

SDZ ENA 713 Study No. B352
 Table 3
 Shift Analysis of Number and Percent of Patients Whose PR Intervals Changed
 From ≤ 260 to > 260 , or > 260 to ≤ 260

BASELINE PR INTERVAL	POST BASELINE PR INTERVAL											
	6-12 mg				1-4 mg				PBO			
	≤ 260		> 260		≤ 260		> 260		≤ 260		> 260	
	N	%	N	%	N	%	N	%	N	%	N	%
≤ 260	222	99.11	1	0.45	221	99.10	1	0.45	229	99.57	0	0
> 260	0	0	1	0.45	0	0	1	0.45	0	0	1	0.43

In the Final Study Report for Study 304, the sponsor notes that 3 drug-treated patients shifted from < 260 to > 260 during the study, while one placebo patients did so.

A similar shift table for the 4 pooled controlled trials, comparing placebo to any Exelon is shown below.

Table 51: Prolonged PR Intervals in Phase 3 Controlled Trials

Post-Baseline PR Interval > 260 msec	
Baseline PR Interval ≤ 260 msec	
Exelon, n=1935	Placebo, n=869
15 (0.78%)	1 (0.12%)

p=0.03, Fisher's Exact Test

8.7.2 Sources of Additional Information

The sponsor has submitted a 120-day safety update. In that update, safety data for the full Study 304 cohort is presented. It includes 332 new patient exposures: 227 Exelon and 105 placebo. (Some information from this expanded Study 304 cohort was presented in the preceding section of this review.)

The safety update also includes more information from the extension studies. Included in the extension study cohort are 585 new exposures to Exelon; these are patients who received placebo in the controlled trials and then entered the extension studies, receiving Exelon for the first time. However, in the safety update, data on these new exposures are not broken out separately and addressed. Given that these data represent uncontrolled information, further information about this cohort was not pursued, but could be in the future.

8.7.3 Additional Analyses

8.7.3.1 Review of ECG Datasets

Based on Dr. Feeney's findings, I reviewed ECG datasets provided by sponsor. I limited my analysis of the raw ECG data to three of the four placebo-controlled trials, B303, B351, B352. I did not use B304 since the active treatment group in this study used a wide, non-randomized range of Exelon dose (2-12mg/d) and the interpretation of any dose-response relationship would be very difficult. I did not use extension study data since it is uncontrolled.

I concentrate my analyses on the PR interval, since Dr. Feeney identified this parameter as being affected by Exelon treatment.

B351 is the best study to analyze because patients were randomized to one of 4 fixed dose groups: 0, 3, 6, or 9 mg/day. The disadvantage is that it did not include 12mg/day, the maximum recommended dose. The other three studies did include 12mg/day but patients were randomized to placebo or a range of Exelon dosing, which complicates the analysis and interpretation.

The ECG dataset for B351 contains ECG data on 702 patients. They were evenly distributed among the 4 treatment groups (178 on 9mg/d, 176 on 6mg/d, 175 on 3mg/d, and 173 on placebo). I analyzed all ECG's performed during the active treatment phase and compared key ECG parameters with baseline values.

Summary statistics for key ECG parameters are shown in Table 52.

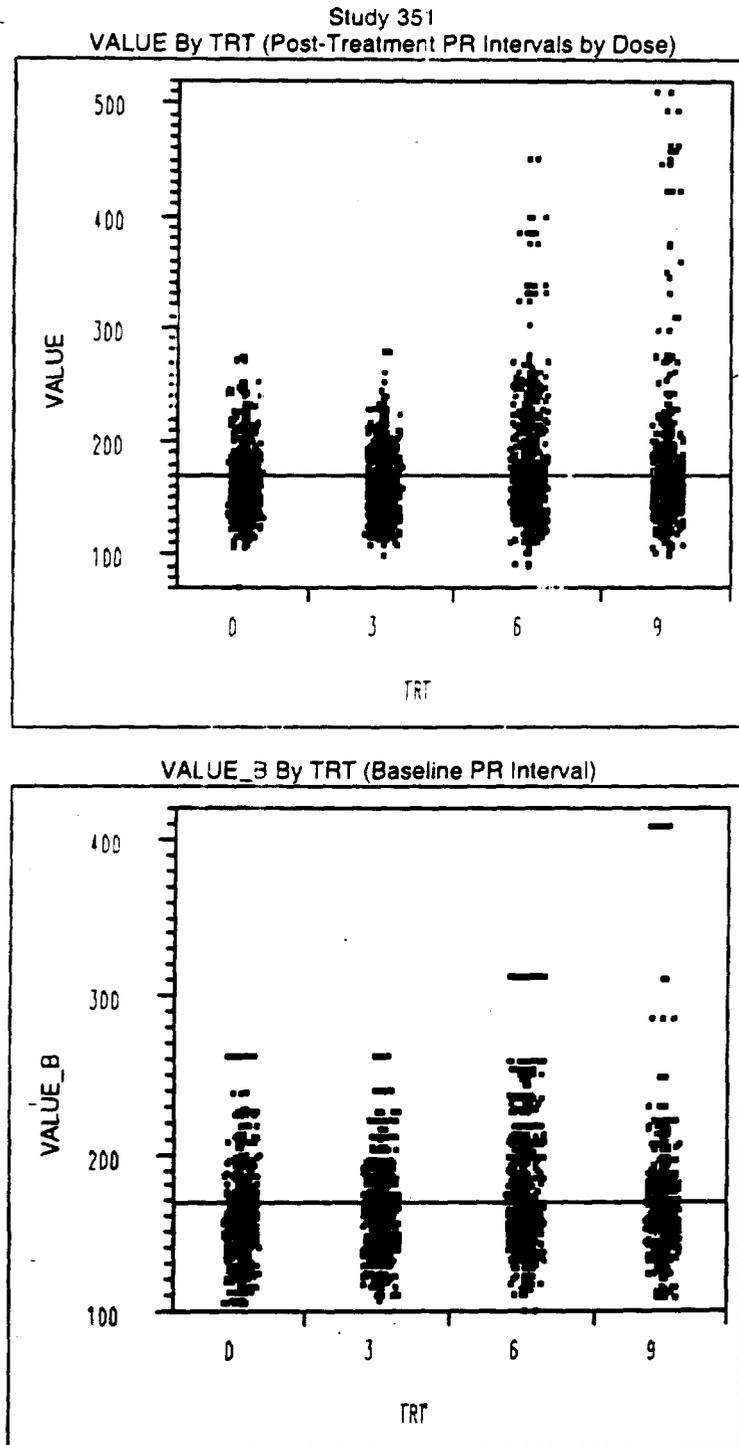
Table 52: ECG Parameters, Study B351

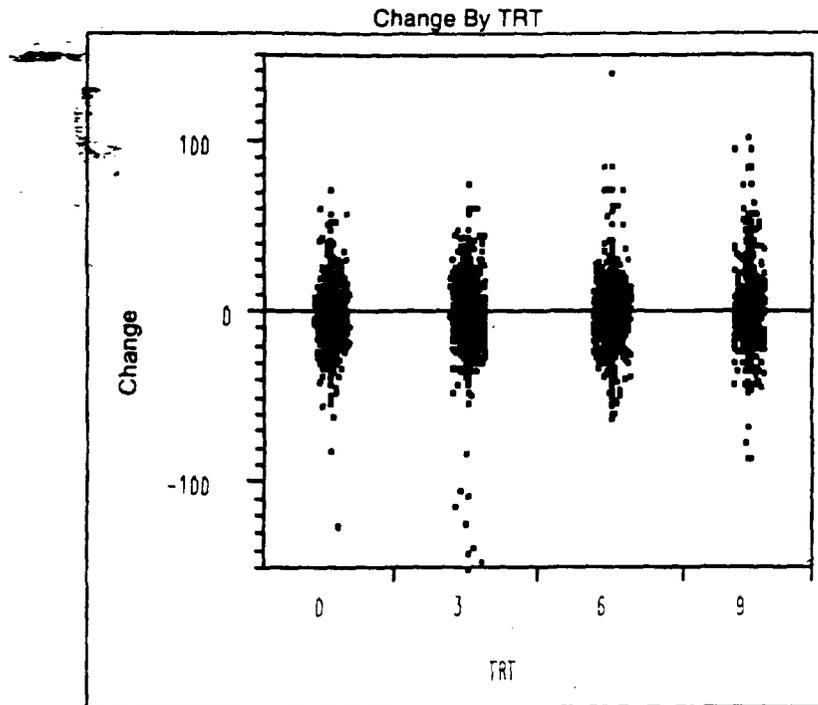
	Dose (mg/d)	Mean Post-Rx Value	Mean Baseline Value	Change
PR	9	173.3	171.2	2.0
	6	178.9	179.0	-0.1
	3	164.6	163.9	1.0
	0	163.5	163.5	0.2
QRS	9	91.3	92.0	-0.7
	6	92.5	92.3	0.2
	3	91.6	91.4	0.2
	0	90.3	89.9	0.4
QTc	9	408.7	413.1	-4.4
	6	410.6	410.3	0.2
	3	409.9	411.5	-1.6
	0	409.9	411.6	-1.7
Ventricular Rate	9	65.8	64.5	1.3
	6	65.5	65.8	-0.3
	3	68.1	68.6	-0.5
	0	68.5	67.1	1.4

There were no clinically significant changes from baseline for all ECG parameters measured. A clear dose-response relationship does not exist for any parameter. When comparing high dose to placebo, the only parameter of note is PR interval. Patients on high dose (9 mg/d) had an average increase in PR interval of a clinically insignificant 2 msec compared to essentially no change (0.2 msec increase) in placebo.

I next looked at outliers. For PR intervals, I plotted post-treatment PR interval (VALUE), baseline PR interval (VALUE_B) and change from baseline (Change) according to treatment group. This is shown in Figure 8. The X axis is dose in mg, and the Y axis is in msec.

Figure 8: PR Intervals in Study B351





In the first plot, it appears that there are more outliers with high PR intervals in the high doses. However, inspection of the second plot indicates that this is also true to a lesser extent at baseline which makes baseline a confounding factor. For example, all patients with PR intervals >400 msec in the 9mg group had baseline PR intervals >400msec.

The third graph shows the change in PR interval from baseline according to dose, and the case for a dose-response relationship is less clear. The greatest changes in PR interval does occur in the 9mg group, but the numbers of patients affected appear small. Still there appears to be a tendency for some patients in the higher doses (6, 9mg/d) to exhibit the greatest increases in PR intervals.

I then looked at the sponsor's criteria for detecting outliers by comparing the number of patients with baseline PR intervals ≤ 260 msec and treatment PR intervals >260 msec, by dose. Using this approach, I found no (0) placebo patients, 1 patient at 3mg, 6 patients at 6mg, and 3 patients at 9mg met the criterion.

Next I looked at studies B303 and B352. These were identical in design. Patients were randomized to 3 dose groups: placebo, 1-4mg/d and 6-12mg/d. I pooled ECG data from these two studies. There were 1422 patients in the combined dataset with ECG data (723 from study B303 and 699 from study B352). Of these, 474 were on placebo, 476 were on 1-4mg/d and 472 were on 6-9mg/d. I analyzed all ECG's performed during the active treatment phase and compared key ECG parameters with baseline values. These are shown in Table 53.

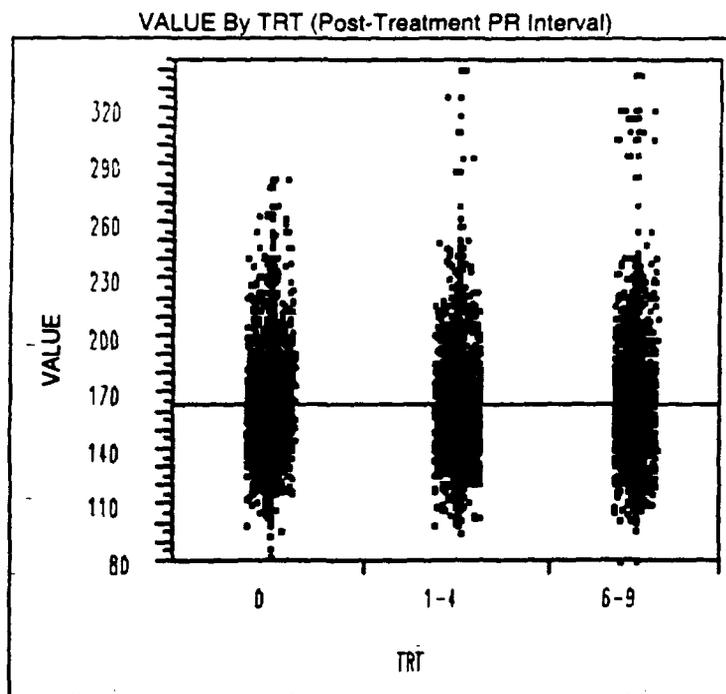
There were no clinically significant changes from baseline in any ECG parameters when analyzed by group means.

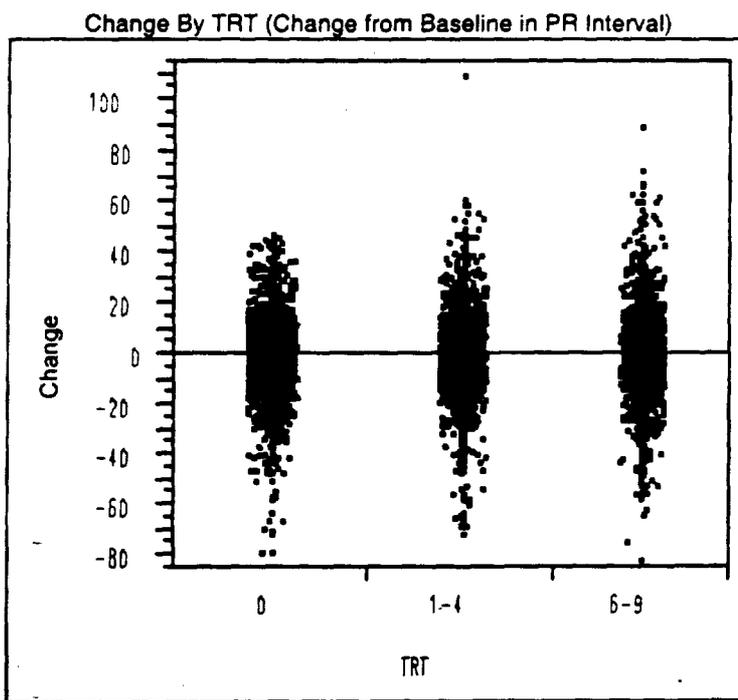
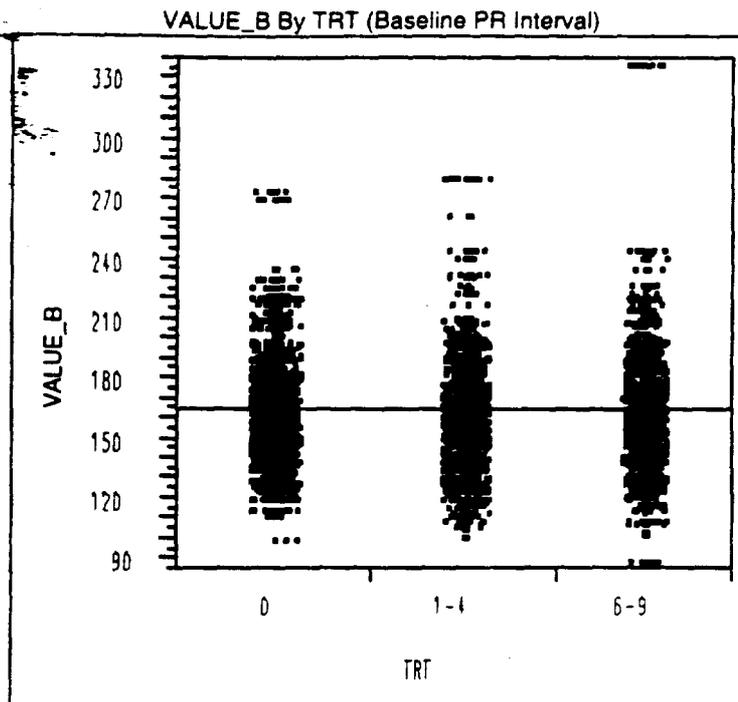
Table 53: Key ECG Parameters, Studies B303, B352

	Dose (mg/d)	Mean	Mean	Change
		Post-Rx Value	Baseline Value	
PR	0	165.4	164.7	0.4
	1-4	164.1	163.3	1.0
	6-9	165.9	165.1	1.0
QRS	0	89.3	88.6	0.7
	1-4	89.0	89.2	-0.2
	6-9	89.4	89.4	-0.1
QTC	0	409.2	409.1	-0.0
	1-4	407.5	407.8	-0.4
	6-9	407.7	408.1	-0.3
ventricular rate	0	68.2	67.5	0.7
	1-4	68.2	68.1	0.1
	6-9	67.1	67.6	-0.5

I then focused on outliers. As in study B351, I plotted PR interval, baseline PR interval, and change in PR interval as a function of dose group. These are shown in Figure 9. Similar to the findings in B351, the increased number of outliers seen with Exelon is partly explained by baseline PR values, however there does appear the suggestion that some patients on Exelon experience greater increases in PR intervals compared to placebo patients. This is not reflected in the group means analysis. The reason for this observation, or its clinical relevance is unclear. The number of outliers (defined by the sponsor as having a baseline PR \leq 260 msec and treatment PR interval $>$ 260 msec) were zero in the placebo group, 1 in the 1-4mg group and 1 in the 6-9mg group.

Figure 9: PR Intervals in Studies B303, B352





This analysis supports the findings seen in B351. There is a subset of patients on Exelon which seem to experience a quantitatively greater degree of PR prolongation compared to placebo patients. Possible risk factors worth considering are baseline PR intervals (*i.e.*, do patients with high baseline PR intervals experience a greater amount of PR prolongation with Exelon treatment?). Other covariates worth considering include age, heart rate, concomitant medications. These may be the focus of additional analyses.

To explore the question of baseline PR interval, I plotted post-treatment PR interval vs. baseline PR interval and sub-grouped by Exelon dose in study B351 and I could not convince myself that baseline PR interval played a significant role.

In the sponsor's own subgroup analysis, Dr. Feeney points out that patients >85 years old experienced a 37% incidence of new or worsening ECG abnormalities, compared to 17% for placebo patients of the same age. However, the incidence of first degree heart block in this population did not exhibit a dose-response relationship.

In summary, this analysis seems to support Dr. Feeney's conclusion about PR intervals. I conclude that, although PR intervals overall do not increase substantially, there is a subset of patients treated with Exelon that experience PR prolongation with treatment. The reason for this finding is unclear.

8.7.3.2 Review of Individual Cases

Dr. Feeney identifies 3 cases worth noting.

B351 02060

The case report form for this patient is not available. Instead, information is obtained from the sponsor provided patient narrative.

This was an 81 y/o male who had a right bundle branch block and 1st degree AV block at baseline – 224 msec. Also noted at baseline and at week 3 were ventricular premature beats (VPC). He was randomized to receive 9 mg/d and was in the titration phase of the study when worsening PR interval prolongation was detected. The dose at the time of discontinuation was 3.5 mg/d. He took Exelon for a total of two weeks (9/7/95-9/22/95). His post-treatment PR interval at week 2 was 312 msec. He was apparently hospitalized because of this finding. Four days after discontinuation, his PR interval was 260 msec.

Concomitant illnesses were diabetes, arthritis, history of myocardial infarction (1975 and 1989), CABG (1975 and 1989), grade 2/6 systolic murmur, BPH.

Concomitant medications were: tylenol, micronase, procardia.

Reviewer's note: this case is supportive of Exelon induced PR prolongation, however it is confounded by first degree AV block already present at baseline, and by the use of procardia, which also affects conduction through the AV node.

B304 3006

The case report form for this patient is not available. Information is obtained from the sponsor provided patient narrative and the electronic datasets.

This was a 67 y/o female who took Exelon, divided three times daily, from 7/13/95 to 1/9/96. All doses were taken per protocol. On 10/5/95, she developed "atrioventricular block" and this continued through the end of the study. From the exposure dataset she was taking 12mg/d on 10/5/95. From the ECG dataset, her PR interval went from a baseline of 172 msec on 7/6/95 to 204 msec on 10/5/97. The PR interval fluctuated between 186 and 204 msec until the end of study participation. There is no indication that she suffered any serious effects from this observation. From the adverse events dataset, the only other AE's reported were dizziness,

headaches, vomiting, and vaginal bleeding. None were serious. The consultant cardiologist, Dr. Morganroth, felt the AV block was of unknown cause.

Reviewer's note: I don't find this case compelling on closer inspection. The degree of AV block is minor and apparently asymptomatic. A causal relation to Exelon appears doubtful, in my opinion.

B353 213002

There is no case report form available for this patient. Information is obtained from the sponsor provided patient narrative (120-Day Safety Update page 19.1719) and the electronic datasets.

After one year on open label Exelon treatment in study B353, this 79 y/o female developed dizziness and a pulse of 30 due to third degree heart block on 3/22/96. From the exposure dataset, she was taking 6mg/d at the time. A pacemaker was placed the next day (3/23/96) and she continued Exelon therapy until 9/18/96. From the ECG dataset, she had a right bundle branch block and left anterior hemiblock at baseline (which was end of study B352). In study B352, she received placebo and also had a right bundle branch block with left anterior hemiblock at baseline and throughout the study.

Concomitant illnesses: plantar wart, left foot.

Concomitant Therapies: Pacemaker, multivitamins, Vitamin E, folic acid, lidocaine 1%, cefazolin, and acetaminophen.

Reviewer's Note: This woman had an abnormal ECG at least 6 months before she received Exelon. It is likely the complete heart block was a result of underlying cardiac disease and not due to Exelon therapy.

8.7.4 Conclusions

The sponsor and the _____, conclude that Exelon has no specific clinically relevant effects on the ECG. Specifically, they conclude that there appears to be no justification for requiring an ECG before treatment with Exelon or to monitor the ECG in any routine way while on Exelon therapy.

The analyses of group means show no clinically relevant overall effect of Exelon on heart rate or EKG intervals.

However, the shift tables demonstrate that there are more patients likely to have their PR interval increase from below 260 msec to above 260 msec while on Exelon than on placebo. Within the controlled trials, there was one discontinuation for what was considered to be a serious prolongation of PR interval from 260 to 360 msec after 2 weeks of treatment. The PR interval for that patient returned to 260 msec after Exelon was discontinued. Review of the ECG datasets support this finding since there does appear to be a subset of patients exposed to Exelon that experience a greater prolongation of their PR intervals compared to placebo. The clinical significance of this is unclear, but should be included in labeling.

At least one patient, Patient 213002, developed complete heart block in an open-label extension trial and required a pacemaker, however this patient had an abnormal baseline ECG (right bundle branch block and left anterior hemiblock) months before receiving Exelon and the complete heart block is more likely due to underlying pre-existing cardiac disease

Therefore, as expected given the pharmacological properties of Exelon, evidence of drug-induced PR interval prolongation emerged from the controlled trial database.

Similarly there were a few patients on Exelon who developed clinically significant bradycardia.

8.8 Vital Signs

The sponsor has presented analyses in the ISS analogous to those for EKGs. Again, the sponsor has pooled the 4 controlled trials assigning patients to 1 of 4 dose groups.

Again, the sponsor presents several types of analyses in the ISS. First, comparisons for placebo vs. any drug for the 4 pooled studies. Second, comparisons for placebo and the 4 assigned dose groups for the 4 pooled studies. Third, comparisons for placebo vs any drug for the 2 U.S. studies. Fourth, comparisons for placebo vs. any drug for the 2 primarily non-U.S. studies. Fifth, comparisons for placebo and the 4 assigned dose groups for the 2 U.S. studies. Sixth, comparisons for placebo and the 4 assigned dose groups for the 2 primarily non-U.S. studies.

In the ISS, comparisons are presented for summary data (means, medians) for pulse, systolic BP, diastolic BP, and weight (Sponsor's Table 8.1.1.1). In the ISS, the results are displayed in summaries titled "Change from Baseline to Endpoint." [Note that analyses could have been done at other time intervals besides endpoint.]

Also presented are shift tables using the following criteria:

Table 54: Vital Signs Normal Ranges

Vital Signs Variable	Normal Range
Heart Rate (bpm)	50-100
Systolic Blood Pressure (SBP)	90-160
Diastolic Blood Pressure (DBP)	55-95
Respiratory Rate (rpm)	8-26
Body Temperature (C/F)	>37.5/>99.5
Weight (kg)	not determined

If a patient had more than one value outside the normal range over the course of the study, the value showing the greatest deviation from normal was taken. For each parameter, the proportion of patients with one or more values outside the normal range over the treatment period was identified.

"Clinically notable" abnormalities for the controlled trials are also analyzed (Sponsor's Table 8.2.1.1). The sponsor defined clinically notable by the following criteria:

Table 55: Criteria for "Clinically Notable" Vital Signs Abnormalities

Variable			
Temperature	≥101 F ≥38.3	and a and	Δ ≥2 F Δ ≥1.1 C
Heart Rate	≥120 bpm ≤50 bpm	and an and a	increase of ≥ 15 bpm decrease of ≥ 15 bpm
Systolic BP	≥180 mm ≤90 mm	and an and a	increase of ≥ 20 mm decrease of ≥20 mm
Diastolic BP	≥105 mm ≤50mm	and an and a	increase of ≥15 mm decrease of ≥15 mm
Weight			change ≥7%

8.8.1 Results

The sponsor reports that, in the pooled controlled trial data, similar values were seen across all treatment groups for the vital signs pulse, SBP, and DBP for change from baseline. Sponsor's Table 9.2 (Table 56) shows the mean changes.

Table 56: Vital Signs, Mean Changes from Baseline, Phase 3 Controlled Studies

Text Table 9.2
 Vital Signs including Weight: Summary of Mean Changes from Baseline to Endpoint
 Phase III Controlled Studies

Treatment Group	Pulse Supine (bpm)	Pulse Standing (1 min)	Pulse Standing (3 min)	Systolic BP Supine (mmHg)	Systolic BP Standing 1 min	Systolic BP Standing 3 min	Diastolic BP Supine	Diastolic BP Standing 1 min	Diastolic BP Standing 3 min	Weight kgs.	Resp. Rate (per min)	Body Temp °C
ElvA 0.12 mg/day	-1.7	-0.4	-0.5	-2.7	-3.7	-2.7	-1.2	-1.0	-1.1	-1.45	-0.1	-0.04
ElvA 0.9 mg/day	-0.3	0.9	1.3	-1.0	-3.0	-2.0	-1.2	-2.0	-1.3	-1.35	-0.1	0.02
ElvA 3.6 mg/day	-1.3	-0.7	-0.5	-2.2	-2.6	-2.2	-0.8	-1.2	-1.3	-0.31	-0.2	-0.02
ElvA 3 mg/day	0.2	0.8	0.1	0.8	-0.9	-0.4	0.8	-0.1	0.1	-0.03	-0.2	-0.01
ElvA Total	-1.0	-0.2	-0.1	-1.8	-2.7	-2.1	-0.8	-1.1	-1.1	-0.79	-0.1	-0.02
Placebo	0.3	0.8	0.8	-1.8	-2.0	-1.8	-0.2	-1.1	-0.3	0.55	0.2	-0.01

The shift tables in the ISS provide the proportions of patients changing from one category (normal, high, low) to another during treatment. No difference between groups was seen for any individual vital sign.

The occurrence of "clinically notable" abnormalities was presented in the ISS. Sponsor's Table 9.3.2.1 (Table 57 below) compares placebo and any drug, while Sponsor's Table 9.3.2.2 (Table 58) compares the 4 assigned dose groups and placebo. Except for weight (discussed separately in section 8.4.6, "Other Significant Adverse Event: Weight Loss", page 49), no obvious differences present themselves.

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Table 57: Clinically Notable Vital Signs Abnormalities, Phase 3 Controlled Studies

Integrated Summary of Safety: Theme 9
 Table 9.3.2.1
 Vital Signs: ENA 713 and Placebo
 Incidence of Clinically Notable Abnormalities
 Phase III Controlled Studies

Parameter	Result	ENA N = 1690		Placebo N = 760		Total N = 2450	
		n (%)	n (%)	n (%)	n (%)		
Pulse Rate (beats/min)	High	20 (1)	8 (1)	28 (1)			
	Low	68 (4)	28 (4)	96 (4)			
	High/Low	1 (<1)	0 (0)	1 (<1)			
Systolic Blood Pressure (mm Hg)	High	146 (9)	67 (9)	213 (9)			
	Low	170 (10)	74 (10)	244 (10)			
	High/Low	5 (<1)	3 (<1)	8 (<1)			
Diastolic Blood Pressure (mm Hg)	High	100 (6)	49 (6)	149 (6)			
	Low	137 (8)	62 (8)	199 (8)			
	High/Low	5 (<1)	3 (<1)	8 (<1)			
Weight (kg)	High	108 (6)	88 (12)	196 (8)			
	Low	215 (13)	39 (5)	254 (10)			
	High/Low	1 (<1)	1 (<1)	2 (<1)			
Body Temperature (Deg. C)	High	3 (<1)	1 (<1)	4 (<1)			

Table 58: Clinically Notable Vital Signs Abnormalities, By Dose Groups, Phase 3 Controlled Studies

Integrated Summary of Safety: Theme 9
 Table 9.3.2.2
 Vital Signs: ENA 713 (>9-12 mg/day, >6-9 mg/day, >3-6 mg/day, <=3 mg/day) and Placebo
 Incidence of Clinically Notable Abnormalities
 Phase III Controlled Studies

Parameter	Result	>9-12 mg N = 476		>6-9 mg N = 295		>3-6 mg N = 681		<=3 mg N = 238		Placebo N = 760	
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)				
Pulse Rate (beats/min)	High	7 (1)	2 (1)	7 (1)	4 (2)	8 (1)					
	Low	15 (3)	9 (3)	34 (5)	10 (4)	28 (4)					
	High/Low	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)					
Systolic Blood Pressure (mm Hg)	High	51 (11)	26 (9)	57 (8)	12 (5)	67 (9)					
	Low	57 (12)	35 (12)	54 (8)	24 (10)	74 (10)					
	High/Low	4 (1)	0 (0)	1 (<1)	0 (0)	3 (<1)					
Diastolic Blood Pressure (mm Hg)	High	39 (8)	12 (4)	39 (6)	10 (4)	49 (6)					
	Low	44 (9)	32 (11)	51 (7)	10 (4)	62 (8)					
	High/Low	3 (1)	1 (<1)	0 (0)	1 (<1)	3 (<1)					
Weight (kg)	High	35 (7)	13 (4)	50 (7)	10 (4)	88 (12)					
	Low	105 (22)	47 (16)	50 (7)	13 (5)	39 (5)					
	High/Low	1 (<1)	0 (0)	0 (0)	0 (0)	1 (<1)					
Body Temperature (Deg. C)	High	0 (0)	1 (<1)	2 (<1)	0 (0)	1 (<1)					

Listings of discontinuations for abnormal vital signs reveal a total of 7 Exelon patients who discontinued for hypertension; 2/7 cases were also classified as serious. There were no placebo discontinuations for hypertension. However, given the greater number of patients randomized to drug than placebo, it is hard to put this finding in perspective.

The 2 serious AE discontinuations for hypertension were Patient 36008 in Study 303 (no narrative located) and Patient 05012 in Study 351.

Patient 36008 was hospitalized at Week 11 due to temporary loss of consciousness, increased BP, and supraventricular arrhythmia. She regained consciousness without treatment and her BP stabilized with nifedipine.

Patient 05012 had two hypertensive episodes during the trial, the first at 3 months and the second at 4 months. The last episode may have contributed to a non-Q wave M.I. The investigator felt these events unrelated to study drug.

8.8.2 Conclusions

The sponsor concludes that no clinically significant effects of Exelon on pulse, SBP, or DBP were demonstrated in the analyses. Dr. Feeney agrees with that assessment. Weight loss and orthostatic changes have been addressed separately in previous sections.¹

8.9 Long Term Safety

8.9.1 Methods

To assess the long term safety of the drug, the incidence rates of newly emergent AE's during short and long-term treatment were compared in a subset of patients who received 26 weeks of treatment during the phase 3 controlled studies, and who then received long term treatment with Exelon during the phase 3 uncontrolled extension studies.

Also compared were the incidence rates of several selected key AE's reported during short and long term Exelon treatment, as well as any clinically notable vital signs and laboratory abnormalities.

The results of the Phase 3 Uncontrolled Extension Studies are based on data from 197 patients who completed 26 weeks of Exelon treatment in the core studies, and who entered the extension studies. Data for another 113 patients in the analyzable extension study database were excluded from this analysis, either because the patients had received placebo during the first 26 weeks, or had discontinued Exelon treatment during that period and later entered the extension, and inclusion of their data would have compromised the valid assessment of the long-term safety of Exelon. The results of the Phase 2 Extension Studies are based on data from all patients from Studies B103 and B104 who entered the extensions (B103E-01,02,04,06, B104E-01,02, B901/902) and received treatment for more than 52 weeks.

8.9.2 Results

The Exelon development program has fulfilled ICH guidelines for long term exposure. A total of 1,249 patients have been exposed for at least 6 months, and 220 have been exposed for at least one year.

Table 59 compares adverse events during the first 26 weeks of Exelon treatment with those occurring up to 52 weeks. Of the 197 patients in the extension studies, 2% experienced AE's resulting in death during weeks 27-52. All of the deaths were considered unrelated or unlikely due to treatment. In addition, 7% of the 197 patients had AE's resulting in discontinuation during weeks 27-52. This rate is lower than that for all Exelon patients in the controlled studies (17%).

Table 59: Adverse Events with Long Term Treatment

	0 - 26	0 - 26	0 - 52	27 - 52
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¹ section 8.4.6, "Other Significant Adverse Event: Weight Loss", page 49; section 8.4.7 Other Significant Adverse Event: Orthostasis, page 51.

Body System/ Preferred Term	Weeks All Pts N = 1696		Weeks Ext. Pts N = 197		Weeks Extension N = 197		Weeks Extension N = 197	
	n	(%)	n	(%)	n	(%)	n	(%)
Death	6	(< 1)	0	(0)	3	(2)	3	(2)
Any SAE	235	(14)	20	(10)	42	(21)	25	(13)
Resulting in Discontinuation	290	(17)	0	(0)	14	(7)	14	(7)
Resulting in Dose Change	733	(43)	69	(35)	134	(68)	112	(57)
Any Severe AE	253	(15)	16	(8)	33	(17)	25	(13)
Adverse Event Requiring Therapy	1035	(61)	148	(75)	148	(75)	148	(75)
Clinically Notable Weight Decrease	216	(13)	30	(15)	59	(30)	41	(21)
At Least One AE	1471	(87)	162	(82)	186	(94)	177	(90)

As in the phase 3 controlled studies, the most common AE's reported were gastrointestinal in nature. Table 60 lists the 10 most common AE's experienced during weeks 1-26 of therapy, and compares their incidences with the 197 patients from the uncontrolled long-term extensions. The incidences of nausea, anorexia, and agitation were increased in patients in the extensions studies during weeks 27-52 compared with both the extensions study patients and all Exelon treated patients in the phase 3 controlled studies during weeks 1-26.

Table 60: Incidence of 10 Most Common AE's During Short-Term vs. Long-Term Treatment

Adverse Event	Phase 3 Controlled Studies Patients Weeks 1-26 (N= 1696)		Extension Study Patients Weeks 1-26 (N= 197)		Extension Study Patients Weeks 27-52 (N= 197)	
	N	%	N	%	N	%
Nausea	598	35	62	31	81	41
Vomiting	362	21	37	19	38	19
Dizziness	325	19	38	19	34	17
Diarrhea	271	16	36	18	30	15
Headache	263	16	25	13	23	12
Anorexia	209	12	19	10	37	19
Abdominal pain	174	10	20	10	20	10
Accidental trauma	155	9	15	8	16	8
Insomnia	148	9	21	11	21	11
Agitation	145	9	11	6	26	13

With respect to age, higher percentages of patients aged 76-85 years, compared with those 65 or younger, experienced serious adverse events (15% vs. 7%) and dizziness (23% vs. 10%) during weeks 27-52. Also, higher percentages of patients aged 66-75 and 76-85 experienced vomiting and anorexia than did patients age 65 or younger.

Consistent with earlier findings, females had a higher incidence of clinically notable weight loss (≥7% loss from baseline) during weeks 27-52 than did males (roughly two-fold, 27% vs. 14%).

There were too few members of non-Caucasian races to make meaningful comparisons based on race.

The incidence of clinically notable elevated BUN was higher (12%) during the extension period than during the initial 26 week treatment period for both extension study patients (8%) and all Exelon treated patients (7%). Of note, no patient in the extension studies had clinically notable elevated levels of alkaline phosphatase, ALT, or AST with up to 52 weeks of Exelon treatment.

Two phase 2 studies (B103 and B104) had extension phases that allowed treatment up to 2 years. Total daily doses of 8-12 mg were used. Patients who completed two years of treatment were then eligible to enter in the compassionate need extensions B901/902.

The incidence rates of AE's leading to death, SAE's, and adverse drop-outs were comparable between patients treated for 27-52 weeks and patients in the phase 2 extensions of B103 and B104 (including B901/902).

8.9.3 Summary

In general, patients who entered the phase 3 uncontrolled extension had similar AE profiles compared to Exelon patients in the phase 3 controlled studies. Most importantly, no unexpected AE's emerged during long term treatment. Furthermore, there were no clinically notable increases in hepatic enzymes indicative of impaired liver function.

Nausea, anorexia, agitation, BUN elevation and weight decreases were more common during long term therapy. Females appeared to be less tolerant of the gastrointestinal effects of Exelon, with more females than males experiencing nausea, vomiting, anorexia, and clinically notable weight loss.

8.10 Drug-Drug Interactions

Exelon binds poorly to plasma proteins and lacks significant metabolism via the hepatic microsomal system. This suggests that clinically important drug interactions would be minimal. The sponsor chose several drugs for specific drug interaction studies based on their narrow margins of safety and/or frequency of use in the target population.

8.10.1 Drug Interaction Studies

Studies were performed in young, healthy subjects to assess possible pharmacokinetic and pharmacodynamic interactions of Exelon with digoxin, warfarin, diazepam, and fluoxetine.

No pharmacokinetic interactions occurred between single doses of Exelon and digoxin (at steady state), warfarin, diazepam, or fluoxetine. The pharmacodynamic effects of digoxin and warfarin were not altered by Exelon. There was a 10% increase in AUC seen for the primary metabolite of rivastigmine, ZNS, which occurred when Exelon and warfarin were co-administered. This is probably not clinically relevant, as ZNS is only 1/10th as active as the parent compound.

Details of these studies are not provided and I refer the reader to Appendix A, "Clinical Pharmacology Studies", page 128 and to the Biopharmaceutical review for more information.

8.10.2 Drug Interactions in Phase 3 Trials

8.10.2.1 Methods

The phase 3 clinical trial population consisted of elderly patients with AD who characteristically took various other concomitant medications (CM's). The sponsor carried out a retrospective analysis on 22 categories or sub-categories of CM's. These categories are listed in Table 61.

Table 61: Categories of Concomitant Medications in Clinical Trials

antacids	alpha blockers	estrogens
drugs for peptic ulcer disease	ACE inhibitors	anilides
antidiarrheals	beta blockers	salicylic acid derivatives
intestinal anti-inflammatories/anti-infectives	calcium channel blockers	non-steroidal anti-inflammatory medications
antiemetics	cardiac therapy	psychotropics
antispasmodic/anticholinergics	digitalis glycosides	aldehydes and derivatives
hypoglycemics	organic nitrates	benzodiazepines
antihypertensives	diuretics	antihistamines

Retrospective analysis was performed on the PK data available from patients in studies B351 and B352. PK analyses sought to determine whether the selected AM's interacted with Exelon to alter systemic concentrations of the parent compound (rivastigmine) or the principal metabolite (ZNS).

PK analyses based on a nonlinear mixed effects model (NONMEM) assessed interactions of Exelon and ZNS with selected, chronically administered CM's (B351/B352 combined analysis). A medication was used chronically if it was taken beginning before the patient's first blood sample until after the patient's last blood sample was taken.

Covariates, including CM's, were included in the models if their inclusion was judged statistically significant at the $p < 0.001$ level.

Retrospective analysis was also done on the pharmacodynamic data from the phase 3 controlled studies to determine whether the incidence of selected AE's was homogenous, controlling for the presence or absence of CM's. Pharmacodynamic analyses were also performed to assess any effects of Exelon on the use of the 22 selected AM's in patients from the phase 3 controlled studies.

For the pharmacodynamic analyses, the selected categories of CM's must have been taken with the study medication (Exelon or placebo) to be considered a concomitantly administered medication. The Breslow-Day test for homogeneity of odds ratio was performed on each selected AE. The incidence of each selected AE in ENA-treated versus placebo-treated patients with the selected CM was compared with or, more specifically, the homogeneity of the odds ratio for patients with and without the CM was tested. A potential drug-drug interaction, involving a particular AE, was determined to occur if the incidence of the selected AE was not homogeneous between those receiving ENA and those receiving placebo, controlling for the presence or absence of the CM. Statistically significant ($p < 0.05$) findings indicated that a drug-drug interaction might exist.

The incidence of patients who required a change in the dosage of one or more of their selected CM's was compared in both active and placebo treatment groups to assess whether Exelon altered the use (and possibly the therapeutic effect) of these CM's.

8.10.2.2 Results - Pharmacokinetic Analyses

The population-pharmacokinetic data set consisted of 1341 observations on 625 patients (348 females) from the three Exelon dose groups in Study B351 (3mg/d, 6mg/d, 9mg/d) and two Exelon dose groups in study B352 (low dose, 1-4 mg/d; and high dose 6-12 mg/d).

Table 62: Number of Exelon patients taking chronic CM's

Target System Category/Subcategory	N=625	
	Exelon Pts Taking CM's	Exelon Pts not Taking CM's
<i>Alimentary Tract and Metabolism</i>		
Antacids, drugs for treatment of peptic ulcer and flatulence	77 (12)	548 (88)
Antidiarrheals, intestinal anti- inflammatory/ anti- infective agents	13 (2)	612 (98)
Antiemetics and antinauseants	0 (0)	625 (100)
Antispasmodic and anticholinergic agents and propulsives	1 (< 1)	624 (100)
Drugs used in diabetes	21 (3)	604 (97)
<i>Cardiovascular System</i>		
Antihypertensives	72 (12)	553 (88)
Alpha- adrenoceptor blocking agents	12 (2)	613 (98)
Converting enzyme blockers	56 (9)	569 (91)
Beta blocking agents	42 (7)	583 (93)
Calcium channel blockers	75 (12)	550 (88)
Cardiac therapy	66 (11)	559 (89)
Digitalis glycosides	33 (5)	592 (95)
Organic nitrates	35 (6)	590 (94)
Diuretics	73 (12)	552 (88)
<i>Genitourinary System and Sex Hormones</i>		
Estrogens	70 (11)	555 (89)
<i>Musculoskeletal System</i>		
Anti- Inflammatory and anti-rheumatic products	79 (13)	546 (87)
<i>Central Nervous System</i>		
<i>Analgesics</i>		
Anilides	65 (10)	560 (90)
Salicylic acid and derivatives	177 (28)	448 (72)
<i>Psychotropics</i>		
Aldehydes and derivatives	16 (3)	609 (97)
Benzodiazepine derivatives	10 (2)	615 (98)
2 (< 1)	623 (100)	
<i>Respiratory System</i>		
Antihistamines for systemic use	15 (2)	610 (98)

In this population of AD patients, there was no significant effect of CM use on systemic Exelon exposure. No effect of CM's was found on systemic ZNS concentrations. C_{max} of ZNS was lower in patients using cardiac therapy than in patients not using cardiac therapy, although ZNS AUC_{0-12} was the same for these two patient populations.

8.10.2.3 Results: Pharmacodynamic Analyses

8.10.2.3.1 EFFECT OF EXELON AND CM'S ON ADVERSE EVENTS

Demographic characteristics for the phase 3 controlled studies group revealed no differences between Exelon treated patients and placebo treated patients for the main demographic parameters (Section 5.1.1.3, Demographics: Patient Treatment Trials, page 12).

For each of the 22 selected AE's, the homogeneity of the odds ratio was tested for patients with and without the CM. This was done for each of the 22 selected CM's. Statistically significant results for selected AE's, controlling for the presence and absence of CM and indicating a

possible drug-drug interaction, were found for 31 of the 484 tests that were performed. Of these 31 tests, 10 indicated the incidence of the selected AE to increase when Exelon was taken by patients with the CM and 21 indicated the incidence of the selected AE to increase when placebo was taken by patients with the CM.

Table 63: Nature of Possible Drug-Drug Interactions, Phase 3 Controlled Studies*

Concomitant Medication	Incidence of Selected AE Increased by CM and Exelon	Incidence of Selected AE Increased by CM and Placebo
Antacids, Drugs for Treatment of Peptic Ulcer and Flatulence Antidiarrheals, Intestinal Anti-Inflammatory/ Anti-infective Agents Antiemetics and Antinauseants		Diarrhea Resulting in Dose Change Abdominal Pain, Sweating Increased SAE, Abdominal Pain Fatigue SAE, Resulting in Dose Change, Requiring Therapy, Dizziness
Antispasmodic and Anticholinergic Agents and Propulsives Drugs Used in Diabetes Antihypertensives	Requiring Therapy Nausea	Resulting in Dose Change, Malaise Weight Decrease Tremor Tremor
Alpha- Adrenoceptor Blocking Agents		
Beta Blocking Agents Cardiac Therapy Digitalis Glycosides Diuretics Estrogens Antilides Salicylic Acid and Derivatives	Dyspepsia Severe Event, Weight Loss Resulting in Discontinuation Clinically Notable Weight Loss, Malaise	Asthenia Malaise
Psychotropics Aldehydes and Derivatives	Dizziness Vomiting	Requiring Therapy Requiring Therapy, Any AE

*Retrospective, Breslow-Day Test for Homogeneity of Odds Ratio

Of the possible interactions seen with Exelon, detailed review of each of them indicated that they are not likely to be relevant clinically. For example, for patients treated with estrogens, the incidence of AE's resulting in discontinuation was greater for patients receiving Exelon (19%) than for patients receiving placebo (0%). This may be compared with the incidence of AE's resulting in discontinuation in patients not treated with estrogens, which was also greater in patients receiving Exelon (17%) than in patients receiving placebo (8%). The differences in magnitude between those patients treated with estrogens vs. those patients not treated with estrogens was mainly attributable to differences on placebo (0% vs. 8%). The same case applies to cardiac therapy and the incidence of dyspepsia, to diuretics and the incidence of severe AE's, and to anti-psychotics and the incidence of dizziness.

Although the incidence of nausea was greater in Exelon treated (22%) than placebo treated (18%) patients who were receiving drugs used for diabetes, the difference is small compared with those patients not receiving drugs used for diabetes (36% for Exelon vs. 12% for placebo). For those patients taking salicylic acid and derivatives, there was a greater incidence of clinically notable weight decrease and malaise in patients receiving Exelon (12% and 5%, respectively) than in patients receiving placebo (2% and 0%, respectively). Such findings are of no clinical relevance when compared with the incidences of clinically notable weight decrease (i.e., 13% vs. 6% in Exelon vs. placebo treated patients, respectively), and malaise (4% vs. 3% in Exelon vs. placebo treated patients, respectively) in patients not taking salicylic acid and derivatives.

The incidence of AE's requiring therapy for patients treated with antispasmodic and anticholinergic agents on propulsives was greater in patients receiving Exelon (98%) than in patients receiving placebo (82%), which was also the case for patients receiving either Exelon and placebo who were not treated with antispasmodic and anticholinergic agents and propulsives, although the incidences were much lower (i.e., 57% and 53%, respectively).

Other findings were of a very small magnitude and may be spurious, owing to the large number of tests that were performed. One example can be found for patients taking diuretics, for whom the difference between the incidence of weight decrease in those treated with ENA versus placebo (i.e., 3% vs. 2%, respectively) was small and slightly smaller compared with that in patients not receiving diuretics (i.e., 2% vs. 0% in ENA-treated vs. placebo-treated patients, respectively). Small differences were also found for patients taking aldehydes and derivatives (e.g., chloral hydrate) with respect to vomiting (i.e., 13% incidence rate of for patients receiving ENA compared with an 11% incidence rate for patients receiving placebo).

8.10.2.3.2 RESULTS: EFFECTS OF EXELON ON CHANGE IN CM DOSE

The second type of pharmacodynamic analysis compared the incidence of Exelon treated patients vs. placebo treated patients who required a change in the dose of one or more of their CM's. This analysis was done by the sponsor in order to assess whether Exelon altered the use (and possibly the therapeutic effect) of any of these CM's. Table 64 lists the results of the analysis. Overall, it shows that the incidence of patients requiring changes in dose of their concomitant medications is about the same for both Exelon and placebo treated groups, with the exception of "antispasmodic and anticholinergic agents and propulsives." In this group, 8% of Exelon patients required a change in dose compared with 2% in placebo patients. Although the analysis presented by the sponsor does not describe whether increases or decreases in dose were more likely in this group, it would be expected that the use of a cholinesterase inhibitor in someone taking an anticholinergic or antispasmodic would require a higher dose of the anticholinergic in order to achieve the same desired clinical effect on gastrointestinal motility.

Table 64: Patients Requiring Change in CM Dose, Phase 3 Controlled Trials

Target System	Exelon N= 1696		Placebo N= 763	
	n	(%)	n	(%)
Antacids, Drugs for Treatment of Peptic Ulcer and Flatulence	175	10	52	7
Antidiarrheals, Intestinal Anti-inflammatory	75	4	20	3
Anti- Infective Agents				
Antiemetics and Antinauseants	36	2	5	1
Antispasmodic and Anticholinergic Agents and Propulsives	134	8	19	2
Drugs Used in Diabetes	22	1	8	1
<i>Cardiovascular System</i>				
Antihypertensives	40	2	9	1
Alpha- Adrenoceptor Blocking Agents	11	1	2	<1
Converting Enzyme Blockers	24	1	6	1
Beta Blocking Agents	27	2	9	1
Calcium Channel Blockers	50	3	20	3
Cardiac Therapy	59	3	18	2
Organic Nitrates	33	2	8	1
Digitalis Glycosides	14	1	6	1
Diuretics	61	4	23	3
<i>Genitourinary System and Sex Hormones</i>				

Natural and Semisynthetic Estrogens, <i>Musculoskeletal System</i>	14	1	6	1
Anti- Inflammatory and Antirheumatics <i>Nervous System</i>	140	8	69	9
<i>Analgesics</i>				
Anilides	204	12	92	12
Salicylic Acid and Derivatives <i>Psychotropics</i>	104	6	46	6
Aldehydes and Derivatives	83	5	31	4
Benzodiazepine Derivatives <i>Respiratory System</i>	85	5	33	4
Antihistamines for Systemic Use	68	4	30	4

8.10.3 Summary

Exelon is only slightly bound to plasma protein and is metabolized mainly through non-hepatic microsomal pathways; therefore it is hypothesized that the drug would not interact with highly protein bound drugs or drugs metabolized via the cytochrome P450 system.

Formal drug-drug interaction studies with ENA with digoxin, warfarin, diazepam, and fluoxetine yielded no clinically meaningful findings with respect to either pharmacokinetic or pharmacodynamic interactions with single doses of ENA in healthy subjects.

The sponsor performed retrospective analyses of 22 selected CMs in patients with AD who received chronic treatment with Exelon. No alteration of plasma concentrations of the parent compound, rivastigmine, or a metabolite (ZNS) were observed except for the finding of lower ZNS C_{max} in cardiac-therapy patients. These pharmacokinetic findings were in agreement with the pharmacodynamic findings, which indicated few statistically significant alterations of the incidence of selected AEs in Exelon patients treated with the selected CM's, some of which were associated with increased incidence with ENA while others were associated with increased incidence with placebo. None was of clinical significance.

No pharmacodynamic effects were found with respect to the usage of concomitant medications in patients treated with Exelon, with the possible exception of antispasmodic and anticholinergic agents and propulsives.

These findings support the conclusion, that there are no systematic, clinically relevant interactions between Exelon and the wide variety of CM's used by elderly patients with Alzheimer's Disease.

8.11 Drug-Disease Interactions

8.11.1 Methods

Safety data were analyzed for potential drug disease interactions, including potential interactions with diseases other than Alzheimer's Disease. Two formal drug-disease interaction studies were conducted in patients with liver impairment and renal disease. Decreased metabolism of the parent drug, rivastigmine, to its primary metabolite, ZNS, appears likely in patients with liver dysfunction. Mildly decreased elimination of ZNS appears to occur in those with renal disease, however a 3 mg dose was well tolerated in both groups. No alteration in dosing is recommended for these groups, since dose titration in clinical practice will be based on drug tolerability. The results of these studies are briefly summarized in Appendix A, beginning on page 128.

The phase 3 clinical population consisted of elderly patients who had various other diseases at baseline. The sponsor carried out retrospective analyses on patients with one or more of the following five concomitant medical conditions present at baseline (CMC's): hypertension, dyspepsia, diabetes mellitus, arthritis, and neoplasms.

The retrospective analyses were performed on PK data and plasma samples obtained on patients from studies B351 and B352. PK analyses sought to determine whether a CMC affected systemic concentrations of rivastigmine or ZNS. The analyses also explored the incidence of selected AE's were in the presence of selected AE's. Safety data from all 4 phase 3 controlled trials were used (B303, B304, B351, B352).

8.11.2 PK Analyses

The PK dataset from B351 and B352 consisted of 1341 observations made on 625 patients (348 or 56% female) from the three Exelon dose groups in B351 (3mg, 6mg, 9mg), and the two dose groups in B352 (1-4mg and 6-12mg). For analysis purposes, they were collapsed into two groups (Table 65): a low dose group (3mg or 1-4 mg) and high dose group (6mg, 9mg, or 6-12mg). Demographic parameters were similar for this subset of patients compared to the overall phase 3 controlled studies population.

Table 65: Distribution of Patients in B351 and B352

Plasma Samples per Patient	Treatment Group		Total
	B351: 6 or 9 mg/ day B352: 6- 12 mg/ day	B351: 3 mg/ day B352: 1- 4 mg/ day	
1	101	51	152
2	137	93	230
3	121	122	243
Total	359	266	625

The incidence of hypertension in this subset was 32%. The incidence of dyspepsia was 7%, for diabetes 6%, for arthritis 30%, and for neoplasms <1%. In this subset population of AD patients, there was no significant effect of CMC on systemic exposure, as measured by AUC₀₋₁₂ or C_{max}. Unfortunately, the sponsor did not include in the NDA the actual PK data from these analyses, and I cannot independently verify their conclusion.

8.11.3 Pharmacodynamic Analysis

The incidence of selected AE's were compared in patients having selected CMC's in the four phase 3 controlled trials (B303, B304, B351, B352). Potential drug-disease interactions were analyzed using the Breslow-Day test for homogeneity of odds ratio. For each of the 22 selected AE's, the homogeneity of the odds ratio was tested for patients with and without the five selected CMC's. Tables summarizing the results for each selected CMC are located in Appendix G, page 166.

Of the 110 tests performed, possible drug-disease interactions were found in five instances. The incidence of Serious Adverse Events was increased in hypertensive Exelon patients, and the incidence of weight decrease was increased in diabetic Exelon patients. In the other three instances, the incidences of SAE, fatigue, and AE's resulting in a dose change of study medication were increased in placebo patients with hypertension, dyspepsia, or neoplasms, respectively (Table 66).

Table 66: Possible Drug-Disease Interactions*

Current Medical Condition	Incidence of Selected AE Increased by CMC and Exelon	Incidence of Selected AE Increased by CMC and Placebo
Diabetes Mellitus	SAE	
Hypertension	Weight Decrease	SAE
Dyspepsia		Fatigue
Neoplasms		Resulting in a Dose Change

* p<0.05 using Breslow-Day Test for Homogeneity of Odds Ratio, in phase 3 controlled studies

The two possible interactions associated with Exelon treatment are shown in Table 67 and discussed below.

Table 67: Possible Drug-Disease Interactions Associated with Exelon, Phase 3 Controlled Trials

	Exelon		PBO		Δ In % Exelon minus PBO	Total		Exelon vs. PBO
	N	n (%)	N	n (%)		N	n (%)	
Hypertension								
weight loss	1696	33 (2)	763	2 (< 1)	?	2459	35 (1)	
With CMC	466	9 (2)	197	2 (1)	<1	663	11 (2)	0.026*
Without CMC	1230	24 (2)	566	0 (0)	?	1796	24 (1)	
Diabetes Mellitus								
Serious AE	1696	235 (14)	763	117 (15)	1	2459	352 (14)	
With CMC	97	20 (21)	46	4 (9)	12	143	24 (17)	0.038*
Without CMC	1599	215 (13)	717	113 (16)	-2	2316	328 (14)	

* p<0.05, Breslow-Day Test for homogeneity of odds ratio

8.11.3.1 SAE's in Exelon Patients with Diabetes Mellitus

For those patients with diabetes mellitus, the incidence of SAE's was greater in patients taking Exelon (21%, or 20/97) compared to placebo (9%, or 4/46). The individual patients, along with SAE reported, are listed in Table 68. Review of the individual cases reveals that the increased incidence is probably without clinical merit. About ¾ of the diabetics on Exelon who reported an SAE had symptoms referable to various body systems that very likely did not result from a drug-disease interaction (e.g. neoplasm, renal calculus, surgery, fracture). The remaining ¼ of these patients had SAE's referable to the cardiovascular system (6/20 for Exelon, and 1/4 for placebo). These rates are comparable between the two groups. The most significant case in the Exelon group was that of patient 351102080, AV Block. This patient had a baseline P-R interval of 0.26 seconds, and he showed prolongation of the P-R with treatment of 0.32 sec.

Table 68 :Diabetic Patients Reporting Serious Adverse Events, Phase 3 Controlled Trials

Patient ID	SAE (Preferred Term)
	Placebo
303143041	Surgery
351103045	Cerebrovascular Disorder
351104036	Skin Neoplasm Malignant
351108029	Carcinoma
	Exelon
303302003	Procedure NOS
303307015	Overdose
303309004	Sudden Death

303313020	Malaise
303322003	Overdose
303324013	Overdose
303334002	Surgery
303334018	Myocardial Infarction
303336008	Arrhythmia
303145005	Angina Pectoris
303145011	Fibrillation Atrial
303145014	Angina Pectoris
303147014	Dehydration
351102080	AV Block
351109011	Bone Fracture
351111011	Carcinoma
351112041	Pneumonia
352202020	Confusion
352209027	Renal Calculus
352220030	Accidental Trauma

8.11.3.2 *Weight Decrease in Exelon Patients with Hypertension*

For those patients with hypertension, the incidence of weight decrease was greater in patients taking Exelon (2%) compared with placebo (1%). This is a small difference and likely attributable to the fact that placebo patients in general gained weight and Exelon patients lost weight.

8.12 *Withdrawal Phenomenon and Abuse Potential*

The possible withdrawal effects and abuse potential of Exelon were examined in rhesus monkeys (study PKF-ZNS/AA2). In one experiment, the possible self administration of the substance was examined, and in a second experiment, animals were observed after terminating an 8 week programmed application of the substance. In both experiments, testing with Exelon was followed with testing of morphine as a positive control.

In the self-administration study, Exelon was made available at doses of 0.0032, 0.0056, and 0.01 mg/kg/infusion. Four of the five animals had typical low rates of self-administering saline. In these animals, response rates were clearly not greater when Exelon solutions were available instead of saline. When morphine was subsequently offered, 3 of the 4 low-baseline animals clearly showed increasing rates of self-administered infusions. This positive control tends to rule out explanations such as inability to learn, or malfunctioning neural reward mechanisms.

In the programmed application study, total daily doses of 0.108 mg/kg of Exelon were attained after a schedule of increasing doses. In the week following cessation of treatment, there were no marked alterations of behavior which might indicate the presence of a withdrawal syndrome. In contrast, when morphine was administered up to a dose of 19.2 mg/kg, a typical withdrawal syndrome was observed after ceasing morphine treatment.

The results of these studies suggest that Exelon does not have significant withdrawal or abuse potential.

8.13 *Human Reproduction Data*

There are no human reproduction data available for Exelon. Across all studies, no female patients reported pregnancy. This is not unexpected, given the elderly population studied (mean age ~ 72 years). Since Exelon is not marketed outside the U.S., no foreign reports exist.

8.14 Overdose

An overdose was defined as an exposure to the drug greater than the prescribed dose. By this definition, an ingestion of as little as an extra capsule was considered an overdose. Of the 3,018 patients who participated in phase 3 studies, 139 of them experienced a total of 181 overdoses (sponsor Table 69). Some patients overdosed more than once. Of the 2,358 patients who received Exelon, 93 (3.9%) experienced 124 overdoses. By comparison, 763 patients received placebo and 46 of them (6%) experienced 57 overdoses. Of the 124 Exelon overdoses, 40 (32.3%) were symptomatic.

Table 69: Overdoses in Phase 3 Studies

Total Overdose Events = 181	Placebo N= 57	ENA N=124			
		<3 mg N= 52 n (%)	3-< 6 mg N= 35 n (%)	6-< 12 mg N= 5 n (%)	Unknown N= 32 n (%)
With Signs/ Symptoms	2 (3.5)	17 (32.7)	16 (45.7)	3 (60)	4 (12.5)
Without Signs/ Symptoms	55 (96.5)	35 (67.3)	19 (54.3)	2 (40)	28 (87.5)

The amount of overdose taken was generally small. The highest overdose seen was 10.5 mg (prescribed: 1.5 mg, taken: 12 mg). However, the amount taken was unknown in 32 cases. These were probably small overdoses as well, as the vast majority (87.5%) of these unknown overdoses were asymptomatic.

As would be expected, the incidence of associated signs and symptoms increased with increasing size of the overdose. The adverse events seen were similar to the commonly reported AE's associated with Exelon (sponsor Table 70). The majority of the overdose associated AE's were gastrointestinal (77.5%), including nausea (65%), vomiting (57.5%), and diarrhea (7.5%). Twenty percent (20%) were considered severe. The severe cases lasted 1 to 12 days. None resulted in discontinuation.

Table 70: Overdose Associated AE's in Phase 3 Trials

Sign/ Symptom	Placebo	<3 mg	3 - <6 mg	6 - <12 mg	Unknown	Total
Asthenia				1		1
Abdominal pain		1		1		2
Chest pain			1			1
Confusion	1				1	2
Diarrhea	1		2	1		4
Dizziness		2		1		3
Drowsiness		2				2
Headache		2			1	3
Lightheadedness			2			2
Loss of appetite		1				1
Malaise					1	1
Nausea		12	10	2	2	26
Stomach cramps			1			1
Tinnitus			1			1
Vertigo					1	1
Vomiting		12	8	2	1	23
Weakness		1				1

8.15 Review of Systems

A systematic review of the safety profile of Exelon is presented in this section according to body system. In general, whenever a particular effect has been discussed in a previous section, I do not repeat the review but rather refer to the appropriate section in this document. In other cases, I reviewed the incidence of a particular effect in the Exelon safety database in order to look for a signal that a particular event may have occurred at a substantially higher rate than placebo (*e.g.*, more than twice the placebo rate, or >1% if there are no placebo cases) before proceeding to a more in depth investigation. It is important to remember that exposures to Exelon were much longer than to placebo, therefore an event that occurs by chance in both groups may show a slight increased incidence in the Exelon group due to the longer exposures.

8.15.1 Cardiovascular

The cardiovascular safety was assessed in human studies by periodic assessment of vital signs, physical examinations, and EKG's. In addition, cardiovascular associated adverse events were elicited. In my opinion, this was an adequate assessment of the cardiovascular system.

The significant cardiovascular effects of Exelon are discussed in previous sections of this review and are not repeated here.

- 8.3.1 Syncope, page 40
- 8.3.2 Other Cardiovascular Events, page 40
- 8.4.7 Other Significant Adverse Event: Orthostasis, page 51
- 8.7 ECG, page 61
- 8.8 Vital Signs, page 79

Syncope occurred more frequently in Exelon patients (1.2% vs. 0.5%). Although an exact mechanism for the syncope was not determined, it is possibly due to Exelon's parasympathetic effects on the cardiovascular system. Myocardial infarction rates and cardiac failure rates were similar in both Exelon and placebo patients. The incidence of other cardiovascular events (Table 71) were similar in both treatment groups.

Table 71: Incidence of Cardiovascular Events, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL CARDIOVASCULAR DIS, GENERAL	224	(7)	67	(7)	287	(7)
HYPERTENSION	87	(3)	25	(3)	111	(3)
EDEMA PERIPHERAL	41	(1)	20	(2)	60	(2)
HYPOTENSION	35	(1)	5	(1)	40	(1)
CHEST PAIN	18	(1)	6	(1)	24	(1)
HYPOTENSION POSTURAL	16	(1)	4	(< 1)	20	(1)
CARDIAC FAILURE	13	(< 1)	2	(< 1)	15	(< 1)
EDEMA	5	(< 1)	3	(< 1)	7	(< 1)
ECG ABNORMAL SPECIFIC	5	(< 1)	1	(< 1)	6	(< 1)
EDEMA PERIORBITAL	5	(< 1)	1	(< 1)	6	(< 1)
ECG ABNORMAL	3	(< 1)	2	(< 1)	5	(< 1)
EDEMA DEPENDENT	4	(< 1)	1	(< 1)	5	(< 1)
PALLOR	4	(< 1)	0	(0)	4	(< 1)
HEART VALVE DISORDERS	3	(< 1)	0	(0)	3	(< 1)

EDEMA GENERALISED	1	(< 1)	2	(< 1)	2	(< 1)
CARDIAC FAILURE RIGHT	1	(< 1)	1	(< 1)	2	(< 1)
CYANOSIS	2	(< 1)	0	(0)	2	(< 1)
EDEMA LEGS	2	(< 1)	0	(0)	2	(< 1)
CARDIOMEGALY	1	(< 1)	0	(0)	1	(< 1)
CARDIOVASCULAR DISORDERS NOS	1	(< 1)	0	(0)	1	(< 1)
FACE OEDEMA	1	(< 1)	0	(0)	1	(< 1)
HYPERTENSION AGGRAVATED	1	(< 1)	0	(0)	1	(< 1)
EDEMA GENITAL	1	(< 1)	0	(0)	1	(< 1)

Table 72 lists the heart rate and rhythm disturbances reported. The overall rate was similar in both treatment groups – 4%. Individual event categories also had similar incidence in the two treatment groups.

Table 72: Heart Rate and Rhythm Disorders, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
HEART RATE AND RHYTHM DISORDERS	120	(4)	35	(4)	154	(4)
PALPITATION	36	(1)	5	(1)	41	(1)
BRADYCARDIA	18	(1)	7	(1)	24	(1)
EXTRASYSTOLES	17	(1)	7	(1)	24	(1)
FIBRILLATION ATRIAL	17	(1)	4	(< 1)	21	(1)
TACHYCARDIA	17	(1)	4	(< 1)	21	(1)
ARRHYTHMIA	9	(< 1)	3	(< 1)	12	(< 1)
AV BLOCK	4	(< 1)	1	(< 1)	5	(< 1)
BUNDLE BRANCH BLOCK	2	(< 1)	3	(< 1)	5	(< 1)
SICK SINUS SYNDROME	0	(0)	3	(< 1)	3	(< 1)
CARDIAC ARREST	2	(< 1)	0	(0)	2	(< 1)
HEART BLOCK	2	(< 1)	0	(0)	2	(< 1)
TACHYCARDIA SUPRAVENTRICULAR	1	(< 1)	1	(< 1)	2	(< 1)
ATRIAL FLUTTER	1	(< 1)	0	(0)	1	(< 1)
JUNCTIONAL RHYTHM	1	(< 1)	0	(0)	1	(< 1)
TACHYCARDIA VENTRICULAR	1	(< 1)	0	(0)	1	(< 1)

8.15.2 Gastrointestinal

The gastrointestinal safety profile of Exelon was assessed in human studies by periodic laboratory assessment of liver function tests and the elicitation of adverse events referable to the gastrointestinal system. In my opinion, this was an adequate assessment of the gastrointestinal system.

Gastrointestinal effects are the most common effects associated with Exelon use. Nausea, vomiting, diarrhea, anorexia, and abdominal pain were the most common gastrointestinal AE's reported (Table 30, Common Adverse Events in All Therapeutic Studies, page 53). The significant gastrointestinal effects of Exelon are discussed in previous sections of this review.

- 8.3.3 Gastrointestinal Hemorrhage, page 40
- 8.4.5 Other Significant Adverse Events - Nausea and Vomiting, page 47
- 8.5.4 Common and Drug-Related Side Effects, page 53
- 8.6 Laboratory Findings, page 56

Six patients (5 drug, 1 placebo) had gastrointestinal hemorrhage. The incidence of these events did not be correlate with the dose taken. Five were women. Three of the six patients had an upper GI hemorrhage. Of these, one was taking non-steroidal anti-inflammatory medications, and the other two had pre-existing medical conditions that probably contributed to the hemorrhage. Two patients had a lower bleed. One had a history of diverticulitis and the other had a prior history of a lower gastrointestinal bleed. The last patient required transfusion for a bleed, but the origin was never found. As a cholinomimetic, there is a theoretical argument that Exelon may induce increased gastric acid secretion, leading possibly to increased upper gastrointestinal hemorrhages in this group. This theory is not clearly supported by the cases discussed above, but remains a possibility.

If upper gastrointestinal bleeding was occurring at a higher rate in Exelon patients, then one might also see an increased incidence in melena. There were 11 cases of melena reported in Exelon patients (0.4%) and only 1 in placebo patients (0.1%). One case was rated as "moderate" and the remainders were rated as mild. No narratives of these cases are presented for review, but the "moderate" case was taking Exelon 1.5 mg. The range of doses seen in the Exelon patients with melena ranged from 1.5 mg to 12 mg (1.5, 3, 3, 4, 6, 9, 10.5, 10.5, 12, unk). There was no clear dose-response relationship as 4 took doses of ≤ 4 mg and 5 took doses ≥ 6 mg. The small numbers again defy drawing any meaningful conclusions, although the incidence is higher for Exelon patients. The possibility remains that Exelon may be associated with increased gastrointestinal bleeding, largely due to theoretical arguments at this point.

There were no clinically significant effects of Exelon on liver function tests.

Table 73 lists the gastrointestinal disorders reported in clinical studies. The most common AE's associated with Exelon use are contained in this table. Nausea, vomiting, diarrhea, abdominal pain, anorexia all occur at significantly higher rates in Exelon patients compared to placebo patients. This is in large part undoubtedly due to its increased parasympathetic effects on the gastrointestinal tract. Other gastrointestinal adverse events occurred with incidence rates comparable in the two treatment groups.

Table 73: *Gastrointestinal Disorders, all clinical studies*

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL GASTROINTESTINAL DISORDERS	1719	(57)	303	(31)	1993	(51)
NAUSEA	1147	(38)	103	(10)	1245	(32)
VOMITING	682	(23)	49	(5)	729	(19)
DIARRHEA	452	(15)	93	(9)	541	(14)
ABDOMINAL PAIN	317	(11)	62	(6)	379	(10)
ANOREXIA	344	(11)	25	(3)	368	(9)
DYSPEPSIA	193	(6)	41	(4)	231	(6)
CONSTIPATION	114	(4)	39	(4)	151	(4)
FLATULENCE	103	(3)	18	(2)	118	(3)
ERUCTATION	47	(2)	7	(1)	54	(1)
TOOTH DISORDER	30	(1)	9	(1)	39	(1)
FAECAL INCONTINENCE	29	(1)	9	(1)	38	(1)
GASTRITIS	19	(1)	5	(1)	24	(1)
GASTROENTERITIS	9	(< 1)	6	(1)	15	(< 1)
GASTROESOPHAGEAL REFLUX	12	(< 1)	2	(< 1)	14	(< 1)
MELENA	11	(< 1)	1	(< 1)	12	(< 1)
SALIVA INCREASED	8	(< 1)	3	(< 1)	11	(< 1)

GASTRO- INTESTINAL DISORDER NOS	8	(< 1)	2	(< 1)	10	(< 1)
ESOPHAGITIS	7	(< 1)	2	(< 1)	9	(< 1)
TOOTH CARRIES	5	(< 1)	4	(< 1)	9	(< 1)
DIVERTICULITIS	6	(< 1)	2	(< 1)	8	(< 1)
HERNIA	8	(< 1)	0	(0)	8	(< 1)
APPETITE INCREASED	6	(< 1)	1	(< 1)	7	(< 1)

The incidence of liver and biliary adverse events are listed in Table 74. The incidence of these disorders were all low and comparable between the Exelon and placebo groups.

Table 74: Liver and Biliary Adverse Events, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL LIVER AND BILIARY SYSTEM	34	(1)	3	(< 1)	37	(1)
CHOLELITHIASIS	7	(< 1)	1	(< 1)	8	(< 1)
HEPATIC FUNCTION ABNORMAL	7	(< 1)	0	(0)	7	(< 1)
GAMMA- GT INCREASED	6	(< 1)	0	(0)	6	(< 1)
HEPATIC ENZYMES INCREASED	4	(< 1)	1	(< 1)	5	(< 1)
HEPATOMEGALY	3	(< 1)	0	(0)	3	(< 1)
SGPT INCREASED	3	(< 1)	0	(0)	3	(< 1)
HEPATITIS	2	(< 1)	0	(0)	2	(< 1)
HEPATOCELLULAR DAMAGE	2	(< 1)	0	(0)	2	(< 1)
CHOLECYSTITIS	1	(< 1)	0	(0)	1	(< 1)
HEPATIC FAILURE	0	(0)	1	(< 1)	1	(< 1)
HEPATITIS CHOLESTATIC	1	(< 1)	0	(0)	1	(< 1)
JAUNDICE	1	(< 1)	0	(0)	1	(< 1)
LIVER FATTY	1	(< 1)	0	(0)	1	(< 1)

8.15.3 Hemic and Lymphatic

The hematological and lymphatic safety profile was assessed in human studies by periodic analysis of the complete blood count as well as elicitation of adverse events referable to the hemic and lymphatic systems. In my opinion, this was an adequate assessment of these systems.

The effects of Exelon on the CBC have already been reviewed in section 8.6 Laboratory Findings, page 56, and are not repeated here. There were no clinically significant effects of Exelon on the CBC. Table 75 lists the red blood cell disorders reported in clinical studies. The incidence rates were comparable between the Exelon and placebo patients.

Table 75: Red Blood Cell Disorders, all clinical trials

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL RED BLOOD CELL DISOR.	17	(1)	6	(1)	23	(1)
ANAEMIA	9	(< 1)	3	(< 1)	12	(< 1)
ANAEMIA HYPOCHROMIC	4	(< 1)	2	(< 1)	6	(< 1)
ANAEMIA MACROCYTIC	1	(< 1)	1	(< 1)	2	(< 1)
ANAEMIA B TWELVE DEFICIENCY	1	(< 1)	0	(0)	1	(< 1)
ANAEMIA HAEMOLYTIC	1	(< 1)	0	(0)	1	(< 1)
SPLEEN DISORDER	1	(< 1)	0	(0)	1	(< 1)

Table 76 lists the white blood cell disorders reported as adverse events in all clinical trials. There were no clinically meaningful differences in incidences between the two treatment groups.

Table 76: White Blood Cell Disorders, all clinical trials

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL WHITE CELL AND RES DISOR.	10	(< 1)	2	(< 1)	12	(< 1)
LYMPHADENOPATHY	6	(< 1)	0	(0)	6	(< 1)
EOSINOPHILIA	2	(< 1)	1	(< 1)	3	(< 1)
GRANULOCYTOSIS	0	(0)	1	(< 1)	1	(< 1)
LEUKOCYTOSIS	1	(< 1)	0	(0)	1	(< 1)
LYMPHOPENIA	1	(< 1)	0	(0)	1	(< 1)

There were 6 reported cases of lymphadenopathy (6/3006, <0.2%) in the Exelon group, and none in placebo. The doses of Exelon ranged from — Three patients experienced lymphadenopathy during the titration phase. Two cases were rated as “moderate”, and the other 4 were rated as “moderate”. The duration of the lymphadenopathy ranged from 1-29 days. The duration of one was unknown. No additional information is available on these cases.

Table 77 lists the platelet and bleeding disorders adverse events reported in clinical trials. The total incidence of this group was actually higher in placebo patients (1% for Exelon, 2% for placebo). There were no clinically substantial differences in the incidence rates of the various disorders between the two groups.

Table 77: Platelet and Bleeding Disorders, all clinical trials

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL PLATELET, BLEEDING AND CLOTTING DISOR.	38	(1)	15	(2)	53	(1)
EPISTAXIS	24	(1)	3	(< 1)	27	(1)
PURPURA	7	(< 1)	5	(1)	12	(< 1)
HAEMATOMA	4	(< 1)	6	(1)	10	(< 1)
THROMBOCYTOPENIA	2	(< 1)	0	(0)	2	(< 1)
HAEMORRHAGE NOS	1	(< 1)	0	(0)	1	(< 1)
THROMBOCYTHAEMIA	0	(0)	1	(< 1)	1	(< 1)

8.15.4 Metabolic and Endocrine

The metabolic effects of Exelon were assessed by periodic measurements of clinical laboratory parameters (blood and urine) and the elicitation of adverse events referable to this system. The endocrine system was assessed by eliciting adverse events. No formal endocrine lab testing was done unless it was deemed necessary by the investigator. In my opinion, this was an adequate assessment of the metabolic and Endocrine systems.

Please refer to section 8.6 Laboratory Findings, page 56, for a description of the chemistry and urinalysis abnormalities seen.

Table 78 lists the incidence of metabolic and nutritional AE's reported in all clinical studies. The overall incidence was slightly higher in the Exelon groups compared to placebo (3% vs. 2%), however the increased incidence was not represented by a single event or condition, but rather was distributed fairly evenly among many conditions which themselves had only 1-3 cases reported.

Table 78: Incidence of Metabolic and Nutritional Adverse Events, All clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL METABOLIC AND NUTRITIONAL	82	(3)	17	(2)	99	(3)
DEHYDRATION	24	(1)	1	(< 1)	25	(1)
DIABETES MELLITUS	10	(< 1)	4	(< 1)	14	(< 1)
HYPERGLYCAEMIA	11	(< 1)	2	(< 1)	13	(< 1)
HYPOKALAEMIA	12	(< 1)	1	(< 1)	13	(< 1)
HYPONATRAEMIA	5	(< 1)	1	(< 1)	6	(< 1)
GOUT	2	(< 1)	3	(< 1)	5	(< 1)
HYPOGLYCAEMIA	2	(< 1)	3	(< 1)	5	(< 1)
HYPERLIPAEMIA	2	(< 1)	2	(< 1)	4	(< 1)
CACHEXIA	3	(< 1)	0	(0)	3	(< 1)
PHOSPHATASE ALKALINE INCREASED	3	(< 1)	0	(0)	3	(< 1)
THIRST	3	(< 1)	0	(0)	3	(< 1)
FLUID OVERLOAD	2	(< 1)	0	(0)	2	(< 1)
GLYCOSURIA	2	(< 1)	0	(0)	2	(< 1)
HYPERCHOLESTEROLAEMIA	1	(< 1)	1	(< 1)	2	(< 1)
CREATINE PHOSPHOKINASE INCREASED	1	(< 1)	0	(0)	1	(< 1)
ELECTROLYTE ABNORMALITY	1	(< 1)	0	(0)	1	(< 1)
HYPERKALAEMIA	1	(< 1)	0	(0)	1	(< 1)
HYPOCHLORAEMIA	1	(< 1)	0	(0)	1	(< 1)
LACTOSE INTOLERANCE	1	(< 1)	0	(0)	1	(< 1)
SERUM IRON DECREASED	1	(< 1)	0	(0)	1	(< 1)

There were very few endocrine disorders reported (Table 79) – 8 for Exelon (0.2%) and 1 for placebo (0.1%). Of the 8 seen in the Exelon group, three were goiters and the others were isolated cases of a variety of other ailments. The numbers were much too small to draw any meaningful conclusions.

Table 79: Incidence of Endocrine Disorders, All clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL ENDOCRINE DISORDERS	8	(< 1)	1	(< 1)	9	(< 1)
GOITER	3	(< 1)	0	(0)	3	(< 1)
HYPOPARATHYROIDISM	1	(< 1)	1	(< 1)	2	(< 1)
BREAST PAIN MALE	1	(< 1)	0	(0)	1	(< 1)
ENDOCRINE DISORDER NOS	1	(< 1)	0	(0)	1	(< 1)
GYNAECOMASTIA	1	(< 1)	0	(0)	1	(< 1)
HYPERTHYROIDISM	1	(< 1)	0	(0)	1	(< 1)

8.15.5 Musculoskeletal

The musculoskeletal system was evaluated by eliciting adverse events referable to that system. In my opinion, this was an adequate assessment of the musculoskeletal system.

The incidence of musculoskeletal adverse events is shown in Table 80. The incidence of musculoskeletal abnormalities as a whole were similar between the two treatment groups (13% for Exelon, and 15% for placebo). Closer inspection of the individual AE's reported show no substantial differences in incidences between the two groups.

Table 80: Incidence of Musculoskeletal Adverse Events, All clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL MUSC/SKELETAL	398	(13)	144	(15)	536	(14)
BACK PAIN	104	(3)	40	(4)	144	(4)
ARTHRALGIA	71	(2)	26	(3)	95	(2)
PAIN	61	(2)	23	(2)	84	(2)
BONE FRACTURE	44	(1)	18	(2)	62	(2)
MYALGIA	38	(1)	8	(1)	46	(1)
CRAMPS LEGS	24	(1)	15	(2)	39	(1)
PAIN LEG(S)	29	(1)	7	(1)	35	(1)
ARTHRITIS	20	(1)	11	(1)	30	(1)
STIFFNESS	23	(1)	3	(< 1)	26	(1)
CRAMPS	16	(1)	3	(< 1)	19	(< 1)
ARTHROPATHY	11	(< 1)	4	(< 1)	14	(< 1)
HERNIA	10	(< 1)	3	(< 1)	13	(< 1)
SURGERY	5	(< 1)	5	(1)	10	(< 1)
ARTHROSIS	5	(< 1)	1	(< 1)	6	(< 1)
BURSITIS	4	(< 1)	1	(< 1)	5	(< 1)
TENDINITIS	4	(< 1)	0	(0)	4	(< 1)
JOINT DISLOCATION	2	(< 1)	1	(< 1)	3	(< 1)
JOINT MALFORMATION	3	(< 1)	0	(0)	3	(< 1)
MUSCLE WEAKNESS	2	(< 1)	1	(< 1)	3	(< 1)
OSTEOPOROSIS	2	(< 1)	1	(< 1)	3	(< 1)
ARTHRITIS AGGRAVATED	1	(< 1)	1	(< 1)	2	(< 1)
BONE DISORDER	2	(< 1)	0	(0)	2	(< 1)

8.15.6 Nervous

The central and peripheral nervous systems were evaluated by eliciting adverse events referable to this system. In my opinion, this was an adequate assessment of the CNS and PNS.

Dizziness and headache were the most commonly reported non-gastrointestinal AE's with Exelon. Dizziness includes lightheadedness, giddiness, wooziness, and related terms. Agitation, insomnia, and confusion were also commonly reported, although the incidence of the latter three were similar in placebo (Table 30, Common Adverse Events in All Therapeutic Studies, page 53).

The more common CNS Effects have already been discussed in previous sections and are not repeated here.

- 8.3.4 Cerebrovascular Disorders, page 40
- 8.4.8 Other Significant Adverse Events: "Evocative" Adverse Events, page 52
- 8.5.4 Common and Drug-Related Side Effects, page 53

The less common CNS and PNS effects seen during drug development are listed below (Table 81 and Table 82). The incidence of dizziness, headache, somnolence, and tremor in Exelon patients are all higher than in placebo patients. The incidence of other AE's are all low and comparable with placebo rates. In particular, convulsions were seen in 9 Exelon patients, and 2 placebo patients, both occurring in <1% of the respective populations (0.3% and 0.2%, respectively).

Table 81: Incidence of CNS and PNS Disorders, all clinical trials

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
CNS and PNS DISORDERS	1093	(36)	234	(24)	1307	(34)
Cerebrovascular Disorders	27	(1)	8	(1)	34	(1)
DIZZINESS	571	(19)	102	(10)	663	(17)
HEADACHE	456	(15)	115	(12)	564	(15)
SOMNOLENCE	139	(5)	19	(2)	156	(4)
TREMOR	90	(3)	12	(1)	102	(3)
VERTIGO	56	(2)	17	(2)	73	(2)
ATAXIA	34	(1)	8	(1)	42	(1)
GAIT ABNORMAL	33	(1)	5	(1)	38	(1)
PARAESTHESIA	30	(1)	4	(< 1)	34	(1)
MUSCLE CONTRACTIONS INVOL.	20	(1)	5	(1)	25	(1)
HYPOAESTHESIA	16	(1)	3	(< 1)	19	(< 1)
CONVULSIONS	9	(< 1)	2	(< 1)	11	(< 1)
HYPOKINESIA	10	(< 1)	0	(0)	10	(< 1)
DYSPHONIA	8	(< 1)	1	(< 1)	9	(< 1)
NEURALGIA	5	(< 1)	3	(< 1)	8	(< 1)
NYSTAGMUS	7	(< 1)	1	(< 1)	8	(< 1)
MIGRAINE	5	(< 1)	2	(< 1)	6	(< 1)
COORDINATION ABNORMAL	3	(< 1)	3	(< 1)	6	(< 1)
EXTRAPYRAMIDAL DISORDER	5	(< 1)	1	(< 1)	6	(< 1)
HYPERTONIA	5	(< 1)	1	(< 1)	6	(< 1)
NEUROPATHY	4	(< 1)	2	(< 1)	6	(< 1)
APHASIA	5	(< 1)	0	(0)	5	(< 1)
CRAMPS	5	(< 1)	0	(0)	5	(< 1)
CEREBRAL HEMORRHAGE	2	(< 1)	2	(< 1)	4	(< 1)

The incidence of autonomic nervous system abnormalities was increased in Exelon patients compared to placebo patients (7% vs. 4%). This appears to be due to Exelon's mechanism of action, which increases parasympathetic cholinergic effects. The increased incidence was largely due to the increased sweating seen in Exelon patients (4% vs. 1%). The incidence of other autonomic AE's were comparable in the two groups.

Table 82: Incidence of Autonomic Nervous System AE's, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL AUTONOMIC NERVOUS SYSTEM DIS.	223	(7)	42	(4)	265	(7)
SWEATING INCREASED	109	(4)	14	(1)	123	(3)
MOUTH DRY	24	(1)	8	(1)	32	(1)
SALIVA INCREASED	20	(1)	1	(< 1)	21	(1)
FLUSHING	15	(< 1)	4	(< 1)	19	(< 1)
FEELING COLD	6	(< 1)	2	(< 1)	8	(< 1)

SKIN COLD CLAMMY	8	(< 1)	0	(0)	8	(< 1)
FECAL INCONTINENCE	1	(< 1)	2	(< 1)	3	(< 1)
PALLOR	2	(< 1)	1	(< 1)	3	(< 1)
URINARY INCONTINENCE	1	(< 1)	1	(< 1)	2	(< 1)
AUTONOMIC INSTABILITY	0	(0)	1	(< 1)	1	(< 1)
HYPOTENSION	1	(< 1)	0	(0)	1	(< 1)
URINARY RETENTION	1	(< 1)	0	(0)	1	(< 1)
VASODILATION	1	(< 1)	0	(0)	1	(< 1)

Table 83 lists the psychiatric adverse events reported in all clinical studies. The most common of these are also discussed in section 8.5.4 Common and Drug-Related Side Effects, page 53. It is worth noting, however, that the incidences were very similar for all categories of behavioral disturbances between drug and placebo and it is difficult to conclude that these relatively common effects (*i.e.*, agitation, insomnia, confusion, depression) are actually caused or worsened by Exelon, but rather most likely represent symptoms or signs common to patients with underlying Alzheimer's Disease. (N.B., "Paroniria" is an unfamiliar term to me and means "bad dreams").

Table 83: Psychiatric Adverse Events, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL PSYCHIATRIC DISORDERS	902	(30)	239	(24)	1119	(29)
AGITATION	242	(8)	66	(7)	303	(8)
INSOMNIA	232	(8)	55	(6)	282	(7)
CONFUSION	195	(6)	61	(6)	252	(6)
DEPRESSION	149	(5)	40	(4)	187	(5)
ANXIETY	124	(4)	25	(3)	146	(4)
NERVOUSNESS	109	(4)	26	(3)	134	(3)
HALLUCINATION	96	(3)	30	(3)	125	(3)
AGGRESSIVE REACTION	88	(3)	18	(2)	104	(3)
DELUSION	52	(2)	16	(2)	67	(2)
PARONIRIA	45	(1)	4	(< 1)	49	(1)
PARANOID REACTION	24	(1)	11	(1)	35	(1)
BEHAVIOURAL DISTURBANCE	23	(1)	7	(1)	29	(1)
SOMNOLENCE	21	(1)	3	(< 1)	24	(1)
EMOTIONAL LABILITY	18	(1)	2	(< 1)	20	(1)
LIBIDO INCREASED	15	(< 1)	0	(0)	15	(< 1)
DREAMING ABNORMAL	10	(< 1)	1	(< 1)	11	(< 1)
SUICIDAL IDEATION	8	(< 1)	3	(< 1)	11	(< 1)
ANOREXIA	8	(< 1)	2	(< 1)	10	(< 1)
AMNESIA	8	(< 1)	1	(< 1)	9	(< 1)
DEPERSONALIZATION	7	(< 1)	0	(0)	7	(< 1)
APATHY	6	(< 1)	0	(0)	6	(< 1)
DEMENTIA	5	(< 1)	1	(< 1)	6	(< 1)

8.15.7 Respiratory

The respiratory system was evaluated by periodic physical examinations and by eliciting adverse events referable to that system. In my opinion, this was an adequate assessment of the respiratory system.

Table 84 lists the respiratory adverse events reported in all clinical studies. The overall incidence of respiratory events were similar between the two treatment groups (12% for Exelon patients, vs. 11% for placebo patients). Review of the individual categories of events shows similar incidences between the two treatment groups. There is no evidence that Exelon is causing a clinically significant increase in respiratory adverse events.

Table 84: Respiratory Adverse Events, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL RESPIRATORY SYSTEM DISOR.	357	(12)	113	(11)	468	(12)
COUGHING	114	(4)	40	(4)	154	(4)
RHINITIS	109	(4)	27	(3)	136	(3)
PHARYNGITIS	51	(2)	22	(2)	73	(2)
BRONCHITIS	48	(2)	16	(2)	63	(2)
DYSPNOEA	51	(2)	11	(1)	62	(2)
SINUSITIS	28	(1)	9	(1)	37	(1)
BRONCHOSPASM	6	(< 1)	4	(< 1)	10	(< 1)
SPUTUM INCREASED	7	(< 1)	2	(< 1)	9	(< 1)
UPPER RESP TRACT INFECTION	6	(< 1)	2	(< 1)	8	(< 1)
CHEST SOUNDS ABNORMAL	5	(< 1)	2	(< 1)	7	(< 1)
HYPERVENTILATION	5	(< 1)	2	(< 1)	7	(< 1)
LARYNGITIS	4	(< 1)	1	(< 1)	5	(< 1)
PLEURISY	0	(0)	3	(< 1)	3	(< 1)
PNEUMONIA	3	(< 1)	0	(0)	3	(< 1)
PULMONARY DISORDER	2	(< 1)	1	(< 1)	3	(< 1)
RESPIRATORY DISORDER	3	(< 1)	0	(0)	3	(< 1)
PNEUMOTHORAX	2	(< 1)	0	(0)	2	(< 1)
PULMONARY OEDEMA	2	(< 1)	0	(0)	2	(< 1)
APNEA	1	(< 1)	0	(0)	1	(< 1)
ATELECTASIS	1	(< 1)	0	(0)	1	(< 1)
HYPOVENTILATION	1	(< 1)	0	(0)	1	(< 1)

8.15.8 Dermatological

The dermatological system was assessed by eliciting adverse events referable to that system. In my opinion, this was an adequate assessment of this system. The incidence of these disorders were the same in both groups (7%). Individual disorders were infrequent and had similar incidences in both groups.

Table 85: Dermatological Adverse Events, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
ALL SKIN AND APPENDAGES DISOR.	208	(7)	72	(7)	276	(7)
RASH	67	(2)	23	(2)	90	(2)
PRURITUS	48	(2)	13	(1)	61	(2)
SKIN DISORDER	13	(< 1)	6	(1)	19	(< 1)
DERMATITIS	12	(< 1)	5	(1)	17	(< 1)
HYPERKERATOSIS	10	(< 1)	3	(< 1)	13	(< 1)
RASH ERYTHEMATOUS	9	(< 1)	4	(< 1)	13	(< 1)
URTICARIA	8	(< 1)	4	(< 1)	12	(< 1)
ECZEMA	8	(< 1)	2	(< 1)	10	(< 1)

DERMATITIS CONTACT	6	(< 1)	2	(< 1)	8	(< 1)
PRURITUS GENITAL	5	(< 1)	3	(< 1)	7	(< 1)
SKIN DRY	7	(< 1)	1	(< 1)	8	(< 1)
ALOPECIA	4	(< 1)	3	(< 1)	7	(< 1)
RASH MACULO-PAPULAR	4	(< 1)	2	(< 1)	6	(< 1)
SKIN ULCERATION	4	(< 1)	2	(< 1)	6	(< 1)
CYST, SKIN	4	(< 1)	0	(0)	4	(< 1)
FURUNCULOSIS	3	(< 1)	1	(< 1)	4	(< 1)
HYPERTRICHOSIS	3	(< 1)	1	(< 1)	4	(< 1)
NAIL DISORDER	3	(< 1)	1	(< 1)	4	(< 1)
RASH PSORIAFORM	3	(< 1)	1	(< 1)	4	(< 1)
ABSCESS	3	(< 1)	0	(0)	3	(< 1)

8.15.9 Special Senses

The special senses were assessed by eliciting adverse events referable to those systems. In my opinion, this was an adequate assessment of the special senses. The reported adverse events in these systems are listed in the next three tables. In all cases, the incidence of the various disorders were comparable in both groups. There's no indication that Exelon use leads to increase incidence of disorders affecting vision, hearing, taste, or smell.

Table 86: Vision Disorders, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
VISION DISORDERS	127	(4)	29	(3)	153	(4)
VISION ABNORMAL	45	(1)	8	(1)	51	(1)
CONJUNCTIVITIS	13	(< 1)	8	(1)	20	(1)
CATARACT	18	(1)	2	(< 1)	20	(1)
EYE ABNORMALITY	12	(< 1)	3	(< 1)	15	(< 1)
EYE PAIN	10	(< 1)	3	(< 1)	13	(< 1)
LACRIMATION ABNORMAL	11	(< 1)	2	(< 1)	13	(< 1)
GLAUCOMA	5	(< 1)	2	(< 1)	7	(< 1)
DIPLOPIA	5	(< 1)	1	(< 1)	6	(< 1)
SURGERY	4	(< 1)	2	(< 1)	6	(< 1)
CONJUNCTIVAL HAEMORRHAGE	3	(< 1)	1	(< 1)	4	(< 1)
BLEPHARITIS	2	(< 1)	0	(0)	2	(< 1)
IRITIS	1	(< 1)	1	(< 1)	2	(< 1)
MACULA LUTEA DEGENERATION	2	(< 1)	0	(0)	2	(< 1)
RETINAL DISORDER	1	(< 1)	1	(< 1)	2	(< 1)
UVEITIS	2	(< 1)	0	(0)	2	(< 1)
CORNEAL ULCERATION	1	(< 1)	0	(0)	1	(< 1)
MIOSIS	1	(< 1)	0	(0)	1	(< 1)
PAPILLOEDEMA	1	(< 1)	0	(0)	1	(< 1)
PHOTOPHOBIA	1	(< 1)	0	(0)	1	(< 1)
THROMBOSIS RETINAL VEIN	0	(0)	1	(< 1)	1	(< 1)

Table 87: Hearing and Vestibular Disorders, all clinical studies

	Exelon N=3006	Placebo N=983	Total N=3886
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Adverse Event	n	%	n	%	n	%
HEARING AND VESTIBULAR DISORDERS	59	(2)	13	(1)	72	(2)
TINNITUS	29	(1)	7	(1)	36	(1)
EAR DISORDER NOS	9	(< 1)	3	(< 1)	12	(< 1)
EARACHE	10	(< 1)	2	(< 1)	12	(< 1)
DEAFNESS	6	(< 1)	1	(< 1)	7	(< 1)
VESTIBULAR DISORDER	3	(< 1)	0	(0)	3	(< 1)
EAR DISCHARGE	1	(< 1)	0	(0)	1	(< 1)
HYPERACUSIS	1	(< 1)	0	(0)	1	(< 1)
TYMPANIC MEMBRANE PERFORATION	0	(0)	1	(< 1)	1	(< 1)

Table 88: Taste and Smell Disorders, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
SPECIAL SENSES OTHER, DISORDERS	23	(1)	3	(< 1)	26	(1)
TASTE PERVERSION	16	(1)	2	(< 1)	18	(< 1)
TASTE LOSS	7	(< 1)	0	(0)	7	(< 1)
PAROSMIA	1	(< 1)	1	(< 1)	2	(< 1)

8.15.10 Genitourinary

The genitourinary system was assessed by analyzing periodic urinalysis collections and by eliciting adverse events referable to that system. A review of the urinalysis findings is contained in section 8.6 Laboratory Findings, page 56. There were no clinically significant changes seen in urinalysis parameters, and most changes that were seen were comparable with placebo. The sole exception was urinary protein, which tended to increase in the Exelon treated patients, but this was not clinically significant, and the incidence of outliers of urinary protein was not higher in the Exelon group.

The genitourinary adverse events reported in clinical studies are shown in the next three tables. There is no evidence to suggest that Exelon use is associated with clinically substantially increased incidence of genitourinary adverse events.

Table 89: Urinary System Disorders, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
URINARY SYSTEM DISORDERS	179	(6)	49	(5)	227	(6)
URINARY INCONTINENCE	76	(3)	18	(2)	93	(2)
MICTURITION FREQUENCY	40	(1)	13	(1)	53	(1)
HAEMATURIA	19	(1)	2	(< 1)	21	(1)
DYSURIA	7	(< 1)	5	(1)	12	(< 1)
URINARY TRACT INFECTION	10	(< 1)	2	(< 1)	12	(< 1)
RENAL CALCULUS	6	(< 1)	2	(< 1)	8	(< 1)
URINARY RETENTION	7	(< 1)	1	(< 1)	8	(< 1)
BLADDER DISORDERS NOS	6	(< 1)	1	(< 1)	7	(< 1)
MICTURITION URGENCY	4	(< 1)	3	(< 1)	7	(< 1)
NOCTURIA	4	(< 1)	1	(< 1)	5	(< 1)
CYSTITIS	2	(< 1)	2	(< 1)	4	(< 1)
POLYURIA	4	(< 1)	0	(0)	4	(< 1)
PYURIA	3	(< 1)	1	(< 1)	4	(< 1)

RENAL CYST	3	(< 1)	0	(0)	3	(< 1)
RENAL FAILURE ACUTE	3	(< 1)	0	(0)	3	(< 1)
URETHRAL DISORDER	2	(< 1)	1	(< 1)	3	(< 1)
ALBUMINURIA	1	(< 1)	1	(< 1)	2	(< 1)
MICTURITION DISORDER	0	(0)	1	(< 1)	1	(< 1)
OLIGURIA	1	(< 1)	0	(0)	1	(< 1)
PROCEDURE NOS	1	(< 1)	0	(0)	1	(< 1)

Table 90: Female Reproductive Disorders, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
REPRODUCTIVE DISORDERS, FEMALE	19	(1)	6	(1)	25	(1)
BREAST PAIN FEMALE	5	(< 1)	2	(< 1)	7	(< 1)
BREAST FIBROADENOSIS	2	(< 1)	1	(< 1)	3	(< 1)
VAGINAL HEMORRHAGE	1	(< 1)	2	(< 1)	3	(< 1)
VAGINITIS	2	(< 1)	1	(< 1)	3	(< 1)
PERINEAL PAIN FEMALE	2	(< 1)	0	(0)	2	(< 1)
VAGINITIS ATROPHIC	2	(< 1)	0	(0)	2	(< 1)
BREAST MALFORMATION	0	(0)	1	(< 1)	1	(< 1)
CERVICAL UTERINE POLYP	0	(0)	1	(< 1)	1	(< 1)
GENITALIA ABNORMAL FEMALE	1	(< 1)	0	(0)	1	(< 1)
LEUKORRHEA	1	(< 1)	0	(0)	1	(< 1)
MENORRHAGIA	1	(< 1)	0	(0)	1	(< 1)
MENSTRUAL DISORDER	1	(< 1)	0	(0)	1	(< 1)
POST- MENOPAUSAL BLEEDING	1	(< 1)	0	(0)	1	(< 1)
SURGERY	1	(< 1)	0	(0)	1	(< 1)
UTERINE DISORDER NOS	0	(0)	1	(< 1)	1	(< 1)

Table 91: Male Reproductive Disorders, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
REPRODUCTIVE DISORDERS, MALE	20	(1)	11	(1)	31	(1)
PROSTATIC DISORDER	15	(< 1)	7	(1)	22	(1)
IMPOTENCE	2	(< 1)	3	(< 1)	5	(< 1)
SURGERY	1	(< 1)	1	(< 1)	2	(< 1)
ANORGASMIA, MALE	1	(< 1)	0	(0)	1	(< 1)
PERINEAL PAIN MALE	1	(< 1)	0	(0)	1	(< 1)

8.15.11 Miscellaneous

The incidence of neoplasm in both Exelon and placebo groups was small, and similar in both groups. There's no evidence that Exelon use is associated with an increased incidence of neoplasms.

Table 92: Neoplasms, all clinical studies

Adverse Event	Exelon N=3006		Placebo N=983		Total N=3886	
	n	%	n	%	n	%
NEOPLASMS	27	(1)	16	(2)	43	(1)

SKIN NEOPLASM MALIGNANT	7	(< 1)	6	(1)	13	(< 1)
BASAL CELL CARCINOMA	6	(< 1)	3	(< 1)	9	(< 1)
CARCINOMA	6	(< 1)	3	(< 1)	9	(< 1)
BREAST NEOPLASM MALIGNANT FEMALE	2	(< 1)	2	(< 1)	4	(< 1)
ADENOCARCINOMA NOS	1	(< 1)	1	(< 1)	2	(< 1)
BLADDER CARCINOMA	0	(0)	2	(< 1)	2	(< 1)
COLON CARCINOMA	2	(< 1)	0	(0)	2	(< 1)
MELANOMA MALIGNANT	2	(< 1)	0	(0)	2	(< 1)
GASTRIC CARCINOMA	1	(< 1)	0	(0)	1	(< 1)
HEPATIC NEOPLASM	1	(< 1)	0	(0)	1	(< 1)
LYMPHOMA MALIGNANT	0	(0)	1	(< 1)	1	(< 1)

8.16 Summary of Key Adverse Events

The key adverse events associated with Exelon use fall under three broad categories: gastrointestinal, cardiovascular (orthostasis syncope), and central nervous system. These are briefly summarized below.

8.16.1 Nausea and Vomiting

Nausea and vomiting are the most common adverse events associated with Exelon use. In all clinical trials, 38% of Exelon patients reported nausea, compared with 10% of placebo patients. Twenty-three percent (23%) of Exelon patients had at least one vomiting episode, compared to 10% of placebo patients. This is undoubtedly due to Exelon's mechanism of action as a cholinesterase inhibitor, resulting in increased parasympathetic gastrointestinal activity. I have reviewed nausea and vomiting in previous sections:

- 8.4.4 Adverse Dropouts (ADO) , page 46
- 8.4.5 Other Significant Adverse Events - Nausea and Vomiting, page 47
- 8.5.4 Common and Drug-Related Side Effects, page 53
- 8.15.2 Review of Systems, Gastrointestinal, page 95

8.16.2 Anorexia and Weight Loss

Anorexia and weight loss are also among the most frequent adverse effects associated with Exelon use are. Anorexia was reported by 11% of Exelon patients, compared with 3% of placebo patients. In phase 3 trials (B303, B304, B351, B352), Exelon treated patients lost weight (-0.8 kg at endpoint) whereas placebo patients gained weight (+0.6 kg at endpoint). Furthermore, 13% of Exelon treated patients (n=216) and 5% of placebo treated patients (n=40) experienced clinically notable weight loss, defined as a $\geq 7\%$ change from baseline. Anorexia and weight loss are previously discussed in these sections:

- 8.4.4 Adverse Dropouts (ADO) , page 46
- 8.4.6 Other Significant Adverse Event: Weight Loss, page 49
- 8.5.4 Common and Drug-Related Side Effects, page 53
- 8.15.2 Review of Systems, Gastrointestinal, page 95

8.16.3 Abdominal Pain

The incidence of abdominal pain among Exelon patients was roughly twice that of placebo patients (11% vs. 6%), making it among the most common treatment related adverse effects reported. Again, this is likely due to Exelon's effects on the gastrointestinal tract. Abdominal pain is reviewed in previous sections:

- 8.4.4 Adverse Dropouts (ADO) , page 46
- 8.4.5 Other Significant Adverse Events - Nausea and Vomiting, page 47
- 8.5.4 Common and Drug-Related Side Effects, page 53

- 8.15.2 Review of Systems, Gastrointestinal, page 95

8.16.4 Diarrhea

Also related to increased gastrointestinal motility, diarrhea was reported by 15% of Exelon patients, compared with 9% of placebo patients. Diarrhea is reviewed in previous sections:

- 8.4.4 Adverse Dropouts (ADO) , page 46
- 8.5.4 Common and Drug-Related Side Effects, page 53
- 8.15.2 Review of Systems, Gastrointestinal, page 95

8.16.5 Gastrointestinal Hemorrhage and Melena

There is a theoretical argument that Exelon can lead to increased upper gastrointestinal bleeding due to its ability to increase gastric acid secretion. Empirical data from clinical trials indicate that the association between Exelon therapy and gastrointestinal bleeding and/or melena is not strong, but there is a numerical tendency to see these effects slightly more often in Exelon than in placebo patients (5/3006 vs. 1/983 for gastrointestinal bleeding, and 11/3006 vs. 1/983 for melena). The numbers were much too small to draw any meaningful conclusions; however, the possibility that these effects are increased with Exelon use exists. These effects are discussed further in previous sections:

- 8.3.3 Gastrointestinal Hemorrhage, page 40
- 8.15.2 Review of Systems, Gastrointestinal, page 95

8.16.6 Orthostasis and Syncope

In controlled phase 3 studies, syncope occurred at more than twice the in the Exelon group compared to placebo. (1.2% vs. 0.5%). Syncope tended to be more frequent in women. Breakdown by dose and body weight failed to reveal any patterns. The majority of the events occurred in ages 76-85. Nine (9) patients had a medical condition or were taking medications that could have contributed to a syncopal event. Four (4) additional patients reported syncope as an SAE in uncontrolled trials. All four were taking high dose Exelon (9-12 mg).

Orthostasis, as defined by the sponsor, was a very common finding among all patients, either on Exelon (64%) or placebo (71%). However, orthostasis + "dizziness" (*i.e.*, this subgroup of symptomatic orthostasis) was more common among Exelon patients compared to placebo patients (22% vs. 14%, respectively). Syncope and orthostasis are reviewed in previous sections:

- 8.3.1 Syncope, page 40
- 8.4.7 Other Significant Adverse Event: Orthostasis, page 51

8.16.7 Dizziness

Dizziness was the most commonly reported non-gastrointestinal adverse effect. Dizziness includes lightheadedness, giddiness, wooziness, and related terms. The incidence among Exelon patients was about twice that seen among placebo patients (19% vs. 10%). Dizziness is also discussed in the following sections:

- 8.5.4 Common and Drug-Related Side Effects, page 53
- 8.15.6 Review of Systems, Nervous, page 100

8.17 Analyses of Safety after Exclusion of _____ Centers

Drs. _____ are under investigation by HFD-340, and by criminal investigators, for alleged improper investigational practices. The Division formally requested Novartis on 7/11/97 to submit analyses which excluded the _____ centers.

Drs. _____ participated in two Phase 3 controlled studies, B303 (Center No. 43) and B351 (Center No. 4), as well as in the titration study, B355. After exclusion of these centers, the sponsor recalculated AE incidences of the most common adverse events associated with Exelon treatment.

There were no clinically meaningful differences in AE incidence rates after exclusion of this center in either study (sponsor Table 93 and Table 94). Since AE incidence rates did not change substantially after exclusion of these centers, I decided not to pursue re-analyses of other safety data.

Table 93: Study B351 - Adverse Events Incidences, excluding Center 4

Adverse Event	9 mg %	6 mg %	3 mg %	PBO %
<i>Nausea</i>				
All Centers	36	33	22	12
without center 4	35	32	22	11
Center 4	50	45	17	17
<i>Vomiting</i>				
All Centers	23	21	8	6
without center 4	21	21	7	4
Center 4	42	18	17	33
<i>Anorexia</i>				
All Centers	13	8	8	4
without Center 4	13	8	8	4
Center 4	8	9	0	0
<i>Dyspepsia</i>				
All Centers	9	8	9	8
without Center 4	10	8	10	7
Center 4	0	0	0	8
<i>Abdominal Pain</i>				
All Centers	14	13	9	6
without Center 4	13	14	9	6
Center 4	8	9	8	0
<i>Diarrhea</i>				
All Centers	18	15	12	12
without Center 4	19	15	12	12
Center 4	8	9	8	17
<i>Accidental Trauma</i>				
All Centers	8	7	11	8
without Center 4	9	7	11	7
Center 4	0	9	0	17
<i>Syncope</i>				
All Centers	3	4	1	1
without Center 4	3	4	1	1
Center 4	0	0	0	0
<i>SAE's</i>				
All Centers	12	14	11	9
without Center 4	13	14	8	9
Center 4	0	0	33	17
<i>ADO's</i>				

All Centers	34	21	11	12
without Center 4	34	20	10	12
Center 4	33	27	8	17

Table 94: Study B303 - Adverse Events Incidences, excluding Center 45

Adverse Event	6-12 mg %	1-4 mg %	PBO %
Nausea			
All Centers	50	17	10
without center 45	49	16	10
Center 45	64	30	9
Vomiting			
All Centers	34	8	6
without center 45	34	7	5
Center 45	36	20	18
Anorexia			
All Centers	14	3	2
without Center 45	14	3	2
Center 45	18	10	0
Dyspepsia			
All Centers	6	2	3
without Center 45	5	2	3
Center 45	27	10	9
Abdominal Pain			
All Centers	12	5	3
without Center 45	12	5	3
Center 45	14	25	0
Diarrhea			
All Centers	17	10	9
without Center 45	16	10	9
Center 45	18	0	0
Accidental Trauma			
All Centers	5	7	8
without Center 45	4	6	8
Center 45	18	30	9
Syncope			
All Centers	2	2	1
without Center 45	2	1	>0
Center 45	9	10	9
SAE's			
All Centers	18	17	20
without Center 45	19	17	20
Center 45	9	30	9
ADO's			
All Centers	23	7	7
without Center 45	23	7	6
Center 45	9	20	18

8.18 120-Day Safety Update

The sponsor submitted the 120 day safety update on 8/27/97. The update is a cumulative in nature. That is, data collected for the ISS are pooled with subsequent data. Unfortunately, the sponsor does not present the new data in isolation. In order to detect any differences from the

ISS, I have compared the new totals with the ISS totals to decide whether there is a significant change in safety parameters.

In addition to the ISS data, the following information is included in the update:

- Patients who completed clinical pharmacology studies by 6/30/97 (ISS cutoff date was 6/30/96)
- Complete safety report for study B304 (the ISS contained an interim report with cutoff date 10/31/95)
- All data from week 27 to 52 for patients enrolled in phase 3 uncontrolled studies (B305 or B353) before 6/1/96 (52 week data)
- All data from week 27 to 78 for patients enrolled in phase 3 uncontrolled studies prior to 1/1/96 (78 week data)
- Weeks 15-26 for all patients who entered phase 3 uncontrolled titration study (B355)
- All adverse events that resulted in death, premature discontinuation, or were serious, through 3/31/97

8.18.1 New Data Sources

8.18.1.1 New Patients

Only two studies contributed new patient data: B304, and P106-A1. B304 was a large, phase 3 controlled trial. It contributed 322 additional patients since the ISS. Although these 322 patients were not included in the ISS itself, the safety data from these patients were available in the safety datasets from the original NDA submission, and I have already included these data in my analyses. P106-A1 was a small clinical pharmacology trial and only one new patient was exposed for only one day.

8.18.1.2 New Data on Old Patients

All other data pertain to patients already enrolled in previous studies. These are the phase 3 uncontrolled extensions (B305 and B353) and a phase 3 uncontrolled titration study (B355).

The ISS contained data on 310 patients for weeks 27-52 of uncontrolled studies B305 and B353. In the update, there are now 1734 patients with extension data for these same weeks, 609 of which have data past 52 weeks (52-78 weeks). Of these 1734 patients, 585 received placebo during controlled trials so they were receiving Exelon for the very first time in the extension trial. Final study reports will be submitted at a future date.

The ISS contained data on 544 patients for weeks 1-14 in the uncontrolled titration study B355. The safety update contains additional data for these 544 patients, namely weeks 15-26 of the maintenance phase. A final study report for B355 is included in the safety update.

8.18.1.3 Corrected Data

The database for weeks 1-14 (included in the ISS) of Study B355 and the databases for weeks 27-52 of studies B305 and B353 were re-opened and corrected for the 120 Day Safety Update because of errors detected after the database was locked for the ISS.

8.18.2 Exposures

Based on the new data submitted, Table 95 presents the new patient exposures. It replaces Table 6, on page 18, which was submitted in the ISS. In the ISS, safety data from 3006 patients exposed to Exelon were presented. The 120 day safety update reports data on 3233 Exelon patients, an increase of less than 10%.

Table 95: Exposures in Phase 2 and Phase 3 Clinical Studies (Updated in 120-Day Safety Update)

Study No.	Location	N (PBO)	N (Exelon)
Phase 2 Controlled			
B103	EUR, CAN	133	269
B104	EUR, CAN	24	90
B105	US	10	40
OR1/ALZ/PH2L/01	JAP	53	117 [116] ^a
<i>Extension</i>			
B103-E-01	EUR, CAN	50 ^b	119 ^b
B103-E-04	EUR, CAN	27 ^b	64 ^b
Sub-Total		220	516 [515]^a
Phase 3 Controlled			
B303	EUR, CAN, US	239	486 [484] ^a
B304	EUR, S. AFR, AUSTR	222	456 [455] ^a
B351	US	173	529 [522] ^a
B352	US	235	464 [462] ^a
Sub-Total		869	1935 [1923]^a
Total Controlled		1089	2451 [2438]^a
Phase 2 Uncontrolled			
AD/EP-II	JAP		71
AD/VD-II	JAP		62
<i>Extension</i>			
B103-E06	EUR, CAN		43 ^c
B104-E01	EUR, CAN		49 ^c
B104-E02	EUR, CAN		41 ^a
<i>Compassionate Use</i>			
B901	EUR		20 ^c
B902	EUR		12 ^c
Sub-Total			133
Phase 3 Uncontrolled			
<i>Extension</i>			
B305	EUR, CAN, S. AFR, AUSTR		734 [256] ^c
B353	US		1000 [329] ^c
<i>Titration</i>			
B354	US		15
B355	EUR, US, AUSTR		548 [544] ^a
Sub-Total			2297 [2293]^a
Total Uncontrolled			2430 [2426]^a
TOTAL - ALL PHASE 2/3 Studies		1089	3250 [3223]^a

^a () patients who actually received study medication

^b Patients who participated in previous controlled studies are not counted in the total unless they previously received placebo.

^c Patients who received placebo in a previous controlled trial

8.18.3 Deaths

The cutoff date for deaths in the 120 Day Safety update was 12/31/96. A death was included in the safety database if it occurred during the conduction of a trial, or if it occurred within 30 days after the last dose of study drug was taken. For completeness, any information regarding death reports received after the 12/31/96 cutoff date up until 3/31/97 have also been included, as well as any deaths which occurred >30 days after the last dose of medication, although these are not included in any analyses. These numbers are listed in Table 96.

Table 96: Deaths, 120 Day Safety Update

	Exelon	Placebo	Total
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