Primary system organ class Preferred term	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Total patients who died	5 (1.7)**	4 (1.4)*	2 (0.7)	3 (1.0)#
Cardiac disorders	2 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)
Cardiac failure	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
General disorders & administration site conditions	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Sudden death	1 (0.3)[a]	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Injury, poisoning & procedural complications	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Head injury	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Subdural hematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Nervous system disorders	0 (0.0)	2 (0.7)	1 (0.3)	1 (0.3)
Cerebrovascular accident	0 (0.0)	2 (0.7)	1 (0.3)	1 (0.3)
Respiratory, thoracic & mediastinal disorders	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory failure	2 (0.7)[b]	0 (0.0)	0 (0.0)	0 (0.0)

* An additional patient died from cardiac arrest 7 days after discontinuation of study treatment due to an SAE of delirium
** One of these patients died whilst receiving 5 cm^2 patch treatment (no up-titration had occurred)
# An additional patient died from cardiac arrest 17 days after discontinuation
[a] Attributed by the investigator to progression of chronic ischemic heart disease
[b] respiratory failure was secondary to pneumonia

I have read the narratives for the deaths listed in the above table. All deaths that occurred in this study appear to be due to incidental illnesses that are common in the elderly; none is easily attributable to study drug.

7.2.4.4.2.2 Serious Adverse Events

The number and percentage of patients with serious adverse events in each treatment group in specific system organ classes are in the following table, which I have copied from the submission. As the table indicates, the most common serious adverse events were disorders of nervous system, cardiac disorders, and gastrointestinal disorders.

Primary system organ class	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Total patients with SAEs	36 (11.9)	23 (7.9)	21 (7.1)	26 (8.6)
Nervous system disorders	10 (3.3)	6 (2.1)	6 (2.0)	5 (1.7)
Cardiac disorders	8 (2.6)	3 (1.0)	2 (0.7)	4 (1.3)
Gastrointestinal disorders	7 (2.3)	2 (0.7)	2 (0.7)	2 (0.7)
Infections & infestations	4 (1.3)	3 (1.0)	4 (1.4)	4 (1.3)
General disorders & administration site conditions	3 (1.0)	1 (0.3)	0 (0.0)	1 (0.3)
Metabolism & nutrition disorders	3 (1.0)	1 (0.3)	1 (0.3)	2 (0.7)
Psychiatric disorders	3 (1.0)	5 (1.7)	3 (1.0)	3 (1.0)
Injury, poisoning & procedural complications	2 (0.7)	3 (1.0)	0 (0.0)	8 (2.6)
Investigations	2 (0.7)	0 (0.0)	1 (0.3)	1 (0.3)
Respiratory, thoracic & mediastinal disorders	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.3)
Hepatobiliary disorders	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.3)
Renal & urinary disorders	1 (0.3)	2 (0.7)	0 (0.0)	1 (0.3)
Surgical & medical procedures	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Musculoskeletal & connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Neoplasms benign, malignant & unspecified	0 (0.0)	3 (1.0)	1 (0.3)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

System Organ Class ordered by descending frequency in the Exelon 20 cm^2 treatment group

The incidence of specific nervous system, cardiac, and gastrointestinal serious adverse events (as classified by preferred term) which occurred in ≥ 2 patients in any treatment group is in the following table.

Serious Adverse Event N (%)	Treatment Group			
	Exelon® 20 cm^2 N = 303	Exelon® 10 cm^2 N = 291	Exelon® Capsule N = 294	Placebo N = 302
Cardiac failure	3 (1.0)	0 (0.0)	0 (0.0)	2 (0.7)
Angina pectoris	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.7)
Cerebrovascular accident	3 (1.0)	2 (0.7)	1 (0.3)	1 (0.3)
Dizziness	2 (0.7)	1 (0.3)	1 (0.3)	0 (0.0)
Transient ischemic attack	2 (0.7)	1 (0.3)	1 (0.3)	0 (0.0)
Vomiting	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2(0.7)	0 (0.0)	0 (0.0)	1 (0.3)

As the table above indicates, the incidence of vomiting, as a serious adverse event, was highest in the Exelon® 20 cm^2 patch group.

A review of the listings for serious adverse events strongly suggests that with the exception of those occurrences that were attributable to the cholinomimetic effects of Exelon®, such as nausea and vomiting, the serious adverse events could be attributed to incidental illnesses common in the elderly.

7.2.4.4.2.3 Discontinuations Due To Adverse Events

The number and percentage of patients with discontinuations due to adverse events in each treatment group in specific system organ classes are in the following table, which I have copied from the submission. As the table indicates, the most common categories of adverse events leading to treatment discontinuation were disorders of the gastrointestinal and nervous systems, and of the skin and subcutaneous tissues.

	Exelon 20 cm^2 N = 303 n (%)	**Exelon 10 cm^2 N = 291 n (%)**	**Exelon capsule N = 294 n (%)**	**Placebo N = 302 n (%)**
Any primary system organ class	31 (10.2)	31 (10.7)	25 (8.5)	18 (6.0)
Gastrointestinal disorders	10 (3.3)	3 (1.0)	13 (4.4)	4 (1.3)
Nervous system disorders	9 (3.0)	9 (3.1)	8 (2.7)	4 (1.3)
Skin & subcutaneous tissue disorders	5 (1.7)	2 (0.7)	3 (1.0)	1 (0.3)
General disorders & administration site conditions	4 (1.3)	8 (2.7)	1 (0.3)	1 (0.3)
Psychiatric disorders	3 (1.0)	6 (2.1)	1 (0.3)	2 (0.7)
Cardiac disorders	2 (0.7)	1 (0.3)	3 (1.0)	4 (1.3)
Investigations	2 (0.7)	4 (1.4)	2 (0.7)	1 (0.3)
Metabolism & nutrition disorders	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)
Blood & lymphatic system disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Ear & labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Infections & infestations	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
Injury, poisoning & procedural complications	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Renal & urinary disorders	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
Respiratory, thoracic & mediastinal disorders	0 (0.0)	1 (0.3)	2 (0.7)	0 (0.0)

System Organ Class ordered by descending frequency in the Exelon 20 cm^2 treatment group
Some patients experienced events in more than one system organ class

The incidence of specific nervous system, gastrointestinal, and skin and subcutaneous tissue adverse events (as classified by preferred term) that lead to treatment discontinuation and which occurred in ≥ 2 patients in any treatment group is in the following table.

Adverse Event Leading To Treatment Discontinuation N (%)	**Treatment Group**			
	Exelon® 20 cm^2 N = 303	**Exelon® 10 cm^2 N = 291**	**Exelon® Capsule N = 294**	**Placebo N = 302**
Cardiac failure	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.7)
Nausea	5 (1.7)	2 (0.7)	5 (1.7)	4 (1.3)
Vomiting	5 (1.7)	0 (0.0)	6 (2.0)	1 (0.3)
Erythema	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pruritus	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.3)

A review of the listings for adverse events that led to treatment discontinuation strongly suggests that with the exception of those events that were attributable to

the cholinomimetic effects of Exelon®, such as nausea and vomiting, and to the local effects of the Exelon®/placebo patch, these occurrences could be attributed to incidental illnesses common in the elderly.

7.2.4.5 Nausea And Vomiting

The tablet formulation of Exelon® has been associated with a high incidence of nausea and vomiting, leading to a bolded warning in the current product labeling for that formulation.

The overall incidence of nausea and vomiting, and of discontinuations due to nausea and vomiting was highest in the Exelon® 20 cm^2 and Exelon® capsule groups, as indicated by the following table, the data for which have been extracted from a table contained in the submission.

Parameter	**Treatment Group**			
	Exelon® 20 cm^2	**Exelon® 10 cm^2**	**Exelon® Capsule**	**Placebo**
Total N	303	291	294	302
Nausea and/or vomiting – N (%)	84 (27.7)	32 (11.0)	84 (28.6)	20 (6.6)
Discontinuations due to nausea and/or vomiting – N (%)	8 (2.6)	2 (0.7)	8 (2.7)	4 (1.3)

7.2.4.6 Vital Signs

Among changes in these parameters described by the sponsor were the following:

- Small decreases in mean pulse rate and systolic blood pressure in the Exelon® treatment groups than in the placebo group
- Higher rates of body weight reductions ≥ 7% in the Exelon® treatment groups than in the placebo group. The incidence of body weight reductions ≥ 7% in each treatment group was as follows:

Treatment Group	**Incidence of body weight reductions ≥ 7%**
Exelon® 20 cm^2 patch	12.2%
Exelon® 10 cm^2 patch	8.2%
Exelon® capsule	10.9%
Placebo	6.0%

7.2.4.7 Electrocardiograms

Among changes in these parameters described by the sponsor were the following:

- Small decreases in mean ventricular rate in the Exelon® treatment groups than in the placebo group; the greatest changes were seen in those administered the Exelon® 20 cm^2 patch

- Slight prolongation of the mean P-R interval in those administered the Exelon® 20 cm^2 patch

The sponsor has concluded that no clinically meaningful electrocardiogram abnormalities were seen with Exelon®.

7.2.4.8 Skin Irritation

The incidence of severe skin irritation due to placebo or Exelon® patches of any size appears to have been very low, as indicated by the table below, but higher in those administered the Exelon® patch than in those administered placebo patches.

	Exelon patch size				Placebo patch size			
Skin irritation	**20 cm^2**	**15 cm^2**	**10 cm^2**	**5 cm^2**	**20 cm^2**	**15 cm^2**	**10 cm^2**	**5 cm^2**
Patients with any rating - N	177	234	537	556	203	243	547	560
Patients with no skin irritation	105 (59.3)	145 (62.0)	276 (51.4)	427 (76.8)	136 (67.0)	196 (80.7)	408 (74.6)	492 (87.9)
Patients with no, slight or mild skin irritation	164 (92.7)	215 (91.9)	481 (89.6)	546 (98.2)	192 (94.6)	238 (97.9)	530 (96.9)	558 (99.6)
- Any severe rating – n (%)	2 (1.1)	4 (1.7)	12 (2.2)	2 (0.4)	2 (1.0)	1 (0.4)	1 (0.2)	0 (0.0)
Erythema - N	177	234	537	556	203	243	547	559
- No, slight or mild – n (%)	166 (93.8)	221 (94.4)	496 (92.4)	549 (98.7)	195 (96.1)	241 (99.2)	538 (98.4)	557 (99.6)
- Moderate or severe – n (%)	11 (6.2)	13 (5.6)	41 (7.6)	7 (1.3)	8 (3.9)	2 (0.8)	9 (1.6)	2 (0.4)
Edema- N	177	234	537	556	203	243	547	559
- No, slight or mild – n (%)	175 (98.9)	232 (99.1)	527 (98.1)	553 (99.5)	202 (99.5)	243 (100.0)	546 (99.8)	559 (100.0)
- Moderate or severe– n(%)	2 (1.1)	2 (0.9)	10 (1.9)	3 (0.5)	1 (0.5)	0 (0.0)	1 (0.2)	0 (0.0)
Scaling - N	177	234	537	556	203	243	547	560
- No, dryness, glossy effect, or mild – n (%)	176 (99.4)	234 (100.0)	530 (98.7)	554 (99.6)	203 (100.0)	243 (100.0)	545 (99.6)	560 (100.0)
- Moderate or severe– n (%)	1 (0.6)	0 (0.0)	7 (1.3)	2 (0.4)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Fissures - N	177	234	537	556	203	243	547	560
- No or superficial – n (%)	177 (100.0)	233 (99.6)	535 (99.6)	556 (100.0)	203 (100.0)	243 (100.0)	547 (100.0)	560 (100.0)
- Single or deep – n (%)	0 (0.0)	1 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus - N	177	234	537	556	203	243	547	560
- Negative, slight or mild – n (%)	171 (96.6)	223 (95.3)	501 (93.3)	550 (98.9)	197 (97.0)	239 (98.4)	537 (98.2)	560 (100.0)
- Moderate or severe – n (%)	6 (3.4)	11 (4.7)	36 (6.7)	6 (1.1)	6 (3.0)	4 (1.8)	10 (2.1)	0 (0.0)
Pain, stinging and/or burning- N	177	234	537	556	203	243	547	560
- No, slight or mild – n (%)	177 (100.0)	232 (99.1)	531 (98.9)	555 (99.8)	199 (98.0)	243 (100.0)	547 (100.0)	560 (100.0)
- Moderate or severe– n (%)	0 (0.0)	2 (0.9)	6 (1.1)	1 (0.2)	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)

N= total number of patients with evaluations for that patch size
The most severe rating was used for patients with multiple occurrences of an irritation sub-category

The incidence of treatment discontinuation due to skin irritation in each treatment group is displayed in the following table, which I have copied from the submission.

Treatment Group	Incidence of treatment discontinuation due to skin irritation
Exelon® 20 cm^2 patch	2.3%
Exelon® 10 cm^2 patch	2.4%
Exelon® capsule	1.4%
Placebo	0.3%

7.3 Sponsor's Conclusions

The sponsor's main conclusions were as follows:

- Both the 20 cm^2 and 10 cm^2 Exelon® patch treatments had efficacy in the **treatment of Alzheimer's Disease as compared with placebo. Also see the sponsor's discussion of the two-step primary efficacy analysis summarized in** Section 7.2.3.3.1.2.
- The 10 cm^2 Exelon® patch had efficacy similar to that of the 20 cm^2 patch but was better tolerated
- The safety and tolerability profile of the 20 cm^2 Exelon® patch was similar to that of the Exelon® capsule administered in a dose of 6 mg BID. Discontinuations due to gastrointestinal adverse events in patients administered the Exelon® patch were infrequent, and adverse events reported in other system organ classes with the Exelon® patch were consistent with the known safety profile for Exelon® capsules. The causes of death seen in this study were as expected for an elderly population, and no clinically meaningful abnormalities were seen on electrocardiograms
- The transdermal formulation of Exelon® demonstrated good skin tolerability and adhesiveness

7.4 Agency Biometrics Reviewer's Comments

The Agency Biometrics reviewer of this submission was Dr Tristan Massie.

His main comments on the results of the primary efficacy analysis may be summarized as follows:

- The two-step hierarchical primary analysis agreed to a priori by this Division required that the superiority of the 20 cm^2 Exelon® patch over placebo be first established on both the ADAS-Cog and ADCS-CGIC at a significance level of 0.05, before proceeding to the second step of the analysis involving the comparison of the 10 cm^2 Exelon® patch with placebo.

- **The sponsor's analysis at the first** step yielded a p-value of 0.054 for the comparison of the 20 cm^2 Exelon® patch with placebo on the ADCS-CGIC on the primary intent-to-treat last-observation-carried-forward dataset; the corresponding primary analysis of the ADAS-Cog on the same dataset, yielded clearly statistically significant results in favor of the 20 cm^2 Exelon® patch, and nominally statistically significant results were seen when the ADCS-CGIC analysis was repeated using confirmatory datasets.

Based on the first step of the primary efficacy analysis not achieving true statistical significance on the ADCS-CGIC, the study could technically be viewed as having failed.

- Dr Massie has expressed further concerns regarding the first-step comparison of the Exelon® 20 cm^2 patch with placebo on the ADCS-CGIC. These concerns may be summarized as follows:
    - According to the protocol, any ADCS-CGIC score recorded more than 2 days after the last dose of study medication was to be excluded from the primary efficacy analysis.
    - Dr Massie has found 16 instances (8 originally assigned to placebo, and 8 originally assigned to the 20 cm^2 patch of Exelon®) where the Week 24 ADCS-CGIC was excluded from the primary efficacy analysis, with the **Week 16 score being carried forward instead; the sponsor's explanation** for excluding those 16 Week 24 ADCS-CGIC scores was that they were recorded during the open-label phase. However, Dr Massie has found that in all but 2 of the 16 instances, the Week 24 score was rated only 1 day after the end of the double-blind phase, and it was unclear if the ratings were indeed made during the open-label phase
    - Dr Massie has further noted that if all those (n = 14) for whom the Week 24 ADCS-CGIC score was recorded 1 day after the end of the double-blind phase were included in the primary comparison of the 20 cm^2 Exelon® dose with placebo using their Week 24 scores on that measure, the p-value for the comparison was 0.109. He has also drawn attention to additional uncertainties regarding this group such as whether open-label medication (10 cm^2 Exelon® patch) was indeed administered to any of these subjects prior to the assessment being carried out and whether transdermal Exelon® might be expected to be efficacious in only one day
    - Among the analyses that he has performed comparing the 20 cm^2 Exelon® patch with placebo on the ADCS-CGIC is one in which all patients (n = 16) whose Week 24 scores may have been recorded during the open-label phase were excluded. For this analysis, he noted a p-value of 0.055.
- Dr Massie does also note the following, however.
    - The p-values for the comparison of the 20 cm^2 (and 10 cm^2) patch on the co-primary efficacy measure, the ADAS-Cog were considerably lower than 0.05
    - The p-value for the comparison of the 10 cm^2 patch with placebo on the ADCS-CGIC would have achieved nominal statistical significance even after a Bonferroni adjustment to account for multiple comparisons
    - Both strengths of Exelon® patch showed a nominally statistically significant superiority to placebo on 2 secondary efficacy measures, the ADCS-ADL and the Mini-Mental Status Examination

- The established efficacy of the oral formulations of Exelon® do lend some support to the potential efficacy of the transdermal formulation, including the 20 cm^2 patch

- Dr Massie considers the 20 cm^2 Exelon® to show no clear advantage in its efficacy when compared with the 20 cm^2 patch.

Please see Dr Massie's full review for further details.

7.5 Reviewer's Comments

7.5.1 Efficacy

Dr Massie's concerns regarding the results of the primary analysis comparing the effect of the 20 cm^2 Exelon® patch with placebo on the ADCS-CGIC have been noted.

Overall, the results of the study do provide sufficient evidence of the efficacy of the 20 cm^2 and 10 cm^2 patches of Exelon® over placebo on both primary efficacy measures, although the 20 cm^2 patch appears to have little advantage over the 10 cm^2 patch.

7.5.2 Safety

As noted by the sponsor, the qualitative spectrum of adverse events in patients administered the transdermal formulation of Exelon® was no different from that seen with the capsule formulation. The incidence of specific, common, mainly gastrointestinal, adverse events was higher in those receiving the 20 cm^2 patch than in those receiving 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.

It is noteworthy that the titration schedule for the capsule formulation of Exelon® in Study 2320, involved dose increases that were made more slowly than in the pivotal trials of the capsule formulation of Exelon® and more slowly than what is recommended in the current approved label; for example, the current approved label recommends that increases (1.5 mg BID → 3.0 mg BID → 4.5 mg BID → 6.0 mg BID) that were made not more often than every 4 weeks in Study 2320 are made not more frequently than every 2 weeks.

7.5.3 Overall

Based on the results of this study, the 20 cm^2 Exelon® patch appeared to offer no advantage in regard to its efficacy, and was less tolerable in regard to the incidence of adverse events, as compared with the 10 cm^2 patch.

8. Efficacy Of Exelon® Patch Transdermal System In Mild To Moderate Dementia Associated With Parkinson's Disease

8.1 Background

In the current application, the sponsor has sought the approval of the Exelon® Patch transdermal system for the treatment of mild to moderate dementia **associated with Parkinson's Disease.**

As already noted in this review, the immediate-release capsule and oral solution formulations of Exelon® were approved by this Agency for the treatment of mild to moderate dementia associated **with Parkinson's Disease on June 27, 2006 (as** the sponsor points out there is currently no other drug approved for the same indication). A meeting of the Peripheral and Central Nervous System Drugs Advisory Committee preceded that action.

The evidence for the efficacy and safety of the oral formulations of Exelon® that the sponsor provided under NDA 20823 (SE1-016) is summarized below

8.2 Summary Of Efficacy And Safety Of Exelon® Capsules In Dementia Associated With Parkinson's Disease

The sponsor had earlier provided evidence from two completed clinical studies in support of the efficacy and safety of Exelon® for the proposed new indication (these data are also summarized in the current submission). These were:

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

The data for these studies as they pertained to the efficacy and safety of Exelon® in this population are summarized below.

8.2.1 Efficacy

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

- This was a randomized (2:1 [Exelon®:Placebo]), double-blind, placebo-controlled, parallel-arm study
- The key selection criteria for the study were as follows
    - **Clinical diagnosis of idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria**

- Clinical diagnosis of dementia according to DSM-IV criteria for Dementia Due To Other General Medical Conditions (Code 294.1x), with onset of symptoms of dementia at least 2 years after the first diagnosis of **idiopathic Parkinson's Disease**
- The exclusion of alternate causes of dementia
- **Mini-Mental Status Examination score of 10 – 24 at entry**

- **The study was of 24 weeks' duration**

- The 2 parallel treatment arms were:

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

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

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

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

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

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

Key results for this study were as follows.

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

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

The main efficacy results of this study were as follows

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

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

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

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

8.2.2 Safety

8.2.2.1 Study 2311

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

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

8.2.2.2 Study 2311E1

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

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

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

8.3 Basis For Agency Approval Of Orally-Administered Formulations Of Exelon® For The Treatment Of Dementia Associated With Parkinson's Disease

Key Advisory Committee and Agency conclusions that underlay the approval of the orally-administered formulations Exelon® for the above indication were as follows:

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

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

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

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

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

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

- The results of Study 2311 did <u>not</u> need replication to confirm that rivastigmine **had efficacy in the treatment of dementia associated with Parkinson's Disease.** The following were the reasons for that view

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

Note that this reviewer continued to feel that the results of Study 2311 **<u>did</u>** warrant replication to confirm that rivastigmine had efficacy in the treatment of dementia associated with Parkinson's Disease. **The following were the reasons** for that view:

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

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

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

This reviewer had, therefore, recommended that the application not be approved, and that the sponsor should be asked to conduct a second adequate and well-controlled trial of rivastigmine in dementia **associated with Parkinson's Disease,** to confirm its efficacy in the treatment of that condition, prior to approval.

8.4 Clinical Trials Of Exelon® Patch In Dementia Associated With Parkinson's Disease

No clinical trials of the proposed transdermal formulation, controlled or otherwise, have been reported in this submission or elsewhere as having been conducted in patients with dementia associated **with Parkinson's Disease.**

8.5 Rationale For Seeking Approval Of Exelon® Patch In Dementia Associated With Parkinson's Disease Using Existing Data

The rationale for seeking the approval of the proposed rivastigmine transdermal formulation for the treatment of dementia **associated with Parkinson's Disease,** as outlined by the sponsor in the current submission, 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, given that** compliance with oral medication may be poor in patients with dementia, and **swallowing may be impaired in patients with Parkinson's Disease.**

- The efficacy of Exelon® immediate-release capsules in the treatment of **dementia associated with Parkinson's Disease was demonstrated in Study 2311.** The safety of Exelon® immediate-release capsules in the treatment of dementia **associated with Parkinson's Disease was demonstrated in both Study 2311 and** its open-label uncontrolled extension Study 2311E. The mean doses of Exelon® used in Study 2311 (at Week 24) and in Study 2311E1 (at Week 24 of that study) were 8.7 mg/day and 8.5 mg/day, respectively.

- The 10 cm^2 and 20 cm^2 Exelon® patches have efficacy in the treatment of mild to **moderate Alzheimer's Disease, as demonstrated by the results of Study 2320.**

The safety and tolerability of the 20 cm^2 Exelon® patch is similar to that of Exelon® capsules in a dose of 6 mg BID, but the 10 cm^2 Exelon® patch is better tolerated, based again on the results of Study 2320. Support for the safety of the 10 cm^2 and 20 cm^2 Exelon® patches in patients with Alzheimer's Disease is also derived from the open-label uncontrolled extension study 2320E1 included in the current submission.

- The open-label study D2331 compared the pharmacokinetics of the 5 cm^2, 10 cm^2, 15 cm^2, and 20 cm^2 Exelon® patches used once daily with Exelon® capsules used in a dose of 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg BID, in patients with mild to moderate Alzheimer's Disease. This study indicated that the range of exposure to rivastigmine, based on AUC_{0-24}, with the above Exelon® patch sizes 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.

- 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.

Thus, according to the sponsor, the transdermal formulation of Exelon® proposed for marketing would be expected to be both effective and safe in the treatment of dementia associated with Parkinson's Disease.

8.6 Reviewer's Comments

The sponsor was earlier required to conduct a separate randomized controlled efficacy study of the proposed transdermal formulation of Exelon® in mild to moderate Alzheimer's Disease on account of the expected differences in the plasma time-concentration curves for rivastigmine when comparing that formulation with the oral formulations of Exelon®, and concern that such differences could alter the efficacy of the transdermal formulation in an unfavorable manner. This requirement was imposed by the Agency despite the efficacy of the immediate-release capsule formulation of Exelon® having been demonstrated in multiple controlled clinical studies, all prior to approval of that formulation.

The same requirement should be imposed for demonstrating the efficacy of the proposed transdermal formulation of Exelon® in dementia associated with Parkinson's Disease, especially since the earlier evidence for the efficacy of the immediate-release capsule formulation of Exelon® was obtained from only a single study and since dementia associated with Parkinson's Disease is pathologically distinct from Alzheimer's Disease.

While the sponsor has further contended that 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

that the mechanism of action of rivastigmine in both conditions appears to be similar, and that these contentions provide further support for why a formal efficacy study of the proposed transdermal formulation of Exelon® in dementia **associated with Parkinson's Disease is** not needed, both assertions are open to question for the following reasons:

- A cholinergic deficiency state may not be the main pathophysiological mechanism underlying the dementia that occurs in patients with relatively early **Alzheimer's Disease, or the only** pathophysiological mechanism underlying **dementia associated with Parkinson's Disease**
- Acetylcholinesterase inhibitor drugs may have mechanisms of action in **Alzheimer's Disease that extend beyond merely enhancing cholinergic function** via an increase in the availability of acetylcholine at synapses

The above points are discussed further in the next 2 subsections.

In my view, and for the above reasons, the sponsor has not provided evidence of the efficacy of the proposed transdermal formulation of Exelon® in dementia **associated with Parkinson's Disease.**

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

The purported similarity in pathophysiology between both disorders may be summarized as follows: in both disorders, there is reported to be a cholinergic deficiency state secondary to pathological abnormalities that are mainly in the nucleus basalis of Meynert and, to a lesser extent, in the pedunculopontine nucleus (the pathological abnormalities in these two locations consist of neuronal loss in both conditions and Lewy bodies and neurofibrillary tangles in **Parkinson's Disease Dementia and Alzheimer's Disease, respectively), and it has been** hypothesized that the cholinergic deficiency state is the basis for the cognitive deficits in both disorders.

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

- In patients with **Parkinson's Disease and dementia**, the severity of dementia appears to generally correlate with the extent of neocortical Lewy bodies (although, as stated by Braak et al [*Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in Parkinson disease. Neurology 2005;64:1404-10*]: **"In some individuals, however,** cognitive decline can develop in the presence of mild Parkinson disease-related cortical pathology, and, conversely, **widespread cortical lesions do not lead to cognitive decline.").**

  Reductions in choline acetyltransferase and acetylcholinesterase activity in the cerebral cortex have also been demonstrated in dementia **associated with Parkinson's Disease, and to a greater extent than in Alzheimer's** Disease; these reductions have been correlated with impaired performance on tests of attention and executive function. However, these observations do not establish that reduced cortical cholinergic activity is the sole or main pathophysiological basis **for dementia associated with Parkinson's** Disease Dementia; it has been suggested for example, that abnormalities of dopaminergic, noradrenergic, and serotoninergic pathways may also contribute to the cognitive deficits seen in that disorder (see *Pillon B, Czernecki V, Dubois B. Dopamine and cognitive function. Curr Opin Neurol 2003;16 Suppl 2:S17-22*)

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

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

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

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

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

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

> CONTEXT: A central tenet of Alzheimer disease (AD) is the loss of cortical cholinergic function and cholinergic markers in postmortem brain specimens. Whether these profound deficits in cholinergic markers found in end-stage patients are also found in patients with much earlier disease is not known.
>
> OBJECTIVE: To determine whether cholinergic deficits in AD precede, follow, or occur in synchrony with the earliest signs of cognitive deterioration.
>
> DESIGN, SETTING, AND PATIENTS: Postmortem study of nursing home residents with Clinical Dementia Rating (CDR) Scale scores of 0.0 to 2.0 and 4.0 to 5.0 who underwent autopsy between 1986 and 1997, comparing the activity of the cholinergic marker enzymes in the cortices of 66 elderly subjects with no (CDR score = 0.0; n = 18), questionable (CDR score = 0.5; n = 11), mild (CDR score = 1.0; n = 22), or moderate (CDR score = 2.0; n = 15) dementia vs subjects with severe dementia (CDR score = 4.0-5.0; n = 15).
>
> MAIN OUTCOME MEASURES: Activity of the cholinergic marker enzymes choline acetyltransferase and acetylcholinesterase in 9 neocortical brain regions. RESULTS: The activity of choline acetyltransferase and acetylcholinesterase in 9 neocortical brain regions did not differ significantly in subjects with CDR scores of 0.0 to 2.0, but was significantly lower in subjects with severe dementia (CDR score = 4.0-5.0). Choline acetyltransferase levels were significantly correlated with severity of neuropathological lesions of AD, as measured by density of neuritic plaques and neurofibrillary tangles.
>
> CONCLUSIONS: Although neocortical cholinergic deficits are characteristic of severely demented AD patients, in this study, cholinergic deficits were not apparent in individuals with mild AD and were not present until relatively late in the course of the disease. These results suggest that patients with more severe disease should be a target for cholinergic treatment.

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

    Note that in the 3 key efficacy studies of **rivastigmine in Alzheimer's Disease that are** described in the approved product labeling, the mean Mini-Mental Status Examination

score at entry ranged from 19.7 to 20, indicating that these subjects did not have advanced Alzheimer's Disease.

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

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

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

9. Integrated Summary Of Safety

9.1 Summary Of Animal Studies

According to the sponsor:

- Rivastigmine had earlier been evaluated by other than the topical route in general acute and chronic general toxicity studies, as well as reproductive, carcinogenicity, and genotoxicity studies.
- In addition, topical formulations of rivastigmine have been evaluated in chronic general toxicity studies (up to 26 weeks) and in carcinogenicity, phototoxicity, irritation, and sensitization studies in appropriate species.

The sponsor further states that, based on the above studies of topical formulations of rivastigmine:

- The dermal administration of rivastigmine did not result in "marked" systemic or target organ toxicity
- The systemic effects seen with the patch formulation in toxicology studies were similar to those seen with the oral formulation

9.2 Clinical Sources Of Safety Data

Safety data were obtained from the following groups of one or more clinical trials.

Note that I have reviewed the safety data for each trial listed by reading each (individual) study report.

9.2.1 Placebo-Controlled Trial In Alzheimer's Disease

This is Study 2320, which was described in detail earlier in this review and is summarized in the sponsor table below

Study No.	Study objective, population	Patients randomized	Treatment duration	Treatment/dose (mg)	Type of control/blinding
2320	Efficacy, safety, and tolerability of Exelon Patch in patients with probable AD (MMSE 10-20)	1195	24 weeks	Exelon patch titrated from 5 to 10 cm^2 Exelon patch titrated from 5 to 20 cm^2 Exelon capsule titrated from 3 to 12 mg/day Placebo patch/capsule	Placebo, active Double-blind, Double-dummy
			4 week follow-up		

9.2.2 Long-Term Open-Label Uncontrolled Clinical Trial In Alzheimer's Disease

This was Study 2320E1, the open-label extension to Study 2320, which is summarized in the sponsor table below.

Study	Study objectives	Patients enrolled	Treatment duration	Treatment/dose (mg)	Type of control/blinding
2320E1	Long-term efficacy, safety, and tolerability of Exelon patch in patients with probable AD (MMSE 10-20)	871*	28 weeks	Exelon patch titrated from 10 to 20 cm^2	Uncontrolled Open-label
			4 week follow-up		

* Interim report on a subset of 632 patients included in submission

Note that interim data on a subset of 632 patients participating in this ongoing trial was included in the initial submission under this IND. All data for this study in this section of the review (Section 9) are derived from this subset. This subset appears to consist of all patients who entered this open-label extension study through July 20, 2005; the cut-off date for data from this subset was February 22, 2006.

Further details about the dose titration regimen and study schedule for this trial/phase of trial are below.

9.2.2.1 Dose-Titration

The dose titration regimen for this study (referred to as the **"open-label treatment phase") is summarized in the table below, which I have copied from the** submission.

Double-blind Treatment Phase								Open-label Treatment Phase					
Exelon® Patch, Capsule or Placebo								Exelon® patch size 10 cm^2 to 20 cm^2					
Period	**SCR**	**BSL**	**Titration**				**Maint**	**Titration**			**Maintenance**		
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13 or PD
Week	-4 to -1	0	1-4	5-8	9-12	13-16	17-24	25-28	29-32	33-36	37-40	41-46	47-52
DL	See Study 2320 for details							DL2	DL3	DL4	DL4	DL4	DL4
Patch size								10 cm^2	15 cm^2	20 cm^2	20 cm^2	20 cm^2	20 cm^2

SCR = screening, BSL = baseline, Maint = maintenance, DL = dose level, PD = premature discontinuation

9.2.2.2 Visit And Safety Assessment Schedule

Study visits were to be at Weeks 24 (end of double-blind treatment), 28, 32, 23, 40, 46, and 52.

Safety assessments were to be made as follows:

- Adverse events were to be evaluated continually
- Vital signs and skin irritation assessments were to checked at every visit
- Physical and neurological examinations were to be performed at Week 52

9.2.3 Other Open-Label Uncontrolled Trials In Alzheimer's Disease

These are summarized in the next sponsor table.

Study	Study objectives	Patients enrolled	Treatment duration	Treatment/dose (mg)	Type of control/blinding
1201	Safety, tolerability, skin irritation & skin adhesion, PK, and efficacy of Exelon Patch in Japanese patients with probable AD (MMSE 10-20)	64	24 weeks 4 week follow-up	Exelon patch titrated from 5 to 20 cm^2 using a 5-step titration (Group A) or 4-step titration (Group B)	Uncontrolled Open-label
0401	Adhesiveness, skin irritation, and safety of different sizes of Exelon Patch in patients with probable AD (MMSE 8-28)	64	42 days 4 week follow-up	Exelon patch titrated from 10 to 20 cm^2	Uncontrolled Open-label

An additional clinical trial conducted by the sponsor **in patients with Alzheimer's** Disease is not listed in this grouping, in the Summary of Safety, contained in this submission.

Trial Number	N	Phase	Study Design	Treatments	Treatment Duration	Locale
C152	40	IIa	Open-label	Exelon patch prototype patches 2.5-30 cm^2	Up to 6 weeks	US

Safety assessments in these trials, although variable across studies, included the following: Adverse events, vital signs, safety laboratory tests, electrocardiograms, physical examinations, and measures of skin irritation at the site of patch application.

9.2.4 Clinical Pharmacology Trials

These are listed below, in a table copied from the submission.

Trial Number	N	Study Design	Treatment	Treatment Duration	Locale
Alzheimer's Disease patients					
2331	51	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	21	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	48	Open-label, crossover in HV age 60-85	3 mg oral solution, 10 cm^2 patch	Single applications	US
2333	46	Double-blind w/placebo in HV age 18-75 (phototoxicity study)	5 cm^2 or 7.5 cm^2 patch	Single applications	US
2334	63	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	40	Open-label in young HV (Caucasian and Japanese)	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 (Japanese)	5 cm^2, 7,5 cm^2 and 10 cm^2 patch	Multiple applications	Japan

HV: Healthy volunteers

9.3 Groupings For The Assessment Of Safety Data

The sponsor has proposed 4 groupings for safety analysis. These groupings are summarized in the following table, which I have copied from the submission. Note the number of subjects in each grouping and the specific safety subjects addressed by the sponsor in each instance. Much, but not all, of the safety data included in this submission has been according to these groupings.

Database	Studies	Number of patients (safety population)	Safety topics Subgroup analyses
Group 1 (All Exelon patch-, capsule- and placebo-treated AD patients in double-blind controlled studies)	2320	1190	Topics: deaths, SAEs, other significant AEs, all AEs, skin irritation, patch adhesion, vital signs, ECGs Subgroups: by age group, gender, baseline weight and MMSE at baseline
Group 2 (All Exelon patch treated patients in Study 2320 and Study 2320E1)	2320, 2320E1	919	Topics: deaths, SAEs, other significant AEs, all AEs, skin irritation, vital signs
Group 3 (All Exelon patch-treated AD patients)	2320, 2320E1, 0401, 1201 and 2331	1071*	Topics: deaths, SAEs, other significant AEs, skin irritation
Group 4 (All Exelon patch patch-treated healthy volunteers)	W155, W159, W160, 2332, 2333, 2334, 2335, 2338, and 1101	432	Topics: deaths, SAEs, other significant AEs, all AEs, skin irritation, patch adhesion

* One patient in Study 1201 commenced treatment but was lost to follow-up and did not return for any evaluations. As a result, the patient was excluded from the safety population.

AE: Adverse Event
SAE: Serious Adverse Event
ECGs: Electrocardiograms
MMSE: Mini-Mental Status Examination
AD: Alzheimer's Disease

9.3.1 Additional Grouping

Data from Study 1201 included in Group 3 are also described separately, since subjects enrolled in that study reportedly had an unusually high incidence of adverse events.

9.4 Exposure Data

Exposure data for each study grouping are below.

9.4.1 Group 1

See Section 7.2.4.1.

9.4.2 Group 2

The duration of exposure to the study drug in Group 2 (all Exelon® patch-treated patients in Study 2320 and its open-label extension, Study 2320E1) is summarized in the following table, which I have copied from the submission.

Duration of Exposure (weeks)	All Exelon patch N = 919 n (%)
Any exposure	919 (100.0)
≥ 4 weeks	894 (97.3)
≥ 8 weeks	853 (92.8)
≥ 12 weeks	818 (89.0)
≥ 16 weeks	773 (84.1)
≥ 20 weeks	731 (79.5)
≥ 24 weeks	673 (73.2)
≥ 28 weeks	481 (52.3)
≥ 32 weeks	305 (33.2)
≥ 36 weeks	290 (31.6)
≥ 40 weeks	280 (30.5)

Duration of Exposure (weeks)	All Exelon patch N = 919 n (%)
≥ 44 weeks	274 (29.8)
≥ 48 weeks	267 (29.1)
≥ 52 weeks	212 (23.1)
Descriptive statistics (weeks)	
n	919
Mean ± SD	31.5 ± 15.7
Median	28.0
Range	0.1 - 68.1

The sponsor further points out that:

- 508 (80.4%) of the 632 patients who received open-label medication completed Study 2320E1
- 453 (71.7%) of patients achieved a patch size of 20 cm^2, with 353 (55.9%) maintaining that dose for the rest of the study

9.4.3 Group 3

The exposure in this group, consisting **of all patients with Alzheimer's Disease** exposed to the Exelon® patch, is summarized in the following table:

Duration of Exposure	All Exelon patch N = 1071 n (%)
Any exposure	1071 (100.0)
≥ 4 weeks	1039 (97.0)
≥ 8 weeks	922 (86.1)
≥ 12 weeks	869 (81.1)
≥ 16 weeks	820 (76.6)
≥ 20 weeks	772 (72.1)
≥ 24 weeks	706 (65.9)
≥ 28 weeks	481 (44.9)
≥ 32 weeks	305 (28.5)
≥ 36 weeks	290 (27.1)
≥ 40 weeks	280 (26.1)
≥ 44 weeks	274 (25.6)
≥ 48 weeks	267 (24.9)
≥ 52 weeks	212 (19.8)
Descriptive statistics (weeks)	
Mean ± SD	28.7 ± 16.4
Median	27.3
Range	0.1 - 68.1

One patient exposed to Exelon patch was lost to follow-up and was excluded from the safety population as no safety assessments were provided

9.4.4 Group 4

432 healthy volunteers were exposed to the Exelon® patch for a maximum of 3 weeks.

9.4.5 Additional Grouping: Study 1201

In this study, a total of 64 patients, **all Japanese, and all with Alzheimer's** Disease, received treatment with the Exelon® patch.

The study had two titration regimens which are explained in the following table; in each instance, the dose was increased at 4-week intervals.

Titration Regimen	Titration Sequence by Patch Size
A	5 cm^2 → 7.5 cm^2 → 10 cm^2 → 15 cm^2 → 20 cm^2
B	5 cm^2 → 10 cm^2 → 15 cm^2 → 20 cm^2

The duration of exposure to study drug by titration sequence is summarized in the following table, which I have copied from this submission.

Duration of exposure	Titration A N = 32 n (%)	Titration B N = 31 n (%)
Any exposure	32 (100.0)	31 (100.0)
0 - 4 weeks	3 (9.4)	0 (0.0)
5 - 8 weeks	2 (6.3)	3 (9.7)
9 - 12 weeks	2 (6.3)	2 (6.5)
13 - 16 weeks	1 (3.1)	3 (9.7)
17 - 20 weeks	5 (15.6)	1 (3.2)
21 - 24 weeks	14 (43.8)	19 (61.3)
> 24 weeks	5 (15.6)	3 (9.7)
Mean duration (days)	128.4	141.4
Median duration (days)	161.0	168.0
Range (days)	5.0 - 175.0	41.0 - 175.0

One patient was lost to follow-up and was excluded from the safety population as no safety assessments were provided

9.5 Disposition

9.5.1 Group 1

See Section 7.2.1

9.5.2 Group 2

Patient disposition for this group (Studies 2320 and [a subset from] 2320E1) is in the following table, which I have copied from the submission.

Disposition/Reason	All Exelon Patch n (%)
Total number of patients	
Exposed to study drug	919 (100.0)
Completed	671 (73.0)
Discontinued	248 (27.0)
Adverse event(s)	109 (11.9)
Subject withdrew consent	74 (8.1)
Lost to follow-up	21 (2.3)
Unsatisfactory therapeutic effect	15 (1.6)
Death	14 (1.5)
Protocol violation	7 (0.8)
Administrative problems	7 (0.8)
Abnormal laboratory value(s)	1 (0.1)

The most common reason for discontinuation was the occurrence of adverse events.

9.5.3 Group 3

The disposition of patients in this **grouping (all Alzheimer's Disease patients** treated with transdermal Exelon®) is summarized in the following table, which I have copied from the submission.

Disposition/Reason	All Exelon patch n (%)
Total number of patients	
Exposed to study drug	1072 (100.0)
Completed	782 (72.9)
Discontinued	290 (27.1)
Adverse event(s)	143 (13.3)
Subject withdrew consent	80 (7.5)
Lost to follow-up	22 (2.1)
Unsatisfactory therapeutic effect	15 (1.4)
Death	14 (1.3)
Protocol violation	8 (0.7)
Administrative problems	7 (0.7)
Abnormal laboratory value(s)	1 (0.1)

In this grouping too, the most common reason for discontinuation was the occurrence of adverse events.

9.5.4 Group 4

Out of 432 healthy subjects exposed to the Exelon® patch, 391 completed treatment. Subject participation and withdrawal is summarized in the next table.

Disposition/Reason	All Exelon patch n (%)
Total number of patients	
Randomized	433 (100.0)
Exposed to study drug	432 (99.8)
Completed	391 (90.3)
Discontinued	41 (9.5)
Adverse event(s)	18 (4.2)
Lost to follow-up	9 (2.1)
Protocol violation	8 (1.8)
Subject withdrew consent	5 (1.2)
Abnormal laboratory value(s)	1 (0.2)

9.5.5 Additional Grouping: Study 1201

The disposition of patients in this study is in the next table, which indicates that a relatively higher proportion, than in the other groupings, developed adverse events leading to treatment discontinuation.

Disposition/Reason	Total n (%)	Titration A n (%)	Titration B n (%)
Screened	85		
Randomized	64	32	32
Exposed to study drug	64 (100.0)	32 (100.0)	32 (100.0)
Completed	40 (62.5)	18 (56.3)	22 (68.8)
Discontinued	24 (37.5)	14 (43.8)	10 (31.3)
Adverse event(s)	20 (31.3)	12 (37.5)	8 (25.0)
Subject withdrew consent	3 (4.7)	2 (6.3)	1 (3.1)
Lost to follow-up	1 (1.6)	0 (0.0)	1 (3.1)

9.6 Common Adverse Events

9.6.1 Group 1

See Section 7.2.4.4.1

9.6.2 Group 2

Nausea, vomiting, and diarrhea were the most commonly experienced adverse events in this grouping as indicated by the following table

	All Exelon patch N = 919 n (%)
Total no. of patients with AEs	591 (64.3)
Preferred Term	
Nausea	179 (19.5)
Vomiting	156 (17.0)
Diarrhea	100 (10.9)
Dizziness	67 (7.3)
Weight decreased	63 (6.9)
Anorexia	46 (5.0)

	All Exelon patch N = 919 n (%)
Total no. of patients with AEs	591 (64.3)
Preferred Term	
Decreased appetite	36 (3.9)
Asthenia	33 (3.6)
Depression	33 (3.6)
Headache	32 (3.5)
Insomnia	31 (3.4)
Abdominal pain	30 (3.3)
Urinary tract infection	30 (3.3)
Fall	29 (3.2)
Agitation	23 (2.5)
Anxiety	23 (2.5)
Abdominal pain upper	22 (2.4)
Nasopharyngitis	20 (2.2)
Hypertension	19 (2.1)
Influenza	19 (2.1)

AEs are listed by descending frequency in the all Exelon patch group

In the open-label phase/study 2320E1 alone, the overall incidence of adverse events was 57.6%, with 10.3% being graded as severe (the rest were mild to

moderate). The most commonly experienced adverse events were nausea, vomiting, and diarrhea.

9.6.3 Group 3

67.7% of all patients with Alzheimer's Disease who were exposed to the Exelon® patch had at least one adverse event with nausea, vomiting, and diarrhea again being the most common.

9.6.4 Group 4

In all healthy volunteers exposed to the Exelon® patch, 42.8% of subjects experienced adverse events, the most common of which were headache, nausea, and vomiting.

9.6.5 Additional Grouping: Study 1201

As the sponsor table below indicates, the incidence of all adverse events and of individual common adverse events was substantially higher (regardless of titration scheduled) in this study conducted exclusively in Japanese patients with **Alzheimer's Disease, than in the other groupings, although the qualitative pattern** of adverse events was similar. The table below indicates the incidence of adverse events that occurred in at least 10% of patients in either treatment group.

	Titration A N = 32 n (%)	**Titration B N = 32 n (%)**
Total no. of patients with AEs	32 (100)	31 (100)
Preferred term		
Application site erythema	16 (50.0)	17 (54.8)
Application site pruritus	14 (43.8)	15 (48.4)
Nausea	14 (43.8)	14 (45.2)
Vomiting	13 (40.6)	16 (51.6)
Anorexia	8 (25.0)	7 (22.6)
Weight decreased	6 (18.8)	5 (16.1)
Headache	5 (15.6)	8 (25.8)
Diarrhea	4 (12.5)	5 (16.1)
Dizziness	4 (12.5)	3 (9.7)
Nasopharyngitis	4 (12.5)	7 (22.6)

9.7 Adverse Event Severity

9.7.1 Group 1

See Section 7.2.4.4.1

9.7.2 Group 2

The majority of adverse events seen in this grouping 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.

	All Exelon patch N = 919 n (%)
Total no. of patients with AEs	591 (64.3)
Mild	189 (20.6)
Moderate	282 (30.7)
Severe	120 (13.1)
Nausea	179 (19.5)
Mild	93(10.1)
Moderate	73 (7.9)
Severe	13 (1.4)
Vomiting	156 (17.0)
Mild	70 (7.6)
Moderate	71 (7.7)
Severe	15 (1.6)
Diarrhea	100 (10.9)
Mild	67 (7.3)
Moderate	30 (3.3)
Severe	3 (0.3)
Dizziness	67 (7.3)
Mild	42 (4.6)
Moderate	19 (2.1)
Severe	6 (0.7)
Weight decreased	63 (6.9)
Mild	32 (3.5)
Moderate	27 (2.9)
Severe	4 (0.4)
Anorexia	46 (5.0)
Mild	25 (2.7)
Moderate	19 (2.1)
Severe	2 (0.2)
Decreased appetite	36 (3.9)
Mild	25 (2.7)
Moderate	9 (1.0)
Severe	2 (0.2)
Asthenia	33 (3.6)
Mild	13 (1.4)
Moderate	20 (2.2)
Severe	0 (0.0)

	All Exelon patch N = 919 n (%)

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.

9.7.3 Group 3

No data regarding severity are presented for this grouping.

9.7.4 Group 4

No data regarding severity are presented for this grouping.

9.7.5 Additional Grouping: Study 1201

No data regarding severity are presented for this grouping.

9.8 Relationship Of Adverse Events To Plasma Concentrations

9.8.1 Group 1

See Section 7.2.4.4.1

9.8.2 Group 2

No data are provided for this grouping as a whole.

9.8.3 Group 3

No data are provided for this grouping as a whole.

9.8.4 Group 4

No data are provided for this grouping as a whole.

9.8.5 Data For Additional Individual Studies

Data are provided only for Studies 2331 and 1201.

9.8.5.1 Study 2331

This was an open-label, parallel-arm study comparing escalating doses of the Exelon® patch (5 cm^2, 10 cm^2, 15 cm^2, and 20 cm^2) each administered for 2 weeks with escalating doses of Exelon® capsules (1.5 mg, 3.0 mg, 4.5 mg, and 6 mg BID), each also administered for **2 weeks in patients with Alzheimer's** Disease. 49 patients completed the study, with 23 and 26 patients in the patch and capsule treatment groups, respectively.

The sponsor states that on account of the small number of patients enrolled in this study and the low incidence of adverse events, a conclusive dose-exposure relationship could not be established; there was, however, a suggestion that the risk of nausea and vomiting increased with increasing average plasma concentration and C_{max} of both rivastigmine and NAP226-90.

9.8.5.2 Study 1201

As noted earlier, in this study, a total of 64 patients, all Japanese, and all with **Alzheimer's Disease, received treatment** with the Exelon® patch. The study had

two titration regimens which are explained in the following table; in each instance, the dose was increased at 4-week intervals.

Titration Regimen	Titration Sequence by Patch Size
A	5 cm^2 → 7.5 cm^2 → 10 cm^2 → 15 cm^2 → 20 cm^2
B	5 cm^2 → 10 cm^2 → 15 cm^2 → 20 cm^2

Trough plasma concentrations of rivastigmine achieved in Japanese patients in this study were about 1.6-fold higher than those achieved with the corresponding patch sizes in Study 2331, which enrolled non-Japanese patients. The sponsor believes that these concentrations were responsible for the higher adverse event incidence in this study.

9.9 Deaths

9.9.1 Group 1

See Section 7.2.4.4.2.1

9.9.2 Group 2 (Open-Label Study 2320E1 Only)

There were a total of 5 deaths that occurred during Study 2320E1 or within 30 days after study drug discontinuation; a further death occurred about 7 weeks following study drug discontinuation. All 6 deaths occurred within the period of cut-off for the interim report, i.e., prior to February 22, 2006. The deaths are summarized in the next table.

Age/Sex	Exelon® patch size	Day* of last dose of Exelon®	Day* of death	Cause of death	Other relevant past or concomitant medical conditions
83/F	20 cm^2	126	137	Stroke	Coronary artery disease; hypertension
75/F	20 cm^2	149	150	Cerebral hemorrhage	Hypertension
69/F	15 cm^2	108	108	Pneumonia	Pulmonary tuberculosis, coronary artery disease
52/M	5 cm^2	12	14	Cardiac failure; respiratory failure	Emphysema
74/M	20 cm^2	75	77	Cardiogenic shock	Autopsy indicated that death was due to hemorrhagic shock following gastroduodenal ulceration
81/M	20 cm^2	144	195	Stroke	Atrial fibrillation; myocardial infarction

*Day of open-label phase

I have read the narratives for the above deaths. There is no reason to believe that these events were other than secondary to intercurrent illnesses common in older individuals.

An additional 4 deaths in this study occurred prior to May 31, 2006. These are listed in the next table.

Age/Sex	Exelon® patch size	Day* of last dose of Exelon®	Day* of death	Cause of death	Other relevant past or concomitant medical conditions
83/M	20 cm^2	148	153	Cardiac failure; renal failure	Pneumonia; coronary artery disease
82/F	15 cm^2	166	173	**"Cardiovascular insufficiency"**	Hypertension, coronary artery disease; atrial fibrillation; episodes of bradycardia and hypotension in double-blind phase
83/M	20 cm^2	118	132	Congestive heart failure	Hypertension; stroke; myocardial ischemia; pneumonia
88/F	15 cm^2	101	101	Cardiac disorder	Transient ischemic attack; hypertension; congestive heart failure; renal failure; alcoholism; tobacco use; aspiration pneumonia

I have read the narratives for the above deaths as well. There is again no reason to believe that these events were other than secondary to intercurrent illnesses common in older individuals.

9.9.3 Group 3

There were no reported deaths in this group other than those which occurred in Studies 2320, 2320E1, and 1201, and which are addressed separately in this **section on "Deaths."**

9.9.4 Group 4

There were no deaths in the clinical trials included in this group.

9.9.5 Additional Grouping: Study 1201

A single patient participating in this study (and in Titration Regimen A) died. This 67 year old man with a previous history of bronchiectasis was diagnosed to have a non-tuberculous mycobacterial infection about 3 weeks after the study drug was discontinued (he received study drug for 140 days); the illness may have developed while on study drug. The patient died of respiratory failure about 6 weeks after study drug was stopped.

9.10 Serious Adverse Events (Including Fatal Serious Adverse Events)

9.10.1 Group 1

See Section 7.2.4.4.2.2.

9.10.2 Group 2 (Open-Label Study 2320E1 Only)

63 patients enrolled in this open-label uncontrolled extension study experienced serious adverse events either while receiving study drug or within 30 days after study drug discontinuation, prior to the cut-off date of February 22, 2006.

The incidence of such adverse events in specific primary system organ classes are in the sponsor table below.

Primary system organ class	Total N = 632 n (%)
Total patients with SAEs	63 (10.0)
Infections & infestations	15 (2.4)
Gastrointestinal disorders	12 (1.9)
Cardiac disorders	10 (1.6)
Injury, poisoning & procedural complications	9 (1.4)
Nervous system disorders	9 (1.4)
Metabolism & nutrition disorders	8 (1.3)
Respiratory, thoracic & mediastinal disorders	6 (0.9)
Psychiatric disorders	5 (0.8)
Surgical & medical procedures	2 (0.3)
Vascular disorders	2 (0.3)
Ear & labyrinth disorders	1 (0.2)
Investigations	1 (0.2)
Musculoskeletal & connective tissue disorders	1 (0.2)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	1 (0.2)
Renal & urinary disorders	1 (0.2)

System Organ Class ordered by descending frequency

I have read the narratives for the serious adverse events. All appear attributable either to intercurrent illnesses generally common in such a population or to predictable cholinomimetic effects of rivastigmine. No skin reactions at the site of Exelon® patch application were classed as serious adverse events.

A further 17 patients experienced serious adverse events (fatal or non-fatal) in this study through May 31, 2006. Narratives for these events have also been reviewed and again suggest that these events were attributable to intercurrent illnesses common in this population or to predictable cholinomimetic effects of rivastigmine.

9.10.3 Group 3

124 patients in this grouping experienced serious adverse events through February 22, 2006. The overall incidence and qualitative pattern of serious adverse events in this population is similar to that seen in the subsets in Groups 1 and 2, as indicated by the following table.

Primary system organ class class	All Exelon patch N = 1071 n (%)
Total patients with SAEs	124 (11.6)
Nervous system disorders	28 (2.6)
Infections & infestations	24 (2.2)
Cardiac disorders	21 (2.0)
Gastrointestinal disorders	21 (2.0)
Injury, poisoning & procedural complications	14 (1.3)
Psychiatric disorders	13 (1.2)
Metabolism & nutrition disorders	12 (1.1)
Respiratory, thoracic & mediastinal disorders	9 (0.8)
General disorders & administration site conditions	4 (0.4)
Neoplasms benign, malignant & unspecified(incl cysts & polyps)	4 (0.4)
Renal & urinary disorders	4 (0.4)
Surgical & medical procedures	4 (0.4)
Investigations	3 (0.3)
Vascular disorders	2 (0.2)
Blood & lymphatic system disorders	1 (0.1)
Ear & labyrinth disorders	1 (0.1)
Hepatobiliary disorders	1 (0.1)
Musculoskeletal & connective tissue disorders	1 (0.1)

I have read the narrative for these serious adverse events; my conclusions are similar to those made for Groups 1 and 2.

9.10.4 Group 4

No serious adverse events occurred in this population.

9.10.5 Additional Grouping: Study 1201

5/64 patients enrolled in this study experienced serious adverse events: these were wound infection, mycobacterial infection, cerebral embolism, thermal burn, and laryngeal cancer. None of these events was attributable to study drug.

9.11 Discontinuations Due To Adverse Events

9.11.1 Group 1

See Section 7.2.4.4.2.3

9.11.2 Group 2 (Open-Label Study 2320E1 Only)

56 patients enrolled in this open-label uncontrolled extension study experienced adverse events that led to treatment discontinuation either while receiving study

drug or within 30 days after study drug discontinuation, prior to the cut-off date of February 22, 2006.

The incidence of such adverse events in different primary system organ classes and the maximum and mode patch sizes in each instance are in the sponsor table below.

	Exelon 20 cm²		Exelon 15 cm²		Exelon 5-10 cm²		Total
	Max	Mode	Max	Mode	Max	Mode	
	N = 453	N = 353	N = 107	N = 82	N = 72	N = 197	N = 632
Primary system organ class	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any primary system organ class	20 (4.4)	6 (1.7)	19 (17.8)	10 (12.2)	17 (23.6)	40 (20.3)	56 (8.9)
General disorders & administration site conditions	5 (1.1)	1 (0.3)	7 (6.5)	5 (6.1)	9(12.5)	15 (7.6)	21 (3.3)
Gastrointestinal disorders	5 (1.1)	1 (0.3)	9 (8.4)	2 (2.4)	6 (8.3)	17 (8.6)	20 (3.2)
Nervous system disorders	5 (1.1)	3 (0.8)	0 (0.0)	1 (1.2)	2 (2.8)	3 (1.5)	7 (1.1)
Skin & subcutaneous tissue disorders	0 (0.0)	0 (0.0)	2 (1.9)	0 (0.0)	2 (2.8)	4 (2.0)	4 (0.6)
Cardiac disorders	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)	3 (1.5)	3 (0.5)
Metabolism & nutrition disorders	2 (0.4)	0 (0.0)	0 (0.0)	1 (1.2)	1 (1.4)	2 (1.0)	3 (0.5)
Infections & infestations	2 (0.4)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	2 (0.3)
Injury, poisoning & procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)	1 (0.2)

23 patients (4.0%) discontinued the study on account of skin reactions at the application site (these included 13/51 patients enrolled in the study at sites in Israel); 19 of these patients were listed in the above table under "General disorders and administrative site conditions" and 4 patients were listed under "Skin and subcutaneous tissue disorders."

I have read the narratives for the above adverse events. All appear attributable either to intercurrent illnesses generally common in such a population, to skin reactions at the site of Exelon® patch administration, or to predictable cholinomimetic effects of rivastigmine.

9.11.3 Group 3

153 (14.3%) of patients in this grouping discontinued study medication on account of adverse events. The incidence of such adverse events in different primary system organ classes is in the table below, which I have abstracted from data contained in the submission. The pattern of adverse events is similar to that seen in Groups 1 and 2.

Primary system organ class	N	%
Any	153	14.3
Blood and lymphatic system disorders	1	0.1

Primary system organ class	N	%
Cardiac disorders	9	0.8
Gastrointestinal disorders	52	4.9
General disorders and administration site conditions	39	3.6
Infections and infestations	4	0.4
Injury, poisoning and procedural complications	2	0.2
Investigations	7	0.7
Metabolism and nutritional disorders	12	1.1
Neoplasms benign, malignant, and unspecified	4	0.4
Nervous system disorders	30	2.8
Psychiatric disorders	11	1.0
Renal and urinary disorders	1	0.1
Respiratory, thoracic, and mediastinal disorders	2	0.2
Skin and subcutaneous tissue disorders	12	1.1
Vascular disorders	1	0.1

I have read the narratives for the above adverse events. As with adverse events leading to treatment discontinuation in Groups 1 and 2, the events for Group 3 appear attributable either to intercurrent illnesses generally common in such a population, to skin reactions at the site of Exelon® patch administration, or to predictable cholinomimetic effects of rivastigmine.

9.11.4 Group 4

21/432 (4.9%) subjects in this grouping discontinued treatment on account of adverse events. The incidence of such adverse events in different primary system organ classes is in the table below, which I have abstracted from data contained in the submission.

Primary system organ class	N	%
Any	21	4.9
Cardiac disorders	1	0.2
Gastrointestinal disorders	12	2.8
General disorders and administration site conditions	3	0.7
Infections and infestations	1	0.2
Investigations	1	0.2
Metabolism and nutritional disorders	1	0.2
Nervous system disorders	8	1.9
Pregnancy, puerperium, and perinatal conditions	1	0.2
Psychiatric disorders	3	0.7
Vascular disorders	5	1.2

Among the gastrointestinal adverse events above were nausea (seen in 2.5% of patients) and vomiting (seen in 1.9%).

I have read through the list of individual adverse events that lead to treatment discontinuation. All were largely minor and/or consistent with the cholinomimetic effects of rivastigmine; the exception was a single patient who became pregnant during the study.

9.11.5 Additional Grouping: Study 1201

In Treatment Group A, 12 (37.5%) of patients discontinued treatment on account of adverse events. The specific adverse events seen included application site dermatitis, application site pruritus, application site erythema, decreased weight,

anorexia, nausea, vomiting, reflux esophagitis, dizziness, somnolence, ventricular extrasystoles, bradycardia, atrial fibrillation, tachycardia, reflux esophagitis.

In Treatment Group B, 8 (25.8%) of patients discontinued treatment on account of adverse events. The specific adverse events seen included application site dermatitis, application site pruritus, application site erythema, application site edema, decreased weight, headache, loss of control of legs, anorexia, nausea, vomiting, epigastric discomfort, abdominal pain, cerebral embolism.

These adverse events were all attributable to incidental illnesses, patch application site reactions, and predictable cholinomimetic effects of rivastigmine.

9.12 Specific Adverse Events: Skin Irritation At Administration Site

9.12.1 Group 1

See Section 7.2.4.8.

9.12.2 Group 2

In this pooled dataset, the majority of skin reactions were classed as slight or mild.

The overall incidence of all skin reactions and of skin reactions in various categories was comparable between those who had the Exelon® patch applied for any length of time and those whose patch was applied for 52 weeks as indicated in the following table (percentages are in parentheses).

Skin irritation	All Exelon Patch N = 919	Exelon patch 52 weeks N = 212
Patients with any rating - N	896	212
Patients with no skin irritation	331 (36.9)	64 (30.2)
Patients with no, slight or mild skin irritation	709 (79.1)	161 (75.9)
- Any severe rating – n (%)	43 (4.8)	9 (4.2)
Erythema - N	896	212
- No, slight or mild – n (%)	748 (83.5)	175 (82.5)
- Moderate or severe – n (%)	148 (16.5)	37 (17.5)
Edema- N	896	212
- No, slight or mild – n (%)	860 (96.0)	203 (95.8)
- Moderate or severe– n(%)	36 (4.0)	9 (4.2)
Scaling - N	896	212
- No, dryness, glossy effect, or mild – n (%)	862 (96.2)	205 (96.7)
- Moderate or severe– n (%)	34 (3.8)	7 (3.3)
Fissures - N	896	212
- No or superficial – n (%)	879 (98.1)	209 (98.6)
- Single or deep – n (%)	17 (1.9)	3 (1.4)
Pruritus - N	896	212
- Negative, slight or mild – n (%)	780 (87.1)	181 (85.4)
- Moderate or severe – n (%)	116 (12.9)	31 (14.6)
Pain, stinging and/or burning- N	896	212
- No, slight or mild – n (%)	871 (97.2)	205 (96.7)
- Moderate or severe– n (%)	25 (2.8)	7 (3.3)

9.12.3 Group 3

The incidence of various application site adverse reactions, classed according to preferred term in this grouping (N = 1071) is below, in a table that I have abstracted from data contained in the submission.

Preferred Term	N (%)
Application site erythema	41 (3.8)
Application site pruritus	38 (3.5)
Application site irritation	12 (1.1)
Application site dermatitis	10 (0.9)
Application site edema	7 (0.7)
Application site reaction	4 (0.4)
Application site exfoliation	2 (0.2)
Application site pain	2 (0.2)
Application site discomfort	1 (0.1)
Application site eczema	1 (0.1)
Application site swelling	1 (0.1)
Application site vesicles	1 (0.1)

9.12.4 Group 4

The incidence of various application site adverse reactions, classed according to preferred term in this grouping (N = 432) is below, in a table that I have abstracted from data contained in the submission.

Preferred Term	N (%)
Application site pruritus	7 (1.6)
Application site erythema	2 (0.5)
Application site pain	2 (0.5)
Application site warmth	1 (0.2)

9.12.5 Individual Studies

9.12.5.1 Study W160

The key statements made by the sponsor include the following:

- 138 patients were enrolled in the study
- About 80% of those enrolled had little or only mild erythema
- 25 (18.1%) of subjects had a skin irritation score ≥ 2 (at least intense erythema). The incidence of intense erythema was much higher in female subjects (24%) than in male subjects (6.5%)
- Only 6 subjects showed a skin irritation score of 3 (erythema with induration and vesicles); all were female and aged between 52 and 75 years
- There were no severe skin reactions (grade 4) during the study

9.12.5.2 Study 0401

The incidence of several types of skin abnormality are summarized in the following table

Abnormality	Incidence	Rater
Slight erythema	91%	Clinician
Mild erythema	55%	Clinician
Very slight edema	17%	Clinician
Very slight pruritus	16%	Clinician
Moderate erythema	14%	Clinician
Moderate pruritus	5%	Clinician
Moderate edema	2%	Clinician
Mild erythema	73%	Caregiver
Mild pruritus	13%	Caregiver

There were no instances of severe skin reaction.

9.13 Adverse Events Associated With Transition From Double-Blind To Open-Label Treatment

An evaluation was performed of the incidence of all adverse events, serious adverse events, and discontinuations due to adverse events during the first 4 weeks of open-label treatment during Study 2320E1 (when all patients received the 10 cm^2 Exelon® patch), based on treatment received during the double-blind study 2320.

9.13.1 All Adverse Events (Transitional Period Only)

As the following sponsor table indicates, the overall incidence of all adverse events, and the incidence of nausea and vomiting, in particular, during the first 4 weeks of Study 2320 was highest in those who received placebo during the double blind phase and least in those who received the 20 cm^2 patch during the double-blind phase ; the incidence of adverse events during the transition from the capsule formulation of Exelon® to the Exelon® patch in a 10 cm^2 dose was low.

	DB Exelon			DB Placebo	Total
	20 cm^2 patch	10 cm^2 patch	Capsule		
	N = 152	N = 155	N = 148	N = 177	N = 632
	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any AE	18 (11.8)	24 (15.5)	25 (16.9)	53 (29.9)	120 (19.0)
Nausea	2 (1.3)	4 (2.6)	4 (2.7)	17 (9.6)	27 (4.3)
Vomiting	0 (0.0)	3 (1.9)	3 (2.0)	13 (7.3)	19 (3.0)
Diarrhea	1 (0.7)	2 (1.3)	2 (1.4)	4 (2.3)	9 (1.4)
Dizziness	0 (0.0)	4 (2.6)	0 (0.0)	3 (1.7)	7 (1.1)
Anorexia	1 (0.7)	2 (1.3)	2 (1.4)	1 (0.6)	6 (0.9)
Decreased appetite	1 (0.7)	0 (0.0)	1 (0.7)	4 (2.3)	6 (0.9)
Urinary tract infection	0 (0.0)	1 (0.6)	0 (0.0)	4 (2.3)	5 (0.8)
Weight decreased	0 (0.0)	1 (0.6)	2 (1.4)	2 (1.1)	5 (0.8)
Bradycardia	0 (0.0)	2 (1.3)	0 (0.0)	2 (1.1)	4 (0.6)
Vertigo	0 (0.0)	1 (0.6)	1 (0.7)	2 (1.1)	4 (0.6)
Abdominal pain upper	2 (1.3)	0 (0.0)	1 (0.7)	1 (0.6)	4 (0.6)
Confusional state	0 (0.0)	1 (0.6)	1 (0.7)	2 (1.1)	4 (0.6)
Hypertension	1 (0.7)	0 (0.0)	0 (0.0)	3 (1.7)	4 (0.6)
Asthenia	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.1)	3 (0.5)
Irritability	0 (0.0)	1 (0.6)	1 (0.7)	1 (0.6)	3 (0.5)
Influenza	2 (1.3)	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.5)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.7)	3 (0.5)
Insomnia	0 (0.0)	1 (0.6)	1 (0.7)	1 (0.6)	3 (0.5)
Cough	2 (1.3)	0 (0.0)	1 (0.7)	0 (0.0)	3 (0.5)
Pruritus	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.1)	3 (0.5)

DB = double blind
AEs ordered by descending frequency in the total group

9.13.2 Serious Adverse Events (Transitional Period Only)

The overall incidence of serious adverse events during the first 4 weeks of Study 2320E1 was low, but as the next sponsor table indicates was also highest in those who received placebo during the double-blind phase/study 2320.

	DB Exelon			DB Placebo	Total
	20 cm^2 patch	10 cm^2 patch	Capsule		
Primary system organ class	N = 152	N = 155	N = 148	N = 177	N = 632
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1 (0.7)	3 (1.9)	0 (0.0)	5 (2.8)	9 (1.4)
Cardiac disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac failure	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Ear and labyrinth disorders	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Vertigo	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Irritable bowel syndrome	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Injury, poisoning & procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Clavicle fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.3)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Hemiparesis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Sciatica	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Anxiety disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (0.7)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.3)
Aspiration	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory failure	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

9.13.3 Discontinuations Due To Adverse Events (Transitional Period Only)

The overall incidence of discontinuations due to adverse events during the first 4 weeks of Study 2320E1 was low, but as the next sponsor table indicates was again highest in those who received placebo during the double-blind phase/study 2320.

Primary system organ class Preferred term	20 cm^2 patch N = 152 n (%)	DB Exelon 10 cm^2 patch N = 155 n (%)	Capsule N = 148 n (%)	DB Placebo N = 177 n (%)	Total N = 632 n (%)
Total	1 (0.7)	2 (1.3)	4 (2.7)	9 (5.1)	16 (2.5)
Cardiac disorders	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.3)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Cardiac failure	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	0 (0.0)	1 (0.6)	1 (0.7)	4 (2.3)	6 (0.9)
Nausea	0 (0.0)	1 (0.6)	0 (0.0)	3 (1.7)	4 (0.6)
Diarrhea	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.6)	2 (0.3)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
General disorders & administration site conditions	0 (0.0)	1 (0.6)	2 (1.4)	3 (1.7)	6 (0.9)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.3)
Application site dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Application site erythema	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Application site irritation	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Application site pain	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Application site pruritus	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Injury, poisoning & procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Metabolism & nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.3)
Balance disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Respiratory, thoracic & mediastinal disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Respiratory failure	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Skin & subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.1)	3 (0.5)
Pruritus	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.6)	2 (0.3)
Skin irritation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.2)

9.14 Clinical Laboratory Evaluations

9.14.1 Study 2320

No routine post-baseline laboratory assessments were performed. Any laboratory abnormalities reported as adverse events were not considered clinically significant (and have been reviewed by me).

9.14.2 Study 2320E1

No routine post-baseline laboratory assessments were performed.

9.14.3 Additional Studies

9.14.3.1 Study 1201

No clinically significant laboratory abnormalities were noted in this study.

9.14.3.2 Study 0401

No clinically significant laboratory abnormalities were noted in this study.

9.14.3.3 Study 2331

No clinically significant laboratory abnormalities were noted in this study.

9.15 Vital Signs

9.15.1 Group 1

See Section 7.2.4.6

9.15.2 Group 2: Study 2320E1 only

Among the changes seen (from Week 24) in the open-label extension study were the following:

- A small increase in mean sitting pulse rate
- Small mean reductions in sitting and standing systolic and diastolic blood pressure
- A mean reduction in body weight of 1.16 kg from Week 24. A reduction in weight ≥ 7% occurred in 16.8% of patients, and an increase in body weight ≥ 7% occurred in 4.9% of patients.

9.16 Electrocardiograms

Electrocardiogram evaluations were performed only in Group 1. See Section 7.2.4.7 for further details.

9.17 Sponsor's Conclusions

The sponsor has concluded, based on the entire clinical development program for Exelon® that the patches of 10 cm^2 and 20 cm^2 size were well-tolerated in **patients with Alzheimer's Disease, and** that no new or unexpected safety concerns were made apparent by the development program.

9.18 Reviewer's Comments

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.

10. 120-Day Safety Update

This update contains the full clinical study report for Study 2320E1 which is now complete, as well as the 120-Day Safety Update proper, whose data are derived entirely from Study 2320E1.

The main contents of this update that pertain to safety will be summarized under the following headings. As might be obvious, a subset of the data described in this update has already been summarized in the interim report for Study 2320E in the Integrated Summary of Safety contained in the original NDA.

Where considered important specific safety data have been compared between the interim report (Interim Clinical Study Report; Interim CSR; interim report) included in the original submission of this application and the final report for Study 2320E1 (Final Clinical Study Report; Final CSR; final report) included in the 120-Day Safety Update. The populations included in the interim and final reports are also referred to as interim and final cohorts, respectively.

10.1 Disposition

The 120-day safety update includes information for 238 additional patients who entered Study 2320E1 after July 20, 2005. Of the total of 870 patients who entered this open-label phase/study received at least one dose of open-label study medication, of whom 704 (80.9%) completed the extension. As the next (sponsor) table indicates, 8.3% of patients discontinued on account of adverse events.

The disposition of patients included in the interim report included in the original submission of this application is compared with that of the patients in the final report for Study 2320E1 in the following sponsor table.

	Interim CSR 04-Aug-06 N= 632	Final CSR 24-Oct-06 N = 870
Disposition/Reason for discontinuation	**n (%)**	**n (%)**
No. of patients who received OL medication	632 (100.0)	870 (100.0)
No. of patients who completed OL extension	508 (80.4)	704 (80.9)
No. of patients who discontinued	124 (19.6)	166 (19.1)
Adverse event(s)	55 (8.7)	72 (8.3)
Subject withdrew consent	34 (5.4)	47 (5.4)
Lost to follow-up	15 (2.4)	17 (2.0)
Unsatisfactory therapeutic effect	8 (1.3)	10 (1.1)
Death	5 (0.8)	8 (0.9)
Administrative problems	4 (0.6)	7 (0.8)
Protocol deviation	3 (0.5)	5 (0.6)

10.2 Exposure

The duration of exposure to study medication in the interim and final reports is compared in the following table, which I have copied from the submission.

	Interim CSR 04-Aug-06	Final CSR 24-Oct-06
Duration of Exposure	**n (%)**	**n (%)**
Any exposure	632 (100.0)	870 (100.0)
≥ 4 weeks	613 (97.0)	848 (97.5)
≥ 8 weeks	595 (94.1)	826 (94.9)
≥ 12 weeks	571 (90.3)	793 (91.1)
≥ 16 weeks	546 (86.4)	763 (87.7)
≥ 20 weeks	529 (83.7)	739 (84.9)
≥ 24 weeks	516 (81.6)	716 (82.3)
≥ 28 weeks	381 (60.3)	512 (58.9)
Mean ± SD	25.4 ± 7.34	25.6 ± 7.03
Median	28.0	28.0
Range	0.1- 44.4	0.1 – 44.4

The duration of exposure by mode patch size in the entire study population, based on the final report alone, is in the following sponsor table.

	Patient's mode patch size			
	Exelon 20 cm^2	Exelon 15 cm^2	Exelon 5-10 cm^2	Total
Duration of Exposure	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any exposure	501 (100.0)	120 (100.0)	249 (100.0)	870 (100.0)
≥ 4 weeks	501 (100.0)	120 (100.0)	227 (91.2)	848 (97.5)
≥ 8 weeks	501 (100.0)	119 (99.2)	206 (82.7)	826 (94.9)
≥ 12 weeks	501 (100.0)	113 (94.2)	179 (71.9)	793 (91.1)
≥ 16 weeks	492 (98.2)	106 (88.3)	165 (66.3)	763 (87.7)
≥ 20 weeks	482 (96.2)	100 (83.3)	157 (63.1)	739 (84.9)
≥ 24 weeks	468 (93.4)	95 (79.2)	153 (61.4)	716 (82.3)
≥ 28 weeks	327 (65.3)	70 (58.3)	115 (46.2)	512 (58.9)
Mean ± SD	27.8 (3.12)	25.6 (5.78)	21.1 (10.38)	25.6 (7.03)
Median	28.0	28.0	27.9	28.0
Range	12.0 – 44.4	7.9 – 32.0	0.1 - 41.3	0.1 – 44.4

10.3 All Adverse Events

As the sponsor table below indicates, 57.6% of all patients participating in this study developed adverse events. The incidence of adverse events that occurred in more than 2% of patients in cohorts included in the interim and final study reports are displayed in the following table, which I have copied from the submission. As the table indicates, nausea, vomiting, and diarrhea were the most frequent of adverse events in both cohorts.

Preferred term	Interim CSR 04-Aug-06 N = 632 n (%)	Final CSR 24-Oct-06 N = 870 n (%)
Patients with AEs	364 (57.6)	501 (57.6)
Nausea	107 (16.9)	137 (15.7)
Vomiting	92 (14.6)	124 (14.3)
Diarrhea	53 (8.4)	68 (7.8)
Dizziness	40 (6.3)	53 (6.1)
Weight decreased	35 (5.5)	52 (6.0)
Anorexia	28 (4.4)	37 (4.3)
Urinary tract infection	21 (3.3)	28 (3.2)
Fall	19 (3.0)	25 (2.9)
Asthenia	20 (3.2)	24 (2.8)
Decreased appetite	21 (3.3)	24 (2.8)
Headache	13 (2.1)	21 (2.4)
Insomnia	15 (2.4)	20 (2.3)
Hypertension	13 (2.1)	20 (2.3)
Abdominal pain	14 (2.2)	18 (2.1)
Abdominal pain upper	13 (2.1)	17 (2.0)
Gastritis	12 (1.9)	17 (2.0)
Nasopharyngitis	12 (1.9)	17 (2.0)

As the incidence of agitation was 15 (1.7) in the final CSR, this AE is not reported in the table. The incidence of agitation in the interim report was 14 (2.2).

10.4 Deaths, Serious Adverse Events, And Discontinuations Due To Adverse Events

The overall incidence of deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs) in the interim and final cohorts is compared in the following sponsor table, which I have copied from the submission. As the table indicates, the incidence of these events was similar in the two populations.

Patients with serious or significant AEs	Interim CSR 04-Aug-06 N = 632 n (%)	Final CSR 24-Oct-06 N = 870 n (%)
Death	5 (0.8)	8 (0.9)
SAEs	63 (10.0)	82 (9.4)
Discontinued due to AEs	56 (8.9)	73 (8.4)
Discontinued due to SAEs	9 (1.4)	15 (1.7)
Discontinued due to non-serious AEs	47 (7.4)	58 (6.7)

10.4.1 Deaths

There were no deaths in this study other than those described in the Summary of Safety contained in the original submission under this IND and in Section 9.9.2 of this review.

10.4.2 Serious Adverse Events

The overall incidence of serious adverse events (SAEs) in specific primary organ system classes in the interim and final cohorts is compared in the following sponsor table, which I have copied from the submission. As the table indicates, the incidence of the 3 most common categories of these events was similar in the two populations.

	Interim CSR 04-Aug-06	**Final CSR 24-Oct-06**
Primary system organ class	**N = 632 n (%)**	**N = 870 n (%)**
Total patients with SAEs	63 (10.0)	82 (9.4)
Gastrointestinal disorders	12 (1.9)	17 (2.0)
Infections & infestations	15 (2.4)	17 (2.0)
Cardiac disorders	10 (1.6)	15 (1.7)
Nervous system disorders	9 (1.4)	13 (1.5)
Injury, poisoning & procedural complications	9 (1.4)	12 (1.4)
Metabolism & nutrition disorders	8 (1.3)	11 (1.3)
Respiratory, thoracic & mediastinal disorders	6 (0.9)	9 (1.0)
Psychiatric disorders	5 (0.8)	5 (0.6)
Renal & urinary disorders	1 (0.2)	4 (0.5)
Musculoskeletal & connective tissue disorders	1 (0.2)	2 (0.2)
Surgical & medical procedures	2 (0.3)	2 (0.2)
Vascular disorders	2 (0.3)	2 (0.2)
Ear & labyrinth disorders	1 (0.2)	1 (0.1)
Hepatobiliary disorders	0 (0.0)	1 (0.1)
Investigations	1 (0.2)	1 (0.1)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	1 (0.2)	1 (0.1)
Skin & subcutaneous disorders	0 (0.0)	1 (0.1)

I have read the narratives for all additional serious adverse events tabulated in the 120-Day Safety Update (a number of these narratives were also included in the original submission under the IND); all appear attributable to intercurrent illnesses or predictable cholinomimetic effects of the study drug.

10.4.3 Discontinuations Due To Adverse Events

The overall incidence of adverse events leading to treatment discontinuations (SAEs) in specific primary organ system classes in the interim and final cohorts is compared in the following sponsor table, which I have copied from the

submission. As the table indicates, the incidence of the 3 most common categories of these events was similar in the two populations.

Primary system organ class	Interim CSR 04-Aug-06 N = 632 n (%)	Final CSR 24-Oct-06 N = 870 n (%)
Any primary system organ class	56 (8.9)	73 (8.4)
General disorders & administration site conditions	21* (3.3)	33* (3.8)
Gastrointestinal disorders	20 (3.2)	25 (2.9)
Nervous system disorders	7 (1.1)	10 (1.1)
Cardiac disorders	3 (0.5)	6 (0.7)
Metabolism & nutrition disorders	3 (0.5)	3 (0.3)
Infections & infestations	2 (0.3)	2 (0.2)
Injury, poisoning & procedural complications	1 (0.2)	1 (0.1)

Primary system organ class	Interim CSR 04-Aug-06 N = 632 n (%)	Final CSR 24-Oct-06 N = 870 n (%)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	1 (0.2)	1 (0.1)
Renal and urinary disorders	0 (0.0)	1 (0.1)
Respiratory, thoracic & mediastinal disorders	1 (0.2)	1 (0.1)
Skin & subcutaneous tissue disorders	4* (0.6)	1* (0.1)
Vascular disorders	1 (0.2)	1 (0.1)

* In the interim CSR, AEs for 3 patients who were discontinued were incorrectly coded under the SOC Skin & subcutaneous tissue disorders. However, in the final CSR, these events were correctly recoded as application site reactions under the SOC General disorders & administration site conditions.

I have read the narratives for all the additional discontinuations due to adverse events that have been tabulated in the 120-Day Safety Update. All appear attributable to either well-established adverse effects of rivastigmine (i.e., cholinomimetic effects) or to intercurrent illnesses common in the elderly. None were clearly attributable to the study drug.

10.5 Vital Signs

Among the changes seen (from Week 24) in the entire (final) cohort participating in open-label extension study were the following:

- Small mean reductions in sitting and standing systolic and diastolic blood pressure
- A mean reduction in body weight of 1.05 kg from Week 24. A reduction in weight ≥ 7% occurred in 15.7% of patients, and an increase in body weight ≥ 7% occurred in 5.4% of patients.

Note that the incidence of weight loss was slightly smaller in the full study cohort as compared with the interim cohort.

10.6 Adverse Events Associated With Transition From Double-Blind To Open-Label Treatment

An evaluation was performed for the entire study population of the incidence of all adverse events, serious adverse events, and discontinuations due to adverse events during the first 4 weeks of open-label treatment during Study 2320E1 (when all patients received the 10 cm^2 Exelon® patch), based on treatment received during the double-blind study 2320.

10.6.1 All Adverse Events (Transitional Period Only)

As the following sponsor table indicates, the overall incidence of all adverse events, and the incidence of nausea and vomiting, in particular, during the first 4 weeks of Study 2320 was highest in those who received placebo during the double blind phase and least in those who received the 20 cm^2 patch during the double-blind phase; the incidence of adverse events during the transition from the capsule formulation of Exelon® to the Exelon® patch in a 10 cm^2 dose was low. The table below is based on the entire study cohort.

	20 cm^2 patch N = 209 n (%)	DB Exelon 10 cm^2 patch N = 204 n (%)	Capsule N = 209 n (%)	DB Placebo N = 248 n (%)	Total N = 870 n (%)
Patients with any AE	31 (14.8)	31 (15.2)	30 (14.4)	70 (28.2)	162 (18.6)
Nausea	4 (1.9)	5 (2.5)	5 (2.4)	21 (8.5)	35 (4.0)
Vomiting	1 (0.5)	3 (1.5)	4 (1.9)	15 (6.0)	23 (2.6)
Diarrhea	1 (0.5)	2 (1.0)	3 (1.4)	6 (2.4)	12 (1.4)
Dizziness	0 (0.0)	5 (2.5)	0 (0.0)	5 (2.0)	10 (1.1)
Anorexia	2 (1.0)	2 (1.0)	2 (1.0)	1 (0.4)	7 (0.8)
Decreased appetite	1 (0.5)	1 (0.5)	1 (0.5)	4 (1.6)	7 (0.8)
Headache	1 (0.5)	3 (1.5)	0 (0.0)	2 (0.8)	6 (0.7)
Urinary tract infection	0 (0.0)	2 (1.0)	0 (0.0)	4 (1.6)	6 (0.7)
Weight decreased	0 (0.0)	1 (0.5)	3 (1.4)	2 (0.8)	6 (0.7)
Abdominal pain upper	3 (1.4)	0 (0.0)	1 (0.5)	1 (0.4)	5 (0.6)
Bradycardia	0 (0.0)	2 (1.0)	0 (0.0)	2 (0.8)	4 (0.5)
Vertigo	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.8)	4 (0.5)
Application site irritation	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.4)	4 (0.5)
Application site pruritus	0 (0.0)	0 (0.0)	3 (1.4)	1 (0.4)	4 (0.5)
Asthenia	0 (0.0)	0 (0.0)	1 (0.5)	3 (1.2)	4 (0.5)
Fall	1 (0.5)	0 (0.0)	0 (0.0)	3 (1.2)	4 (0.5)
Confusional state	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.8)	4 (0.5)
Depression	1 (0.5)	0 (0.0)	0 (0.0)	3 (1.2)	4 (0.5)
Hypertension	1 (0.5)	0 (0.0)	0 (0.0)	3 (1.2)	4 (0.5)

DB = double blind
AEs ordered by descending frequency in the total group

The incidence of adverse events during this period is compared between the interim and final cohorts in the next table, which I have copied from the submission.

	Interim CSR 04-Aug-06 N = 632 n (%)	Final CSR 24-Oct-06 N = 870 n (%)
Patients with any AE	120 (19.0)	162 (18.6)
Nausea	27 (4.3)	35 (4.0)
Vomiting	19 (3.0)	23 (2.6)
Diarrhea	9 (1.4)	12 (1.4)
Dizziness	7 (1.1)	10 (1.1)
Anorexia	6 (0.9)	7 (0.8)
Decreased appetite	6 (0.9)	7 (0.8)
Headache	0 (0.0)	6 (0.7)
Urinary tract infection	5 (0.8)	6 (0.7)
Weight decreased	5 (0.8)	6 (0.7)
Abdominal pain upper	4 (0.6)	5 (0.6)
Bradycardia	4 (0.6)	4 (0.5)
Vertigo	4 (0.6)	4 (0.5)
Application site irritation	1 (0.2)	4 (0.5)
Application site pruritus	1 (0.2)	4 (0.5)
Asthenia	3 (0.5)	4 (0.5)
Fall	3 (0.5)	4 (0.5)
Confusional state	4 (0.6)	4 (0.5)
Depression	0 (0.0)	4 (0.5)
Hypertension	4 (0.6)	4 (0.5)

As the table above indicates, the overall incidence of adverse events, and the incidence of the most common of adverse events was similar between the 2 populations.

10.6.2 Serious Adverse Events (Transitional Period Only)

The overall incidence of serious adverse events during the first 4 weeks of Study 2320E1 was low, but as the next sponsor table indicates was also highest in those who received placebo during the double-blind phase/study 2320.

	DB Exelon			DB	Total
	20 cm^2 patch	10 cm^2 patch	Capsule	Placebo	
Primary system organ class	N = 209	N = 204	N = 209	N = 248	N = 870
Preferred term	n (%)	n (%)	n (%)	n (%)	n (%)
Total	1 (0.5)	3 (1.5)	0 (0.0)	5 (2.0)	9 (1.0)
Cardiac disorders	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac failure	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ear and labyrinth disorders	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Vertigo	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal disorders	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Irritable bowel syndrome	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Injury, poisoning & procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Clavicle fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.2)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Hemiparesis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Sciatica	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Anxiety disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	2 (0.2)
Aspiration	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory failure	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

The incidence of adverse events during this period is compared between the interim and final cohorts in the next table, which I have copied from the submission.

Primary system organ class Preferred term	Interim CSR 04-Aug-06 N = 632 n (%)	Final CSR 24-Oct-06 N = 870 n (%)
Total	16 (2.5)	21 (2.4)
Cardiac disorders	2 (0.3)	2 (0.2)
Bradycardia	1 (0.2)	1 (0.1)
Cardiac failure	1 (0.2)	1 (0.1)
Gastrointestinal disorders	6 (0.9)	7 (0.8)
Nausea	4 (0.6)	5 (0.6)
Diarrhea	2 (0.3)	2 (0.2)
Abdominal pain upper	1 (0.2)	1 (0.1)
Vomiting	0 (0.0)	1 (0.1)
General disorders & administration site conditions	6 (0.9)	14 (1.6)
Application site irritation	1 (0.2)	4 (0.5)
Application site pruritus	1 (0.2)	4 (0.5)
Application site erythema	1 (0.2)	3 (0.3)
Asthenia	2 (0.3)	3 (0.3)
Application site pain	1 (0.2)	2 (0.2)
Application site dermatitis	1 (0.2)	1 (0.1)
Application site reaction	0 (0.0)	1 (0.1)
Injury, poisoning & procedural complications	1 (0.2)	1 (0.1)
Fall	1 (0.2)	1 (0.1)
Metabolism & nutrition disorders	1 (0.2)	1 (0.1)
Decreased appetite	1 (0.2)	1 (0.1)
Nervous system disorders	2 (0.3)	3 (0.3)
Dizziness	1 (0.2)	2 (0.2)
Balance disorder	1 (0.2)	1 (0.1)
Syncope	1 (0.2)	1 (0.1)
Respiratory, thoracic & mediastinal disorders	1 (0.2)	1 (0.1)
Respiratory failure	1 (0.2)	1 (0.1)
Vascular disorders	1 (0.2)	1 (0.1)
Hypertension	1 (0.2)	1 (0.1)

Primary system organ class Preferred term	Interim CSR 04-Aug-06 N = 632 n (%)	Final CSR 24-Oct-06 N = 870 n (%)
Total	16 (2.5)	21 (2.4)
Cardiac disorders	2 (0.3)	2 (0.2)
Bradycardia	1 (0.2)	1 (0.1)
Cardiac failure	1 (0.2)	1 (0.1)
Gastrointestinal disorders	6 (0.9)	7 (0.8)
Nausea	4 (0.6)	5 (0.6)
Diarrhea	2 (0.3)	2 (0.2)
Abdominal pain upper	1 (0.2)	1 (0.1)
Vomiting	0 (0.0)	1 (0.1)
General disorders & administration site conditions	6 (0.9)	14 (1.6)
Application site irritation	1 (0.2)	4 (0.5)
Application site pruritus	1 (0.2)	4 (0.5)
Application site erythema	1 (0.2)	3 (0.3)
Asthenia	2 (0.3)	3 (0.3)
Application site pain	1 (0.2)	2 (0.2)
Application site dermatitis	1 (0.2)	1 (0.1)
Application site reaction	0 (0.0)	1 (0.1)
Injury, poisoning & procedural complications	1 (0.2)	1 (0.1)
Fall	1 (0.2)	1 (0.1)
Metabolism & nutrition disorders	1 (0.2)	1 (0.1)
Decreased appetite	1 (0.2)	1 (0.1)
Nervous system disorders	2 (0.3)	3 (0.3)
Dizziness	1 (0.2)	2 (0.2)
Balance disorder	1 (0.2)	1 (0.1)
Syncope	1 (0.2)	1 (0.1)
Respiratory, thoracic & mediastinal disorders	1 (0.2)	1 (0.1)
Respiratory failure	1 (0.2)	1 (0.1)
Vascular disorders	1 (0.2)	1 (0.1)
Hypertension	1 (0.2)	1 (0.1)

10.6.3 Discontinuations Due To Adverse Events (Transitional Period Only)

The overall incidence of discontinuations due to adverse events during the first 4 weeks of Study 2320E1 was low, but as the next sponsor table indicates was again highest in those who received placebo during the double-blind phase/study 2320.

Primary system organ class Preferred term	20 cm^2 patch N = 209 n (%)	DB Exelon 10 cm^2 patch N = 204 n (%)	Capsule N = 209 n (%)	DB Placebo N = 248 n (%)	Total N = 870 n (%)
Total	2 (1.0)	2 (1.0)	6 (2.9)	11 (4.4)	21 (2.4)
Cardiac disorders	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.2)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Cardiac failure	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal disorders	0 (0.0)	1 (0.5)	1 (0.5)	5 (2.0)	7 (0.8)
Nausea	0 (0.0)	1 (0.5)	0 (0.0)	4 (1.6)	5 (0.6)
Diarrhea	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)	2 (0.2)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
General disorders & administration site conditions	1 (0.5)	1 (0.5)	5 (2.4)	7 (2.8)	14 (1.6)
Application site irritation	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.4)	4 (0.5)
Application site pruritus	0 (0.0)	0 (0.0)	3 (1.4)	1 (0.4)	4 (0.5)
Application site erythema	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.4)	3 (0.3)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	3 (0.3)
Application site pain	1 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.2)
Application site dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Application site reaction	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.1)
Injury, poisoning & procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Metabolism & nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Nervous system disorders	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)	3 (0.3)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	2 (0.2)
Balance disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Respiratory, thoracic & mediastinal disorders	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory failure	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)

10.7 Skin Irritation

Skin irritation data for the final study cohort are in the following table, and are similar to those in the initial study cohort.

Skin irritation	Exelon Patch size 20 cm^2	15 cm^2	10 cm^2	5 cm^2
Patients with any rating - N	576	702	822	80
Patients with no skin irritation	295 (51.2)	414 (59.0)	495 (60.2)	25 (31.3)
Patients with no, slight or mild skin irritation	526 (91.3)	635 (90.5)	752 (91.5)	60 (75.0)
Any severe rating – n (%)	13 (2.3)	10 (1.4)	15 (1.8)	7 (8.8)
Erythema – N	576	702	822	80
No, slight or mild – n (%)	534 (92.7)	645 (91.9)	769 (93.6)	64 (80.0)
Moderate or severe – n (%)	42 (7.3)	57 (8.1)	53 (6.4)	16 (20.0)
Edema- N	576	702	822	80
No, slight or mild – n (%)	568 (98.6)	690 (98.3)	815 (99.1)	72 (90.0)
Moderate or severe– n (%)	8 (1.4)	12 (1.7)	7 (0.9)	8 (10.0)
Scaling – N	576	702	822	80
No, dryness or mild – n (%)	569 (98.8)	692 (98.6)	809 (98.4)	74 (92.5)
Moderate or severe– n (%)	7 (1.2)	10 (1.4)	13 (1.6)	6 (7.5)
Fissures – N	576	702	822	80
No or superficial – n (%)	572 (99.3)	694 (98.9)	815 (99.1)	77 (96.3)
Single or deep – n (%)	4 (0.7)	8 (1.1)	7 (0.9)	3 (3.8)
Pruritus – N	576	702	822	80
Negative, slight or mild – n (%)	549 (95.3)	667 (95.0)	779 (94.8)	63 (78.8)
Moderate or severe – n (%)	27 (4.7)	35 (5.0)	43 (5.2)	17 (21.3)
Pain, stinging and/or burning- N	576	702	822	80
No, slight or mild – n (%)	569 (98.8)	695 (99.0)	814 (99.0)	75 (93.8)
Moderate or severe– n (%)	7 (1.2)	7 (1.0)	8 (1.0)	5 (6.3)

N= total number of patients with evaluations for that patch size
The most severe rating was used for patients with multiple occurrences of an irritation sub-category.

10.8 Sponsor's Conclusions

The sponsor has concluded that the additional data included in the 120-Day Safety Update did not differ from the safety data included in Summary of Clinical Safety included in the original NDA.

10.9 Reviewer's Comments

The spectrum of adverse events and other safety abnormalities seen in the final cohort for Study 2320E1 as described in the 120-Day Safety Update, is not substantially different from the interim cohort for the same study as originally presented in the original submission of this NDA.

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.

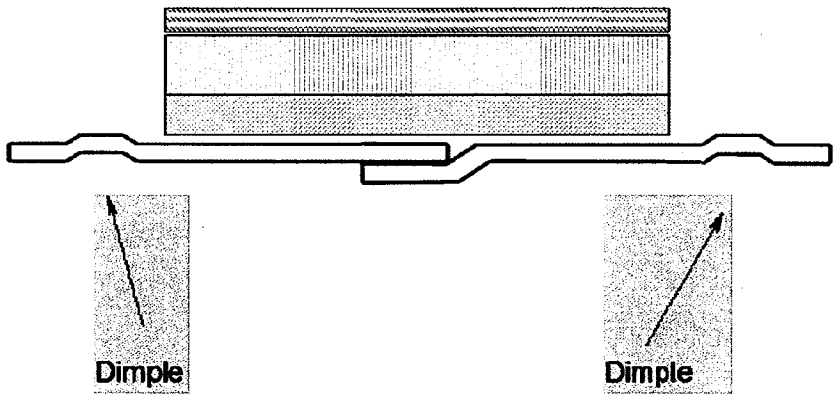
11. Summary Of Clinical Pharmacokinetics Of Exelon® Patch Transdermal System

11.1 Sponsor Summary

The following are the key points contained in the pharmacokinetic summary provided with the sponsor.

(All clinical studies in this application, with the exception of Study W155, used the transdermal formulation of Exelon® that is currently proposed for marketing. The information below is pertinent to the latter formulation only).

- The rivastigmine patch proposed for marketing is diagrammatically represented below in a figure that I have copied from the submission



Layer 1 = Backing film
Layer 2 = Drug product (acrylic) matrix
Layer 3 = Adhesive (silicone) matrix
Layer 4 = (Protective) release liner [redacted] b(4)

- The rivastigmine patch uses [redacted] b(4) ; the oral formulations, on the other hand, use the hydrogen tartrate salt of rivastigmine.

- 5 different sizes (strengths) or rivastigmine patch have been evaluated in clinical trials. These are listed in the table below

Rivastigmine patch size	Rivastigmine content
5 cm^2	9 mg
7.5 cm^2	13.5 mg
10 cm^2	18 mg
15 cm^2	27 mg
20 cm^2	36 mg

- After the application of the rivastigmine patch, the T_{max} was at about 13 to 16 hours after single patch application and 8 hours at steady state

- The rivastigmine patch produced a lower C_{max} and higher AUC_{0-24} as compared with the 2 approved oral formulations of rivastigmine (at matching doses). For example, under steady-state concentrations, the largest size patch (20 cm^2) produced a 1.5-fold lower C_{max} and a 1.8-fold higher AUC_{0-24} as compared with the highest dose of the Exelon® capsule (12 mg/day). The patch also showed less peak-trough fluctuations in plasma concentrations of rivastigmine than the oral formulation

- Over a 24-hour period, about 50% of the drug load in each patch (regardless of size/strength) was released from the system, as assessed by drug residual in each patch, and as shown in the following table

Rivastigmine patch size	**Rivastigmine content**	**Estimated rivastigmine release rates over 24 hours**
5 cm^2	9 mg	4.6 mg
10 cm^2	18 mg	9.5
15 cm^2	27 mg	13.3
20 cm^2	36 mg	17.4

- After the application of a single patch, rivastigmine reached the systemic circulation with an absorption lag time of 0.6 to 1.5 hours after application of a single patch; the principal metabolite of rivastigmine, NAP226-90 was detected in the systemic circulation after a lag time of 1.2 to 2.3 hours. Population pharmacokinetic modeling estimated that the lag time at steady state after application of the rivastigmine patch was 42 minutes and 1.5 hours for rivastigmine and NAP226-90, respectively (the respective lag times for rivastigmine and NAP226-90 after oral administration were 0 and 11 minutes).

- The relative bioavailability of the 3 mg rivastigmine immediate-release coral solution and the 10 cm^2 rivastigmine patch were compared: the AUC_∞ of the patch was 5.2 times higher and the C_{max} 0.8 times lower than after the oral solution. After normalization for dose (mg of rivastigmine released from the patch (and body weight), the relatively bioavailability of the patch versus the oral solution (based on the patch/solution ratio) was 2.5 for AUC_∞ and 0.31 for C_{max}.

- The metabolite-to-parent AUC_∞ ratio was 0.7 after the patch versus 3.5 after oral administration, indicating that the metabolism of rivastigmine was less after transdermal administration than after oral administration.

- Exposure to rivastigmine, based on C_{max} and AUC_∞ increases over-proportionately with increasing dose. On dose escalation through the 5, 10, 15, and 20 cm^2 patch sizes, the increase in rivastigmine exposure to the lowest dose of 5 cm^2 dose was 2.5, 4.9, and 7.8-fold for the 10, 15, and 20 cm^2 patch sizes, respectively (the shift from linear increases in exposure was less with the patch formulation than with oral formulations)

- There was no correlation between the bioavailability of rivastigmine and degree of adhesiveness of the patch

- The intra-subject co-efficient of variation for C_{max} and AUC_{∞} ranged from 19-42% and 18-56%, respectively. The inter-subject coefficient of variation for C_{max} and AUC_{∞} ranged from 44-60% and 52-80%, respectively. The variability was considered moderate, and less than for the oral formulations.

- Elimination half-life ranged from 2.2 to 3.9 hours after patch application versus 1.4 hours after oral or intravenous administration.

- The highest exposure to rivastigmine was obtained when the patch was applied to the upper back, chest or upper arm and lowest when applied to the thigh or lower abdomen.

- After application of the rivastigmine patch, urinary excretion was mainly in the form of NAP266-90 and its sulfate conjugate

11.2 Agency Clinical Pharmacology Review

The Agency Clinical Pharmacology review of this application has been primarily performed by Dr Veneeta Tandon, and assisted by Dr Atul Bhattaram, **Pharmacometrics Reviewer. Dr Tandon's** summary findings and conclusion are below.

11.2.1 Summary Findings

Among Dr Tandon's summary findings were the following (the findings apply to the Final Marketing Image version of the Exelon® patch):

- In the randomized, double-blind, placebo-controlled study 2320, a greater improvement in ADAS-Cog and an increased response rate on the ADCS-CGIC was seen with increased exposure to rivastigmine, based on steady-state plasma concentrations

- In the randomized, double-blind, placebo-controlled study 2320, there was no clear relationship between the incidence of adverse events and steady-state plasma concentrations

- The absorption of rivastigmine from the patch was slow (lag time of about 0.5 to 1.0 hour after the first application) with the T_{max} occurring at a mean of about 14 to 16 hours

- A lower metabolite-to-parent AUC_{0-24} ratio was observed after dermal administration as compared with oral administration, suggesting that much less metabolism occurred after dermal administration than after oral administration (there was no indication of dermal metabolism of rivastigmine)

- After administration of the Exelon® patch, about 3% of the dose was excreted unchanged in the urine; rivastigmine was mainly excreted as the sulfate conjugate of NAP226-90

- The plasma elimination half-life of rivastigmine after application of 20 cm^2 patches in succession for 24 hours each was 3.4 ± 0.7 hours. Steady-state plasma concentrations were reached at the second day of dosing. The transdermal formulation of rivastigmine exhibited non-linear pharmacokinetics although the non-linearity was less-pronounced than with the oral formulation. The pharmacokinetics of rivastigmine and NAP226-90 are similar in patients with **Alzheimer's Disease and in healthy volunteers when the same patch size is** applied to the same body site

- While no new studies have been conducted with Exelon® patches in subjects with renal or hepatic impairment. Based on population analyses, serum creatinine clearance and serum transaminase levels did not show any statistically significant effect on steady-state concentrations of rivastigmine

- Population analyses did not suggest any effect of age, gender, or race on steady-state plasma concentrations or rivastigmine

- Based on modeling and simulation, exposure after the 10 cm^2 patch is about equivalent to exposure after the administration of Exelon® capsules in a dose of 6 mg BID

- The relative bioavailability of the drug at different application sites was assessed. The upper back was used as the reference site (this was used as the application site in most clinical pharmacology studies as well as in the Phase III studies 2320 and 2320E1); compared with the upper back, the chest, abdomen, outer thigh, and upper arm application sites achieved 100%, 80%, 71%, and 92% exposure (based on AUC_∞), respectively

- Dissolution specifications were proposed

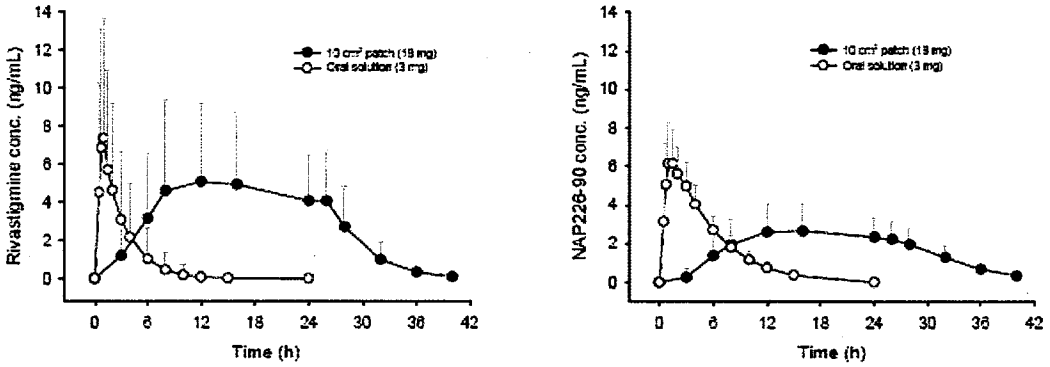
The Agency Clinical Pharmacology review has also summarized the relative bioavailability of the active ingredient in the Exelon® patch with that in the currently marketed oral solution and capsule formulations of Exelon®; each comparison is based on a separate study.

- In Study 2332, the relative bioavailability of the 10 cm^2 Exelon® patch applied to the upper back was compared with that of 3 mg of the oral solution (using single doses of both) in a cross-over study conducted in 30 healthy subjects aged 60 to 85 years. The relative exposure ratios for both rivastigmine and its metabolite NAP226-90 are in the following table which I have copied from the review.

Parameter	Test/Reference (Patch/Solution)	
	Rivastigmine	NAP 226-90
$C_{max,\ norm}$ ratio	0.353 ± 0.173 (49) [0.313]	0.165 ± 0.0599 (36) [0.155]
$AUC_{0\text{-}24h,\ norm}$ ratio	2.46 ± 1.87 (76) [1.93]	0.433 ± 0.144 (33) [0.410]
$AUC_{last,\ norm}$ ratio	3.27 ± 2.45 (75) [2.61]	0.661 ± 0.174 (26) [0.638]
$AUC_{\infty,\ norm}$ ratio	3.07 ± 2.13 (69) [2.50]	0.660 ± 0.166 (25) [0.639]

Values are mean ± SD (%CV) [geometric mean]

The comparative concentration-time profiles for both rivastigmine and NAP226-90 in this study are in the following table, which I have again copied from the Clinical Pharmacology review.



- In Study 2331, an open-label, parallel-arm study, the pharmacokinetics of escalating doses of the Exelon® patch (5 cm^2, 10 cm^2, 15 cm^2, and 20 cm^2), each administered for 2 weeks were compared with those of escalating doses of Exelon® capsules (1.5 mg, 3.0 mg, 4.5 mg, and 6 mg BID), each also **administered for 2 weeks in patients with Alzheimer's Disease. The mean C_{max}** and $AUC_{0\text{-}24}$ ratios for the patch over the capsule formulation are in the following table, which I have also copied from the Clinical Pharmacology review.

		Capsule			
		1.5 mg bid (3 mg/day)	3.0 mg bid (6 mg/day)	4.5 mg bid (9 mg/day)	6.0 mg bid (12 mg/day)
	C_{max}[1] (ng/mL):	3.34 ng/mL	9.70 ng/mL	16.8 ng/mL	29.3 ng/mL
	AUC_{24h} (ng·h/mL):	12.5 ng·h/mL	57.7 ng·h/mL	106 ng·h/mL	191 ng·h/mL
Patch					
5 cm^2	C_{max} = 2.71 ng/mL	0.81	0.28 **	0.16 **	0.09 **
	AUC_{24h} = 46.3 ng·h/mL	3.70 **	0.80	0.44 **	0.24 **
10 cm^2	C_{max} = 7.88 ng/mL	2.36 **	0.81	0.47 **	0.27 **
	AUC_{24h} = 127 ng·h/mL	10.2 **	2.20 **	1.20	0.66
15 cm^2	C_{max} = 14.1 ng/mL	4.22 **	1.45 *	0.84	0.48 **
	AUC_{24h} = 233 ng·h/mL	18.6 **	4.04 **	2.20 **	1.22
20 cm^2	C_{max} = 19.5 ng/mL	5.84 **	2.01 **	1.16	0.67 *
	AUC_{24h} = 345 ng·h/mL	27.6 **	5.98 **	3.25 **	1.81 **

1 morning dose

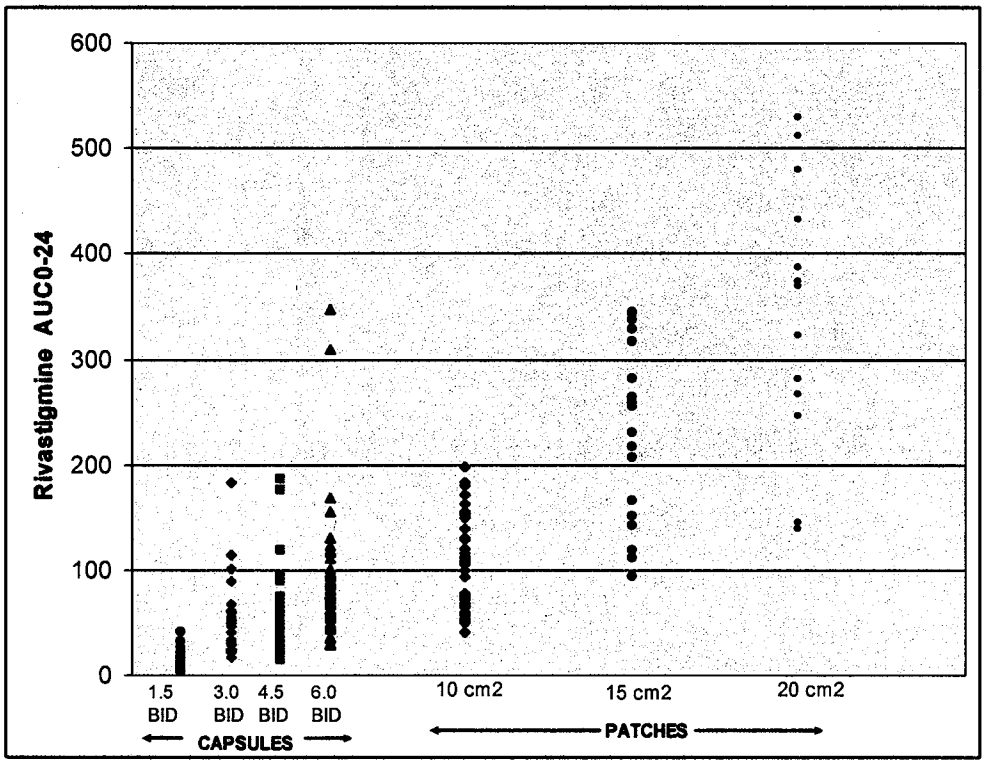
* P≤0.05 (based on ratio of geometric means)

** P≤0.001 (based on ratio of geometric means)

The distribution of individual AUC_{0-24} data in this study is depicted in the following figure, also copied from the Clinical Pharmacology review, which is self-explanatory.

Dr Tandon considers the data in the figure to support the sponsor's proposed dosing schedule for transition from the oral to transdermal administration with **Exelon® recommended in the product label. Under the sponsor's proposal:**

- Those taking an oral dose of < 6 mg/day may be switched directly to the 5 cm^2 Exelon® patch
- Those taking an oral dose of 6 to 12 mg/day may be switched directly to the Exelon® 10 cm^2 patch



11.2.1.1 Relationship Between Selected Exposure Data And Adverse Events

At Dr Tandon's request, I have determined what adverse events occurred in association with high outlier exposure levels after application of the 10 cm^2 patch in Study 401.

Study 401 was an open-label uncontrolled study that was intended to evaluate the safety, tolerability, skin adhesion, skin irritation potential, and pharmacokinetics of 3 different patch sizes (5 cm^2, 10 cm^2, and 15 ^{cm2}; Final Marketing Image) in patients with mild to moderate Alzheimer's Disease. 64 patients were enrolled in the study, of whom 58 completed the study. The dose titration schedule used was as follows.

Study Days	Exelon® Transdermal System Dose
1 to 14	10 cm^2 patch once daily (18 mg daily dose)
15 to 28	15 cm^2 patch once daily (27 mg daily dose)
29 to 42	20 cm^2 patch once daily (36 mg daily dose)

The adverse events (which were obtained from Case Report Tabulations) in 4 patients with high exposure levels were as follows.

ID #	Pharmacokinetic parameters following a single application of a 10 cm^2 patch on Day 1		Adverse events during application of 10 cm^2 patch
	C_{max} (ng/mL)	AUC_{last} (ng.hr/mL)	
50004	30.12	501.34	Nausea, vomiting
130002	18.46	310.24	Nausea, vomiting, tinnitus, headache, hallucinations, nightmares
130010	30.68	525.65	Eczema due to uncleanliness, itching
501009	15.69	277.53	Tearfulness, dermatitis, insomnia

Note that the adverse events seen in the patient with the highest exposure level (Patient 130010) were more likely to be related to Alzheimer's Disease than to Exelon®. In Patient 50004 alone, I was able to confirm that the adverse events listed in the table above (nausea and vomiting) occurred on Day 1.

11.2.2 Conclusion

Dr Tandon considers the application acceptable, provided the labeling recommendations that she has made in her review are accepted by the sponsor.

12. Overall Summary Of Clinical Data

12.1 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.

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**.

12.2 Summary Of Clinical Findings

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

12.2.1 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)

12.2.1.1 —— /13D2320

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

12.2.1.1.1 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
- Exelon® 20 cm^2 patch QD
- 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

12.2.1.1.2 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.

12.2.1.1.3 Reviewer's Conclusion

The results of this study do provide evidence of the efficacy of both the 10 cm^2 and 20 cm^2 Exelon® patches in comparison with placebo, although there is little evidence that the 20 cm^2 patch has a superior effect to the 10 cm^2 patch.

12.2.2 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 receiving the 20 cm^2 patch than in those receiving 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 also 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.

12.2.3 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.

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

12.3.1 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 in 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.**

- 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.

12.3.2 Reviewer's Conclusion

The sponsor has failed to provide evidence of the efficacy of Exelon® in **dementia associated with Parkinson's Disease**. My 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 a separate clinical trial prior to approval.

13. Review Of Labeling

The sponsor's proposed labeling has been reviewed in a separate document.

14. Financial Disclosure Certification

Financial disclosure information has been collected for Study 2320 and its open-label uncontrolled extension 2320E1. The methods of collecting information have been described and are standard.

The sponsor indicates that 97.5% of the clinical investigators participating in Study 2320/2320E1 in the United States, and 98.8% of the clinical investigators participating in Study 2320/2320E1 outside the US. responded to the request for information.

The components of financial disclosure certificate submitted and my comments are below.

14.1 Components Of Certification

This certification provided by the sponsor had a single component.

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

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

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

This certification has been provided on FDA Form 3454.

14.2 Reviewer's Comments

There was no evidence that any study investigators had financial arrangements that may have introduced significant bias into the results of trials submitted with this application.

15. Site Inspection Report

A Clinical Inspection Summary has been completed by Antoine El-Hage, PhD, of the Division of Scientific Investigations. Please see that document for full details.

The study sites inspected are summarized in the table below, which I have copied from the Clinical Inspection Summary.

Name of CI and site #, if known	Country	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Andrzej Potemkowski, M.D. Site #0134	Poland	Pamieci	13D 2320	2/12/07	pending	NAI*
Nikolai Yakhno, M.D Site# 0152	Russia	Moscow	13D 2320	2/19/07	pending	VAI*

b(4)

* based on e-mail summary information or telephone call from the field investigators.

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

The above sites were the largest – in regard to patient enrollment - participating in Study 2320:

- Site #0134 enrolled 41 patients
- Site #0152 enrolled 38 patients

The overall assessment of the Division of Scientific Investigations is that the data from these sites was acceptable for use in support of the pending application.

16. Conclusions

16.1 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 and 20 cm^2, that nominally deliver 9.5 mg/24 hours and 17.4 mg/24 hours of rivastigmine, respectively, has been established to a sufficient degree through the submission of this application. There is, however, little evidence that the 20 cm^2 patch has a beneficial effect superior to that of the 10 cm^2 patch.

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.

16.2 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.

16.3 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. b(4)

17. 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.

Ranjit B. Mani, M.D.
Medical Reviewer

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

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