine

7.1.9.4 Health-Related Quality Of Life Measure

The Alzheimer's Disease Caregiver Preference Questionnaire (ADCPQ) is a measure that was intended to evaluate caregiver acceptance, preference, and satisfaction for a patch and capsule formulation at different timepoints during the study. It was developed specifically for, and will be validated in, this study.

7.1.10 Safety Monitoring

Adverse events, vital signs, skin irritation assessment

7.1.11 Analysis Plan

7.1.11.1 Study Populations

7.1.11.1.1 Intent-To-Treat

All randomized patients who receive at least one dose of study medication and have at least a pre- and post-baseline assessment for one of the primary efficacy variables.

7.1.11.1.2 Intent-To-Treat With Retrieved Dropouts

All randomized patients who received at least one dose of study medication and have at least a pre- and post-baseline assessment for one of the primary efficacy variables.

7.1.11.1.3 Safety

All randomized patients who received at least one dose of study medication and had at least one safety assessment following baseline.

7.1.11.2 Demographic And Other Baseline Characteristics

Data for these characteristics were to be presented by treatment group and country using summary statistics.

7.1.11.3 Exposure To Study Drug, Compliance, And Concomitant Medications

These data were to be presented using summary statistics.

7.1.11.4 Primary Efficacy Analysis

Two separate types of primary efficacy analysis were stipulated a priori by the sponsor, as agreed upon at a Pre-NDA Meeting with this Division that was held on November 8, 2005.

- The first of these types of analysis addressed the original 4 study hypotheses and was planned to meet the requirements of the European Agency for the Evaluation of Medicinal Products (EMEA). This type of analysis is described **below under the heading "Original Proposed Primary Efficacy Analysis"**

- **The second type of primary efficacy analysis was designed to meet this Agency's** requirements for approval and addressed only two of the 4 original study hypotheses. This type of analysis is described below under the heading **"Alternative Primary Efficacy Analysis" in bold font**

7.1.11.4.1 Originally Proposed Primary Efficacy Analysis

As noted earlier, this analysis was planned so as to meet the requirements of the EMEA.

7.1.11.4.1.1 Original Study Hypotheses

Four study hypothesis were to be evaluated in the same numerical order as below.

7.1.11.4.1.1.1 First Study Hypothesis

This (superiority) hypothesis involved the comparison of the 20 cm^2 Exelon® patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 20 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.

7.1.11.4.1.1.2 Second Study Hypothesis

This (non-inferiority) hypothesis was to compare the 20 cm^2 Exelon® patch and Exelon® capsule groups on the ADAS-Cog to demonstrate that the 20 cm^2 patch is non-inferior to Exelon® capsules at the 6 mg BID dose.

7.1.11.4.1.1.3 Third Study Hypothesis

This (superiority) hypothesis involved the comparison of the 10 cm^2 Exelon® patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 10 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.

7.1.11.4.1.1.4 Fourth Study Hypothesis

This superiority hypothesis involved the comparison of the 20 cm^2 Exelon® group with placebo on the ADCS-ADL to demonstrate superiority of the 20 cm^2 Exelon® group over placebo.

7.1.11.4.1.2 Strategy For Confirmatory Testing Of Each Study Hypothesis

According to the sponsor, since the study hypotheses were arranged in order a priori, and as both primary efficacy parameters were be tested simultaneously for the superiority hypotheses, no correction of Type I error was required for testing each hypothesis (i.e., a Type I error of 0.05 [2-sided] could be used to test each hypothesis).

The steps to be taken in the testing process were to be as follows:

Step 1. The superiority of the 20 cm^2 Exelon® patch over placebo was to be demonstrated simultaneously for both primary efficacy variables, the ADAS-Cog and ADCS-CGIC. If for both treatment comparisons, the corresponding 2-sided p-values were less than 0.05, then the superiority of the 20 cm^2 Exelon® patch over placebo was to be regarded as confirmed and it would then be possible to

proceed to Step 2. Otherwise the testing procedure was to be stopped, and none of the confirmatory hypotheses established

Step 2. The non-inferiority of the 20 cm^2 Exelon® patch over Exelon® capsules was to be demonstrated on the ADAS-Cog. If the lower bound of the 2-sided 95% confidence interval for the difference between treatment groups was greater than -1.25, then non-inferiority of the 20 cm^2 Exelon® patch over placebo was to be assumed and it was then to be considered possible to proceed to Step 3. Otherwise the testing procedure was to be stopped, and no further confirmatory hypothesis considered capable of being established.

Step 3. The superiority of the 10 cm^2 Exelon® patch over placebo was to be demonstrated simultaneously for both primary efficacy variables, the ADAS-Cog and ADCS-CGIC. If for both treatment comparisons, the corresponding 2-sided p-values are less than 0.05, then the superiority of the 10 cm^2 Exelon® patch over placebo was to be regarded as confirmed and it would then be possible to proceed to Step 4. Otherwise the testing procedure was to be stopped, and no further confirmatory hypothesis considered capable of being established.

Step 4. The superiority of the 20 cm^2 Exelon® patch over placebo was to be demonstrated for the secondary efficacy variable, the ADCS-ADL. If for this comparison, the corresponding 2-sided p-value was less than 0.05, then the superiority of the 20 cm^2 Exelon® patch over placebo was to be confirmed for this measure. Otherwise the testing procedure was to stop, and the fourth confirmatory hypothesis considered not capable of being established.

7.1.11.4.1.3 Summary Of Hypothesis Testing

The hypotheses and variables for individual treatment comparisons as described above has been summarized in the following table, which I have copied from an earlier submission.

	Variables for individual comparisons			Simultaneous testing required
Hypothesis	**ADAS-Cog**	**ADCS-CGIC**	**ADCS-ADL**	
1 Exelon 20 cm^2 vs Placebo -superiority	X	X	—	X
2 Exelon 20 cm^2 vs Exelon capsules - non-inferiority	X	—	—	—
3 Exelon 10 cm^2 vs Placebo - superiority	X	X	—	X

	Variables for individual comparisons			Simultaneous testing required
Hypothesis	ADAS-Cog	ADCS-CGIC	ADCS-ADL	
4 Exelon 20 cm^2 vs Placebo - superiority for ADCS-ADL	___	___	X	___

7.1.11.4.2 Alternative Primary Efficacy Analysis

The primary efficacy analysis method described below was performed to be consistent with this Agency's criteria for determining the efficacy of drugs intended for the treatment of Alzheimer's Disease. Two hypotheses (the same as Hypotheses 1 and 3 of the original four hypotheses) were to be assessed.

The two hypotheses, and the sequence in which they were to be addressed as part of this alternative analysis strategy, are described below.

7.1.11.4.2.1 Alternative Hypotheses

Two hypothesis were to be evaluated in the same numerical order as below.

7.1.11.4.2.1.1 First Study Hypothesis

This (superiority) hypothesis involved the comparison of the 20 cm^2 Exelon® patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 20 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.

7.1.11.4.2.1.2 Second Study Hypothesis

This (superiority) hypothesis involved the comparison of the 10 cm^2 Exelon® patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 10 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.

7.1.11.4.2.2 Strategy For Confirmatory Testing Of Each Alternative Study Hypothesis

Since the study hypotheses were arranged in order a priori, and as both primary efficacy parameters were be tested simultaneously, no correction of Type I error was considered required for testing each hypothesis (i.e., a Type I error of 0.05 [2-sided] could be used to test each hypothesis).

The steps to be taken in the testing process were to be as follows:

Step 1. The superiority of the 20 cm^2 Exelon® patch over placebo was to be demonstrated simultaneously for both primary efficacy variables, the ADAS-Cog and ADCS-CGIC. If for both treatment comparisons, the corresponding two-sided p-values were less than 0.05, then the superiority of the 20 cm^2 Exelon® patch over placebo was to be regarded as confirmed and it would then be possible to proceed to Step 2. Otherwise the testing procedure was to be stopped, and neither of the confirmatory hypotheses considered established

Step 2. The superiority of the 10 cm^2 Exelon® patch over placebo was to be demonstrated simultaneously for both primary efficacy variables, the ADAS-Cog and ADCS-CGIC. If for both treatment comparisons, the corresponding two-sided p-values were less than 0.05, then the superiority of the 10 cm^2 Exelon® patch over placebo was to be regarded as confirmed. Otherwise the superiority of the 10 cm^2 Exelon® patch over placebo would not be regarded as having been established.

7.1.11.4.3 Statistical Models For Primary Efficacy Analysis

- The statistical methods described below were intended to apply to both sequences of hypothesis testing alluded to earlier.

- Each study hypothesis above, whether one of the original 4 study hypotheses or part of the alternative strategy, was to be tested at a two-sided alpha level of 0.05

- The population for the primary efficacy analysis was to be the intent-to-treat last-observation-carried-forward population

- The primary analysis of cognitive function was to be based on the change from baseline score for the ADAS-Cog. 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 the baseline total ADAS-Cog score

- The primary analysis for the ADCS-CGIC was to be a treatment comparison using a Cochran-Mantel-Haenszel test with modified ridit scores with country as stratification variable

- The primary analysis of activities of daily living was to be based on the change from baseline in the total ADCS-ADL score. The statistical method used was to be the same as that for the ADAS-Cog

- For each superiority hypothesis, the corresponding confirmatory statistical analysis was to be performed and the two-sided p-value for the difference between treatment groups was to be calculated

- For the non-inferiority hypothesis on the ADAS-Cog, the corresponding confirmatory statistical analysis was to be performed and the lower bound of the two-sided 95% confidence interval for the difference between treatment groups calculated. The non-inferiority margin for ADAS-Cog was specified 1.25 points; i.e., the hypothesis of inferiority was to be rejected if the lower bound of the 95% confidence interval was greater than the non-inferiority margin of -1.25 points

7.1.11.4.4 Handling Of Missing Values

Imputation of missing values was to be carried out at 2 levels: individual scale items and total scale scores

The following order was to be used for imputing items

- Efficacy assessments were to be allocated to the appropriate weeks/visits

- Missing scale items were to be imputed

- For scales that consist of several items, the total score was to be calculated for each visit

- Patients were to be assigned to the analysis populations

- The population-specific imputation scheme was to be applied to missing (total) scores at weeks/visits

7.1.11.4.4.1 Imputation Of Missing Individual Scale Items

The following rules were to be used

- Missing baseline items were to be imputed using the baseline mean (from all patients), rounded to the closest integer score for that individual item

- Missing post-baseline items were to be replaced with ratings from the last non-missing prior visit

- In instances where one or more specific scale items were missing at baseline and at all subsequent time points, no total score was to be calculated

These imputation schemes were to be used if at least half the items that comprised the total score were present. If more than half of these items were missing, the corresponding total score was also to be considered missing.

7.1.11.4.4.2 Missing Values For Total Scores

The following imputation schemes were be used.

7.1.11.4.4.2.1 Intent-To-Treat Last-Observation-Carried-Forward

- If available the scheduled assessment was to be used
- If missing, the immediately prior available observation, scheduled or unscheduled, was to be used. Measurements made more than 2 days after the last dose of study drug were not to be carried forward
- Evaluations made more than 2 days after the last dose of study drug were not to be included in the analysis

7.1.11.4.4.2.2 Intent-To-Treat Plus Retrieved Dropouts (Last-Observation-Carried-Forward)

- If available, the scheduled assessment was to be used
- If missing and the patient returned for an efficacy assessment, that retrieved dropout assessment was to be used.
- If no retrieved dropout assessment was available, the immediately prior available observation, scheduled or unscheduled, was to be used.

7.1.11.4.4.2.3 Intent-To-Treat Observed Cases

- No imputation was to occur under this analysis.
- Data was to be reported for all patients in the intent-to-treat population
- Evaluations done more than 2 days after the last known date of study drug would not be included in the analysis

7.1.11.5 Analyses Of Secondary Efficacy Parameters And Other Efficacy Analyses

- For all primary and secondary efficacy parameters, summary statistics were to be provided by treatment group for baseline and post-baseline evaluations for all study populations (datasets) analyzed

- For the ADAS-Cog:
    - A categorical analysis was also to be conducted to determine the percentage of patients who demonstrated a clinically significant improvement (defined as a 4-point or greater improvement from baseline); a Cochran-Mantel-Haenszel test for binary response, blocking for country, was also to be used to compare treatment groups
    - The primary and categorical analysis for this parameter were to be repeated using the retrieved dropouts and observed cases populations to investigate the sensitivity of the conclusions drawn from the primary efficacy analysis
    - A repeated measurement model was to be fitted to the observed total scores of all patients with at least a baseline or a post-baseline total score and estimates for the differences between treatment groups obtained
- For the ADCS-CGIC:
    - A proportional odds regression analysis with treatment and country as explanatory variables was to be performed
    - The ADCS-CGIC score will be dichotomized into responders versus non-responders as follows: scores of 1, 2, and 3 were to be interpreted as a positive response to study treatment; scores of 4, 5, 6, and 7 were to be interpreted as no response. The response variable was to be analyzed using a Cochran-Mantel-Haenszel test blocking for country to compare treatment groups. A logistic regression model with treatment and country as explanatory variables was also be fitted to the dichotomized data
    - The primary analysis and the analysis on dichotomized data was also to be repeated using the retrieved dropouts and observed cases populations to investigate the sensitivity of the conclusions drawn from the primary efficacy analysis
- For the ADCS-ADL:
    - The percentage of patients who showed an improvement on this score were to be compared between treatment groups using the Cochran-Mantel-Haenszel test with country as a stratification variable
    - The primary and categorical analysis for this parameter will be repeated using the retrieved dropouts and observed cases populations, to investigate the sensitivity of the conclusions drawn from the primary efficacy analysis
- For the Neuropsychiatry Inventory:
    - For the total 12-item change from baseline score, 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 the baseline total score. This analysis was to be based on the intent-to-treat last-observation carried forward population

- A dichotomous variable for the Neuropsychiatry Inventory was to be defined as follows: for every post-baseline visit, the ratio of total score (for all 12 items) for the assessment and baseline total score was to be calculated and if there was at least a 30% decrease in this score, this was to be interpreted as a positive response; otherwise, the response was to be interpreted as negative. This dichotomous variable was to be compared between treatment groups using a Cochran-Mantel-Haenszel test with country as a stratification variable

- The same analyses were to be repeated for the original 10-item Neuropsychiatry Inventory

- Change from baseline scores on the Mini-Mental Status Examination and the Ten Point Clock Test will be compared between treatment groups on the intent-to-treat last-observation-carried-forward population using the Cochran-Mantel-Haenszel test with modified ridit scores, using country as stratification

- Change from baseline scores on the Trailmaking Test Part A were to be compared between treatment groups using least square means derived from an analysis of covariance model with the following explanatory variables: treatment, country, and the baseline total Trailmaking Test Part A score

If needed, the statistical analyses for the secondary efficacy variables were to be repeated using the intent-to-treat retrieved dropouts and intent-to-treat observed cases populations to investigate the sensitivity of the conclusions drawn from the analyses performed using the intent-to-treat last-observation-carried-forward population.

7.1.11.6 Analysis Of Safety Parameters

- The safety parameters were to be adverse events, vital signs, and skin irritation index. All were to be described by treatment group using summary statistics

- Adverse events were to 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. Serious adverse events and adverse event discontinuations were to be tabulated. The occurrence of gastrointestinal adverse events (nausea and vomiting), the patient's mean daily degree of burden (defined) due to such adverse events, and discontinuations due to gastrointestinal adverse events were also to be

tabulated and analyzed using the Cochran-Mantel-Haenszel test for binary response with country as stratification to compare all treatment groups.

- For vital signs (including body weight), summary statistics were to be presented by treatment for baseline and post-baseline evaluations as well as the number and proportion of patients with clinically notable abnormalities. Clinically notable abnormalities of body weight were to be flagged in data listings

- For electrocardiograms, summary statistics will be presented by treatment for baseline and post-baseline evaluations as well as the number and proportion of patients with abnormal values. Treatment-emergent abnormalities are to be listed.

- For the skin irritation index, summary statistics were to be provided by time, treatment group and patch size using the intent-to-treat observed cases population.

7.1.11.7 Pharmacokinetic Measures

The plasma concentrations of rivastigmine and its principal metabolite, NAP 226-90, were to be provided using summary statistics.

7.1.11.8 Pharmacogenetic Measures

These analyses were to investigate the associations between genotypes and phenotypes and are further described in the submission.

7.1.11.9 Other Biomarkers

These analyses were to be done to determine if differentially expressed markers existed and if they defined treatment-relevant subgroups.

7.1.11.10 Health-Related Quality Of Life Measure

The Alzheimer's Disease Caregiver Preference Questionnaire (ADCPQ) was the measure to be used; this study was to be used to validate that measure. Summary statistics were to be presented.

7.1.11.11 Sample Size Rationale

The sample size rationale for the primary efficacy analysis is summarized below.

7.1.11.11.1 Assumptions

Assumptions on expected delta and standard deviation (SD) used for the different efficacy variables under each hypothesis are in the following table which I have copied from the submission.

	Superiority Exelon® patch 20 cm^2 over placebo		Non-inferiority Exelon® patch 20 cm^2 to capsules		Superiority Exelon® patch 10 cm^2 over placebo		Superiority Exelon® patch 20 cm^2 over placebo
Hypothesis	H1		H2		H3		H4
Efficacy variables	ADAS-Cog	ADCS-CGIC	ADAS-Cog		ADAS-Cog	ADAS-CGIC	ADCS-ADL
Delta	3.5	.4	1	0	2.5	.35	2.5
SD	7	1.2	7	7	7	1.2	10
Non-inferiority margin			1.25	1.25			

Further details are provided as to the basis for assuming the above delta and standard deviations, and non-inferiority margin. These details are as follows:

- Assumptions for the delta and standard deviation for the ADAS-Cog and ADCS-CGIC were based on 24-week studies of the efficacy of the Exelon® capsule where the ADAS-Cog and CIBIC-Plus (the latter considered similar to the ADCS-CGIC) were used as primary efficacy measures

- Assumptions for the delta and standard deviation for the ADCS-ADL were based on data from a published 5-month trial of galantamine hydrobromide

- For the non-inferiority comparison of the 20 cm^2 Exelon® patch to Exelon® capsules:

    - It was assumed that the 20 cm^2 Exelon® patch with its smoother pharmacokinetic profile would be about 1 point better on the change from baseline to endpoint in ADAS-Cog than Exelon® capsules (delta =1)

    - In a previous similarly-designed placebo-controlled study of Exelon® **capsules in Alzheimer's Disease, a treatment difference in comparison** with placebo in the ADAS-Cog change from baseline score of 2.5 points was noted. A non-inferiority margin of 1.25 points was chosen to preserve 50% of this effect

7.1.11.11.2 Calculated Sample Sizes At Various Power Estimates

This study aimed at control of the Type I error rate at the multiple alpha level of 5% and to have an overall power of at least 80% covering the first three hypotheses. Since the hypotheses were ordered a priori and since there was to be simultaneous testing of the two primary efficacy variables for the superiority hypotheses (if the hypothesis specified two comparisons), no correction of Type I error was to be required, i.e., an alpha level of 0.05 (2-sided) for superiority and non-inferiority was to be used for each individual comparison of variables. The overall power to reject the first three statistical null hypotheses was to be derived

from the product of the individual power for the single efficacy variable comparisons.

The sample size for each single efficacy variable comparison was to be based on two-sided t-tests with an individual Type I error level of 0.05. The sample size had been successively increased to 260 patients per treatment group in order to reach an overall power of 80% for the first three hypotheses. As a result, a total sample size of 1040 patients with at least one post-baseline efficacy assessment on treatment was estimated.

The individual power for the fourth hypothesis was approximately 81% with a sample size of 260 patients per treatment group.

The sample size and power for individual hypotheses and efficacy variables is also summarized in the following table, which I have copied from the submission.

	Superiority Exelon® patch 20 cm^2 over placebo		Non-inferiority Exelon® patch 20 cm^2 to capsules		Superiority Exelon® patch 10 cm^2 over placebo		Superiority Exelon® patch 20 cm^2 over placebo
Hypothesis	H1		H2		H3		H4
Efficacy variable	ADAS-Cog	ADCS-CGIC	ADAS-Cog		ADAS-Cog	ADCS-CGIC	ADCS-ADL
Delta			1	0			
n per group for 90% individual power	86	191	205	660	166	248	338
Individual power (%) with n=260 per group	99%	96%	95%	52%	98%	91%	81%

7.2 Results

This study was conducted at a total of 100 centers in 21 countries. The countries in which the study was conducted were Chile, Czech Republic, Denmark, Finland, Germany, Guatemala, Israel, Italy, Korea, Mexico, Norway, Peru, Poland, Portugal, Russia, Slovakia, Sweden, Taiwan, Uruguay, USA, and Venezuela.

7.2.1 Patient Disposition

Patient disposition is summarized in the following table, which I have copied from the submission.

Disposition/Reason	Exelon 20 cm^2 n (%)	Exelon 10 cm^2 n (%)	Exelon capsule n (%)	Placebo n (%)	Total n (%)
Total number of patients					
Screened					1464
Randomized	303 (100.0)	293 (100.0)	297 (100.0)	302 (100.0)	1195 (100.0)
Exposed to study drug	303 (100.0)	291 (99.3)	294 (99.0)	302 (100.0)	1190 (99.6)
Completed	241 (79.5)	229 (78.2)	234 (78.8)	266 (88.1)	970 (81.2)
Discontinued	62 (20.5)	64 (21.8)	63 (21.2)	36 (11.9)	225 (18.8)
Adverse event(s)	26 (8.6)	28 (9.6)	24 (8.1)	15 (5.0)	93 (7.8)
Subject withdrew consent	19 (6.3)	21 (7.2)	17 (5.7)	6 (2.0)	63 (5.3)
Unsatisfactory therapeutic effect	4 (1.3)	3 (1.0)	8 (2.7)	6 (2.0)	21 (1.8)
Lost to follow-up	4 (1.3)	3 (1.0)	5 (1.7)	3 (1.0)	15 (1.3)
Death	5 (1.7)	4 (1.4)	2 (0.7)	3 (1.0)	14 (1.2)
Administrative problems	2 (0.7)	1 (0.3)	4 (1.3)	2 (0.7)	9 (0.8)
Protocol violation	2 (0.7)	3 (1.0)	2 (0.7)	1 (0.3)	8 (0.7)
Abnormal laboratory value(s)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Subject's condition no longer required study drug	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

As the table indicates, the highest proportion completing the study was in the placebo group. Adverse events were the most common reason for treatment discontinuation.

7.2.2 Protocol Deviations

The incidence of protocol violations in each treatment group is summarized in the following table; the incidence of such violations was least in the placebo group, and highest in the Exelon® 10 cm^2 group.

	Exelon 20 cm^2 N=303 n (%)	Exelon 10 cm^2 N=293 n (%)	Exelon capsule N=297 n (%)	Placebo N=302 n (%)	Total N=1195 n (%)
Patients with at least one protocol violation	63 (20.8)	75 (25.6)	69 (23.2)	59 (19.5)	266 (22.3)
Had at least one laboratory diagnostic test missing	21 (6.9)	16 (5.5)	18 (6.1)	18 (6.0)	73 (6.1)
Screening and baseline examination dates of MMSE were < 7 or > 28 days	16 (5.3)	26 (8.9)	19 (6.4)	12 (4.0)	73 (6.1)
Age < 50 or > 85 years	6 (2.0)	7 (2.4)	5 (1.7)	9 (3.0)	27 (2.3)
Primary efficacy parameter not assessed by certified rater	6 (2.0)	5 (1.7)	4 (1.3)	4 (1.3)	19 (1.6)
Did not have stable dose of psychotropic medication in the 4 weeks prior to randomization	5 (1.7)	9 (3.1)	13 (4.4)	10 (3.3)	37 (3.1)
MMSE score < 10 or > 20	4 (1.3)	8 (2.7)	5 (1.7)	0 (0.0)	17 (1.4)
Took only patches but no capsules for at least 2 days	3 (1.0)	1 (0.3)	4 (1.3)	0 (0.0)	8 (0.7)
Incorrect study medication taken, either dose or treatment	2 (0.7)	1 (0.3)	2 (0.7)	2 (0.7)	7 (0.6)
Had exclusionary laboratory diagnostic screening test results	1 (0.3)	5 (1.7)	6 (2.0)	4 (1.3)	16 (1.3)
Took any excluded concomitant medication prior to randomization	1 (0.3)	3 (1.0)	1 (0.3)	3 (1.0)	8 (0.7)
Took any excluded concomitant medication during the course of the study	1 (0.3)	1 (0.3)	2 (0.7)	2 (0.7)	6 (0.5)
Had no screening ECG	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.3)	3 (0.3)
Did not reside with someone in community or if living alone, had no daily contact to primary caregiver	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	2 (0.2)

7.2.3 Efficacy Evaluation

7.2.3.1 Datasets Analyzed

The number and proportion of patients in each treatment group in each analysis population is in the following table, which I have copied from the submission.

Analysis population	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 293 n (%)	Exelon capsule N = 297 n (%)	Placebo N = 302 n (%)	Total N = 1195 n (%)
All randomized (RND)	303 (100.0)	293 (100.0)	297 (100.0)	302 (100.0)	1195 (100.0)
Safety	303 (100.0)	291 (99.3)	294 (99.0)	302 (100.0)	1190 (99.6)
ITT	264 (87.1)	251 (85.7)	256 (86.2)	282 (93.4)	1053 (88.1)
ITT+RDO	279 (92.1)	267 (91.1)	275 (92.6)	289 (95.7)	1110 (92.9)

ITT: Intent-to-treat
RDO: Retrieved dropouts

A total of 11.9% (n =142) of randomized patients were not included in the intent-to-treat population. 5 of these patients were excluded from the intent-to-treat dataset on account of their never receiving study drug and 137 patients were excluded from the intent-to-treat dataset because they did not have a baseline or post-baseline efficacy assessment for at least one of the primary efficacy variables. The sponsor states that a key reason why a large number of patients

were excluded from the intent-to-treat population was because they did not have a post-baseline efficacy assessment on treatment.

7.2.3.2 Demographic And Other Baseline Characteristics

Important demographic and other baseline characteristics are summarized in the table below. As the table indicates, these variables were broadly comparable across treatment groups.

		Treatment Group			
		Exelon® 20 cm² N=303	**Exelon® 10 cm² N=291**	**Exelon® Capsule N=294**	**Placebo N=302**
Mean age (SD)		74.2 (7.7)	73.6 (7.9)	72.8 (8.2)	73.9 (7.3)
% Women		66.0	68.0	65.6	66.6
Time since first symptoms of Alzheimer's Disease [Mean in years (SD)]		3.3 (2.5)	3.3 (2.2)	3.4 (2.3)	3.5 (2.4)
Mini-Mental Status Examination score at baseline	Mean (SD)	16.6 (2.9)	16.6 (3.1)	16.4 (3.1)	16.4 (3.0)
	Range	10-24	6-24	9-26	10-20

7.2.3.3 Primary Efficacy Analysis

7.2.3.3.1 Overall Analysis Based On Two Sets Of Study Hypotheses

As noted earlier, two separate plans for the primary efficacy analysis were submitted prior to the study blind being broken. The overall results of the primary efficacy analysis, performed according to each plan, are summarized below in this section; the analysis of individual primary efficacy measures is described in the next section.

7.2.3.3.1.1 Four-Objective (Four-Hypothesis) Analysis

As noted earlier, this was the original analysis proposed for this protocol and was created to meet the requirements of the EMEA. The table below, summarizing the results of this analysis, was copied from the submission.

Objective	Variable		
	ADAS-Cog	ADCS-CGIC	ADCS-ADL
1 Superiority of Exelon 20 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	$p < 0.001$	$p = 0.054$	-
2 Non-inferiority of Exelon 20 cm^2 target patch size compared to Exelon 12 mg/day target capsules at Week 24, based on ADAS-Cog	(-2.06, 0.17)*	-	-
3 Superiority of Exelon 10 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	$p = 0.005$	$p = 0.010$	-
4 Superiority of Exelon 20 cm^2 target patch size over placebo at Week 24, based on ADCS-ADL	-	-	$p = 0.017$

* Non-inferiority established, as the 95%-confidence interval for the difference between treatment groups (a negative difference indicates greater efficacy of Exelon 20 cm^2 versus capsule) was entirely below the corresponding predefined non-inferiority margin of 1.25.

The sponsor's interpretation of the results of each step of this analysis is as follows.

7.2.3.3.1.1.1 Step 1

The objective of this step was to demonstrate the superiority of the 20 cm^2 Exelon® patch over placebo at Week 24 by simultaneous testing of the ADAS-Cog and ADCS-CGIC in the intent-to-treat last-observation-carried forward population.

On the ADAS-Cog, the 20 cm^2 Exelon® patch demonstrated a clear statistically significant superiority over placebo ($p < 0.001$).

On the ADCS-CGIC, the treatment difference between the 20 cm^2 Exelon® patch and placebo, which favored the Exelon® patch, yielded a p-value (0.054) that marginally exceeded the pre-specified value of 0.05. However, analyses of this measure using a number of pre-specified alternate datasets yielded consistently statistically significant treatment differences favoring Exelon®. Thus, there was substantial evidence for effectiveness of the 20 cm^2 Exelon® patch.

Testing was therefore continued to Step 2.

7.2.3.3.1.1.2 Step 2

Non-inferiority of the Exelon® 20 cm^2 patch over the Exelon® capsule formulation at Week 24 was established as the 95% confidence interval was below the pre-specified non-inferiority margin of 1.25. Testing therefore proceeded to Step 3.

7.2.3.3.1.1.3 Step 3

Superiority of the 10 cm^2 Exelon® patch over placebo at Week 24 was demonstrated on the both the ADAS-Cog ($p = 0.005$) and on the ADCS-CGIC ($p = 0.010$). Testing then proceeded to Step 4.

7.2.3.3.1.1.4 Step 4

Superiority of the 20 cm^2 Exelon® patch over placebo at Week 24 on the ADCS-ADL was demonstrated ($p = 0.017$).

7.2.3.3.1.2 Two-Objective (Two-Hypothesis) Analysis

As also noted earlier, this analysis was performed at the request of this Agency, based on discussions at a Pre-NDA Meeting held on November 8, 2005. The table below, summarizing the results of this analysis, was copied from the submission.

Objective	Variable	
	ADAS-Cog	ADCS-CGIC
1 Superiority of Exelon 20 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	$p < 0.001$	$p = 0.054$
2 Superiority of Exelon 10 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	$p = 0.005$	$p = 0.010$

The sponsor's interpretation of the results of each step of this analysis is as follows.

7.2.3.3.1.2.1 Step 1

As noted earlier, the objective of this step was to demonstrate the superiority of the 20 cm^2 Exelon® patch over placebo at Week 24 by simultaneous testing of the ADAS-Cog and ADCS-CGIC in the intent-to-treat last-observation-carried forward population.

As also noted earlier:

- On the ADAS-Cog, the 20 cm^2 Exelon® patch demonstrated a clear statistically significant superiority over placebo ($p < 0.001$).
- On the ADCS-CGIC, the treatment difference between the 20 cm^2 Exelon® patch and placebo, which favored the Exelon® patch, yielded a p-value (0.054) that marginally exceeded the pre-specified value of 0.05. However, analyses of this measure at Week 24, comparing the 20 cm^2 group with placebo, and using a two **pre-specified alternate datasets – intent-to-treat plus retrieved dropouts, with last-**

observation-carried-forward imputation; observed cases - yielded consistently statistically significant treatment differences favoring Exelon®; the p-values obtained were 0.034 and 0.029 for the intent-to-treat plus retrieved dropouts, with last-observation-carried-forward imputation and observed cases datasets, respectively.

- Thus, there was substantial evidence for effectiveness of the 20 cm^2 Exelon® **patch in comparison with placebo (although, as the sponsor states, "the first objective was not achieved as planned").**

Testing was therefore continued to Step 2.

7.2.3.3.1.2.2 Step 2

Superiority of the 10 cm^2 Exelon® patch over placebo at Week 24 was demonstrated on the both the ADAS-Cog (p = 0.005) and on the ADCS-CGIC (p = 0.010).

7.2.3.3.2 Analysis Of Individual Primary Efficacy Measures

7.2.3.3.2.1 ADAS-Cog

The results of analyses of this measure (change from baseline score) at Weeks 16 and 24 for the intent-to-treat last-observation-carried-forward population are summarized in the following table. The components that were considered part of the primary efficacy analysis have already been highlighted.

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon Capsule N = 256	Placebo N = 282
Week 16		n	257	248	253	280
	Baseline	Mean	27.5	27.0	27.9	28.5
	Post-baseline	Mean	26.1	26.1	27.4	28.5
	Change	Mean	-1.4	-0.8	-0.5	-0.0
		p-value	0.007*	0.090	0.274	
Week 24		n	262	248	253	281
	Baseline	Mean	27.4	27.0	27.9	28.6
	Post-baseline	Mean	25.8	26.4	27.3	29.5
	Change	Mean	-1.6	-0.6	-0.6	1.0
		p-value	<0.001*	0.005*	0.003*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Negative change score indicates improvement.
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

The following are noteworthy:

- Both the 20 cm^2 and 10 cm^2 Exelon® patches showed a statistically significant superiority to placebo on this measure on the change from baseline score at Week 24

- The effect sizes were small and similar to those seen with the capsule formulation of Exelon® and with other acetylcholinesterase inhibitor drugs **approved for the treatment of mild to moderate Alzheimer's Disease.**

The results of the analysis of the change from baseline in ADAS-Cog score at Week 24 for two additional datasets is in the following table, which I have created from data in the submission.

Dataset	**Parameter**	**Treatment Group**			
		Exelon® 20 cm²	**Exelon® 10 cm²**	**Exelon® Capsule**	**Placebo**
Intent-to-treat plus retrieved dropouts	N	278	263	272	288
	Mean change from baseline at Week 24	-1.6	-0.6	-0.6	1.2
Last-observation carried-forward	p-value (vs placebo)	< 0.001	0.001	0.001	
Intent-to-treat Observed Cases	N	218	209	214	243
	Mean change from baseline	-1.8	-0.6	-0.7	1.0
	p-value (vs placebo)	< 0.001	0.003	0.003	

The results of these analyses are consistent with those used for the primary efficacy analysis (all 3 analyses were consistent across countries), as was an ADAS-Cog categorical analysis of the proportion of those improving in all 3 datasets, which is summarized in the next sponsor table.

Population / Visit		Exelon 20 cm^2	Exelon 10 cm^2	Exelon capsule	Placebo
ITT (LOCF)	N	257	248	253	280
Week 16	n (%)	74 (28.8)	65 (26.2)	70 (27.7)	69 (24.6)
	p-value	0.248	0.685	0.369	
	N	262	248	253	281
Week 24	n (%)	86 (32.8)	68 (27.4)	72 (28.5)	56 (19.9)
	p-value	< 0.001*	0.048*	0.013*	
ITT+RDO (LOCF)	N	278	263	272	288
Week 16	n (%)	77 (27.7)	68 (25.9)	73 (26.8)	69 (24.0)
	p-value	0.245	0.590	0.375	
	N	278	263	272	288
Week 24	n (%)	92 (33.1)	70 (26.6)	79 (29.0)	57 (19.8)
	p-value	< 0.001*	0.061	0.006*	
ITT (OC)	N	256	248	251	280
Week 16	n (%)	74 (28.9)	65 (26.2)	70 (27.9)	69 (24.6)
	p-value	0.235	0.685	0.338	
	N	218	209	214	243
Week 24	n (%)	79 (36.2)	58 (27.8)	64 (29.9)	48 (19.8)
	p-value	< 0.001*	0.034*	0.008*	

Improvement: at least 4 points improvement over baseline
p-values are derived from CMH test blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

The sponsor indicated that in a subgroup analysis on the intent-to-treat last-observation-carried-forward dataset, there was a better mean change from baseline at Week 24 in the 3 active treatment groups on the ADAS-Cog for those with an entry Mini-Mental Status Examination score ≥ 15 than for those with a Mini-Mental Status Examination score < 15. Other subgroup analyses are also described in the submission.

The sponsor also provides evidence that in all 3 of the above populations, non-inferiority of the 20 cm^2 Exelon® patch over the Exelon® capsule was demonstrated at Week 24, based on pre-specified criteria, and as indicated by the following sponsor table.

Population / visit		Exelon 20 cm^2 versus Capsule		
		ITT (LOCF)	ITT+RDO (LOCF)	ITT (OC)
Week 16	LS-Mean	-0.83	-0.78	-0.83
	LB 95%-CI	-1.88	-1.80	-1.89
	UB 95%-CI	0.22*	0.23*	0.22*
Week 24	LS-Mean	-0.95	-0.95	-1.14
	LB 95% CI	-2.06	-2.05	-2.35
	UB 95% CI	0.17*	0.14*	0.08*

A negative LS-mean treatment difference indicates superiority of Exelon 20 cm^2 versus capsule
Mean and 95%-Confidence Interval of LS mean between treatments are derived from two-way analyses of covariance
* upper boundary of 95%-Confidence Interval (UB 95%-CI) for the difference between treatment groups is below the corresponding pre-defined non-inferiority margin 1.25

7.2.3.3.2.2 ADCS-CGIC

The results of analyses of this measure at Weeks 16 and 24 for the intent-to-treat last-observation-carried-forward population are summarized in the following table. The component that was considered part of the primary efficacy analysis has already been highlighted (see Section 7.2.3.3.1.2). As noted earlier, on this measure, the treatment difference between the 20 cm^2 Exelon® patch and placebo, which favored the Exelon® patch, yielded a p-value (0.054) that marginally exceeded the pre-specified alpha of 0.05.

Visit	Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16 – n (%)				
Markedly improved (1)	3 (1.2)	4 (1.6)	1 (0.4)	1 (0.4)
Moderately improved (2)	21 (8.2)	24 (9.7)	20 (8.0)	22 (8.1)
Minimally improved (3)	58 (22.7)	48 (19.4)	48 (19.3)	53 (19.4)
Unchanged (4)	109 (42.7)	104 (42.1)	111 (44.6)	116 (42.5)
Minimally worse (5)	40 (15.7)	53 (21.5)	43 (17.3)	53 (19.4)
Moderately worse (6)	20 (7.8)	14 (5.7)	23 (9.2)	25 (9.2)
Markedly worse (7)	4 (1.6)	0 (0.0)	3 (1.2)	3 (1.1)
n	255	247	249	273
mean	3.9	3.9	4.0	4.0
SD	1.13	1.08	1.10	1.10
p-value	0.177	0.195	0.804	
Week 24 – n (%)				
Markedly improved (1)	5 (1.9)	5 (2.0)	3 (1.2)	2 (0.7)
Moderately improved (2)	32 (12.3)	29 (11.7)	29 (11.5)	26 (9.4)
Minimally improved (3)	48 (18.5)	43 (17.3)	60 (23.7)	50 (18.0)
Unchanged (4)	94 (36.2)	105 (42.3)	96 (37.9)	91 (32.7)
Minimally worse (5)	50 (19.2)	41 (16.5)	30 (11.9)	65 (23.4)
Moderately worse (6)	27 (10.4)	22 (8.9)	30 (11.9)	36 (12.9)
Markedly worse (7)	4 (1.5)	3 (1.2)	5 (2.0)	8 (2.9)
n	260	248	253	278
mean	4.0	3.9	3.9	4.2
SD	1.27	1.20	1.25	1.26
p-value	0.054	0.010*	0.009*	

p-values are derived from CMH test (van Elteren test) blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

The sponsor has also pointed out, however, that analyses of this measure using a number of pre-specified alternate datasets yielded consistently statistically significant treatment differences favoring Exelon®. The sponsor, therefore, considers that there was substantial evidence for effectiveness of the 20 cm^2 and 10 cm^2 Exelon® patches, based on the effects seen on both the ADAS-Cog and ADCS-CGIC.

The sponsor indicates that the above effects of the Exelon® patches were consistent across countries.

The p-values for the comparisons of each active treatment group with placebo on the ADCS-CGIC score at Week 24, for each of these alternate datasets, is in the next table, which I have created from data provided by the sponsor.

Dataset	Treatment Group		
	Exelon® 20 cm² p-value vs placebo	Exelon® 10 cm² p-value vs placebo	Exelon® Capsule p-value vs placebo
Intent-to-treat plus retrieved dropouts Last-observation carried-forward	0.034	0.020	0.007
Intent-to-treat Observed Cases	0.029	0.013	0.013

The sponsor indicated that the proportion of patients showing an improvement on this measure at Week 24 was higher for the 3 active treatment groups than for the placebo in all 3 datasets described above. Those results are in the following sponsor table.

Population/Visit		Exelon 20 cm²	Exelon 10 cm²	Exelon capsule	Placebo
ITT (LOCF)					
Week 16	N	255	247	249	273
	n (%)	82 (32.2)	76 (30.8)	69 (27.7)	76 (27.8)
	p-value	0.266	0.422	0.917	
Week 24	N	260	248	253	278
	n (%)	85 (32.7)	77 (31.0)	92 (36.4)	78 (28.1)
	p-value	0.216	0.473	0.047*	
ITT+RDO (LOCF)					
	N	268	262	266	279
Week 16	n (%)	87 (32.5)	79 (30.2)	73 (27.4)	76 (27.2)
	p-value	0.157	0.359	0.969	
		273	264	271	285
Week 24	n (%)	90 (33.0)	79 (29.9)	94 (34.7)	79 (27.7)
	p-value	0.123	0.521	0.073	
ITT (OC)					
Week 16	N	255	247	249	273
	n (%)	82 (32.2)	76 (30.8)	69 (27.7)	76 (27.8)
	p-value	0.266	0.422	0.917	
Week 24	N	214	206	213	238
	n (%)	77 (36.0)	68 (33.0)	82 (38.5)	70 (29.4)
	p-value	0.069	0.384	0.042*	

Improvement: markedly, moderately, or minimally improved
p-values are derived from CMH test blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

The sponsor further indicated that in a subgroup analysis on the intent-to-treat last-observation-carried-forward dataset, there was a higher percentage of

individuals improving at Week 24 in the 3 active treatment groups on the ADCS-CGIC for those with an entry Mini-Mental Status Examination score < 15 than for those with a Mini-Mental Status Examination score ≥ 15. Other subgroup analyses are also described in the submission.

7.2.3.3.2.3 ADCS-ADL

The results of analyses of this measure (change from baseline score) at Weeks 16 and 24 for the intent-to-treat last-observation-carried-forward population are summarized in the following table. The component that was considered part of the primary efficacy analysis (based on the 4th of the original hypotheses) have already been highlighted.

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	261	247	253	280
	Baseline	Mean	47.5	50.1	49.3	49.2
	Post-baseline	Mean	47.8	49.5	48.9	47.7
	Change	Mean	0.4	-0.6	-0.4	-1.6
		p-value	0.035*	0.226	0.143	
Week 24			263	247	254	281
	Baseline	Mean	47.6	50.1	49.3	49.2
	Post-baseline	Mean	47.6	49.9	48.8	46.9
	Change	Mean	-0.0	-0.1	-0.5	-2.3
		p-value	0.017*	0.013*	0.039*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Positive change score indicates improvement
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

As the above table indicates, all 3 active treatment groups showed at least a nominally statistically significant superiority to placebo on the change from baseline ADCS-ADL score at Week 24.

The results of the analysis of the change from baseline in ADCS-ADL score at Week 24 for two additional datasets is in the following table, which I have created from data in the submission. These results are consistent with those seen for the intent-to-treat last-observation-carried-forward dataset.

Dataset	Parameter	Treatment Group			
		Exelon® 20 cm^2	Exelon® 10 cm^2	Exelon® Capsule	Placebo
Intent-to-treat plus retrieved dropouts	N	278	264	274	288
	Mean change from baseline at Week 24	-0.4	-0.4	-0.5	-1.9
	p-value (vs placebo)	0.008	0.005	0.008	

Dataset	Parameter	Treatment Group			
		Exelon® 20 cm²	Exelon® 10 cm²	Exelon® Capsule	Placebo
Last-observation carried-forward					
Intent-to-treat Observed Cases	N	217	209	219	245
	Mean change from baseline	0.2	-0.1	-0.3	-2.2
	p-value (vs placebo)	0.016	0.021	0.034	

A categorical analysis of the proportion of those improving in all 3 datasets, which is summarized in the next sponsor table, indicated that a greater proportion of patients in the active treatment groups improved as compared with those in the placebo groups on the ADCS-ADL at Week 24.

Population / Visit		Exelon 20 cm²	Exelon 10 cm²	Exelon capsule	Placebo
ITT (LOCF)					
Week 16	N	261	247	253	280
	n (%)	136 (52.1)	115 (46.6)	118 (46.6)	112 (40.0)
	p-value	0.005*	0.138	0.120	
Week 24	N	263	247	254	281
	n (%)	125 (47.5)	111 (44.9)	114 (44.9)	107 (38.1)
	p-value	0.031*	0.121	0.099	
ITT+RDO (LOCF)					
Week 16	N	278	264	274	288
	n (%)	141 (50.7)	119 (45.1)	123 (44.9)	112 (38.9)
	p-value	0.006*	0.182	0.167	
Week 24	N	278	264	274	288
	n (%)	126 (45.3)	114 (43.2)	121 (44.2)	107 (37.2)
	p-value	0.059	0.173	0.087	
ITT (OC)					
	N	261	247	252	280
Week 16	n (%)	136 (52.1)	115 (46.6)	118 (46.8)	112 (40.0)
	p-value	0.005*	0.138	0.106	
Week 24	N	217	209	219	245
	n (%)	105 (48.4)	93 (44.5)	100 (45.7)	91 (37.1)
	p-value	0.017*	0.127	0.054	

Improvement: at least 1 point improvement over baseline
p-values are derived from CMH test blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

7.2.3.4 Analysis Of Secondary Efficacy Measures

7.2.3.4.1 Neuropsychiatry Inventory

There were no differences that were even nominally statistically significant between the active treatment groups and the placebo for the change from baseline in Neuropsychiatry Inventory-12 score, as indicated in the table below.

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	260	248	253	280
	Baseline	Mean	15.0	13.9	15.1	14.8
	Post-baseline	Mean	12.9	12.1	13.6	12.4
	Change	Mean	-2.1	-1.8	-1.5	-2.4
		p-value	0.547	0.684	0.319	
Week 24		n	263	248	253	281
	Baseline	Mean	15.1	13.9	15.1	14.9
	Post-baseline	Mean	12.8	12.2	12.8	13.2
	Change	Mean	-2.3	-1.7	-2.2	-1.7
		p-value	0.686	0.744	0.512	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Negative change scores indicate improvement.
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.

The analysis of the Neuropsychiatry Inventory-10 and caregiver distress scores yielded similar results.

7.2.3.4.2 Mini-Mental Status Examination

As the sponsor table below indicates, all 3 active treatment groups showed at least a nominally statistically significant superiority to placebo on the change from baseline Mini-Mental Status Examination score at Week 24 for the intent-to-treat last-observation-carried-forward population. Similar results were seen for the intent-to-treat plus retrieved dropouts and Observed Cases populations.

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	259	250	256	281
	Baseline	Mean	16.6	16.7	16.4	16.4
	Post-baseline	Mean	17.8	17.7	17.0	16.6
	Change	Mean	1.1	1.0	0.6	0.2
		p-value	< 0.001*	0.007*	0.108	
Week 24		n	262	250	256	281
	Baseline	Mean	16.6	16.7	16.4	16.4
	Post-baseline	Mean	17.6	17.8	17.2	16.4
	Change	Mean	0.9	1.1	0.8	0.0
		p-value	0.002*	< 0.001*	0.002*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Positive change score indicates improvement.
p-values are derived from CMH test (van Elteren test) blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

7.2.3.4.3 Ten-Point Clock Test

There were no differences that were even nominally statistically significant between the active treatment groups and the placebo for the change from baseline in Ten-Point Clock Test score, as indicated in the table below.

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	247	243	245	266
	Baseline	Mean	4.7	4.5	4.5	4.3
	Post-baseline	Mean	4.7	4.6	4.6	4.4
	Change	Mean	0.1	0.1	0.1	0.0
		p-value	0.211	0.194	0.223	
Week 24		n	251	245	246	269
	Baseline	Mean	4.7	4.5	4.4	4.3
	Post-baseline	Mean	4.9	4.6	4.6	4.2
	Change	Mean	0.3	0.1	0.2	-0.1
		p-value	0.077	0.079	0.152	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Positive change score indicates improvement.
p-values are derived from CMH test (van Elteren test) blocking for country and are based on comparison of each Exelon treatment group with placebo.

7.2.3.4.4 Trailmaking Test A

As the sponsor table below indicates, all 3 active treatment groups showed at least a nominally statistically significant superiority to placebo on the change from baseline Trailmaking Test A score at Week 24 for the intent-to-treat last-observation-carried-forward population.

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16		n	233	238	237	257
	Baseline	Mean	174.8	182.6	176.0	177.9
	Post-baseline	Mean	167.9	169.3	167.5	183.0
	Change	Mean	-6.9	-13.2	-8.4	5.2
		p-value	0.010*	< 0.001*	0.004*	
Week 24		n	238	241	240	258
	Baseline	Mean	176.5	183.3	177.2	178.3
	Post-baseline	Mean	170.0	171.0	167.4	186.0
	Change	Mean	-6.5	-12.3	-9.8	7.7
		p-value	0.005*	< 0.001*	< 0.001*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Negative change score indicates improvement.
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo..
* $p < 0.05$

7.2.4 Safety Evaluation

Unless otherwise specified, all safety data below apply to the safety population which was to consist of all randomized patients who received at least one dose of study medication and had at least one safety assessment following baseline.

7.2.4.1 Exposure

The duration of exposure by treatment is summarized in the following table, which I have copied from the submission.

Duration of Exposure	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Any exposure	303 (100.0)	291 (100.0)	294 (100.0)	302 (100.0)
≥ 4 weeks	299 (98.7)	283 (97.3)	288 (98.0)	298 (98.7)
≥ 8 weeks	285 (94.1)	270 (92.8)	276 (93.9)	295 (97.7)
≥ 12 weeks	278 (91.7)	256 (88.0)	268 (91.2)	289 (95.7)
≥ 16 weeks	263 (86.8)	243 (83.5)	251 (85.4)	280 (92.7)
≥ 20 weeks	244 (80.5)	231 (79.4)	241 (82.0)	274 (90.7)
≥ 24 weeks	180 (59.4)	170 (58.4)	179 (60.9)	207 (68.5)
Mean ± SD	22.0 ± 5.5	21.4 ± 6.3	21.8 ± 5.9	23.0 ± 4.2
Median	24	24	24	24
Range	0.6 – 35.0	0.1 – 30.4	0.1 – 31.4	0.4 – 26.9
Patients with mode dose level 4 during maintenance period	165 (62.7)	206 (85.5)	163 (65.2)	-
Target treatment received for:				
≥ 1 day	208 (68.6)	280 (96.2)	186 (63.3)	-
≥ 4 weeks	175 (57.8)	260 (89.3)	169 (57.5)	-
≥ 8 weeks	150 (49.5)	244 (83.8)	156 (53.1)	-
≥ 12 weeks	95 (31.4)	234 (80.4)	97 (33.0)	-

Target treatment duration is based on the sum of the total number of days on target treatment
Mean, median, and range data above are in weeks

A higher proportion of patients in the Exelon® 10 cm^2 patch group received their target treatment for specific periods (≥ 1 day; ≥ 4 weeks; ≥ 8 weeks; and ≥ 12 weeks) as compared with the other 2 Exelon® groups, as indicated by the above table.

7.2.4.2 Patch Adhesion

The number of evaluations of patch adhesion by caregivers, as well as the ratings by caregivers of the extent of patch adhesion, are summarized in the following table, which I have taken from the submission.

	Exelon patch size			
Adhesion	5 cm^2	10 cm^2	15 cm^2	20 cm^2
Total number of evaluations - N	695	1336	301	334
Patch remained completely on – n (%)	588 (84.6)	1131 (84.7)	236 (78.4)	245 (73.4)
Edges of the patch were lifting off – n (%)	85 (12.2)	151 (11.3)	49 (16.3)	69 (20.7)
Patch was mostly half off – n (%)	12 (1.7)	21 (1.6)	8 (2.7)	13 (3.9)
Patch was just hanging on – n (%)	4 (0.6)	16 (1.2)	4 (1.3)	4 (1.2)
Patch was completely detached – n (%)	6 (0.9)	17 (1.3)	4 (1.3)	3 (0.9)

N = total number of evaluations for that patch size.

As the table, the majority of patches remained adherent regardless of size, although the extent of adhesion was best with the smaller patches.

7.2.4.3 Concomitant Medication

There were no major differences between treatment groups in the pattern of concomitant medication use – whether or not those medications were considered to have effects on the central nervous system – either prior to or during treatment. Full data, which I have reviewed, are in the submission but are not reproduced here.

7.2.4.4 Adverse Events

7.2.4.4.1 All Adverse Events

The number and proportion of patients with specific adverse events (AEs) that occurred in at least 3% of patients in any treatment group is summarized in the following table, which I have copied from the submission.

	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Total no. of patients with AEs	200 (66.0)	147 (50.5)	186 (63.3)	139 (46.0)
Preferred Term				
Nausea	64 (21.1)	21 (7.2)	68 (23.1)	15 (5.0)
Vomiting	57 (18.8)	18 (6.2)	50 (17.0)	10 (3.3)
Diarrhea	31 (10.2)	18 (6.2)	16 (5.4)	10 (3.3)
Weight decreased	23 (7.6)	8 (2.7)	16 (5.4)	4 (1.3)
Dizziness	21 (6.9)	7 (2.4)	22 (7.5)	7 (2.3)
Decreased appetite	15 (5.0)	2 (0.7)	12 (4.1)	3 (1.0)
Headache	13 (4.3)	10 (3.4)	18 (6.1)	5 (1.7)
Anorexia	12 (4.0)	7 (2.4)	14 (4.8)	3 (1.0)
Depression	12 (4.0)	11 (3.8)	13 (4.4)	4 (1.3)
Insomnia	12 (4.0)	4 (1.4)	6 (2.0)	6 (2.0)
Abdominal pain	11 (3.6)	7 (2.4)	4 (1.4)	2 (0.7)
Asthenia	9 (3.0)	5 (1.7)	17 (5.8)	3 (1.0)
Anxiety	8 (2.6)	9 (3.1)	5 (1.7)	4 (1.3)
Agitation	7 (2.3)	3 (1.0)	11 (3.7)	5 (1.7)
Fall	7 (2.3)	6 (2.1)	7 (2.4)	10 (3.3)
Hypertension	4 (1.3)	2 (0.7)	12 (4.1)	11 (3.6)

AEs are listed by descending frequency in the Exelon 20 cm^2 treatment group

It is noteworthy that the overall incidence of adverse events, and of nausea and vomiting, was highest (and similar) in the Exelon® 20 cm^2 patch and Exelon® capsule groups, as compared with the Exelon® 10 cm^2 patch and placebo groups. It is also unclear to what extent those listed as having a "decreased appetite" overlapped with those listed as having "anorexia" (i.e., it is unclear if some subjects were listed as having both when referring to the same adverse event)

Analyses of subgroups indicated that the incidence of adverse events was similar in men and in women, but was higher in those aged ≥ 75 years than in younger patients (in both the active drug and placebo groups).

The majority of adverse events seen in this study were mild to moderate in intensity. The basis for that observation and the grouping of specific adverse events by severity are displayed in the next table, which I have copied from the submission.

	Exelon 20 cm^2 N = 303 n (%)	**Exelon 10 cm^2** N = 291 n (%)	**Exelon capsule** N = 294 n (%)	**Placebo** N = 302 n (%)
Total no. of patients with AEs	200 (66.0)	147 (50.5)	186 (63.3)	139 (46.0)
Mild	72 (23.8)	60 (20.6)	70 (23.8)	70 (23.2)
Moderate	91 (30.0)	65 (22.3)	90 (30.6)	53 (17.5)
Severe	37 (12.2)	22 (7.6)	26 (8.8)	16 (5.3)
Nausea	64 (21.1)	21 (7.2)	68 (23.1)	15 (5.0)
Mild	27 (8.9)	11 (3.8)	30 (10.2)	10 (3.3)
Moderate	33 (10.9)	9 (3.1)	32 (10.9)	5 (1.7)
Severe	4 (1.3)	1 (0.3)	6 (2.0)	0 (0.0)

	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Vomiting	57 (18.8)	18 (6.2)	50 (17.0)	10 (3.3)
Mild	18 (5.9)	12 (4.1)	23 (7.8)	6 (2.0)
Moderate	35 (11.6)	6 (2.1)	23 (7.8)	4 (1.3)
Severe	4 (1.3)	0 (0.0)	4 (1.4)	0 (0.0)
Diarrhea	31 (10.2)	18 (6.2)	16 (5.4)	10 (3.3)
Mild	20 (6.6)	15 (5.2)	13 (4.4)	5 (1.7)
Moderate	10 (3.3)	3 (1.0)	3 (1.0)	5 (1.7)
Severe	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	23 (7.6)	8 (2.7)	16 (5.4)	4 (1.3)
Mild	16 (5.3)	1 (0.3)	9 (3.1)	3 (1.0)
Moderate	7 (2.3)	5 (1.7)	6 (2.0)	1 (0.3)
Severe	0 (0.0)	2 (0.7)	1 (0.3)	0 (0.0)
Dizziness	21 (6.9)	7 (2.4)	22 (7.5)	7 (2.3)
Mild	13 (4.3)	5 (1.7)	14 (4.8)	4 (1.3)
Moderate	5 (1.7)	2 (0.7)	8 (2.7)	3 (1.0)
Severe	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	15 (5.0)	2 (0.7)	12 (4.1)	3 (1.0)
Mild	12 (4.0)	2 (0.7)	7 (2.4)	3 (1.0)
Moderate	2 (0.7)	0 (0.0)	4 (1.4)	0 (0.0)
Severe	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Headache	13 (4.3)	10 (3.4)	18 (6.1)	5 (1.7)
Mild	9 (3.0)	8 (2.7)	7 (2.4)	4 (1.3)
Moderate	4 (1.3)	2 (0.7)	9 (3.1)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.3)
Anorexia	12 (4.0)	7 (2.4)	14 (4.8)	3 (1.0)
Mild	6 (2.0)	4 (1.4)	9 (3.1)	2 (0.7)
Moderate	6 (2.0)	2 (0.7)	5 (1.7)	1 (0.3)
Severe	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)

AEs are listed by descending frequency in the Exelon 20 cm^2 patch group
A subject with multiple occurrences of an AE under one treatment is counted only once
A subject with multiple severity ratings for an AE while on a treatment, is only counted under the maximum rating.

The overall pattern of adverse events seen in this study was quite consistent with that seen with the tablet formulation of Exelon® when its safety was reviewed prior to that drug formulation being originally approved for the treatment of **Alzheimer's Disease**.

The sponsor conducted a further analysis to determine if adverse events were related to plasma concentrations of rivastigmine and its metabolite, NAP226-90. Further details of this analysis are below.

- Modeling was performed using data for 310 Exelon®-patch treated patients for whom a single plasma concentration measurement of rivastigmine and/or its

main metabolite (see above) was available at the end of the maintenance period (i.e., at steady state)

- The relationship between the incidence of nausea, vomiting, and dizziness during the maintenance period and steady state concentrations of rivastigmine and its main metabolite (see above) was examined

- The results of the analysis indicated a lack of a relationship between tolerability **and drug exposure. The sponsor's explanation for that is as follows**

    - Blood sampling for pharmacokinetic analysis (limited and sparse as it was) was performed during the maintenance phase

    - Adverse events such as nausea and vomiting occur more commonly during the titration period when pharmacokinetic sampling was not performed

7.2.4.4.2 Deaths, Other Serious Adverse Events, And Discontinuations Due To Adverse Events

The number and proportion of patients in each treatment group who died, had serious adverse events (SAEs), or discontinued due to adverse events (AEs) is summarized in the following table, which I have copied from the submission.

Patients with serious or significant AEs	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Deaths	5 (1.7)**	4 (1.4)*	2 (0.7)	3 (1.0)#
SAEs	36 (11.9)	23 (7.9)	21 (7.1)	26 (8.6)
Discontinued due to AEs	31 (10.2)	31 (10.7)	25 (8.5)	18 (6.0)
Discontinued due to SAEs	12 (4.0)	12 (4.1)	7 (2.4)	9 (3.0)
Discontinued due to non-serious AEs	20 (6.6)	19 (6.5)	19 (6.5)	9 (3.0)

* An additional patient died from cardiac arrest 7 days after discontinuation due to an SAE of delirium
** One patient died whilst receiving 5 cm^2 patch treatment (no up-titration had occurred)
# An additional patient died from cardiac arrest 17 days after discontinuation of study treatment

As the above table indicates, the incidence of deaths was low and without notable differences between the Exelon® patch and placebo groups.

7.2.4.4.2.1 Deaths

The incidence of deaths by specific cause (i.e., system organ class and preferred term) in each treatment group is summarized in the following table, which I have copied from the submission. As might be expected, the incidence of specific causes of death, by preferred term, was very low (not exceeding 0.7%) in each treatment group.

The deaths summarized in the table below are those which occurred during double-blind treatment or within 30 days of completion of that treatment.