EMA/270221/2012
Human Medicines Development and Evaluation

2nd CHMP request for supplementary information to be addressed by the MAH in writing and in an oral explanation

Exelon / Prometax

rivastigmine

EMEA/H/C/000xxx/WS/0132/G

2nd CHMP request for supplementary information as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Recommendation

Based on the review of the data on safety and efficacy, the CHMP considers that the group of variations application EMEA/H/C/xxxx/WS/0132/G for Exelon/Prometax and Prometax (rivastigmine) for the following proposed change:

Extension the indication for the Exelon/Prometax patch to include the symptomatic treatment of mild to moderately severe PDD and to add new safety data in Parkinson's disease dementia to update the labels of Exelon/Prometax capsules and oral solution.

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided below and should be addressed in writing and in an oral explanation. In addition, satisfactory answers must be given to the "other concerns" as detailed in section 2 & 3.

2. Executive Summary

The Exelon/Prometax and Prometax transdermal patch were approved in the European Union (EU) for the symptomatic treatment of mild to moderately severe Alzheimer's dementia (AD) on 17 September 2007 (EMEA/H/C/169/X/38 and EMEA/H/C/255/X/39).

Exelon/Prometax oral formulations (capsule, solution) were first approved in the EU for symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease (PDD) on 28 February 2006 (EMEA/H/C/169/II/33 and EMEA/H/C/255/II/33). Approval of the PDD indication for the Exelon/Prometax capsule in the EU was based on the results of a prospective, randomized, double-blind, placebo-controlled, multicenter trial (Study B2311).

The present type II variation proposed to extend the indication for the Exelon/Prometax patch to include the symptomatic treatment of mild to moderately severe PDD and to add new safety data in Parkinson's disease dementia in the capsules and oral solution formulations based on the results of a new study, Study B2315.

Study B2315 was conducted as a post-approval commitment in the EU for the Exelon/Prometax capsule in the treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease. Based on the request from the CHMP, this 76-week open-label study was designed to provide long-term safety data on the Exelon/Prometax capsule, in particular the effect of Exelon/Prometax on worsening of the underlying motor symptoms of Parkinson's disease in patients with PDD.

Novartis extended the scope of this study to include an Exelon/Prometax patch treatment arm. This arm was added to assess the risk-benefit ratio of the patch in PDD.

A PK substudy within Study B2315 was conducted to investigate the pharmacokinetics of Exelon/Prometax patch at steady state in PDD patients, and to compare (descriptively) the results to historic data in AD patients.

3. Scientific discussion

3.1. Clinical aspects

3.1.1. Clinical efficacy

3.1.1.1. Main study- Study B2315

Study B2315 was a 76-week prospective, open-label, multicenter study to evaluate the long-term effect of Exelon/Prometax capsule and transdermal patch on worsening of the underlying motor symptoms of PD in patients with mild to moderately severe dementia associated with Parkinson's disease (PDD).

Methods

Objectives

Primary objective

To evaluate the long-term safety of Exelon/Prometax capsule (12 mg/day), by assessing the worsening of the underlying motor symptoms of PD in patients with mild to moderately severe PDD.

The primary objective was assessed by measuring:

- Predefined AEs due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, and fall).
- Study drug discontinuations due to predefined AEs due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, and fall).

Secondary objectives

Safety objectives

- To evaluate the long-term safety of Exelon/Prometax patch, by assessing the worsening of the underlying motor symptoms of PD in patients with mild to moderately severe PDD.

This safety objective was assessed by measuring:

1. Predefined AEs due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, and fall).

2. Study drug discontinuations due to predefined AEs due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, and fall).

- To assess the overall long-term tolerability and safety (including the incidence of gastrointestinal AEs, worsening of other PD motor symptoms, and peak expiratory flow [PEF]) of Exelon/Prometax capsule and patch in patients with mild to moderately severe PDD.
- To assess the effect of Exelon/Prometax capsule and patch on:

1. Patients with autonomic symptoms of PD at baseline.

2. Patients with sleep disorder at baseline.

3. Antipsychotic dose changes in patients with hallucinations at baseline.

Efficacy objectives

- To assess the efficacy of Exelon/Prometax capsule and patch on:

    1. Cognition function (including executive functioning and attention).

    2. Neuropsychiatric symptoms.

    3. Ability to perform complex and basic activities of daily living.

Efficacy assessments performed were: the Mattis Dementia Rating Scale (MDRS), Ten Point Clock Test (TPCT), Neuropsychiatric Inventory (NPI), and Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-ADL).

Caregiver evaluation of the medications was assessed at Week 24 or at early discontinuation (ED) if the patient discontinued before Week 24, using the Caregiver Medication Questionnaire (CMQ). Time spent on care giving was collected as exploratory assessments using the caregiver time section of Resource Utilization in Dementia (RUD) Questionnaire.

Efficacy and safety objectives were assessed in subgroups patients with:

• baseline visual hallucinations (frequency of Neuropsychiatric Inventory [NPI] hallucinations item >0 and visual hallucinations ticked "yes" in electronic [eCRF]) versus no visual hallucinations.

• mild dementia (baseline MMSE 18 to 26) versus moderate dementia (baseline MMSE 10 to 17).

• baseline elevated plasma homocysteine (≥14 µmol/L) versus normal/low homocysteine.

Other objectives

- To assess the effects of adhesion of the Exelon/Prometax patch in patients with AD and PDD.
- To investigate the pharmacokinetics of Exelon/Prometax patch at steady state in PDD patients, and to compare (descriptively) to historic data in Alzheimer's disease patients (per Protocol Amendment #4).

The study had 2 phases: a pre-randomization phase followed by the open-label treatment phase.

1. Pre-randomization phase (≤5 weeks)

All patients underwent a preliminary evaluation (screening visit) to assess eligibility. At the baseline visit (at least 1 week after the screening visit but no more than 5 weeks after), eligibility was confirmed and patients were randomly assigned to treatment with the Exelon/Prometax capsule (12 mg/day) or Exelon/Prometax transdermal patch (10 cm^2). The patients also underwent baseline safety and efficacy assessments at the baseline visit as per protocol.

2. Open-label Treatment Phase

The open-label treatment phase comprised 2 periods

Titration Period

• **Exelon/Prometax capsule group (Weeks 1 to 16)**: Following baseline efficacy and safety assessments, patients randomized to capsule began treatment at 3 mg/day (1.5 mg b.i.d) and were titrated in 3 mg/day increments every 4 weeks to reach a 12 mg/day (6 mg b.i.d) target dose. During the titration period, patients underwent safety and efficacy assessments as per protocol.

• **Exelon/Prometax patch group (Weeks 1 to 8)**: Following baseline efficacy and safety assessments, patients randomized to 10 cm2 patch began treatment at 5 cm2 and be titrated after 4 weeks with a single 5 cm2 increment to reach a target patch size of 10 cm2. During the titration period, patients underwent safety and efficacy assessments as per protocol.

Maintenance Period

• Exelon/Prometax capsule group (Weeks 17 to 76): Patients were maintained on the target dose of 12 mg/day (or highest well-tolerated dose) for the remainder of the study and underwent safety and efficacy assessments as per-protocol.

• Exelon/Prometax patch group (Weeks 9 to 76): The patients were maintained on the target patch size of 10 cm2 (or highest well-tolerated dose) for the remainder of the study and underwent safety and efficacy assessments as per protocol.

Diagnosis and main criteria for inclusion and exclusion

The study population consisted of a representative group of male and female patients (50 to 85 years) who have a clinical diagnosis of idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria and of PD dementia according to DSM-IV criteria, with onset of symptoms of dementia at least 1 year after the first diagnosis of idiopathic PD and a Mini-Mental State Examination score (MMSE) of 10 to 26 inclusive.

Patients were excluded if they had a score of 5 in the "on"-state on the Modified Hoehn and Yahr Staging (UPDRS Part V) assessment at screening or baseline; a current diagnosis of any primary neurodegenerative disorder other than idiopathic PD or of any treatable dementia that was verified by the Investigator to be the cause of dementia, or a current diagnosis of probable vascular dementia.

Statistical methods

Approximately 550 patients were planned to be randomized in the study, using a 1:1 randomization scheme, to either the Exelon/Prometax capsule group or the Exelon/Prometax patch group.

The **Safety population** consisted of all patients who have received at least one dose of study drug and have had at least 1 safety measurement after baseline. Patients were analyzed according to treatment received. The statement that a patient had no AEs constitutes a safety assessment.

The **Intent-to-treat (ITT)** population included all randomized patients who received at least 1 dose of study drug and have at least a 1 pre- and a post-baseline assessment for 1 of the efficacy variables (i.e., MDRS, TPCT, NPI, and ADCS-ADL). Following the ITT principle, patients were analyzed according to the treatment they were assigned to at randomization.

Results

- **Participant flow**

Table 1.

Disposition Reason	Exelon/Prometax Capsule N=295 n (%)	Exelon/Prometax Patch N=288 n (%)	Total N=583 n (%)
Screened			738
Randomized	295 (100.0)	288 (100.0)	583 (100.0)
Exposed to study drug	294 (99.7)	288 (100.0)	582 (99.8)

Completed	184 (62.4)	175 (60.8)	359 (61.6)
Discontinued	111 (37.6)	113 (39.2)	224 (38.4)
Reason for discontinuation			
Adverse event(s)	70 (23.7)	60 (20.8)	130 (22.3)
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	4 (1.4)	12 (4.2)	16 (2.7)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	18 (6.1)	24 (8.3)	42 (7.2)
Lost to follow-up	4 (1.4)	1 (0.3)	5 (0.9)
Administrative problems	2 (0.7)	4 (1.4)	6 (1.0)
Death	11 (3.7)	11 (3.8)	22 (3.8)
Protocol deviation	2 0.7)	1 (0.3)	3 (0.5)

Table 2. Patient demographics characteristics by treatment group (Randomized population)

Demographic Characteristic Category Statistic	**Exelon/Prometax Capsule N=295**	**Exelon/Prometax Patch N=288**	**Total N=583**
Sex, n (%)			
Male	207 (70.2)	191(66.3)	398 (68.3)
Female	88 (29.8)	97(33.7)	185 (31.7)
Race, n (%)			
Caucasian	289 (98.0)	284 (98.6)	573 (98.3)
Black	2 (0.7)	1 (0.3)	3 (0.5)
Other	4 (1.4)	3 (1.0)	7 (1.2)
Age (yrs)			
Mean (SD)	72.35 (6.295)	72.26 (6.352)	72.31 (6.318)
Median	73.00	73.00	73.00
Min -Max	52.0 – 85.0	50.0 – 85.0	50.0 – 85.0
Age group (yrs), n (%)			
<65	28 (9.5)	37 (12.8)	65 (11.1)
65 - 80	249 (84.4)	231 (80.2)	480 (82.3)
>80	18 (6.1)	20 (6.9)	38 (6.5)

The CHMP noted that the patient disposition was well-balanced between the treatment groups (295 patients, Exelon/Prometax capsule and 288 patients, Exelon/Prometax patch). Demographics characteritics are similar to those of population included in study 2311.

The overall study completion and discontinuation rates were similar for both groups. The most common reasons for study discontinuation in both groups were AEs (Exelon/Prometax capsule, 23.7% and Exelon/Prometax patch, 20.8%). A higher percentage of patients in the Exelon/Prometax patch group (4.2%) discontinued the study due to an unsatisfactory therapeutic effect compared to the patients in the Exelon/Prometax capsule group (1.4%), respectively.

The mean duration between diagnosis of PD and symptoms diagnosis of PDD was 7.34 and 7.41 years in the Exelon/Prometax capsule and Exelon/Prometax patch groups, respectively. The distribution of PD severity as measured by Hoehn and Yahr (UPDRS part V) staging was similar in the 2 groups and indicated a moderate stage of disability for a majority of the patients. The average MMSE scores in both treatment groups were similar at study entry and indicated a mild to moderate stage of dementia. Patients characteristics are similar to those included in study 2311.

- **Outcomes and estimation**

Table 3. Number (%) of patients in analysis populations by treatment group (Randomized Population)

Population	Exelon/Prometax Capsule n (%)	Exelon/Prometax Patch n (%)	Total n (%)
Randomized	295 (100.0)	288 (100.0)	583 (100.0)
Safety	294 (99.7)	288 (100.0)	582 (99.8)
Intent-to-treat (ITT)			
ITT-LOCF	273 (92.5)	273 (94.8)	546 (93.7)
ITT-OC	273 (92.5)	273 (94.8)	546 (93.7)

Primary efficacy results

No primary efficacy evaluation was performed for this study.

Secondary efficacy results

Table 4. Change from baseline in Mattis Dementia Rating Scale (MDRS) total score by treatment group and visit

Population Visit	Exelon/Prometax Capsule n Mean			Exelon/Prometax Patch n Mean		LS Mean and 95% CI for Exelon/Prometax Capsule-Patch
ITT-LOCF						
	Baseline	273	109.5	273	109.4	
Week 16	Change	273	5.4	273	3.4	2.2 (0.3, 4.1)
Week 24	Change	273	6.5	273	4.4	2.3 (0.2, 4.4)
Week 52	Change	273	4.6	273	1.3	3.5 (1.1, 5.9)
Week 76	Change	273	3.9	273	-1.4	5.5 (2.6, 8.4)
ITT-OC						
Week 16	Baseline	264	109.8	261	109.8	
	Change	264	5.6	261	3.5	2.3 (0.3, 4.2)
Week 24	Baseline	225	109.5	231	109.5	
	Change	225	7.8	231	5.1	2.8 (0.6, 5.1)
Week 52	Baseline	197	110.1	204	109.9	
	Change	197	6.2	204	1.0	5.4 (2.5, 8.3)
Week 76	Baseline	178	111.6	169	109.8	
	Change	178	6.2	169	-1.6	8.2 (4.5, 11.9)

The CHMP noted that for both treatment groups in the ITT-LOCF population, improvements from baseline were seen in the MDRS total scores with greater increases (improvement) seen with the Exelon/Prometax capsule compared to the Exelon/Prometax patch at Week 16 and 24. At Week 76, the mean MDRS total score for the Exelon/Prometax patch group was just below the baseline value (−1.4). The LS means difference between treatments groups was statistically significant in favour of Exelon/Prometax capsule during all the study duration.

Table 5. Alzheimer's Disease Cooperative Study –Activities of Daily Living(ADCS-ADL)

Population Visit	Exelon/Prometax Capsule n Mean			Exelon/Prometax Patch n Mean		LS Mean and 95% CI for Exelon/Prometax Capsule-Patch
ITT-LOCF						
	Baseline	273	49.2	270	50.1	
Week 16	Change	273	-0.4	270	-1.3	0.8 (-0.8, 2.5)
Week 24	Change	273	-0.6	270	-1.5	0.8 (-0.9, 2.6)
Week 52	Change	273	-2.2	270	-5.4	3.1 (1.1, 5.2)
Week 76	Change	273	-4.4	270	-7.8	3.4 (1.0, 5.7)
ITT-OC						
Week 16	Baseline	269	49.1	265	50.2	
	Change	269	-0.4	265	-1.3	0.8 (-0.9, 2.5)
Week 24	Baseline	226	48.3	230	49.4	
	Change	226	-0.1	230	-0.3	0.1 (-1.7, 1.9)
Week 52	Baseline	197	48.7	203	50.5	
	Change	197	-1.4	203	-5.5	4.1 (1.7, 6.4)
Week 76	Baseline	185	50.0	171	49.9	
	Change	185	-4.4	171	-7.8	3.5 (0.5, 6.5)

The CHMP noted the decline in ADSC-ADL over time compared to baseline, observed in both groups up to Week 24. At Weeks 52 and 76 total scores continued to decline in both groups. The LS means difference between treatments group was statistically significant in favour of Exelon/Prometax capsule group at Week 52 and 76.

Table 6. Neuropsychiatric Inventory (NPI)

Population	**Exelon/Prometax Capsule**			**Exelon/Prometax Patch**		**LS Mean and 95%CI for Exelon/Prometax Capsule-Patch**
Visit	**n Mean**			**n Mean**		
ITT-LOCF						
	Baseline	273	11.3	273	11.4	
Week 16	Change	273	-3.3	273	-0.5	-2.8 (-4.3, -1.2)
Week 24	Change	273	-2.6	273	-1.0	-1.7 -3.2, -0.1)
Week 52	Change	273	-1.7	273	-0.3	-1.5 (-3.1, 0.2)
Week 76	Change	273	-1.6	273	0.7	-2.4 (-4.1, -0.7)
ITT-OC						
Week 16	Baseline	270	11.4	268	11.4	
	Change	270	-3.4	268	-0.6	-2.8 (-4.3, -1.2)
Week 24	Baseline	228	11.3	236	11.7	
	Change	228	-3.1	236	-2.2	-1.0 (-2.5, 0.4)
Week 52	Baseline	203	11.7	204	11.5	
	Change	203	-2.5	204	-1.1	-1.4 (-3.2, 0.4)
Week 76	Baseline	184	11.1	175	11.5	
	Change	184	-2.8	175	-0.2	-2.8 (-4.7, -0.9)

The CHMP noted the improvements seen for both treatment groups in the NPI total scores up to Week 24, which continued throughout week 52. At week 76 an increase (worsening) was observed in the mean NPI total scoreof the Exelon/Prometax patch group.

Table 7. Ten-Point Clock Test (TPCT)

	Exelon/Prometax Capsule			**Exelon/Prometax Patch**	
Population Visit	**n Mean**			**n Mean**	
ITT-LOCF					
	Baseline	273	4.8	273	4.7
Week 16	Change	273	0.5	273	0.4
Week 24	Change	273	0.6	273	0.3
Week 52	Change	273	0.3	273	-0.1
Week 76	Change	273	0.0	273	-0.3
ITT-OC					
Week 16	Baseline	257	4.8	262	4.7
	Change	257	0.6	262	0.4
Week 24	Baseline	222	4.8	231	4.7
	Change	222	0.8	231	0.3
Week 52	Baseline	197	4.9	200	4.9
	Change	197	0.6	200	-0.1

Week 76	Baseline	176	5.1	164	4.8
	Change	176	0.1	164	-0.3

The CHMP noted that for the ITT-LOCF population, improvements in the scores were seen in both treatments groups up to Week 24. Then, the mean scores increased in the Exelon/Prometax capsule group up to Week 52 and returned to baseline levels at Week 76, while for the Exelon/Prometax patch group, there were small decreases from baseline observed at Weeks 52 and 76.

Tolerability/acceptability

For caregivers of patients treated with the Exelon/Prometax patch, the results of the CMQ assessment of preference for Exelon/Prometax patch treatment indicate superiority of preference for the Exelon/Prometax patch vs. receiving the medication in the form of an oral capsule: 82.2% preferred the Exelon/Prometax patch vs. 17.8% who would prefer the medication in the form of an oral capsule.

Pharmacokinetics investigation

Pharmacokinetic behaviour of Exelon/Prometax patch has been extensively characterized in healthy volunteers and Alzheimer patients. However, a PK investigation has been performed by the MAH in a sub-group of patients enrolled in the 76-week prospective clinical study (ENA713B2315).

Because of the exploratory nature of the PK evaluation in this study, no sample size calculation was done for PK, and it was considered that 15 to 20 patients should be sufficient to meet the PK objective of the study.

Blood sampling

Blood samples (3 mL each) for the assessment of the pharmacokinetic plasma profiles of rivastigmine (ENA713) and its inactive metabolite (NAP226-90) at steady state after patch administration were collected within a same 24-h once-daily patch application at the following time points in each of the patients who agreed to participate in the sub-PK part of the study: 1, 3, 6, 8, 12 and 24* h after patch application (* immediately prior to next patch application).

Pharmacokinetic data analysis

A total of nineteen (19) patients participated in the PK part of the study. There were 12 males and 7 females enrolled in the PK part. Their mean (±SD) age was 71.9 ± 5.2 years (range 63-84 years). All but one patient were Caucasians.

All 19 patients completed their treatment assignment. Eighteen (18) patients were treated with the 10 cm2 (9.5 mg/24 h) patch, whereas one patient was treated with the 5 cm^2 (4.6 mg/24 h) patch.

All patients with evaluable concentrations of rivastigmine were included in the PK subpopulation.

The following pharmacokinetic parameters for rivastigmine and NAP226-90 were determined by non-compartmental methods using Phoenix 6 (Pharsight, Mountain View, CA): Cmax, Cmin, Cavg, Tmax, AUC0-24h and fluctuation index (FI = (Cmax-Cmin)/Cavg). The actual sampling times (calculated by the pharmacokineticist based on data recorded in the paper CRFs) were used for the PK analysis.

In order to reduce the burden to the patients, no 0-h sample was taken. However, for graphic presentation and for the PK calculation of AUC0-24h, the 0-h time concentration value was considered to be the same as the trough concentration observed at time-point 24 h (steady-state conditions).

Descriptive statistics of the PK parameters included mean, standard deviation, coefficient of variation (CV), median, range, geometric mean (and CV geo. mean).

Results

Descriptive statistics of the PK parameters included mean, standard deviation, coefficient of variation (CV), median, range, geometric mean (and CV geo. mean) are tabulated below.

Table 8. Summary statistics (mean ± SD (CV%)) of PK parameters of rivastigmine and NAP226-90 following 24 h application of Exelon/Prometax patch 10 cm2 (9.5 mg/24 h) in 18 PDD patients

Parameter	Rivastigmine (n=18)	NAP226-90 (n=18)
Cmax (ng/mL)	6.72 ± 3.23 (48%)	3.04 ± 0.97 (32%)
Cmin (ng/mL)	2.62 ± 1.64 (63%)	1.86 ± 0.720 (39%)
Cavg (ng/mL)	4.94 ± 2.52 (51%)	2.51 ± 0.734 (29%)
Tmax (h) (median and range)	8.00 (0.00-13.0)	9.00 (0.00-13.0)
AUC0-24h (ng·h/mL)	117 ± 62.1 (53%)	60.6 ± 17.9 (30%)
FI ((Cmax-Cmin)/Cavg)	0.85 ± 0.35 (42%)	0.47 ± 0.31 (65%)

Table 9. Inter-study comparison:

Parameter	Parkinson Patients (ENA713B2315)	Alzheimer Patients (ENA713D2331)
Cmax (ng/mL)	6.72 ± 3.23 (48%)	7.88 ± 2.88 (36.6%)
AUC0-24h (ng·h/mL)	117 ± 62.1 (53%)	127 ± 41.4 (32.6%)
FI ((Cmax-Cmin)/Cavg)	0.85 ± 0.35 (42%)	0.77 ± 0.32 (42.2%)

3.1.1.2. Analysis performed across trials

Novartis provided additional indirect analysis of the efficacy data focusing on the results from the Exelon/Prometax patch and capsule arm of Study B2315 compared to the historic data from the placebo and Exelon/Prometax capsule arm of Study B2311 to show that relative to the placebo arm in the pivotal, double-blind Study B2311, treatment with the Exelon/Prometax patch in Study B2315 showed an improvement in patient's cognitive abilities, considerably less deterioration in activities of daily living and behavioural symptoms over 6 months.

Analysis population

The primary analysis population was ITT-LOCF in Study B2315 and ITT+RDO in Study B2311. The ITT+RDO population was the most similar to the ITT-LOCF population in Study B2315, it included all randomized patients who received at least one dose of study drug and had at least a pre-baseline assessment and a post-baseline assessment for one of the primary efficacy variables, either under treatment or not. It also included patients who discontinued study treatment early and continued to attend scheduled visits for efficacy evaluation.

Cognition

In Study B2315, improvement in cognition, as measured by mean change from baseline in MDRS total score, was observed for the ITT-LOCF population in the Exelon/Prometax patch group at Week 24 (4.4 points); similar results were observed in the ITT-OC population.

In the placebo group from Study B2311, a worsening in cognition as measured by mean change from baseline in ADAS-cog total scores was observed at Week 24 in both the ITT+RDO population (-0.7); similar results were observed in the ITT-OC population.

The use of MDRS in Study B2315 and ADAS-Cog in Study B2311 resulted in a greater variability of reported outcomes and greater difficulty in comparing data across studies.

Fortunately, though the scoring systems for these cognitive scales differ, there is considerable overlap between the scales regarding the actual cognitive functions evaluated. Therefore, a method which standardizes results obtained using different cognitive scales was used as a means of facilitating the comparison of outcome data. Following transformation of the original MDRS/ADAS-cog scores to standardized scale scores, mean change from baseline to the different timepoints were assessed and expressed in standardized units (mean:SD).

In Study B2315 for the ITT-LOCF population, the MDRS change from baseline ratio mean: SD at Week 24 was 0.50 for the Exelon/Prometax capsule and 0.34 for the Exelon/Prometax patch. Similar results were seen in the ITT-OC population (Table 10).

In Study B2311 for the ITT+RDO population, the ADAS-cog change from baseline ratio mean: SD at Week 24 was 0.26 for the Exelon/Prometax capsule and -0.09 for placebo. Similar results were seen in the ITT-OC population (Table 10).

The data indicate that the effects of the Exelon/Prometax patch on cognitive measures in Study B2315 and Study B2311 were better than placebo.

Table 10. Ratios of Mean/SD for MDRS change from baseline in Study B2315 and ADAS-cog change from baseline in Study B2311

	Study B2315		Study B2311	
	Cognition (MDRS)		Cognition (ADAS-cog)	
	Exelon patch	Exelon capsule	Exelon capsule	Placebo
	ITT-LOCF		ITT+RDO	
Week 24	n = 273	n = 273	n = 329	n = 161
Mean	4.4	6.5	2.1	-0.7
SD	12.85	12.98	8.2	7.5
Mean/SD	0.34	0.50	0.26	-0.09
	ITT-OC		ITT-OC	
Week 24	n = 231	n = 225	n = 256	n = 139
Mean	5.1	7.8	2.9	-1.0
SD	12.51	12.83	8.3	7.6
Mean/SD	0.41	0.61	0.35	-0.13

Function (activities of daily living)

At Week 24, less functional decline, as measured by mean change from baseline in ADSC-ADL total score, was observed for the ITT-LOCF population in the Exelon/Prometax patch group from Study B2315 compared to the ITT-RDO population in the placebo group from Study B2311 (-1.5 vs. -3.6 points, respectively). For the ITT-OC populations the difference in decline between the

Exelon/Prometax patch group and the placebo group was greater in favor of the Exelon/Prometax patch (-0.3 vs. -3.5 points, respectively) (Table 11).

Additionally, the decline in the ADCS-ADL score at Week 24 for the Exelon/Prometax patch and Exelon/Prometax capsule groups in Study B2315 were similar to that observed in the Exelon/Prometax capsule group and considerably less than observed in the placebo group from Study B2311 (Table 11).

Table 11. Change from baseline in ADCS-ADL total score at Week 24 (Study B2315-ITT-LOCF and ITT-OC populations; Study B2311-ITT+RDO and OC populations)

	Study B2315		Study B2311	
	Activities of daily living (ADCS-ADL)		Activities of daily living (ADCS-ADL)	
	Exelon patch mean (SD)	Exelon capsule mean (SD)	Exelon capsule mean (SD)	Placebo mean (SD)
	ITT-LOCF		ITT+RDO	
Week 24	n = 270	n = 273	n = 333	n = 165
Change from baseline	**-1.5** (10.91)	**-0.6** (10.12)	**-1.1** (12.6)	**-3.6** (10.3)
LS Means difference	0.8		2.51	
95% CI	(-0.9, 2.6)		(0.35, 4.67)	
p-value	-		0.023*	
	ITT-OC		ITT-OC	
Week 24	n = 230	n = 226	n = 260	n = 142
Change from baseline	**-0.3** (9.55)	**-0.1** (10.24)	**-0.3** (13.1)	**-3.5** (10.7)
LS Means difference	0.1		3.20	
95% CI	(-1.7, 1.9)		(0.77, 5.62)	
p-value	-		0.010*	

Positive change scores indicate improvement from baseline.

Study B2315: LS Mean and 95% confidence intervals (CI) (capsule-patch) were from an analysis of covariance (ANCOVA) model with treatment and country as factors and the baseline ADCS-ADL as a covariate.

Study B2311: p-value based on analysis of covariance model using treatment and country as factors and baseline ADCS-ADL as a covariate; 95% confidence interval calculated for the difference between LeastSquares Means (LSMEANS). * : p<0.05

Behaviour

At Week 24, greater improvement in neuropsychiatric symptoms, as measured by mean change from baseline in NPI-10 total score, was observed for the ITT-LOCF population in the Exelon/Prometax patch group from Study B2315 compared to the ITT-RDO population in the placebo group from Study B2311 at Week 24 (-1.0 and -2.6 points, respectively); similar results were observed in the ITT-OC population (Table 13).

Additionally, the improvement in the NPI-10 score at Week 24 for the Exelon/Prometax patch and Exelon/Prometax capsule groups in Study B2315 were similar to that observed in the Exelon/Prometax capsule group and considerably greater than observed in the placebo group from Study B2311(Table 12).

Table 12. Change from baseline in NPI-10 total score at Week 24 (Study B2315-ITT-LOCF and ITT-OC populations; Study B2311-ITT+RDO and OC populations)

	Study B2315		Study B2311	
	Behavior (NPI-10)		Behavior (NPI-10)	
	Exelon patch mean (SD)	Exelon capsule mean (SD)	Exelon mean (SD)	Placebo mean (SD)
	ITT-LOCF		ITT+RDO	
Week 24	n = 273	n = 273	n = 334	n = 166
Change from baseline	**-1.0** (10.27)	**-2.6** (10.31)	**-2.0** (10.0)	**0.0** (10.4)
LS Means difference	-1.7		-2.15	
95% CI	(-3.2, -0.1)		(-3.88, -0.43)	
p-value			0.015*	
	ITT-OC		ITT-OC	
Week 24	n = 236	n = 228	n = 262	n = 144
Change from baseline	**-2.2** (8.79)	**-3.1** (10.22)	**-2.5** (10.5)	**-1.1** (9.2)
LS Means difference	-1.0		-1.16	
95% CI	(-2.5, 0.4)		(-2.87, 0.55)	
p-value			0.182	

Negative change scores indicate improvement from baseline.
Study B2315: LS Mean and 95% confidence intervals (CI) (capsule-patch) were from an ANCOVA model with treatment and country as factors and the Baseline NPI-10 score as a covariate.
Study B2311: p-value based on analysis of covariance model using treatment and country and as factors and baseline NPI-10 as covariate. 95% confidence interval calculated for the difference between Least Squares Means (LSMEANS) * $p < 0.05$

Efficacy of the Exelon/Prometax patch at Weeks 52 and 76 in Study B2315

Cognition

Improvement in cognition, as measured by mean change from baseline in MDRS total score, was still evident at Week 52 in the Exelon/Prometax patch group (1.3 points). At Week 76, a decrease (worsening) in the mean MDRS total score just below baseline was observed for the ITTLOCF and ITT-OC populations in the Exelon/Prometax patch group (-1.4 and -1.6 points, respectively) (Table 13). Taking into account the mean ADAS-cog scores at Week 24 in the placebo group of Study B2311 (1.0 point below baseline in the OC population and the expected rate of disease progression, the minor decrease in MDRS total score in the Exelon/Prometax patch group at Week 76 indicates that the effect of Exelon/Prometax patch persisted over the entire study duration.

Table 13. Change from baseline in MDRS total scores at Weeks 52 and 76 (Study B2315-ITT-LOCF and ITT-OC populations)

	Cognition (MDRS)	
	Study B2315	
	Exelon patch mean (SD)	
	Week 52	Week 76
	ITT-LOCF	ITT-LOCF
n	273	n = 273
Change from baseline	**1.3** (15.07)	**-1.4** (17.43)
	ITT-OC	ITT-OC
n	n = 204	n = 169
Change from baseline	**1.0** (15.28)	**-1.6** (16.88)

Positive change scores indicate improvement from baseline.

Function (activities of daily living)

Mean ADSC-ADL total scores continued to decline in the Exelon/Prometax patch group at Week 52 and Week 76 (-5.4 and -7.8 points, respectively) in the ITT-LOCF population; similar results were observed in the ITT-OC population (Table 14). However, this worsening in activities of daily living should be considered in the context of the 3.6 point decline in mean ADSC-ADL total scores observed in the placebo group at Week 24 in Study B2311 (Table 11).

Table 14. Change from baseline in ADCS-ADL total score at Weeks 52 and 76 (Study B2315-ITT-LOCF and ITT-OC populations)

	Activities of daily living (ADCS-ADL)	
	Study B2315	
	Exelon patch mean (SD)	
	Week 52	Week 76
	ITT-LOCF	ITT-LOCF
n	n = 270	n = 270
Change from baseline	-5.4 (13.57)	-7.8 (15.62)
	ITT-OC	ITT-OC
n	n = 203	n =171
Change from baseline	-5.5 (13.49)	-7.8 (15.71)

Positive change scores indicate improvement from baseline.

Additional analyses on MDRS, ADAS-cog and ADL

To further take into account the absence of a placebo group in Study B2315, statistical modelling was performed to compare treatment groups across studies in one common model.

Results of these analyses confirm the findings of the already reported descriptive analyses i.e. that the capsule is more efficacious at certain timepoints, but also shows that there is an advantage of the patch against placebo.

The following describes the modelling approach taken:

In order to evaluate the efficacy of Exelon/Prometax patch compared to placebo, an analysis of repeated measures for change from baseline cognitive outcome measures (MDRS for B2315, ADAScog for B2311) using the pooled data from studies B2315 and B2311/E1 was carried out. For Study B2311E1 only the patients who had been treated with Exelon/Prometax capsule during the core study B2311 were included. The mean change from baseline for each outcome measure (MDRS and ADAS-cog) was standardized via division by the standard deviation of all observation per time point within study and treatment group. The analysis model included the terms of treatment, time, study, and treatment by time interaction. Graphs for the mean observed and predicted standardized efficacy parameters change from baseline by treatment and visit were also produced. A similar analysis (without standardization) was performed for the efficacy parameter ADCS-ADL.

This analysis was performed on the pooled Study B2315 and Studies B2311/E1 ITT population which includes Study B2315 and study B2311 ITT Observed Case (OC) patients as defined in the individual study report, and Study B2311E1 Observed Case (OC) patients as defined in the B2311E1study report.

This model allows to inferentially compare treatments (Exelon/Prometax capsule vs. patch, Exelon/Prometax capsule vs. placebo and Exelon/Prometax patch vs. placebo at different time points), thus providing a more formalized structure for the treatment comparisons and complement the descriptive analyses already submitted in the original summary documents of the registration dossier. The model makes mild assumptions on the data: the covariance matrix for the repeated measures

from a given subject is "unstructured" there is no interaction between treatment and study, which implies that the time profile of the population-average response to treatment is assumed to have the same shape for the same treatment in different trials. Since Exelon/Prometax capsule is the only common treatment used in trials Study B2315 and Studies B2311/E1, this means that the response to Exelon/Prometax capsule can differ in magnitude, but is assumed to have the same shape in these trials.

The results of these analyses indicate that for the cognitive domain, both the Exelon/Prometax capsule and the Exelon/Prometax patch are significantly better than placebo at Week 24 and that Exelon/Prometax capsule is always numerically superior to the Exelon/Prometax patch and significantly better at Weeks 16, 52 and 76 (Table 15, Figure 1-1). For the functional domain these analyses show that Exelon/Prometax capsule is significantly better than placebo at Week 24, Exelon/Prometax patch is numerically superior to placebo at Week 24 and Exelon/Prometax capsule is always numerically superior to the Exelon/Prometax patch and significantly better at Weeks 52 and 76 (Table 16, Figure 1-2).

Table 15. Repeated measures mixed model analysis for standarized cognitive scale (MDRS and ADAS-cog) change from baseline by visit (combined B2315 and B2311 ITT population)

	Exelon Capsule vs. Placebo		Exelon Patch vs. Placebo		Exelon Capsule vs. Patch	
	DLSM / 95% CI	p-value	DLSM / 95% CI	p-value	DLSM / 95% CI	p-value
Week 16	0.2919 (0.097, 0.487)	0.0034*	0.1041 (-0.149, 0.357)	0.4191	0.1878 (0.021, 0.355)	0.0277*
Week 24	0.4810 (0.279, 0.683)	<0.001*	0.3545 (0.095, 0.614)	0.0075 *	0.1265 (-0.048, 0.301)	0.1554
Week 52	-	-	-	-	0.2828 (0.092, 0.474)	0.0038*
Week 76	-	-	-	-	0.4005 (0.189, 0.612)	<0.001*

Pooled ITT population includes both studies B2315 and B2311 ITT populations
Cognitive scales (MDRS for B2315 and ADAS-cog for B2311) was standardized by dividing by the standard deviation of all observation per time point within study and treatment group
Least Square Means (LSM), p-value and 95% confidence interval (CI) were based on an MMRM model including treatment, time, study and treatment by time interaction
A positive Difference in LSM (DLSM) indicates an improved change from baseline of the first treatment in each column compared to the second.

Figure 1-1 Modeled MDRS and ADAS-cog effect change (combined B2315 and B2311 ITT population)

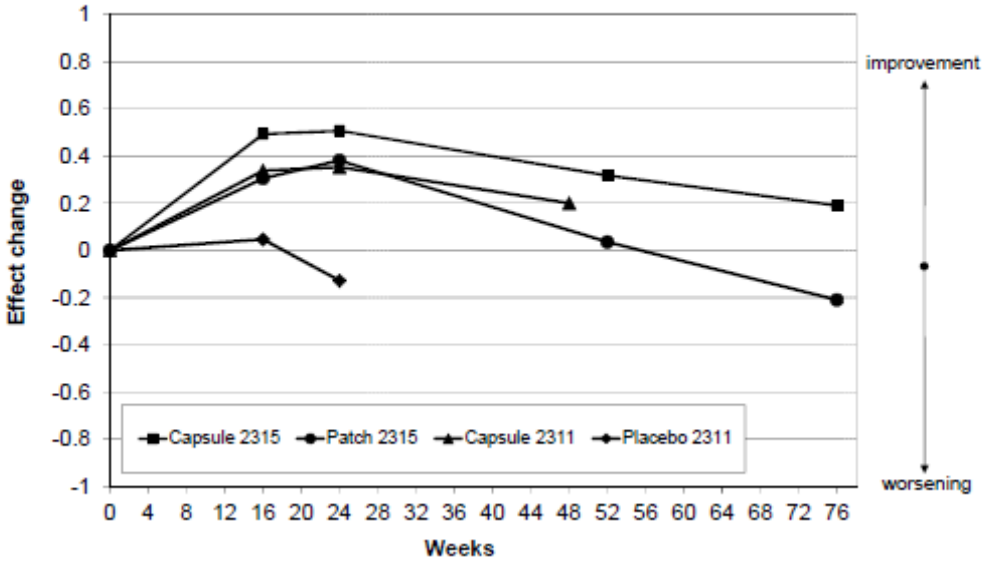


Table 16. Repeated measures mixed model analysis for ADCS-ADL change from baseline by visit (combined B2315 and B2311 ITT population)

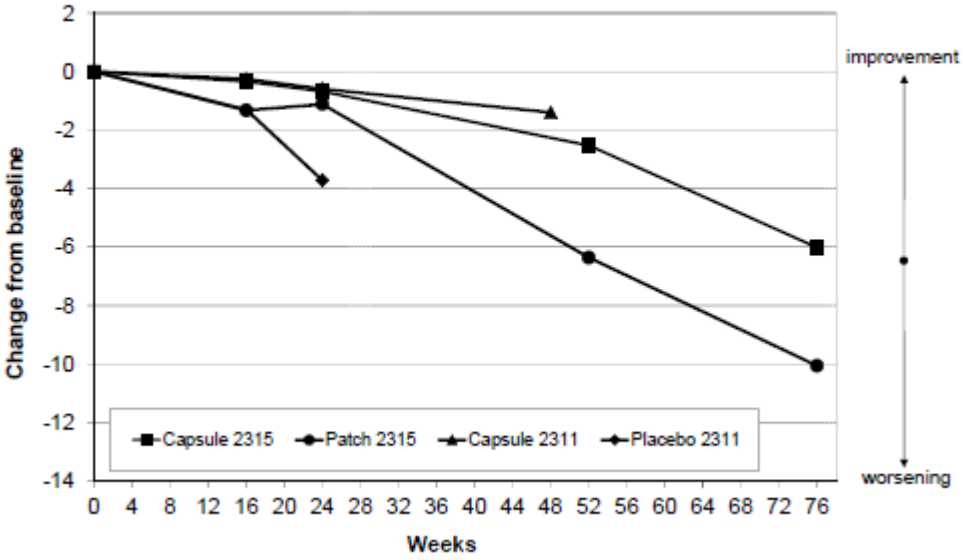
	Exelon Capsule vs. Placebo		Exelon Patch vs. Placebo		Exelon Capsule vs. Patch	
	DLSM / 95% CI	p-value	DLSM / 95% CI	p-value	DLSM / 95% CI	p-value
Week 16	1.0487 (-0.962, 3.060)	0.3064	0.0665 (-2.571, 2.703)	0.9605	0.9822 (-0.759, 2.724)	0.2687
Week 24	3.1318 (0.913, 5.350)	0.0057*	2.6922 (-0.152, 5.536)	0.0635	0.4396 (-1.485, 2.364)	0.6541
Week 52	-	-	-	-	3.8349 (1.392, 6.278)	0.0021*
Week 76	-	-	-	-	4.0486 (0.936, 7.161)	0.0108*

Pooled ITT population includes both studies B2315 and B2311 ITT populations

Least Square Means (LSM), p-value and 95% confidence interval (CI) were based on an MMRM model including treatment, time, study and treatment by time interaction

A positive Difference in LSM (DLSM) indicates an improved change from baseline of the first treatment in each column compared to the second.

Figure 1-2 Modeled ADCS-ADL change from baseline (combined B2315 and B2311 ITT population)



Overall efficacy discussion

The CHMP noted that the objective of Study CENA713B2315 was to provide long-term safety data for Exelon/Prometax capsule and transdermal patch treatments, in particular the effect of Exelon/Prometax on worsening of the underlying motor symptoms of Parkinson's disease (PD), in patients with mild to moderately severe dementia associated with PD. The MAH extended the scope of this study to include an Exelon/Prometax patch treatment arm to assess the risk-benefit ratio of the patch in PDD. This study used a randomized, open-label, parallel-group design. Efficacy was a secondary endpoint. Thus, this study was not designed as a non-inferiority efficacy study.

No significant differences in baseline demographic and background characteristics were observed between the 2 treatment patients. 583 patients were randomized, 295 for Exelon/Prometax capsules and 288 for Exelon/Prometax patch. Of these, 359 (61.6%) completed the study. The most common reason for study discontinuation in both groups was Adverse Events (AEs) (23.7% in the Exelon/Prometax capsules group and 20.8% in the Exelon/Prometax patch group). Unsatisfactory therapeutic effect was observed in 1.4% of patients in the Exelon/Prometax capsule group compared to 4.2% in the Exelon/Prometax patch group.

Both Exelon/Prometax groups showed an effect in the treatments of clinical symptoms of PDD (cognition, executive functioning/visuospatial skills, behaviour). Similar results (but in favour of Exelon/Prometax capsules in all domains, except for NPI) were observed in both treatments during the first 24 weeks of the study; however, the Exelon/Prometax capsule was clearly superior to the Exelon/Prometax patch at week 52 and 76.

Taking into account the open nature of this study with absence of placebo group and the absence of predefined non-inferiority hypothesis, the numerical inferiority, sometimes statistically significant, of the transdermal patch group compared to the hard capsules, is difficult to interpret.

The findings of the PK investigation conducted in a sub-group of Parkinson patients in study ENA713B2315 showed a systemic exposure to rivastigmine is of the same magnitude than that observed in Alzheimer disease patients under similar dosing conditions i.e. once daily repeated application of the 10 cm^2 patch. However, it was considered of concern that the doses used for the patch and the capsule in Study B2315 resulted in estimated substantially higher Cmax in the patients on capsule therapy which could have explained that the efficacy results of the different analysis from the main study B2315 indicate that for the cognitive and functional domains Exelon capsules are superior to Exelon patch in dementia associated with Parkinsons disease.

Since Alzheimer disease and dementia in Parkinson disease have different underlying aetiologies and pathogenetic mechanisms, patients might consequently, react differently to therapy. Therefore, the dose/response relationship could be different in PDD and ADD, and the respective role of Cmax and AUC in efficacy must be further clarified to allow bridging of efficacy based on PK data.

To shed more light on the results the MAH has compared and analysed the results from the Study B2315 with the 24 week, double-blind, placebo controlled Study B2311. The ITT-LOCF results for the patch in Study B2315 have been compared to ITT-RDO results for placebo in Study B2311 at Week 24. These analysis showed that relative to the placebo arm in the pivotal Study B2311, treatment with the Exelon/Prometax patch in Study B2315 showed an improvement in patient's cognitive abilities, considerably less deterioration in activities of daily living and behavioural symptoms over 6 months. However, even if this indirect comparison favours the patch, this comparison has its limitations.

Overall efficacy conclusion

The results of the different analysis indicate that efficacy of Exelon/Prometax patch was observed across multiple domains in PDD patients for the cognitive and functional domains, but also that Exelon/Prometax capsules are superior to Exelon/Prometax patch. Nevertheless, Study 2315 was an open study that was not design to assess efficacy and a non-inferiority limit was not pre-defined. All the analysis provided are descriptive and they are based according to a model without taking account the imprecisions of each study.

The indirect comparisons showed that Exelon/Prometax patch is superior to placebo treatment and that Exelon/Prometax patch in Study B2315 led to improvements in patient's cognitive abilities (including executive function), behavioural symptoms and considerably less deterioration in activities of daily living over 24 weeks. However, the interpretation of these results has its limitations.

Furthermore, the findings of the PK investigation conducted in a sub-group of Parkinson patients in study ENA713B2315 need to be further clarified to allow bridging of efficacy based on PK data.

3.1.2. Clinical safety

3.1.2.1. Safety Analysis

The objective of the safety analysis made by the MAH is to present the safety results of Study B2315 in the context of those reported in the pivotal registration Study B2311 and its long-term extension Study B2311E1. Therefore, the safety results of Study B2315 are presented by the MAH side-by-side with those from Studies B2311 and B2311E1 according to the following groupings:

Dataset A:

• Study B2315: 76-week safety data

• Studies B2311 plus B2311E1: 48-week safety data (core and extension phase)

Dataset B:

• Study B2315: Week 0 to Week 24 safety data

• Study B2311: Week 0 to Week 24 safety data (core phase)

This data set is the key dataset used by the MAH to support the claim to extend the indication for the Exelon/Prometax patch to patients with PDD.

Dataset C:

• Study B2315: Week 24 to Week 48 safety data

• Study B2311E1: Week 24 to Week 48 safety data (extension phase)

Dataset D:

• Study B2315: >48 weeks safety data

A primary objective of study B2315 was to assess the long-term effect of Exelon/Prometax (capsule and patch) on worsening of the underlying motor symptoms of Parkinson's disease in patients with mild to moderately severe dementia associated with PD. To accomplish this objective, data from the following 3 sources were analyzed by the MAH as follows:

- Predefined AEs due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, fall) in studies B2315, B2311, and B2311E1.
- The motor score, collected from the UPDRS part III scale (study B2315)
- The use of anti-parkinsonian medication (study B2315)

It should be underlined that comparison of the safety results between these two studies is indirect.

Patient exposure

◇ Concomitant medications

o CNS-related concomitant medications

CNS-related concomitant medications were used by a similar percentage of patients in all treatment groups in all studies (91.6% - 100%). 'Dopa and dopa derivatives' represented the most widely used ATC class in all treatment groups and in all studies. In study B2315, 'dopa and dopa derivatives'were used by 98.6% of patients in the Exelon/Prometax capsule group, and in 97.6% of patients in the Exelon/Prometax patch group.Other CNS medications used during this study in the Exelon/Prometax patch group were antidepressants (35.8%), antipsychotics (30.9%), and hypnotics/anxiolytics (23.3%).

o Newly introduced CNS medication

In the Exelon/Prometax patch group, 36.8 % of the patients began new CNS medications during the study. Of these, 21.2% were taking antiparkinsonian agents, 7.3% were taking antidepressants, 10.8% antipsychotics, and 8.0% were taking hypnotics/anxiolytics. In comparison, in the Exelon/Prometax capsule group, 27.6% of the patients began new CNS medications during the study. Of these, 17.7% were taking antiparkinsonian agents 7.1% were taking antipsychotics, 4.8% hypnotics/anxiolytics, and 4.1% were taking antidepressants.

o Discontinuation of CNS medications after the start of the study

For any CNS-related concomitant medication, a higher percentage of patients in the Exelon/Prometax patch group (34.4% of patients) had discontinued their CNS-related concomitant medication than in the Exelon/Prometax capsule group (21.4% of patients). In particular, an increased incidence of discontinuation was seen with antidepressants (Exelon/Prometax patch, 8.0% of patients and Exelon/Prometax capsule, 4.4% of patients), antiparkinsonian agents (Exelon/Prometax patch, 25.3% of patients and Exelon/Prometax capsule 13.9% of patients), and hypnotic/anxiolytic agents (Exelon/Prometax patch, 6.9% of patients and Exelon/Prometax capsule, 4.8% of patients).

o Dopaminergic agents

In the Exelon/Prometax patch group, more patients had newly introduced and discontinued antiparkinsonian agents after the start of the study.

Table 17. Usage pattern of antiparkinsonian (dopaminergic) agents (Study B2315- safety population)

Timepoint in study	Exelon Capsule N=294 n (%)	Exelon Patch N=288 n (%)
Prior to start of study	291(99.0)	283(98.3)
Concomitant medications	293(99.7)	284(98.6)
Newly introduced after start of study	52(17.7)	61(21.2)
Discontinued after start of the study	41(13.9)	73(25.3)

Note: Prior medications were any medications started prior to first dose of study medication.
Concomitant medication/therapy was any drug or non-drug therapy that was active on or after the first dose of study drug.
A concomitant medication was considered 'introduced newly' when the start date of this medication was after the start of the study drug and the medication did not continue at the time of start of study drug.
Any CNS medication considered as 'discontinued' if that medication was discontinued after start of study drug.
Source: [Study B2315-PT-Table 14.3-1.5], [Study B2315-PT-Table 14.3-1.6], [Study B2315-PT-Table 14.3-1.7], and [Study B2315-PT-Table 14.3-1.8].

A total of 97.6% of the patients in the Exelon/Prometax patch group used any L-Dopa medication during the study B2315. L-Dopa medications were newly introduced in 15.6% of patients in the Exelon/Prometax patch group, compared to 10.2% of patients in the Exelon/Prometax capsule group. Overall, an increase in L-Dopa dose was seen in both groups. For patients in the Exelon/Prometax capsule group who completed the study, a decrease in L-Dopa dose was seen at the end of study. However, for patients the Exelon/Prometax capsule group who discontinued the study, an increase in the L-Dopa dose was seen at the end of study. For patients in the Exelon/Prometax patch group, an increase in the L-Dopa dose was observed by the end of study regardless of completion status.

The MAH was requested to further discuss the fact that more patients began new CNS medications (antiparkinsonian agents, antidepressants, antipsychotics, hypnotics/anxiolytics) during study B2315 in the Exelon/Prometax patch group, the fact that a higher percentage of patients in the Exelon/Prometax patch group had discontinued their CNS-related concomitant medication than in the Exelon/Prometax capsule group, in particular with regard to data on worsening effect on the PD symptoms and the fact that a higher percentage of patients in the Exelon/Prometax patch group were newly treated by L-Dopa medications than in the Exelon/Prometax capsule group.

The MAH provided a detailed analysis and the CHMP were reassured that the concerns initially rose, may be explained by the patient's characteristics at baseline (medication, medical history). In addition no significant difference may be considered between Exelon/Prometax formulations regarding new CNS medications, discontinued CNS medications, and new L-Dopa medications.

- o Withdrawals

The most common reasons for study discontinuation in the both groups were AEs (23.7% for Exelon/Prometax capsule and 20.8% for patch), withdrawal of consent (6.1% and 8.3%, respectively), and death (3.7% and 3.8%, respectively). A higher percentage of patients in the Exelon/Prometax patch group (4.2%) discontinued the study due to an unsatisfactory therapeutic effect compared to the patients in the Exelon/Prometax capsule group (1.4%).

The MAH was requested to further discuss the fact that a higher percentage of patients in the Exelon/Prometax patch group (4.2%) discontinued the study due to an unsatisfactory therapeutic effect compared to the patients in the Exelon/Prometax capsule group (1.4%).

The MAH clarified that for the majority of the patients who were discontinued due to lack efficacy, the overall duration of treatment with the Exelon/Prometax patch and Exelon/Prometax capsule was short(treatment with the target dose was either very brief or not achieved in many cases). The short duration and suboptimal dosing no doubt contributed to the Investigator's assessment of "unsatisfactory therapeutic effect" in both treatment groups. However, the fact that improvement was shown on 1 or more of the efficacy scales for more than half the patients in both treatment groups suggest that, in some cases, reasons other than lack of efficacy may have played role in the discontinuation of these patients. Based on this case review, the significance of the imbalance between the treatment groups is not considered meaningful.

The CHMP agreed with the MAH's conclusion.

Adverse events

The most frequently affected system organ classes in study B2315 were gastrointestinal disorders, nervous system disorders and psychiatric disorders and the most common AEs were nausea, vomiting, and parkinsonian rest tremor. These events were reported in the highest percentage of patients during the initial 24 weeks of treatment in both the Exelon/Prometax capsule and the Exelon/Prometax patch groups. Except for the rate of fall, which remained relatively unchanged in the Exelon/Prometax

capsule group and in the Exelon/Prometax patch group after Week 24, the percentages of patients with these events trend to progressively decrease over time.

The most frequently reported AEs in the Exelon/Prometax capsule group were nausea, vomiting, Parkinsonian rest tremor, and fall; with the exception of fall, the incidence rates of these events were substantially lower in the Exelon/Prometax patch group.

The most frequently reported AEs in the Exelon/Prometax patch group were fall, application site erythema, Parkinsonian rest tremor and confusional state:

- the most frequent AE in the Exelon/Prometax patch group was fall, which was reported in 20.1% of patients compared to 17.0% in the Exelon/Prometax capsule group during the 76 weeks of study B2315; this was markedly higher than in patients treated with the Exelon/Prometax capsule over the 48 weeks of studies B2311+B2311E1 (7.7%).

- psychiatric events, in particular depression during the initial 24 weeks of treatment., were reported most frequently by patients in the Exelon/Prometax patch group (45.1% vs 32% capsule).

- a total of 25.3% of patients in the Exelon/Prometax patch group reported an application site reaction AE. over the 76 weeks of study B2315 The most frequently reported event was application site erythema (13.9% of patients).

◇ Analysis by dataset

- **Common AEs and affected SOCs in Dataset A (full duration 76 and 48 week safety data; Study B2315 & Studies B2311+B2311E1)**

Table 18. Number (%) of patients with adverse events (at least 5% in any treatment group) by SOC, preferred term, treatment group and study (Dataset A: full duration 76 and 48 weeks- safety population)

	Study B2315		Studies B2311+B2311E1	
	Exelon capsule	Exelon patch	Exe/Exe* (capsule)	Plc/Exe** (capsule)
	N=294	N=288	N=362	N=179
	n (%)	n (%)	n (%)	n (%)
Any system organ class	274 (93.2)	263 (91.3)	323 (89.2)	154 (86.0)
Primary system organ class				
AE Preferred term				
Gastrointestinal disorders				
-Total	182 (61.9)	84 (29.2)	203 (56.1)	79 (44.1)
Nausea	119 (40.5)	24 (8.3)	119 (32.9)	46 (25.7)
Vomiting	45 (15.3)	8 (2.8)	70 (19.3)	22 (12.3)
Diarrhea	27 (9.2)	16 (5.6)	29 (8.0)	12 (6.7)
Constipation	21 (7.1)	21 (7.3)	21 (5.8)	14 (7.8)
Abdominal pain upper	13 (4.4)	8 (2.8)	20 (5.5)	3 (1.7)
Nervous system disorders				
-Total	174(59.2)	156(54.2)	147 (40.6)	69 (38.5)
Parkinsonian rest tremor [1]	72 (24.5)	28 (9.7)	0 (0.0)[1]	0 (0.0) [1]
Dizziness	27 (9.2)	23 (8.0)	23 (6.4)	4 (2.2)
Somnolence	24 (8.2)	19 (6.6)	17 (4.7)	12 (6.7)
Parkinsonian gait	18 (6.1)	14 (4.9)	0 (0.0)	0 (0.0)
Bradykinesia	15 (5.1)	18 (6.3)	9 (2.5)	3 (1.7)
Headache	15 (5.1)	12 (4.2)	20 (5.5)	8(4.5)
On and off phenomenon	15 (5.1)	16 (5.6)	1 (0.3)	3 (1.7)
Syncope	15 (5.1)	5 (1.7)	5 (1.4)	8 (4.5)
Cogwheel rigidity	12 (4.1)	15(5.2)	0 (0.0)	0 (0.0)
Tremor	3 (1.0)	1 (0.3)	41 (11.3)	20 (11.2)
Psychiatric disorders				
-Total	94 (32.0)	130 (45.1)	117 (32.3)	53 (29.6)
Confusional state	23 (7.8)	27 (9.4)	22 (6.1)	15 (8.4)
Hallucination	20 (6.8)	25 (8.7)	25 (6.9)	22 (12.3)
Anxiety	18 (6.1)	23 (8.0)	13(3.6)	4 (2.2)
Hallucination, visual	15 (5.1)	19 (6.6)	14 (3.9)	8 (4.5)
Insomnia	14 (4.8)	23 (8.0)	14 (3.9)	5 (2.8)
Depression	6 (2.0)	23 (8.0)	12 (3.3)	4 (2.2)
Infections and infestations				
-Total	73 (24.8)	74 (25.7)	66 (18.2)	36 (20.1)
Urinary tract infection	19 (6.5)	23 (8.0)	16 (4.4)	13 (7.3)
Injury, poisoning and procedural complications				
-Total	72 (24.5)	73 (25.3)	48(13.3)	27(15.1)
Fall	50 (17.0)	58 (20.1)	28 (7.7)	17 (9.5)
General disorders and administration site conditions				
-Total	61 (20.7)	108 (37.5)	57(15.7)	32(17.9)

	Study B2315		Studies B2311+B2311E1	
	Exelon capsule	Exelon patch	Exe/Exe* (capsule)	Plc/Exe** (capsule)
	N=294	N=288	N=362	N=179
	n (%)	n (%)	n (%)	n (%)
Fatigue	21 (7.1)	13 (4.5)	19 (5.2)	8 (4.5)
Application site erythema	0 (0.0)	40 (13.9)	0 (0.0)	0 (0.0)
Vascular disorders				
-Total	60 (20.4)	46 (16.0)	45 (12.4)	42 (23.5)
Hypotension	24 (8.2)	10 (3.5)	27 (7.5)	18 (10.1)
Orthostatic hypotension	19 (6.5)	17 (5.9)	10 (2.8)	12 (6.7)
Hypertension	16 (5.4)	14 (4.9)	7 (1.9)	8 (4.5)
Musculoskeletal and connective tissue disorders				
-Total	53(18.0)	60 (20.8)	41 (11.3)	18 (10.1)
Back pain	15 (5.1)	16 (5.6)	10 (2.8)	4 (2.2)
Metabolism and nutrition disorders				
-Total	38 (12.9)	31 (10.8)	49 (13.5)	18 (10.1)
Decreased appetite	18 (6.1)	13 (4.5)	34 (9.4)	14 (7.8)
Investigations				
-Total	34 (11.6)	29 (10.1)	20 (5.5)	15 (8.4)
Weight decreased	19 (6.5)	19 (6.6)	12 (3.3)	10 (5.6)

* Exelon capsule group in the core study (B2311) **plus** Exelon capsule group in the extension study (B2311E1)

Placebo group in the core study (B2311) **plus Exelon capsule group in the extension study (B2311E1)

[1] In Study B2311+ Study B2311E1, events of parkinsonian rest tremor are captured under the preferred term AE 'Tremor'

Primary system organ classes with AEs occurring in ≥ 5% of patients in any treatment group are presented in descending frequency, as reported in Study B2315 Exelon Capsule column.

Preferred terms are sorted within SOCs in descending frequency, as reported in Study 2315 Exelon Capsule column.

A patient with multiple AEs within a primary system organ class was counted only once.

Studies included: [Study B2315], [Study B2311], [Study B2311E1]

Source: [SCS Appendix 1-PT-Table 2.1-1]

- **Common AEs and affected SOCs in Dataset B (Initial 24-week, open-label/ double-blind safety data; Studies B2315 & B2311)**

Table 19. Number (%) of patients with adverse events (at least 5% in any treatment group) by SOC, preferred term, treatment group, and study (Dataset B: Initial 24 weeks-safety population)

	Study B2315 (Week 0-24)		Study B2311	
	Exelon capsule	Exelon patch	Exelon capsule	Placebo
	N=294	N=288	N=362	N=179
	n (%)	n (%)	n (%)	n (%)
Any system organ class	259(88.1)	230(79.9)	303(83.7)	127(70.9)
Primary system organ class				
AE Preferred term				
Gastrointestinal disorders				
-Total	168 (57.1)	61 (21.2)	183 (50.6)	48 (26.8)
Nausea	113 (38.4)	19 (6.6)	105 (29.0)	20 (11.2)
Vomiting	38 (12.9)	5 (1.7)	60 (16.6)	3 (1.7)
Diarrhea	24 (8.2)	11 (3.8)	26 (7.2)	8 (4.5)
Constipation	16 (5.4)	11 (3.8)	17 (4.7)	12 (6.7)
Nervous system disorders				
-Total	145 (49.3)	119 (41.3)	121 (33.4)	47 (26.3)
Parkinsonian rest tremor	66 (22.4)	20 (6.9)	0 (0.0)[1]	0 (0.0)[1]
Dizziness	24 (8.2)	16 (5.6)	20 (5.5)	2 (1.1)
Somnolence	18 (6.1)	12 (4.2)	13 (3.6)	5 (2.8)
Tremor	3 (1.0)	1 (0.3)	37 (10.2)	7 (3.9)
Psychiatric disorders				
-Total	60 (20.4)	89 (30.9)	86 (23.8)	40 (22.3)
Confusional state	14 (4.8)	13 (4.5)	13 (3.6)	10 (5.6)
Anxiety	13 (4.4)	15 (5.2)	11 (3.0)	1 (0.6)
Hallucination	10 (3.4)	15 (5.2)	17 (4.7)	17(9.5)
Insomnia	7 (2.4)	18 (6.3)	10 (2.8)	4 (2.2)
Depression	1 (0.3)	16 (5.6)	6 (1.7)	3 (1.7)

	Study B2315 (Week 0-24)		Study B2311	
	Exelon capsule	Exelon patch	Exelon capsule	Placebo
	N=294	N=288	N=362	N=179
	n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions				
-Total	45 (15.3)	81 (28.1)	44 (12.2)	22 (12.3)
Fatigue	16 (5.4)	10 (3.5)	14 (3.9)	5 (2.8)
Application site erythema	0 (0.0)	31 (10.8)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications				
-Total	41 (13.9)	48 (16.7)	36 (9.9)	17 (9.5)
Fall	29 (9.9)	34 (11.8)	21 (5.8)	11 (6.1)
Vascular disorders				
-Total	30 (10.2)	28 (9.7)	30 (8.3)	31 (17.3)
Orthostatic hypotension	13 (4.4)	10 (3.5)	6 (1.7)	9 (5.0)
Hypotension	9 (3.1)	7 (2.4)	19 (5.2)	14 (7.8)
Metabolism and nutrition disorders				
-Total	26 (8.8)	19 (6.6)	38 (10.5)	9 (5.0)
Decreased appetite	14 (4.8)	9 (3.1)	28 (7.7)	8 (4.5)

[1] In Study B2311 events of parkinsonian rest tremor are captured under the preferred term AE 'Tremor'.

Primary system organ classes with AEs occurring in ≥ 5% of patients in any treatment group are presented in descending frequency, as reported in Study B2315 Exelon Capsule column.

Preferred terms are sorted within SOCs in descending frequency, as reported in Study B2315 Exelon Capsule column.

A patient with multiple AEs within a primary system organ class was counted only once.

Studies included: [Study B2315], [Study B2311]

Source: [SCS Appendix 1-PT-Table 2.1-2]

- **Common AEs and affected SOCs in Dataset C (Weeks 24-48 open-label safety data; Studies B2315 & B2311E1)**

Table 20. Number (%) of patients with adverse events (at least 5% in any treatment group) by SOC, preferred term, treatment group, and study (Dataset C: 24 to 48 weeks-safety population)

	Study B2315 (Week 24-48)		Study B2311E1	
	Exelon capsule	Exelon patch	Exe-Exelon* (capsule)	Plc-Exelon** (capsule)
	N=228	N=235	N=211	N=123
	n (%)	n (%)	n (%)	n (%)
Any system organ class	134 (58.8)	144 (61.3)	158 (74.9)	93 (75.6)
Primary system organ class				
AE Preferred term				
Nervous system disorders				
-Total	51 (22.4)	49 (20.9)	51 (24.2)	38 (30.9)
Parkinson's rest tremor[1]	11 (4.8)	4 (1.7)	0 (0.0)	0 (0.0)
Somnolence	6 (2.6)	7 (3.0)	5 (2.4)	7 (5.7)
Tremor	0 (0.0)	0 (0.0)	8 (3.8)	15 (12.2)
Gastrointestinal disorders				
-Total	33 (14.5)	25 (10.6)	58 (27.5)	47 (38.2)
Nausea	16 (7.0)	4 (1.7)	29 (13.7)	33 (26.8)
Vomiting	7 (3.1)	3 (1.3)	17 (8.1)	20 (16.3)
Psychiatric disorders				
-Total	31 (13.6)	46 (19.6)	49 (23.2)	23 (18.7)
Hallucination	6 (2.6)	5 (2.1)	9 (4.3)	7 (5.7)
Confusional state	5 (2.2)	10 (4.3)	10 (4.7)	7 (5.7)
Injury, poisoning and procedural complications				
-Total	25 (11.0)	21 (8.9)	15 (7.1)	14 (11.4)
Fall	19 (8.3)	16 (6.8)	7 (3.3)	9 (7.3)
Infections and infestations				
-Total	21 (9.2)	28 (11.9)	32 (15.2)	18 (14.6)
Urinary tract infection	3 (1.3)	10 (4.3)	4 (1.9)	7 (5.7)

* Patients who received Exelon capsule during the core study (B2311)

** Patients who received placebo during the core study (B2311)

[1] Although reported in <5% of patients AEs of Parkinson's rest tremor are presented because the preferred term 'tremor' in Study B2311 and B2311E1 includes AEs of Parkinson's rest tremor.

Primary system organ classes with AEs occurring in ≥ 5% of patients in any treatment group are presented in descending frequency, as reported in Study B2315 Exelon Capsule column.
Preferred terms are sorted within SOCs in descending frequency, as reported in Study B2315 Exelon Capsule column.
A patient with multiple AEs within a primary system organ class was counted only once.
Studies included: [Study B2315], [Study B2311E1]
Source: [SCS Appendix 1-PT-Table 2.1-3]

- **Common AEs and affected SOCs in Dataset D (>48 weeks, open-label safety data; Study B2315)**

Table 21. Number (%) of patients with adverse events (at least 5% in any treatment group) by SOC, preferred term, treatment group, and study (Dataset D: >48 weeks- safety population)

	Study B2315	
	Exelon capsule (>48 weeks) N=203 n (%)	Exelon patch (>48 weeks) N=205 n (%)
Any system organ class	116 (57.1)	115 (56.1)
Primary system organ class		
AE Preferred term		
Nervous system disorders		
-Total	38 (18.7)	37 (18.0)
Injury, poisoning and procedural complications		
-Total	29 (14.3)	23 (11.2)
Fall	17 (8.4)	19 (9.3)
Psychiatric disorders		
-Total	26 (12.8)	30 (14.6)
Infections and infestations		
-Total	25 (12.3)	28 (13.7)
Gastrointestinal disorders		
-Total	25 (12.3)	14 (6.8)

System organ classes were sorted in descending frequency, as reported in the Exelon Capsule column.
A patient with multiple AEs within a primary system organ class was counted only once.
Studies included: [Study B2315]
Source: [SCS Appendix 1-PT-Table 2.1-4]

Consistently with the known safety profile of Exelon, the frequently affected SOCs over 76 weeks were for capsule gastrointestinal disorders (61.9%), nervous system disorders (59.2%), and psychiatric disorders (32%), and for patch, nervous system disorders (54.2%), psychiatric disorders (45.1%), and general disorders and administration site conditions (37.5%).

The most frequently reported AEs in the Exelon/Prometax capsule group were nausea (40.5%), vomiting (15.3%), parkinsonian rest tremor (24.5%), and fall (17%).

The most frequently reported AEs in the Exelon/Prometax patch group were fall (20.1%), application site erythema (13.9%), Parkinsonian rest tremor (9.7%) and confusional state (9.4%).Psychiatric events were reported most frequently by patients in the Exelon/Prometax patch group (45.1% vs 32% for capsule), particularly depression (8% vs 2% for capsule).

The incidence of gastrointestinal AEs was significantly lower in the Exelon/Prometax patch group(29.2%) than in the Exelon/Prometax capsule group 61.9%), and application site reaction AEs were commonly reported with Exelon/Prometax patch over the 76 weeks of study B2315. The percentage of patients in the Exelon/Prometax patch group with an AE of parkinsonian rest tremor over the 76 weeks was lower than in the Exelon/Prometax capsule group (9% vs 24.5%, respectively), and similar to the percentage of patients in the Exelon/Prometax capsule with tremor (including Parkinson's rest tremor) reported over the 48 weeks of studies B2311/B2311E1.

The highest incidence rates of AEs were observed during the initial 24 weeks of treatment in both the Exelon/Prometax capsule and Exelon/Prometax patch groups.

In conclusion, the Exelon/Prometax capsule safety data and the Exelon/Prometax patch safety data from study B2315 are consistent with the known safety profile of Exelon/Prometax in PD population, and no major differences in safety profile (excepted the higher frequency of tremor with oral form) are observed in this study between the two Exelon/Prometax formulations.

- **Severity of AEs**

In study B2315, the incidence rates of mild, moderate and severe AEs were similar in the Exelon/Prometax capsule group and the Exelon/Prometax patch group (respectively, mild 15.6%vs 12.5%, moderate 52.4% vs 50.3%, severe 25.2% vs 28.5%).

The incidence rates of moderate and severe AEs in both treatment groups in study 2315 were generally about 10 - 20% higher than those in the Exelon/Prometax treatment groups of study B2311 and study B2311E1, which is according to the MAH, not unexpected with longer study duration.

- **Serious adverse events and deaths**

Table 22. Number of patients who died or experienced other serious or clinically significant adverse events (Study B2315- Safety population)

	Exelon capsule N=294 n (%)	Exelon patch N=288 n (%)
Patient with serious or significant AEs		
Deaths	11 (3.7)	11 (3.8)
SAEs	87 (29.6)	83 (28.8)
Discontinued due to AEs[(a)]	80 (27.2)	71 (24.7)

(a) Deaths were included.
Source: [Study B2315-Table 12-5]

- **Deaths**

In study B2315, a total of 22 patients died during the 76-week study period (11 patients in each treatment group). The frequency of deaths was 3.7% (11/294) for Exelon/Prometax capsule and 3.8% (11/288) for Exelon/Prometax patch. Of these, none was attributed to the use of study drug by the investigator, except for 1 death in the Exelon/Prometax patch group reported as suspected to be related to the study drug (acute myocardial infarction).

Pneumonia was the most common reason for death (Exelon/Prometax capsule, 5 patients and Exelon/Prometax patch, 2 patients). In the Exelon/Prometax patch group, 1 patient died due to progression of PD. Deaths due to pulmonary embolism were reported in 2 patients (1 patient in each group), cardiac failure (Exelon/Prometax patch, 2 patients), and cardiac arrest (Exelon/Prometax capsule, 2 patients).

The frequency of deaths in patients who were exposed to Exelon/Prometax in all 3 studies, was the same or lower than the incidence in the placebo group (3.9%) from the pivotal double-blind core study (2311).

The causes of death were typical for the elderly patients with underlying PD enrolled in this study, in particular pneumonia. Regarding the case of acute myocardial infarction (diagnosis mentioned in death certificate), the investigator suspected a relationship between this event and Exelon, however no other informative data on possible alternative event origins was available (i.e ventricular arrhythmia, pulmonary embolism). No other concomitant medications were reported for this patient, and the patient's baseline ECG results were within normal values.

- **SAEs**

The overall incidence of serious adverse events (SAEs) was similar for both treatment groups (Exelon/Prometax capsule: 29.6%; Exelon/Prometax patch: 28.8%) during study B2315 .The most frequently affected SOCs were nervous system disorders, injury, poisoning and procedural complications, and infections and infestations**.**

Dataset A (full duration 76 and 48 week safety data; Studies B2315 & B2311+B2311E1)

The overall incidence of SAEs was similar across studies and treatment groups (22.1% to 29.6%). The most frequently affected SOCs were:

- Nervous system disorders (8.5% and 9.0%, capsule and patch respectively in study B2315).

No unexpected SAEs were reported. The most frequent nervous system-related SAE was syncope, reported in 1.7% of the Exelon/Prometax capsule group and 0.3% of the Exelon/Prometax patch group in study B2315. The percentage of patients in study B2311 + study B2311E1 reporting an AE of syncope was similar: 0.3% in the Exelon/Exelon/Prometax group and 1.7% in the Placebo/Exelon/Prometax group.

- Injury, poisoning and procedural complications (8.2% and 6.9%, capsule and patch respectively in study B2315)

No unexpected SAEs were reported. Only femur fracture, hip fracture and fall occurred in 1% or more of the patients in any treatment group. The most frequent SAE was fall, reported in 3.1% of patients in the Exelon/Prometax patch group and in less than 1% of patients in the other groups.

- Infections and infestations (7.5% and 4.9%, capsule and patch respectively in study B2315)

No unexpected SAEs were reported. Only pneumonia and urinary tract infection occurred in 1% or more of the patients in any treatment group. The most frequent SAE was pneumonia, reported in 3.1% of patients in the Exelon/Prometax capsule group and in 2.4% the patch group in study B2315. In study B2311 + study B2311E1, the percentage of patients with an SAE of pneumonia was 1.1% of patients in the Exelon/Exelon/Prometax treatment group and 3.4% of patients in the Placebo/Exelon/Prometax group.

- Gastrointestinal disorders (5.4% and 4.2%, capsule and patch respectively in study B2315)

No unexpected gastrointestinal-related SAEs were reported. Only diarrhea, inguinal hernia, and vomiting were reported in 1% or more of the patients in any treatment group. Except for diarrhea, which was reported in 3 (1.0%) patients in the Exelon/Prometax patch group in study 2315, all SAEs occurred in only 1 or 2 patients.

- Cardiac disorders (4.1% and 3.5%, capsule and patch respectively in study B2315)

No unexpected cardiac-related SAEs were reported, with only atrial fibrillation occurring in 1% or more of the patients. Atrial fibrillation was reported as an SAE in 1.0% of patients in the Exelon/Prometax capsule group and was not reported in the other 3 treatment groups.

- Psychiatric disorders

The incidence of psychiatric-related SAEs were higher in the Exelon/Prometax patch group than in Exelon/Prometax capsule (7.3% vs. 2.7%) in study B2315, and than in the Exelon-Exelon/Prometax or the Placebo-Exelon/Prometax groups (3.6% and 5.0%, respectively) in study B2311. No unexpected SAEs were reported and only AEs of confusional state, hallucination, and hallucination visual were reported in 1% or more of the patients in any treatment group.

Dataset B (Initial 24-week, openlabel/ double-blind safety data; Studies B2315 & B2311)

The most frequently affected SOCs and the most common SAEs during the first 24 weeks of study B2315 were generally similar to those in the 24-week pivotal registration study B2311.

The incidence of SAEs in each of these SOCs was less than 5% in each treatment group. Overall, no unexpected SAEs were reported and few events occurred in 1% or more of the patients in any treatment group.

The most frequently affected SOCs were nervous system disorders, injury, poisoning and procedural complications, psychiatric disorders, and metabolism and nutrition disorders.

- Nervous system disorders (4.8% and 4.9%, capsule and patch respectively in study B2315)

Only cogwheel rigidity and Parkinsonian rest tremor, dyskinesia and syncope occurred in 1% or more of the patients in any treatment group. With the exception of syncope, these SAEs were only reported in study B2315 occurring in 3 (1.0%) patients in the Exelon/Prometax capsule group and 1 (0.3%) patient in the Exelon/Prometax patch group.

- Injury, poisoning and procedural complications (3.7% and 3.5%, capsule and patch respectively in study B2315)

Only femur fracture and fall occurred in 1% or more of the patients in any treatment group. An SAE of fall was reported in 3 (1.0%) patients in the Exelon/Prometax patch group of study B2315 and in 1 (0.3%) patient in the Exelon/Prometax capsule group in study B2311.

- Psychiatric disorders

Confusional state was the only psychiatric disorder SAE occurring in 1% or more of the patients in any treatment group. The highest percentage of patients with this SAE (1.4%) was in the Exelon/Prometax patch group during the first 24 weeks of study B2315 and was similar to that observed in the placebo group during the 24 weeks of study B2311 (1.1%).

- Metabolism disorders

Dehydration was the only metabolism and nutrition disorder SAE occurring in 1% or more of the patients in any treatment group. The highest percentage of patients with this SAE (1.4%) was in the Exelon/Prometax capsule group during study B2311 and was similar to that observed in the placebo group (1.1%).

Dataset C (Weeks 24-48 open-label safety data; Studies B2315 & B2311E1)

During weeks 24 to 48 of study B2315, the overall incidence rate of SAEs in the Exelon/Prometax capsule and Exelon/Prometax patch groups was lower (11.4% and 14.9%, respectively) than in either the Exelon-Exelon/Prometax or Placebo-Exelon/Prometax group in study B2311E1 (17.5% and 16.3%, respectively).

The most frequently affected SOCs were nervous system disorders, cardiac disorders, and infections and infestations.

In study B2315, other than syncope and atrial fibrillation, which were each reported in 3 (1.3%) patients in the Exelon/Prometax capsule group, pneumonia reported by 3 (1.3%) patients in each group, and urinary tract infection reported by 3 (1.3%) in the Exelon/Prometax patch group, all SAEs during weeks 24 to 48 were single-patient events.

Dataset D (>48 weeks, open-label safety data; Study B2315)

During the period of treatment after week 48, the overall incidence rate of SAEs was similar in the Exelon/Prometax capsule and Exelon/Prometax patch treatment groups (12.3% and 14.6%, respectively) and to the rates observed during weeks 24 to 48 of study B2315 (11.4% and 14.9%).

The most frequently affected SOCs were injury, poisoning and procedural complications, infections and infestations, vascular disorders, respiratory, thoracic and mediastinal disorders, cardiac disorders, renal and urinary retention disorders, nervous system disorders, psychiatric disorders, and metabolism and nutrition disorders. The incidence rates of SAEs in the SOCs of nervous system disorders, psychiatric disorders, or metabolism and nutrition disorders were higher in the Exelon/Prometax patch group;

SAEs of fall, rib fracture, dizziness, and cardiac failure occurred only in the Exelon/Prometax patch group (2.4%, 1.0%, 1.0%, and 1.0%, respectively). SAEs of hypotension, dyspnea, pulmonary embolism, and urinary retention, occurred only in the Exelon/Prometax capsule group (1.0% for each event). Pneumonia was reported by 5 (2.5%) patients in the Exelon/Prometax capsule group and 2 (1.0%) patients in the Exelon/Prometax patch group, dehydration was reported in 3 (1.5%) patients in the Exelon/Prometax patch group and 1 (0.5%) in the Exelon/Prometax capsule group; all other SAEs were single patient events in the Exelon/Prometax capsule group or events reported by 2 patients in the Exelon/Prometax patch group.

- **AEs leading to discontinuation**

The total percentage of patients in the Exelon/Prometax patch group who discontinued Study B2315 due to an AE was similar to that observed in the Exelon/Prometax capsule group (24.7% and 27.2%, respectively) and to the total percentage of patients treated with the Exelon/Prometax capsule during Studies B2311 and B2311E1 (Exelon/Exelon/Prometax group) who discontinued due to an AE (23.8%).

The most frequently reported AEs leading to discontinuation across all studies and treatment groups were nausea, vomiting, and Parkinsonian rest tremor or tremor. In study B2315, with the exception of 5 events, all AEs leading to discontinuation reported in ≥ 1% of patients occurred during the initial 24 weeks of treatment. These 5 events were reported by 1 patient in the Exelon/Prometax capsule group who discontinued from the study due to an AE of vomiting, 1 patient in the Exelon/Prometax patch group who discontinued from the study due to an AE of hallucination during weeks 24 to 48, and 3 patients in the Exelon/Prometax capsule group who discontinued due to pneumonia after week 48.

The rate of discontinuation due to AEs was higher in the Exelon/Prometax capsule and Exelon/Prometax patch groups in Study B2315 than in the Exelon/Prometax capsule group in study B2311 and study B2311E1 (17.1% and 7.1%, respectively).

- **Worsening of Parkinson's disease motor symptoms**

The objectives of study B2315 was to evaluate the long-term safety of Exelon/Prometax capsule (primary objective) and Exelon/Prometax patch (secondary objective), by assessing the worsening of the underlying motor symptoms of PD in patients with mild to moderately severe PDD.

This primary objective was assessed by measuring:

- Predefined AEs due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, and fall).
- Study drug discontinuations due to predefined AEs due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, and fall).

- **Worsening of Parkinson's disease motor symptoms in Dataset A (full duration 76 and 48 week safety data; Studies B2315 & B2311+B2311E1)**

The number (%) of patients in Dataset A with predefined worsening of PD motor symptoms are presented in the table below:

Table 23. Number (%) of patients with worsening of Parkinson's disease motor symptoms by treatment group (Dataset A: full duration 76 and 48 weeks- safety population)

	Study B2315		Studies B2311+B2311E1	
	Exelon capsule N=294	Exelon patch N=288	Exe/Exe* capsule N=362	Plc/Exe** capsule N=179
	n (%)	n (%)	n (%)	n (%)
Any preferred term	107 (36.4)	93 (32.3)	73 (20.2)	35 (19.6)
Predefined AEs				
Any tremor[1]	73 (24.8)	29 (10.1)	41 (11.3)	20 (11.2)
Any muscle rigidity[2]	13 (4.4)	15 (5.2)	1 (0.3)	1 (0.6)
Fall	50 (17.0)	58 (20.1)	28 (7.7)	17 (9.5)
Bradykinesia	15 (5.1)	18 (6.3)	9 (2.5)	3 (1.7)

* Exelon capsule group in the core study (B2311) **plus** Exelon capsule group in the extension study (B2311E1)

Placebo group in the core study (B2311) **plus Exelon capsule group in the extension study (B2311E1)

[1]'Any Tremor' comprises the preferred terms 'Parkinsonian rest tremor' and 'Tremor'

[2]'Any Muscle rigidity' comprises the preferred terms 'Cogwheel rigidity' and 'Muscle rigidity'

Studies included: [Study B2315], [Study B2311], [Study B2311E1]
Source: [SCS Appendix 1-PT-Table 2.1-13]

During the 76 weeks of study B2315, a total of 36.4% of patients in the Exelon/Prometax capsule group and 32.3% of patients in the Exelon/Prometax patch group reported predefined AEs due to worsening of PD motor symptoms. During the 48 weeks of study B2311 + study B2311E1, the rates were 20.2% in the Exelon-Exelon/Prometax group and 19.6% in the Placebo-Exelon/Prometax group.

In study 2315, tremor was reported in a higher percentage of patients in the Exelon/Prometax capsule group than in the Exelon/Prometax patch group (24.8% vs. 10.1%, respectively). In study B2311 + study B2311E1, the percentage of patients with an AE of tremor in either the Exelon/Exelon/Prometax or the Placebo/Exelon/Prometax group (11.3% and 11.2%, respectively) was similar to that reported in the Exelon/Prometax patch group.

In study B2315, a similar percentage of patients in the Exelon/Prometax capsule and Exelon/Prometax patch groups experienced muscle rigidity (4.4 % and 5.2%, respectively) or bradykinesia (5.1% and 6.3%, respectively). A higher percentage of patients treated with the Exelon/Prometax patch reported an AE of fall than those treated with the Exelon/Prometax capsule (20.1% vs. 17.0% respectively).

The percentages of patients with AEs of muscle rigidity, fall or bradykinesia in either treatment group in study B2315 were higher than those reported for the Exelon/Prometax capsule group and the Placebo-Exelon/Prometax group in study B2311 + study B2311E1.

- **Worsening of Parkinson's disease motor symptoms in Dataset B (Initial 24-week, open-label/double-blind safety data; Studies B2315 & B2311)**

The number (%) of patients in Dataset B with predefined worsening of PD motor symptoms are presented in the table below:

Table 24. Number (%) of patients with worsening of Parkinson's disease motor symptoms by treatment group (Dataset B: Initial 24 weeks- safety population

	Study B2315 (Week 0-24)		Study B2311	
	Exelon capsule N=294 n (%)	Exelon patch N=288 n (%)	Exelon capsule N=362 n (%)	Placebo N=179 n (%)
Any preferred term	86 (29.3)	59 (20.5)	64 (17.7)	19 (10.6)
Predefined AEs				
Any tremor[1]	67 (22.8)	21 (7.3)	37 (10.2)	7 (3.9)
Any muscle rigidity[2]	9 (3.1)	8 (2.8)	1 (0.3)	0 (0.0)
Fall	29(9.9)	34 (11.8)	21 (5.8)	11 (6.1)
Bradykinesia	9 (3.1)	10 (3.5)	9 (2.5)	3 (1.7)

AEs were sorted in descending frequency, as reported in Study B2315 Exelon Capsule column

[1] 'Any Tremor' comprises the preferred terms 'Parkinsonian rest tremor' and 'Tremor'

[2] 'Any Muscle rigidity' comprises the preferred terms 'Cogwheel rigidity' and 'Muscle rigidity'

Studies included: [Study B2315], [Study B2311]
Source: [SCS Appendix 1-PT-Table 2.1-14]

In study B2315 (weeks 0-24), the incidence of predefined AEs due, or potentially due, to worsening of PD motor symptoms was higher in the Exelon/Prometax capsule group (29.3%) than in Exelon/Prometax patch group (20.5%), both being higher than the rates observed in the Exelon/Prometax capsule group (17.7%) and the placebo group (10.6%) in study B2311.

During the first 24 weeks of Study B2315, tremor was reported in a higher percentage of patients in the Exelon/Prometax capsule group than in the Exelon/Prometax patch group (22.8% vs. 7.3%, respectively). During the 24-week study B2311, 10.2% of patients in the Exelon/Prometax capsule group and 3.9% in the placebo group reported an AE of tremor.

In study B2315, a similar percentage of patients in the Exelon/Prometax capsule and Exelon/Prometax patch groups experienced muscle rigidity (3.1 % and 2.8%, respectively) or bradykinesia (3.1% and 3.5%, respectively). A higher percentage of patients treated with the Exelon/Prometax patch reported an AE of fall than those treated with the Exelon/Prometax capsule (11.8% vs. 9.9%, respectively).

The percentages of patients with AEs of muscle rigidity, fall or bradykinesia in either treatment group in study B2315 were higher than those reported for the Exelon/Prometax capsule group and the placebo group in study B2311.

- **Worsening of Parkinson's disease motor symptoms in Dataset C (Weeks 24-48 open-label safety data; Studies B2315 & B2311E1)**

The number (%) of patients in Dataset C with predefined worsening of PD motor symptoms are presented in the table below:

Table 25. Number (%) of patients with worsening of Parkinson's disease motor symptoms by treatment group (Dataset C: Weeks 24 to 48- safety population)

	Study B2315 (Week 24-48)		Study B2311E1	
	Exelon capsule	Exelon patch	Exe-Exelon* (capsule)	Plc-Exelon** (capsule)
	N=228	N=235	N=211	N=123
	n (%)	n (%)	n (%)	n (%)
Any preferred term	28 (12.3)	24 (10.2)	16 (7.6)	23 (18.7)
Predefined AES				
Any tremor[1]	11 (4.8)	4 (1.7)	8 (3.8)	15 (12.2)
Any muscle rigidity[2]	3 (1.3)	5 (2.1)	0 (0.0)	1 (0.8)
Fall	19 (8.3)	16 (6.8)	7 (3.3)	9 (7.3)
Bradykinesia	3 (1.3)	5 (2.1)	1 (0.5)	0 (0.0)

* Patients who had received Exelon capsule during the core study (B2311)

** Patients who had received placebo during the core study (B2311)

[1] 'Any Tremor' comprises the preferred terms 'Parkinsonian rest tremor' and 'Tremor'

[2] 'Any Muscle rigidity' comprises the preferred terms 'Cogwheel rigidity' and 'Muscle rigidity'

Studies included: [Study B2315], [Study B2311E1]
Source: [SCS Appendix 1-PT-Table 2.1-15]

During the 24 to 48 weeks of study B2315, tremor was reported in a higher percentage of patients in the Exelon/Prometax capsule group than in the Exelon/Prometax patch group (4.8% vs. 1.7%, respectively). In study B2311E1, the percentage of patients with an AE of tremor was 3.8% in the Exelon-Exelon/Prometax group and 12.2% in the Placebo-Exelon/Prometax group.

In study B2315, a similar percentage of patients in the Exelon/Prometax capsule and Exelon/Prometax patch treatment groups experienced muscle rigidity (1.3 % and 2.1%, respectively) or bradykinesia (1.3% and 2.1%, respectively). A lower percentage of patients treated with the Exelon/Prometax patch reported an AE of fall than those treated with the Exelon/Prometax capsule (6.8% vs. 8.3%, respectively).

The percentages of patients with AEs of muscle rigidity, fall or bradykinesia in either treatment group in study B2315 were higher than those reported for the Exelon-Exelon/Prometax or Placebo-Exelon/Prometax groups in study B2311E1.

- **Worsening of Parkinson's disease motor symptoms in Dataset D (> 48 weeks, open-label safety data; Study B2315)**

The number (%) of patients in Dataset D with predefined worsening of PD motor symptoms are presented in the table below:

Table 26. Number (%) of patients with worsening of Parkinson's disease motor symptoms by treatment group (Dataset D: >48 weeks- safety population)

	Study B2315 (>48 weeks)	
	Exelon capsule	Exelon patch
	N=203	N=205
	n (%)	n (%)
Any preferred term	29 (14.3)	27 (13.2)
Predefined AES		
Any tremor[1]	7 (3.4)	4 (2.0)
Any muscle rigidity[2]	3 (1.5)	4 (2.0)
Fall	17 (8.4)	19 (9.3)
Bradykinesia	4 (2.0)	4 (2.0)

[1] 'Any Tremor' comprises the preferred terms 'Parkinsonian rest tremor' and 'Tremor'

[2] 'Any Muscle rigidity' comprises the preferred terms 'Cogwheel rigidity' and 'Muscle rigidity'

Studies included: [Study B2315]
Source: [SCS Appendix 1-PT-Table 2.1-16]

During the period of treatment after week 48, a similar percentage of patients in the Exelon/Prometax capsule and Exelon/Prometax patch groups reported tremor (3.4% and 2.0%, respectively). This was also the case for muscle rigidity (1.5 % and 2.0%, respectively), fall (8.4% vs. 9.3%, respectively); bradykinesia was reported by and 2.0% of percentage of patients in both groups.

- **Time-to-first PD motor symptoms**

In study B2315, analysis of the time-to-first PD motor symptoms AEs (tremor, muscle rigidity, bradykinesia, and fall) was performed using the Kaplan-Meier method of life-table estimation. This analysis was not performed in study B2311 or study B2311E1.

Overall, the greatest between-treatment difference in the time-to-first PD motor symptom during the first 24 weeks of therapy was for tremor. At week 24, the survival function for the time-to-first PD motor symptom of tremor in the Exelon/Prometax capsule group was 0.758 (95% confidence interval (CI) =0.706, 0.809), while for the Exelon/Prometax patch it was approximately 0.924 (95% CI=0.893, 0.955) (observed at week 25)

Little or no differences between the treatment groups were seen in the time-to-first AEs of muscle rigidity, bradykinesia, and fall.

- **Discontinuations rate due to worsening of Parkinson's disease motor symptoms**

In study B2315, the overall discontinuation rate due to worsening of PD motor symptoms was 4.4% for the Exelon/Prometax capsule group and 2.4% for the Exelon/Prometax patch group. In the Exelon/Prometax capsule group, tremor was the most frequently reported PD motor symptom AE that led to study discontinuation (2.4%), while fall was the most frequently reported AE leading to discontinuation in the Exelon/Prometax patch group (1.4%). Few patients in each group discontinued the study because of muscle rigidity (0.3% in each) or bradykinesia (1% vs. 0.0%, respectively). These data are similar to what was observed in Study B2311 and Study B2311E1.

Table 27. Discontinuation rate due to worsening of Parkinson's disease motor symptoms, by treatment group (Study B2315- safety population)

	Exelon Capsule N=294		Exelon Patch N=288	
Event	n	%	n	%
Total	**13**	**4.4**	**7**	**2.4**
Tremor	7	2.4	2	0.7
Muscle rigidity	1	0.3	1	0.3
Bradykinesia	3	1.0	0	0.0
Fall	3	1.0	4	1.4

Patients with multiple occurrences of the same AEs were counted only once in each category.
Ninety-five percent (95%) CI were calculated for proportions using normal approximation.
Worsening of PD motor symptoms were pre-defined based on the following preferred terms: fall; bradykinesia; cogwheel rigidity (for muscle rigidity); and parkinsonian rest tremor (for tremor).
Source: [Study B2315-PT-Table 14.3.1-3.2]

- **Time to first event of tremor leading to study discontinuation**

In study B2315, analysis of the time-to-first PD motor symptom AEs (tremor, muscle rigidity, bradykinesia, and fall) leading to study discontinuation was performed using the Kaplan-Meier method of life-table estimation. Overall, little or no changes were seen between the Exelon/Prometax capsule and Exelon/Prometax patch groups or the time-to-first PD motor symptom AEs of tremor, muscle rigidity , bradykinesia , and fall that led to discontinuation of the study drug.

- **UPDRS Part III scores in Study B2315**
  - **UPDRS Part III: Total**

UPDRS Part III total scores (used as a safety parameter to assess changes in PD motor symptoms) were compared at weeks 8, 16, 24, 52, and 76 in both groups. The changes from baseline are summarized below:

Table 28. Change from baseline in UPDRS Part III total score, by treatment group and visit (Study B2315- safety population)

		Exelon Capsule		Exelon Patch	
Visit		**n**	**Mean**	**n**	**Mean**
Week 8	Baseline	276	29.3	277	30.2
	Change	276	-0.4	277	-0.9
Week 16	Baseline	254	29.5	252	29.9
	Change	254	0.5	252	-1.7
Week 24	Baseline	229	29.6	237	30.0
	Change	229	0.1	237	-1.4
Week 52	Baseline	203	29.7	206	29.2
	Change	203	0.7	206	1.6
Week 76	Baseline	183	28.8	175	29.3
	Change	183	2.1	175	2.1

n is the number of patients with non-missing baseline and post-baseline respective measurement.
LS Mean and 95% CI were from an analysis of covariance (ANCOVA) model with treatment and country as factors and the baseline UPDRS Part III score as a covariate.
Negative change scores indicate improvement from baseline.
Source: [Study B2315-PT-Table 14.3-2.5]

Improvements from baseline were seen with the Exelon/Prometax capsule at Weeks 8, and in the Exelon/Prometax patch group at Weeks 8, 16, and 24. A small and similar deterioration was observed in both groups at weeks 52 and 76.

- **UPDRS Part III: Patients who experienced worsening of Parkinson's Disease motor symptoms**

Summary statistics for the UPDRS Part III total scores and Part III item scores in patients who experienced worsening of PD motor symptoms were provided for baseline, week 8, week 16, 24, 52, and 76.

In the subgroup of patients who reported predefined AEs due, or potentially due to worsening of PD motor symptoms, similar results in the UPDRS Part III total scores were seen to those results observed in the total safety population. In general with long-term treatment, the changes from baseline in the UPDRS Part III total scores with the Exelon/Prometax capsule increased slightly or remained unchanged in patients who experienced worsening of their PD. At week 76, the change from baseline was 2.6 in the UPDRS Part III total scores.

Patients in the Exelon/Prometax patch group who experienced worsening of their PD motor symptoms also continued to show improvements or remain unchanged. At week 76, the change from baseline was 3.1 in the UPDRS Part III total scores. For the patients in the Exelon/Prometax patch group who experienced worsening of PD, slightly numerically greater improvements were seen in the UPDRS Part III total scores at weeks 8 and 24 compared to those patients in the Exelon/Prometax capsule group. Statistically significant differences were seen in the changes from baseline in the UPDRS Part III total scores at week 16 in the Exelon/Prometax patch group compared to the Exelon/Prometax capsule group (−2.2 vs. 1.0, respectively).

Other than a slight improvement from baseline at week 76 in the 'tremor at rest' sub-item score in the Exelon/Prometax patch group (-0.6), and in the 'rigidity' sub-item score in the Exelon/Prometax capsule group (-0.1), changes from baseline at week 76 ranged from 0.0 to 0.4 in the Exelon/Prometax capsule group and 0.0 to 0.5 in the Exelon/Prometax patch group.

Summary of worsening of Parkinson's disease motor symptoms

During the 76 weeks of study B2315, a total of 36.4% of patients in the Exelon/Prometax capsule group and 32.3% of patients in the Exelon/Prometax patch group reported predefined AEs due, or potentially due to worsening of PD motor symptoms. The most commonly reported predefined AEs were tremor in the Exelon/Prometax capsule group (24.8% vs 9.7% patch) and fall in the Exelon/Prometax patch group (20.1% vs 17% patch). A similar percentage of patients in the Exelon/Prometax capsule and Exelon/Prometax patch groups experienced muscle rigidity (4.4% and 5.2%, respectively) or bradykinesia (5.1% and 6.3%, respectively)

The majority of events of tremor, muscle rigidity, bradykinesia, or fall occurred during the first 24 weeks of treatment. Except for the rate of fall, which remained between 8.3% and 8.4% in the Exelon/Prometax capsule group and 6.8% to 9.3% in the Exelon/Prometax patch group after week 24, with these events progressively decreased during weeks 24 to 48 and after week 48.

During the first 24 weeks of treatment, a significant higher percentage of patients in the Exelon/Prometax capsule group from study B2315 reported an AE of tremor compared to the Exelon/Prometax capsule group in study B2311 (22.8% vs. 10.2%, respectively). This was also the case for an AE of fall in both the Exelon/Prometax capsule and Exelon/Prometax patch groups (9.9% and 11.8%, respectively vs. 5.8%)

The overall discontinuation rate due to these predefined AEs or due to tremor was low (oral : 4.4% / patch : 2.4%) and similar to those observed in studies B2311 and B2311E1. In the Exelon/Prometax capsule group, tremor was the most frequently reported PD motor symptom AE that led to study

discontinuation (2.4% vs 0.7% patch), while fall was the most frequently reported AE leading to discontinuation in the Exelon/Prometax patch group (1.4%). Few patients in each group discontinued the study because of muscle rigidity (0.3% in each) or bradykinesia (1% vs. 0.0%, respectively). These data are similar to what was observed in study B2311 and study B2311E1

- **Application site reactions**

In study B2315, application site skin reactions and irritations, defined as either application site erythema, pruritus, hypersensitivity, eczema, irritation, and inflammation was reported by 25.3% of the patients who were treated with Exelon/Prometax patch, with application site erythema reported most often (13.9%).

Application site reaction AEs lead to discontinuations in 3.8% (11/288) of patients over 76 weeks. These events included the following: erythema in 4 (1.4%) patients, irritation in 3 (1.0%) patients, and single-patient events of hypersensitivity, inflammation, eczema or pruritus.

Laboratory findings (study B2315)

Clinical chemistry, haematology, urinalysis, special tests

Overall, no clinically relevant changes in laboratory values were observed in study B2311. As a result, laboratory evaluations were only performed at screening and baseline in Study B2315.

Electrocardiograms, vital signs, body weight and physical examinations

No clinically relevant electrocardiogram (ECG) changes were observed in study B2311. As a result, ECG data were only recorded as source data in Study B2315 and not captured in the clinical database.

Significant decreases in body weight (≥7% from baseline) occurred in a higher percentage of patients treated with the Exelon/Prometax patch compared to the Exelon/Prometax capsule (10.4% vs. 7.8%, respectively).

The results of the Schellong Test for orthostatic hypotension at weeks 8, 24, 52, and 76 showed no increases in the incidences of orthostatic hypotension over time from baseline with Exelon/Prometax capsule or Exelon/Prometax patch treatment.

In both Exelon/Prometax groups, there were similar mean decreases up to 3.6 mmHg in supine systolic BP. Greater mean decreases were seen in standing systolic BP in the Exelon/Prometax patch group compared to the Exelon/Prometax capsule group (3.9 mmHg vs. 1.6 mmHg, respectively). However, the percentage of patients who had notable decreases in standing systolic BP was greater in the Exelon/Prometax capsule group compared to the Exelon/Prometax patch group (3.1% vs. 0.7%, respectively).

In the Exelon/Prometax capsule group, small decreases in mean standing (1.2 beats per minute [bpm]) and supine (0.3 bpm) pulse rate were seen. Small increases were seen in mean standing (0.3 bpm) and supine (0.7 bpm) pulse rate for the Exelon/Prometax patch group. Overall, few patients had notable increases or decreases in supine or standing pulse rates.

Discussion on safety

The 76-week open-label study B2315 was designed to provide long-term safety data, in particular the effect of Exelon/Prometax on worsening of the underlying motor symptoms of Parkinson's disease in patients with PDD.

Regarding long term safety data, study B2315 is considered well designed to answer to the request. The results of this study identify no unexpected adverse events during long-term treatment with Exelon/Prometax capsule or Exelon/Prometax patch in PD population.

Consistently with the known safety profile of Exelon, the frequently affected SOCs over 76 weeks were for Exelon/Prometax capsule gastrointestinal disorders (61.9%), nervous system disorders (59.2%), and psychiatric disorders (32%), and for Exelon/Prometax patch, nervous system disorders (54.2%), psychiatric disorders (45.1%), and general disorders and administration site conditions (37.5%).

The most frequently reported AEs in the Exelon/Prometax capsule group were nausea (40.5%), vomiting (15.3%), parkinsonian rest tremor (24.5%), and fall (17%).

The most frequently reported AEs in the Exelon/Prometax patch group were fall (20.1%), application site erythema (13.9%), Parkinsonian rest tremor (9.7%) and confusional state (9.4%).Psychiatric events were reported most frequently by patients in the Exelon/Prometax patch group (45.1% vs 32% for capsule), particularly depression (8% vs 2% for capsule). A slightly higher percentage of patients treated with the Exelon/Prometax patch reported an AE of fall than those treated with the Exelon/Prometax capsule (20.1% vs. 17.0% respectively).The incidence of gastrointestinal AEs was significantly lower in the Exelon/Prometax patch group than in the Exelon/Prometax capsule group, and application site reaction AEs were very commonly (25.3%) reported with Exelon/Prometax patch over the 76 weeks of study B2315. The percentage of patients in the Exelon/Prometax patch group with an AE of Parkinson's rest tremor was lower than in the Exelon/Prometax capsule group, and similar to the percentage of patients in the Exelon/Prometax capsule with tremor (including Parkinson's rest tremor) reported over the 48 weeks of studies B2311/B2311E1.

The highest incidence rates of AEs, including majority of worsening of PD motor symptoms, were observed during the initial 24 weeks of treatment in both the Exelon/Prometax capsule and Exelon/Prometax patch groups. Incidences of worsening of PD motor symptoms trend to decrease during weeks 24 to 48 and after week 48, excepted the AE of fall, remaining between 8.3% and 8.4% in the Exelon/Prometax capsule group, and between 6.8% and 9.3% in the Exelon/Prometax patch group.

The overall discontinuation rate due to these worsening of PD motor symptoms was low (capsule : 4.4% ; patch : 2.4%) and similar to those observed in studies B2311 and B2311E1. In the Exelon/Prometax capsule group, tremor was the most frequently reported PD motor symptom AE that led to study discontinuation (2.4% vs 0.7% patch), while fall was the most frequently reported AE leading to discontinuation in the Exelon/Prometax patch group (1.4%).

In conclusion, the Exelon/Prometax capsule safety data and the Exelon/Prometax patch safety data from study B2315 are overall consistent with the known safety profile of Exelon/Prometax in PD population, and no major differences in safety profile (excepted tremor) are observed in this study between the two Exelon/Prometax formulations.

For the safety analysis, the MAH made a comparison between ADR incidences in study B2315 and incidences in the Exelon/Prometax capsule or placebo groups from the pivotal double-blind core study 2311. This was based on the MAH's consideration that the patient populations, with regard to

demographic and background characteristics, were sufficiently similar in study B2315 and study B2311 to allow for meaningful comparisons of efficacy and safety outcomes. The only noteworthy difference was the mean MMSE, which was slightly more pronounced (2 points higher) in Study B2315 than in Study B2311.

However, to answer to the questions related to the high incidence over 76 weeks of adverse events due to worsening of PD motor symptoms in both treatment groups in study B2315 (capsule 36.1%, 95% CI [30.6%-41.8%], patch 31.9%, 95% CI [26.6%-37.7%]), in particular tremor for capsule, fall, bradykinesia and muscle rigidity for both formulations, and related to the important difference with the projected rate (23% [lower limit 18%, upper limit 28%, 95% confidence interval]), the MAH performed an additional analysis. This post-hoc review of the data relating to the higher frequency of tremor in the Exelon capsule group and fall in both treatment groups observed in Study B2315 compared to Studies B2311/2311E1 did not reveal an explanation for these results. Unlike Study B2311, which was a pivotal double-blind efficacy and safety study, Study B2315 was open-label and designed as a safety trial in which the primary objectives were to assess:

> *predefined adverse events (AEs) due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, fall)
>
> *study drug discontinuations due to predefined AEs due, or potentially due, to worsening of PD motor symptoms (tremor, muscle rigidity, bradykinesia, fall)

The setting for Study B2311 was, therefore, quite different from Study B2315 in so far as the monitoring and reporting of PD-related motor symptoms. During Study B2311, onset or worsening of these events were no doubt considered by many of the investigators, patients and caregivers to be part of the disease course and not reported as AEs. In Study B2315, not only was reporting PD motor symptoms required, but information regarding the possible onset or worsening of these events was solicited because of their status as a primary endpoint of the Study. This fact together with the open-label nature of the study would be sufficient to account for the higher reporting rate of these events in Study B2315 compared to Study B2311.

The CHMP agreed with these conclusions. These considerations may also explain the higher frequency of tremor with Exelon oral and the higher frequency of fall with both Exelon formulations in study B2315. Analysis of risk factors for fall did not reveal orthostatic hypotension nor other AEs possibly related to rivastigmine as a causal factor.

It was also observed that in the Exelon/Prometax patch group, more patients had newly introduced (21.2% vs 17.7% oral) and discontinued (25.3% vs 13.9%) antiparkinsonian agents after the start of the study. L-Dopa medications were newly introduced in 15.6% of patients in the Exelon/Prometax patch group, compared to 10.2% of patients in the Exelon/Prometax capsule group. However the MAH provide additional data indicating that the introduction of "new antiparkinsonian medication" was not driven by worsening of PD motor symptom AEs as some of these patients had just a change in the dose of their existing medications or a change in the name of the medication being received

No new signal raised from study B2315 regarding application site reactions that occurred at an expected frequency, based on the known safety profile of Exelon/Prometax patch. However, concern has been raised from post-marketing data regarding skin reactions with Exelon/Prometax patch. It appears that rivastigmine may induce two types of skin reactions, mainly application site reactions (allergic dermatitis, prurit, irritation) due to contact hypersensitivity (Exelon/Prometax patch), but also generalized allergic reactions due to systemic hypersensitivity to oral rivastigmine, in some patients previously sensitized by Exelon/Prometax patch. The MAH was requested to discuss in detail the

mechanism of delayed type hypersensitivity reaction possibly induced by rivastigmine, and to provide data on rivastigmine cutaneous metabolism, with information on implicated enzymes and metabolites potentially implicated in the mechanism of hypersensitivity. In addition, the MAH was requested to further investigate in context of the risk minimisation measures, the possibilities to generalize the use of allergological tests in case of serious application site reactions, or before switching from patch to oral formulations in patients developing skin reactions under Exelon/Prometax patch, in order to avoid the risk of systemic hypersensitivity. The MAH provided an in-depth analysis of the serious cases of application site reactions reported with Exelon/Prometax, and a detailed research on the use of allergological testing and desensitization protocols concluding that by contraindicating the use of any Exelon formulation following occurrence of serious skin reactions additional risk minimization activities would not be necessary.

The CHMP however was of the opinion that in order to minimize the risk of serious skin reactions, the MAH should enlarge the proposed contraindication to the use of any Exelon/Prometax formulation if any skin reaction with Exelon/Prometax patch occurs.

4. Overall conclusion and Benefit-risk assessment

Overall conclusion on efficacy

Exelon capsules administered twice daily are the only available treatment approved for use in patients with PDD. Compliance with oral dosage regimens is often problematic for patients with PDD and availability of an Exelon patch would meet a currently unmet need for these patients.

Furthermore, the drug-release characteristics of the Exelon patch would allow for once daily administration, thus improving patient and caregiver convenience, which may in turn increase patient acceptability and compliance.

However, even if efficacy for the Exelon/Prometax patch was observed across multiple domains in PDD patients, the interpretation of the efficacy results of Study 2315 is difficult.

While the MAH believes that there is sufficient direct and indirect evidence available for bridging of indication between capsules and the patch, the Committee expressed their concerns and highlighted that the different efficacy results between capsule and patch in AD and Parkinsons disease could be explained by the difference in exposure/PK profile of the formulations

Alzheimer disease and dementia in Parkinson disease have different underlying aetiologies and pathogenetic mechanisms. Consequently, the two diseases could react differently to therapy. Since the dose/response relationship could be different in PDD and ADD, the respective role of Cmax and AUC in efficacy must be further clarified to allow bridging of efficacy based on PK data.

Overall conclusion on safety

Overall, the Exelon/Prometax capsule safety data and the Exelon/Prometax patch safety data from study B2315 are consistent with the known safety profile of Exelon/Prometax in PD population, and no major differences in safety profile are observed in this study between the two formulations. The most frequently reported AEs in the Exelon/Prometax patch group were fall (20.1%), application site erythema (13.9%), Parkinsonian rest tremor (9.7%) and confusional state (9.4%). Psychiatric events were reported most frequently by patients in the Exelon/Prometax patch group (45.1% vs 32% for capsule), particularly depression (8% vs 2% for capsule). The incidence of gastrointestinal AEs was significantly lower in the Exelon/Prometax patch group (29.2%) than in the Exelon/Prometax capsule group (61.9%).

Regarding long term safety data, study B2315 is considered well designed. The results of this study do not identify any unexpected adverse events during long-term treatment with Exelon/Prometax capsule or patch in the PD population.

No new signal was raised from study B2315 regarding application site reactions (which occurred at an expected frequency). However, concern has been raised from post-marketing data regarding skin reactions with Exelon/Prometax patch. It appears that rivastigmine may induce two types of skin reactions, mainly application site reactions (allergic dermatitis, pruritus, irritation) due to contact hypersensitivity (Exelon/Prometax patch), but also generalized allergic reactions due to systemic hypersensitivity to oral rivastigmine, in some patients previously sensitized by Exelon/Prometax patch. Therefore, in order to minimize the risk of serious skin reactions and maintain a favourable benefit/risk of Exelon/Prometax patch the MAH is requested to enlarge the contraindication to the use of any Exelon/Prometax formulation if any skin reaction with Exelon/Prometax patch occurs.

Conclusion on benefit risk

The benefit/risk balance of Exelon/Prometax patch for the treatment of mild to moderate severe dementia in patients with idiopathic Parkinson's disease can only be considered positive provided that satisfactory clarifications are given the objections raised below and the MAH agrees to enlarge the contraindication to the use of any Exelon/Prometax formulation if any skin reaction with Exelon/Prometax patch occurs.

5. Request for supplementary information

Clinical aspects

5.1. Major objections

1. Alzheimer disease and dementia in Parkinson disease have different underlying aetiologies and pathogenetic mechanisms. Consequently, the two diseases could react differently to therapy. Since the dose/response relationship could be different in PDD and ADD, the respective role of Cmax and AUC in efficacy must be further clarified to allow bridging of efficacy based on PK data. The discussion should be based on a qualitative summary of available scientific knowledge on the respective diseases and the pharmacology of the drug, also on quantitative PK/PD modelling based on clinical or pharmacodynamic outcomes (e.g. enzyme inhibition).

5.2. Other concerns

2. Since the MAH does not foresee additional risk minimization activities such as general allergological testing or a desensitization protocol, in order to minimize the risk of serious skin reactions the MAH should enlarge the current contraindication to the use of any Exelon/Prometax formulation if any skin reaction with Exelon/Prometax patch occurs.
3. The RMP should be updated to reflect the above mentioned contraindication and the risk of elevated liver function tests. In addition, the summary tables 5-1 and 5-2 should include relevant SmPC wording and not just references to Annex 2.
4. The paediatric full waiver must be mentioned in the SmPC as per the QRD template and the comments highlighted in annex I should be taken into account.