Table 4. Mortality Rates by Age, Sex and Prior Exposure to Drug in RCT for All Patients in RCT Extensions

	PYRs	Deaths	Rate per 1000 PYRs
Drug In RCT			
Yes	1347	22	16.3
No (placebo)	641	13	20.3
Age Group			
<=73	1036	9	8.7
73+	952	26	27.3
Gender			
Males	919	17	18.5
Females	1069	18	16.8

Table 5. Mortality Rates by Dose Group for Patients in RCT Extensions Who Were Assigned Drug in the RCT (95% CI)

Dose Group	PYRs	Deaths	Rate per 1000 PYRs
1-4 mg	79	0	0
5-6 mg	354	4	11.3 (4.2,30.1)
7-9 mg	194	1	5.2 (0.7, 36.6)
10-12 mg	719	17	23.6 (14.7, 38.0)

Note: The LRT for the variable "dose group" had a p value of 0.06

Table 6. Mortality Rates by Dose Group for Patients in An Extension Who Were Assigned Placebo in the RCT (95% CI)

Dose Group	PYRs	Deaths	Rate per 1000 PYRs
1-4 mg	56	3	53.6 (17.3, 166.3)
5-6 mg	222	2	9.0 (2.2,35.9)
7-9 mg	91	2	21.9 (5.5, 87.8)
10-12 mg	272	6	22.1 (9.9,49.2)

Note: The LRT for the variable "dose group" had a p value of 0.27

Table 5A. Mortality Rates by Dose Group for Patients in RCT Extensions Who Were Assigned Drug in the RCT Using deaths That were within 7 days of the Last Dose (95% CI)

Dose Group	PYRs	Deaths	Rate per 1000 PYRs
1-4 mg	79	0	0
5-6 mg	354	1	2.8
7-9 mg	194	1	5.2
10-12 mg	719	11	15.3

Note: The LRT for the variable "dose group" had a p value of 0.09

Table 6A. Mortality Rates by Dose Group for Patients in An Extension Who Were Assigned Drug in the RCT (95% CI) Using deaths That were within 7 days of the Last Dose

Dose Group	PYRs	Deaths	Rate per 1000 PYRs
1-4 mg	56	1	17.9
5-6 mg	222	2	4.5
7-9 mg	91	2	21.9
10-12 mg	272	3	11.0

Note: The LRT for the variable "dose group" had a p value of 0.56

Table 7. Mortality Rates for the 10/12 mg Dose Group Compared to Doses < 10 mg for Patients in RCT Extensions (95% CI)

	PYRs	Deaths	Rate per 1000 PYRs
All Patients			
10,12 Mg[1]	991	23	23.2 (15.4, 34.9)
< 10 Mg	997	12	12.0 (6.6,21.2)
Drug in RCT			
10,12 Mg[2]	719	17	23.6 (14.7,38.0)
< 10 Mg	628	5	8.0 (3.3,19.1)
Placebo in RCT			
10,12 Mg[3]	272	6	22.1 (9.9,49.2)
< 10 Mg	370	7	18.9 (9.0,39.7)

1) The LRT for the variable comparing 10/12 mg with lower doses had a p value of 0.06.
2) The LRT for the variable comparing 10/12 mg with lower doses had a p value of 0.02.
3) The LRT for the variable comparing 10/12 mg with lower doses had a p value of 0.8.

Table 8. Mortality Rate per 1000 PYRs by Time Since Entering Extension for Patients with and without Prior Exposure in the RCTs
(Deaths, PYRs)

	First 60 Days	Days 61-180	Days 181-365	Days 365+
Drug in RCTs	0 (0,212)	23.8 (9,378)	19.4 (9,465)	13.8 (4,290)
Placebo in RCTs	9.5 (1,106)	27.3 (5,183)	23.0 (5,218)	14.9 (2,134)

Table 9. Mortality Rates per 1000 PYRs by Time Since Entering Extension for All Patients In an Extension
(Deaths, PYRs)

Dose Group	First 60 Days	Days 61-180	Days 181-365	Days 365+
1-4 mg	0 (0,57)	37.9 (1,26)	31.1 (1,32)	49.8 (1,20)
5-6 mg	7.7 (1,129)	13.0 (2,154)	16.1 (3,186)	0 (0,108)
7-9 mg	0 (0,52)	12.6 (1,79)	20.5 (2,98)	0 (0,56)
10-12 mg	0 (0,81)	33.1 (10,302)	21.8 (8,367)	20.8 (5,241)

Table 10. Mortality Rates per 1000 PYRs by Time Since Entering Extension for Patients Exposed in RCTs
(Deaths, PYRs)

Dose Group	First 60 Days	Days 61-180	Days 181-365	Days 365+
1-4 mg	0 (0,36)	0 (0,13)	0 (0,18)	0 (0,11)
5-6 mg	0 (0,83)	10.8 (1,93)	26.5 (3,113)	0 (0,65)
7-9 mg	0 (0,35)	0 (0,53)	14.9 (1,67)	0 (0,40)
10-12 mg	0 (0,58)	36.4 (8,220)	18.7 (5,267)	22.9 (4,175)

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Table 11. Mortality Rates per 1000 PYRs by Time Since Entering Extension for Patients Assigned Placebo in the RCTs (Deaths, PYRs)

Dose Group	First 60 Days	Days 61-180	Days 181-365	Days 365+
1-4 mg	0 (0,21)	76.9 (1,13)	71.4 (1,14)	111.1 (1,9)
5-6 mg	21.7 (1,46)	16.4 (1,61)	0 (0,73)	0 (0,42)
7-9 mg	0 (0,17)	37.0 (1,27)	32.3 (1,31)	0 (0,17)
10-12 mg	0 (0,23)	24.4 (2,82)	30.0 (3,100)	16.4 (1,66)

Table 12. Unadjusted and Adjusted Rate Ratios for the 10/12 mg Dose Group compared to Doses < 10 mg for Patients in RCT Extensions (95% CI)

	Rate	Unadjusted Rate Ratio	Adjusted Rate Ratio*
All Patients			
10,12 Mg	23.2	1.9 (0.96,3.9)	1.8 (0.9,3.7)
< 10 Mg	12.0		
Drug in RCT			
10,12 Mg	23.6	3.0 (1.1,8.0)	2.8 (1.01,7.5)
< 10 Mg	8.0		
Placebo in RCT			
10,12 Mg	22.1	1,2 (0.4,3.5)	1.0 (0.3, 3.0)
< 10 Mg	18.9		

*Adjusted for age, sex and time since study entry

Table 14. Mortality rates by dose category and time from the beginning of the study (Phase 3). Exelon June 30, 1997 database

Phase 3 Randomized Clinical trials						
Dose	≤100 days			>100 days		
(mg/day)	Deaths	P.years	Inc. Rate/ 1000 p.y.	Deaths	P.years	Inc. Rate/ 1000 p.y..
0	0	225.6	0.0	1	170.5	5.9
>0 to < 4	1	171.5	5.8	0	47.0	0.0
4 to 6	3	153.0	19.6	1	130.2	7.7
>6 to 9	0	85.8	0.0	0	58.8	0.0
>9	0	65.4	0.0	1	99.4	10.1
TOTAL	4	701.3	5.7 (1.6-14.6)	3	505.8	5.9 (1.2-17.3)

Phase 3 Extension of RCT						
Dose	≤100 days			>100 days		
(mg/day)	Deaths	P.years	Inc. Rate/ 1000 p.y.	Deaths	P.years	Inc. Rate/ 1000 p.y.
>0 to < 4	0	66.1	0.0	3	67.7	44.3
4 to 6	1	181.8	5.5	5	395.0	12.7
>6 to 9	0	78.7	0.0	3	206.2	14.5
>9	2	187.1	10.7	21	803.5	26.1
TOTAL	3	513.8	5.8 (0.4-14.1)	32	1472.5	21.7 (14.7-30.1)

Phase 3 Titration studies						
Dose	≤100 days			>100 days		
(mg/day)	Deaths	P.years	Inc. Rate/ 1000 p.y.	Deaths	P.years	Inc. Rate/ 1000 p.y.
>0 to < 4	0	35.1	0.0	2	68.7	29.1
4 to 6	2	34.1	58.7	3	78.6	38.2
>6 to 9	2	25.3	78.9	3	59.1	50.8
>9	0	35.4	0.0	2	99.5	20.1
TOTAL	4	129.8	30.8 (8.3-78.9)	10	305.9	32.7 (15.6-60.1)

able 12. Mortality rates by dose category. Exelon June 30, 1997 database

ıase 2 trials					Phase 3 Randomized clinical trials				
	Deaths	P.years	Inc. rate/ 1000 py.	95% C.I.		Deaths	P.years	Inc. rate/ 1000 py.	95% C.I.
acebo	1	92.6	10.8	(0.2-60.2)	Placebo	1	396.1	2.5	(0.1-14.0)
0 to < 4 mg/day)	0	48.5	0.0	(0.0-76)	(>0 to < 4 mg/day)	1	218.5	4. 6	(0.1-25.4)
to 6 mg/day)	2	194.5	10.3	(1.2-37.1)	(4 to 6 mg/day)	4	283.2	14.1	(3.9-36.2)
6 to 9 mg/day)	0	6.1	0.0	(0.0-604)	(>6 to 9 mg/day)	0	144.6	0.0	(0.0-25.4)
9 mg/day)	0	87.7	0.0	(0.0-42.1)	(>9 mg/day)	1	164.8	6.1	(0.2-33.7)
OTAL	3	429.4	7.0	(1.4-20.4)	TOTAL	7	1207.2	5.8	(2.8-14.4)

ıase 3 Extension trials					Phase 3 Titration trials				
	Deaths	P.years	Inc. rate/ 1000 py.	95% C.I.		Deaths	P.years	Inc. rate/ 1000 py.	95% C.I.
) to < 4 mg/day)	3	133.8	22.4	(4.6-65.5)	(>0 to < 4 mg/day)	2	103.8	19.3	(2.3-69.6)
to 6 mg/day)	6	576.9	10.4	(3.8-22.6)	(4 to 6 mg/day)	5	112.6	44.4	(14.4-103)
6 to 9 mg/day)	3	285.0	10.5	(2.1-30.8)	(>6 to 9 mg/day)	5	84.4	59.2	(2.2-30.7)
9 mg/day)	23	990.6	23.2	(13.7-32.7)	(>9 mg/day)	2	134.9	14.8	(13.7-32.7)
OTAL	35	1986.3	17.6	(11.7-23.4)	TOTAL	14	435.7	32.1	(1.8-53.5)

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Review and Evaluation of Clinical Data

NDA (Serial Number)	**20-823**
Sponsor:	**Novartis**
Drug:	**Exelon**
Proposed Indication:	**Alzheimer's dementia**
Material Submitted:	**NDA Amendment**
Correspondence Date:	**5/12/98**
Date Received / Agency:	**5/13/98**
Date Review Completed	**5/28/98**
Reviewer:	**Armando Oliva, MD**

1. Introduction

In response to the Division's concerns regarding an apparent increased mortality rate in Exelon treated patients seen in previous safety databases, the sponsor now submits the results of their mortality analyses on all deaths occurring in all therapeutic studies (phase 2/3) through 6/30/97. This database contains additional data which has not previously been seen by the review team. Unlike previous databases, the 6/30/97 database contains all deaths that occurred until that time. No criteria for meeting a particular exposure window were applied.

2. Mortality Analyses

As of 6/30/97, the sponsor reports a total of 62 deaths have occurred in all therapeutic studies. Sixty (60) occurred in the Exelon group and 2 occurred on placebo. Of the 60 Exelon deaths, 3 occurred outside the 30-day post-treatment window and were excluded from the analysis. Of the remaining 57 Exelon deaths, 55 occurred in phase 3 and 2 occurred in phase 2 studies.

My review of all submitted information results in different numbers. I have identified 76 deaths (Appendix A, page 13). Seven (7) occurred during phase 2 trials. Apparently the sponsor did not include certain phase 2 trials in their calculation, including two Japanese studies. The remaining 69 occurred in phase 3 trials. Of these, 9 either occurred after the 30 day cutoff or the date of death was unknown (2 of the 9) and were not included in the analyses. Of the remaining 60 patients, 3 were identified by Novartis MedWatch forms only and, presumably, the case report form had not yet been received by Novartis to be included in the safety database. The remaining 57 patients coincide with the 57 described by the sponsor in this report.

The development program contains 4,058.6 patient years of therapeutic experience (sum of the totals in Table 12, page 32 of the submission). Of these, 488.7 patient-yrs represent placebo experience and 3,569.9 represent Exelon experience. The calculated mortality rates are shown in Table 1.

Table 1: Mortality Rates in All Therapeutic Studies

Rx	Deaths	Patient-Time (yrs)	Mortality Rate (per 1,000 pt-yrs)
Exelon	57	3,569.9	16
Placebo	2	488.7	4
TOTAL	59	4,058.6	14.5

This suggests that there is 4 fold increase in mortality rate for Exelon patients. In an attempt to control for time as a confounding variable, the sponsor divided deaths and person-time according to time since initial dose (≤100 days or >100 days). Using this approach, 1545.3 patient-years occurred in patients undergoing ≤100 days of therapy, and 2513.3 patient-yrs occurred in patients treated >100 days. This is shown in Table 2 (from Tables 13 and 14, page 33-34 of the submission).

Table 2: Mortality Rates in All Therapeutic Studies, by Treatment Duration

	≤100 days			> 100 days		
Rx	Deaths	Pt-Time (yrs)	Mortality Rate (/ 1,000 pt-yrs)	Deaths	Pt-Time (yrs)	Mortality Rate (/1,000 pt-yrs)
Exelon	11	1260.5	8.7	46	2309.4	20
Placebo	0	284.8	0	2	203.9	9.8
TOTAL	11	1545.3	7.1	48	2513.3	19

Despite this breakdown by the sponsor, Exelon patients still appear to experience greater mortality rates. Dr. Burkhart's separate analysis by time indicates that time is not significant confounding factor. I refer the reader to his memo for a more detailed analysis of time.

Another approach is to analyze mortality rates by study type. This is only possible with phase 2 and phase 3 RCT's, since only these included placebo. Unfortunately, most of the patient time experience and deaths occur in the extensions, so this analysis excludes valuable data. This information is derived from sponsor Table 12, page 32.

Table 3: Mortality Rates in RCT's

Rx	Deaths	Patient-Time (yrs)	Mortality Rate (per 1,000 pt-yrs)
Phase 2			
Exelon	2	336.8	5.9
Placebo	1	92.6	10.8
TOTAL	3	429.4	7.0
Phase 3			
Exelon	6	811.1	7.4
Placebo	1	396.1	2.5
Total	7	1207.2	5.8

The Exelon mortality rate was lower than placebo in the phase 2 RCT's, but the numbers were small. In the phase 3 studies, there was a 3 fold increase in mortality associated with Exelon use.

Since placebo was not used in the extension and titration studies, the sponsor (and the Division) analyzed the data according to dose groups to look for a dose response relationship. The dose groups used were >0 to <4, 4-6, >6-9, and >9 mg/d. The results are shown in Table 4 and are taken from sponsor Table 12, page 32.

Table 4: Mortality in Open Label Studies, by Dose Groups

Rx	Deaths	Patient-Time (yrs)	Mortality Rate (per 1,000 pt-yrs)
EXT			
>0 to <4	3	133.8	22.4
4-6	6	576.9	10.4
>6 to 9	3	285.0	10.5
>9	23	990.6	23.2
TOTAL	35	1986.3	17.6
TITR			
>0 to <4	2	103.8	19.3
4-6	5	112.6	44.4
>6 to 9	5	84.4	59.2
>9	2	134.9	14.8
TOTAL	14	435.7	32.1

These data show no clear dose-response relationship. In the extension trial, the lowest and highest dose groups have the highest mortality rates. In the Titration studies, it's just the opposite: the two middle dose groups have the highest rates. The sponsor also performed this analysis for the phase 2 and 3 RCT's, but no dose-response relationship was apparent.

The sponsor split the data according to time (≤100 or >100 days) in their table 14, page 34. I only present the data for the extension studies since it represents the largest single group of deaths and patient years.

Table 5: Mortality Rates by Dose Groups and Time

	≤100 days			> 100 days		
Rx	Deaths	Pt-Time (yrs)	Mortality Rate (/ 1,000 pt-yrs)	Deaths	Pt-Time (yrs)	Mortality Rate (/1,000 pt-yrs)
EXT						
>0 to <4	0	66.1	0	3	67.7	44.3
4 - 6	1	181.8	5.5	5	395.0	12.7
>6 to 9	0	78.7	0	3	206.2	14.5
>9	2	187.1	10.7	21	803.5	26.1
TOTAL	3	513.8	5.8	32	1472.5	21.7
TITR						

Rx	≤100 days Deaths	Pt-Time (yrs)	Mortality Rate (/ 1,000 pt-yrs)	> 100 days Deaths	Pt-Time (yrs)	Mortality Rate (/1,000 pt-yrs)
>0 to <4	0	35.1	0	2	68.7	29.1
4 to 6	2	34.1	58.7	3	78.6	38.2
>6 to 9	2	25.3	78.9	3	59.1	50.8
>9	0	35.4	0	2	99.5	20.1
TOTAL	4	129.8	30.8	10	305.9	32.7

This last table shows that in the extension studies, mortality overall increased from 5.8 to 21.7 when comparing ≤100 to >100 days. The highest dose group mortality rate also increased from 10.7 to 26.1, only a 2.4 fold increase. The highest mortality rate was seen in the lowest dose (44.3). This supports the sponsor's statement that mortality in the extension studies appears more a function of time rather than dose. However, the amount of patient time experience <100 days is relatively small and difficult to compare with the much larger subsequent experience.

The sponsor then conducted a Poisson regression analysis of the four Exelon dose groups. I do not include the details here, as they deal with largely epidemiological rather than clinical arguments and are addressed by Dr. Burkhart. The sponsor concludes that there is no dose-response relationship and that mortality is more dependent on time and age.

The sponsor then includes a section discussing Dr. Burkhart's finding that patients exposed to Exelon in RCT's had a significantly higher mortality rate if exposed to >9 mg/day (compared to ≤9 mg/d, 11/449 yrs vs. 0/410 yrs, respectively). By comparison, patients exposed to placebo in RCT's had mortality rates of 5/259 in the ≤9mg/d group vs. 3/174 in the >9mg/d group. This suggests that pre-treatment with Exelon in the RCT was associated with increased mortality with treatment in the extension with >9 mg/d.

The sponsor argues that the Fisher's exact test is inappropriate for this analysis because it should be used to compare proportions, and not rates. They also argue that the post-hoc nature of the analysis without an a priori hypothesis about mortality, the choice of dose categories, and the lack of correction for multiple comparisons make interpretation of the analysis difficult.

They reanalyzed the data using the 6/30/97 database and the new rates are the following:

*Table 6: **Exelon Deaths in Extension Studies According to Prior RCT Treatment***

RCT Treatment	≤9 mg/d	>9 mg/d
Exelon	4/628 (6.4*)	18/720 (25*)
Placebo	9/370 (24.3*)	5/272 (18.3*)

* rates in deaths per 1,000 patient years

This still shows a substantial difference in mortality rates for the subgroup of patients previously exposed to Exelon in an RCT.

3. Mortality Rates in Other Cholinomimetics

In order to get an idea whether the increased mortality rate seen in Exelon is unique to Exelon or whether it may be a class effect, I reviewed the mortality rates in RCT's for Exelon, Aricept, [redacted]. For Aricept, I used Dr. Levin's safety review, plus a study report recently submitted to the division (E2020-A044-304) [redacted]

Also available were data from the physostigmine NDA. I chose not to use these data since the study designs were quite complex and the drop-out rates were so high in the physostigmine group, making comparisons difficult.

3.1 Exelon

In all phase 3 RCT's, there were eight deaths, 7 on Exelon and 1 on placebo. There were 1923 patients exposed to Exelon and 869 exposed to placebo (Table 95 of my safety review, page 113). The mortality incidences are shown in Table 7.

Table 7: Mortality in Exelon RCT's (303, 304, 351, 352)

Treatment	N	Deaths	Incidence
Exelon	1923	7	0.36%
Placebo	869	1	0.11%

There was a greater than 3 fold incidence of deaths in the Exelon treated group. When expressed as mortality rates according to patient time, then the rates are as follows (taken from sponsor's 5/12/98 submission, Table 12, page 32):

Table 8: Mortality Rates in Exelon RCT's

Treatment	Pt-yrs	Deaths	Rate per 1,000 pt-yrs
Exelon	811.1	6	7.4
Placebo	396.1	1	2.5

It is unclear to me why the sponsor only shows 6 deaths in the Exelon group in this table. Even with the 7th Exelon death excluded, the mortality rate remains roughly 3 times higher than placebo.

3.2 Aricept

The Aricept NDA contains data from 3 RCT's (201, 301, and 302). There were four deaths. Three occurred on placebo (N=355) and 1 occurred on Aricept (N=747). Dropout rates were similar for placebo (14%) and Aricept (18%). The mortality incidences are shown in Table 9.

Table 9: Mortality in Aricept RCT's Included in the Original NDA (201, 301, 302)

Treatment	N	Deaths	Incidence
Aricept	747	1	0.13%
Placebo	355	3	0.84%

Mortality was higher in placebo patients.

Patient exposure information was not readily available so I was unable to calculate mortality rates in patient years, but with similar dropout rates between the two treatment groups, it is unlikely the patient exposures per group are proportionately different than the number of patients exposed.

The sponsor subsequently submitted results of a fourth RCT (304). This was a 30 week randomized, double-blind, placebo-controlled trial during which patients were randomized to Aricept or placebo for 24 weeks. A six week placebo washout period followed. Two dose groups were used, 5mg, and 10mg.

There were 274 patients in the placebo group and 544 patients in the two Aricept groups. Drop-out rates were somewhat higher in the Aricept patients: 24% vs. 20% for placebo. There were 5 deaths, 2 on placebo and 3 on drug (Table 10).

Table 10: Aricept Mortality, Study 304

Treatment	N	Deaths	Incidence
Aricept	544	3	0.55%
Placebo	274	2	0.73%

Mortality was still higher in the placebo group. Again, accurate patient exposure data were unavailable to calculate accurate mortality rates. The combined mortality of all patients in Aricept RCT's are shown in Table 11.

Table 11: Aricept Mortality, All RCT's (201, 301, 302, 304)

Treatment	N	Deaths	Incidence
Aricept	1291	4	0.31%
Placebo	629	5	0.79%

Mortality remains higher for placebo in this pooled descriptive analysis.

3.3

Placebo	493	2	0.41%

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4. Weight Analysis

4.1 Background

Since Exelon causes weight loss, I decided to undertake a separate analysis of weight loss and death since it seems clinically possible that increased weight loss in the elderly population can lead to increased mortality from multiple causes due to malnutrition, general poor health and a nonspecific and ill-defined "decreased resistance" against other diseases.

There were 3350 patients in all phase 3 therapeutic trials. In only 35% of the cases (1178/3350) was the last weight recorded on the last visit. In the other cases, the date of the last weight recorded preceded the last visit by several (sometimes many) days. The median interval was 109 days (mean 147 days, range 1-460 days). Therefore, the last weight recorded may not be an accurate measurement of the last weight at the end of the study or death. The last visit recorded often lagged, by many days, the date medication was stopped. The last recorded weight was recorded a median of 50 days before medication was stopped, although in some cases, it occurred after.

With this limitation in mind, I focused my analysis on patients treated in RCT's and extensions. This consisted of 2,791 patients, 43 of which died during treatment or within 30 days of treatment. Only one of these occurred on placebo during an RCT.

I looked at several variables:

- % change in weight using the difference in the last recorded weight from baseline
- last prescribed dose (PBO, ≤9 mg, >9 mg)
- use of Exelon vs. PBO during the RCT portion

In settings where I state a p value, the purpose is for description only since p values in this setting (retrospective, multiple comparisons, non-randomized data) cannot be used for statistical inference.

4.2 Results - Overall Population

The mean weight loss of the entire RCT-EXT (phase 3 RCT and extension) population of 2,791 patients was -1.4% (S.D. = 6.12%). The mean weight loss by last prescribed dose is shown in Table 18. Patients exposed to high dose numerically lost the most weight as a percentage of baseline.

Table 18: Mean Weight Loss in RCT-EXT Studies, by Last Prescribed Dose

Last Dose	N	% Δ Weight
missing	6	0.3
PBO	187	0.5
≤9 mg/d	1536	-1.4
>9 mg/d	1062	-1.7
TOTAL	***2791***	***-1.4***

The mean weight loss according to treatment in the RCT is shown in Table 19. Patients lost twice as more weight if they were exposed to Exelon in the RCT.

Table 19: Mean Weight Loss in RCT-EXT Studies, by RCT Treatment

RCT Rx	N	% Δ Weight
PBO	868	-0.8
Exelon	1923	-1.7

p=0.0007 (t test)

Next, I analyzed the weights of patients who died. Those who died numerically lost more weight, but the difference was not statistically significant.

Table 20: Mean Weight Loss in RCT-EXT Deaths

Status	N	% ΔWeight
Alive	2748	-1.4
Died	43	-2.5

p=.23 (t test)

Next I analyzed the weights of patients who died based on their treatment in the RCT (Table 21). Patients who survived numerically lost more weight (1.7%) if they received Exelon during the RCT compared to those who lived and received placebo. The numbers for the patients who died looked similar.

Table 21: Mean Weight Loss in RCT-EXT Deaths, by Prior RCT Treatment

Status	PBO in RCT N (%)	%Δ Wt	Exelon in RCT N (%)	%Δ Wt
Alive	854 (98.4)	-0.8	1894 (98.5)	-1.7
Died	14 (1.6)	-2.3	29 (1.5)	-2.6

Next I analyzed the weights of patients who died based on their last prescribed dose.

Table 22: Mean Weight Loss in RCT-EXT Deaths, by Last Prescribed Dose

	Missing	%Δ Wt missing	PBO N (%)	%Δ Wt PBO	≤9mg N (%)	%Δ Wt ≤9 mg	>9mg N (%)	%Δ Wt ≥9 mg
Alive	6	0.3	186 (99.5)	0.5	1519 (98.9)	-1.5	1037 (97.7)	-1.6
Died	0	0	1 (0.5)	0	17 (1.1)	+1.7	25 (2.3)	-5.5

The finding in this analysis is striking. Patients who died AND received high dose prior to death had much more weight loss than any other group (5.5%).

Subdividing Table 22 by prior treatment in an RCT results in Table 23.

Table 23: Mean Weight Loss in RCT-EXT, by Last Prescribed Dose and Prior RCT Rx

	Placebo Treatment During RCT						
	N	PBO	%	LO	%	HI	%
Alive	852	186	0.5	396	-1.1	270	-1.3
Died	14	1	0.0	7	+2.1	6	-7.9

	Exelon Treatment During RCT				
	N	LO	%	HI	%
Alive	1890	1123	-1.6	767	-1.7
Died	29	10	+1.4	19	-4.7

Last Prescribed Dose: LO = ≤9mg, HI = >9mg
*excluded from these tables are 6 patients who had no recorded last prescribed dose

The pattern remains the same, regardless of whether patients received Exelon or placebo during the RCT, patients who died and were exposed to high dose also had more weight loss.

One possible explanation for this finding which Dr. Burkhart suggested is that patients close to death may be sicker, may be followed more closely and may have more recent recorded weights. In order to explore this possibility, I analyzed the mean time (in days) between the last recorded weight and the last visit for each group (weight to last, or WL interval).

Table 24: No. of Days between Last Recorded Weight and the Last Visit (WL interval)

	N	Mean WL interval	Median WL interval
Alive	2748	102	34
Died	43	56	39

Although the mean WL interval was substantially shorter for patients who died, the data points are not normally distributed. The median WL interval are comparable between the two groups.

Another possible explanation is that time is a confounding factor. That is, if all patients lose weight over time independent of dose, then patients at high doses may lose the most weight simply because they are on the drug for a longer period of time. A third possibility is that only weight loss associated with malnutrition (*e.g.*, a low albumin) would be clinically significant and a better predictor of increased mortality. I have not pursued these strategies but they would be reasonable next steps to investigate this preliminary signal further. It also remains to be established that weight loss itself is a risk factor for all cause mortality. Dr. Jim Knudsen, one of our safety reviewers, informs me that this has been shown in other settings, although the body mass index (BMI) may be a better predictor.

4.3 Conclusion

In summary, this analysis suggests that patients who died and had the last prescribed dose >9 mg also had the greatest percentage of weight loss when compared to any other group (*i.e.*, compared to patients who died and took low dose (≤9 mg), patients who survived and took high dose, and patients who survived and took low dose). This finding was present regardless of prior treatment in the RCT.

This conclusion has one plausible clinical interpretation. Patients who lose the greatest amount of weight are the most malnourished, are generally in poorer health and are less able to tolerate the complications associated with other illnesses of any type and are at higher risk for death. Since we know that Exelon is associated with increased weight loss in a dose dependent fashion, prolonged high doses of Exelon may result in more weight loss in certain individuals, which may, in turn, result in increased risk of death due to multiple and apparently unrelated causes.

As is the case with retrospective ad hoc analyses of uncontrolled data of this type, one can imagine many other factors which may explain this observation. If this analysis can be confirmed after additional and independent scrutiny, the drug may be approvable with appropriate warnings to prescribers and patients to monitor weight carefully and discontinue the drug if significant weight loss occurs.

5. Comments

There is a persistent increase in mortality associated with Exelon use. Admittedly, this signal is not robust, and no easily identifiable clinical reason for this increase has been identified. This finding appears to be unique to Exelon and is not likely to be a "class effect" of cholinomimetics since similar mortality patterns are not evident in Aricept and metrifonate RCT's.

It can be argued that the numbers in the RCT's are small, and that the safety data in the extension studies are not randomized and open to multiple confounding factors. This may very well be true. However, the signal persists despite multiple analyses, it has not been adequately explained on a clinically identifiable and preventable basis, and therefore cannot be dismissed.

The weight analysis shows that patients who died after taking high dose also lost substantially more weight than any other group. In particular, those who died after taking low dose actually gained weight, and those who took high dose but did not die hardly lost any weight at all. This preliminary signal may provide insight into the increased mortality seen at high doses. The sponsor should consider exploring this signal further but should also look at other covariates.

Given that Exelon does not appear to offer any substantial benefit to patients above what is currently available on the market, there seems little reason to grant approval to a drug that may be associated with increased mortality. With this in mind, I continue to support a non-approvable action.

As a response to the non-approvable action, the sponsor should consider the following strategies:

1. demonstrate using additional safety data that the signal goes away.
2. explain the increased mortality on the basis of some confounding clinical factor that can be described in labeling.
3. provide compelling evidence that the drug represents a substantial benefit over existing therapy which would alter the risk-benefit ratio in favor of approval.

/s/

Armando Oliva, M.D.
Medical Reviewer

R. Levin, M.D. R.L. (see note)

ao 5/28/98
cc:
HFD-120
NDA 20-823
electronic copy-Levin

Appendix A - All Deaths in Exelon Therapeutic Trials

*Table 25 - All Deaths as of June 30, 1997 in Exelon Therapeutic Trials**

	PATIENT ID	FDA NO.	Phase	Age	Sex	Last Dose	Death Date	Cause	Notes
1	ADEPII220-01	.	2	79	M	3		sudden death	
2	B129 UK	.	2	83	F	8		aspiration pneumonia	died on day 53 of 56 day study
3	VDEPII280-13	.	2	67	F	3		intracerebral hemorrhage	
4	B103 005 002	10305002	2	71	M	4		MVA	last dose unknown Oct ? 1991, MVA 11/19/91
5	B103 033 004	10333004	2	80	M	6		pneumonia & pyelonephritis	
6	B103 035 007	10335007	2	85	F	4		pneumonia	
7	B104 100 001	10400001	2	72	M	0		?PE after aortofem bypass	
8	B305 302 004	30302004	3	80	M	8	2/28/96	hip fx, sepsis, death	
9	B305 304 001	30304001	3	73	M	12	11/17/95	sudden death	
10	B305 305 010	30305010	3	82	M	8	1/23/97	MI, pneumonia	massive MI one day after pneumonia sxs
11	B303 009 004	30309004	3	67	M	5	5/12/95	sudden death-heart failure	dyspnea, cardiac failure, died suddenly 12 days later
12	B305 312 016	30312016	3	83	M	12	5/30/96	hemorrhage	bleeding on anticoagulation after hip fracture
13	B305/0/326/4/1/CDN	30326041	3	53	F	8		breast ca, metastatic	197 days on open label rx,
14	B305 329 008	30329008	3	83	F	8	12/28/96	sudden death (asystole)	dyspnea, collapsed, died
15	B305 331 002	30331002	3	84	F	10	5/1/97	stroke	
16	B303 034 018	30334018	3	75	M	12	5/13/96	sudden death in sleep	found dead in bed, no cardiac history
17	B305/0/336/15/1/D	30336151	3	69	F	2		cardiac failure, death 3d latr	653 days in 305
18	B305 342 006	30342006	3	73	M	12	7/13/96	sudden death	died suddenly during a walk
19	B305 342 008	30342008	3	75	M	12	2/22/97	pneumonia	died in hosp pneumonia, no other info, exact last dose date?
20	B305 402 009	30402009	3	86	M	2		bronchial pneumonia	died ? 1/26/97 (per CRF)
21	B305/0/402/5/2/GB	30402052	3	81	M	12		stroke with death in 3 days	583 days in 305
22	B305 403 009	30403009	3	70	F	6	5/15/97	pneumonia	
23	B305/0/406/13/1/GB	30406131	3	77	M	6		fever, chest infection	724 days in 305
24	B304 007 010	30407010	3	83	M	5		stroke	drug dced 2 months p.t. death due to stroke
25	B304 008 006	30408006	3	90	M	0		femoral fracture	PBO dced 2 months prior to death
26	B304 009 003	30409003	3	70	F	5	6/28/96	gi hemorrhage	breast ca, massive hematemesis
27	B304 011 001	30411001	3	79	F	0	11/1/95	broken leg, pneumonia, PE	PBO dced 3 wks prior to death
28	B305 411 003	30411003	3	76	F	6	10/1/96	pneumonia	
29	B305 413 010	30413010	3	76	F	12	11/1/96	colon ca	12mg/d dc'ed wk 61, she died 18 days later
30	B305 413 013	30413013	3	77	M	12	8/10/96	malignant thymoma	hemopericardium from thymoma
31	B305 417 011	30417011	3	76	M	6	1/18/97	MI	MI from physical exertion, died 5 days later reinf
32	B305 425 004	30425004	3	85	M	12	10/16/96	sudden death	sudden death 2 hours after study drug in sleep
33	B305 431 015	30431015	3	84	M	2	8/22/96	septicemia	viral bronchitis, femoral fx, UTI, sepsis
34	B353 102 071	35102071	3	72	M	6	1/6/97	sudden death	suddenly unresonsive
35	B351 003 011	35103011	3	83	M	1	2/18/95	prostate ca	died 4 days after diagnosis (had N/V/anorexia)
36	B351 005 003	35105003	3	77	M	4	3/22/95	stroke	
37	B353 105 021	35105021	3	68	F	2	12/28/96	sudden death	"cardiac arrhythmia, asystole" 26d after d/c med
38	B353 106 045	35106045	3	78	F	12	7/15/96	diverticulitis	also had hematemesis, paralytic ileus
39	B351 011 013	35111013	3	76	M	3		MVA	exact death date not known, 3-13 wks from last dose

	PATIENT ID	FDA NO.	Phase	Age	Sex	Last Dose	Death Date	Cause	Notes
40	B353/0/111/2/1/USA	35111021	3	73	M	12		ruptured AAA	
41	B353 111 049	35111049	3	75	F	12	10/18/96	respiratory failure	confusion, ? viral meningitis, sepsis
42	B353 112 014	35112014	3	87	M	12	2/3/97	died during sleep	ruptured AAA (death certificate, ? autopsy)
43	B353 202 038	35202038	3	78	F	12	6/19/97	died during sleep-sudden death	? acute MI, h/o SVT, DM, no mention of autopsy
44	B353 203 002	35203002	3	75	F	10	4/25/97	sudden death	death (?MI) 3 days after inpt rx for pneumonia, no autopsy
45	B353 203 003	35203003	3	82	F	10	6/10/96	pancreatic ca	
46	B353 203 023	35203023	3	74	M	12	4/28/97	MI	
47	B353 203 025	35203025	3	80	F	12	6/12/96	MI	inferior wall MI, died 3 days later
48	B353 204 022	35204022	3	80	F	4	3/8/96	metastatic brain ca	abnl CXR, likely lung primary
49	B353 204 042	35204042	3	82	F	12	12/9/96	stroke	malignant hypertension, intracerebral hemorrhage
50	B353 206 021	35206021	3	78	M	4	6/17/96	diverticulitis, septicemia	pneumonia, pelvic abcess, sepsis
51	B353 207 028	35207028	3	73	F	12	12/21/96	sudden death	cardiac arrest
52	B353 209 022	35209022	3	75	M	10	11/7/96	MI ? sudden death	drug d/c'ed 9 days prior to ? 2nd MI
53	B353 211 009	35211009	3	78	F	2	1/14/97	metastatic brain ca	unknown primary
54	B353 213 004	35213004	3	88	M	12	2/21/96	pneumonia	general physical deterioration
55	B353 213 019	35213019	3	69	F	12	8/5/96	lung cancer	metastatic small cell ca
56	B353 215 011	35215011	3	70	F	12	6/14/96	acute heart failure	death in sleep "terminal Alzheimers"
57	B352 015 039	35215039	3	83	F	6	11/11/95	poss MI-sudden death	died suddenly, no more info
58	B353 220 009	35220009	3	73	M	10	4/1/96	cardiac arrest	drug dced 2 wks prio to death, colectomy sepsis
59	B353 222 027	35222027	3	83	M	12	1/25/97	progressive deterioration	drug dced 8 days prior to death in hospice
60	B355 002 104	35502104	3	62	M	6	6/9/97	ASCVD/arteriosclerosis	
61	B355 007 104	35507104	3	80	M	6		intracerebral hemorrhage	drug dced 140 days prior to death
62	B355 007 116	35507116	3	86	F	6	6/6/96	sudden death	found dead on bathroom floor
63	B355 007 118	35507118	3						no information provided
64	B355 010 117	35510117	3	57	M	12	9/15/96	suicide	gunshot wound to the head
65	B355 015 108	35515108	3	76	F	3	9/30/96	MI ? sudden death	pneumonia, intubation, cardiac arrest in hosp
66	B355 016 101	35516101	3	77	M	?	5/14/97	MI	
67	B355 016 104	35516104	3	73	F	9	11/26/96	MVA	trauma
68	B355 018 102	35518102	3	75	F	9	7/31/96	poss stroke	drug dced 5 days prior "massive stroke" no more info
69	B355 019 113	35519113	3	72	M	6		lung ca	drug dced 38 days prior to death
70	B355 022 103	35522103	3	84	M	9	1/29/97	bronchitis, renal failure	drug dced 28 days prior to death
71	B355 024 116	35524116	3	70	F	3	6/26/96	stroke	drug dced 3 days prior to death (when stroke occurred)
72	B355 026 102	35526102	3	77	M	12	5/3/97	shock	
73	B355 028 101	35528101	3	75	F	3	4/6/96	pelvic ca	
74	B355 028 105	35528105	3	85	F	12	11/5/96	post op wound infection	staph infection after left femoral fx
75	B355 028 121	35528121	3	86	F	9	5/16/96	met colon ca	
76	B355 028 126	35528126	3	85	M	6	10/17/96	pneumonia, DVT, PE	autopsy proven PE

*The 57 patients included in the 6/30/97 database are in black bold (56 on Exelon, 1 on PBO); those in blue were excluded from the 6/30/97 database
empty cells indicate unknown or missing values

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: 5/30/98
From: Randy Levin, M.D., Neurology Team Leader
Subject: NDA 20-823 Exelon (rivastigmine tartrate)
To: file

Exelon (rivastigmine tartrate) is a acetylcholinesterase inhibitor for the symptomatic treatment for mild to moderate Alzheimer's dementia.

The NDA was submitted on 4/7/97. Upon finding evidence for an increase in mortality, reviewers worked with the sponsor to obtain an update on deaths occurring in the ongoing trials. The original due date was extended 3 months to 7/7/98 after the sponsor amended the NDA with the data.

Chemistry:

Conclusions: Dr. Rzeszotarski has reviewed the CMC section and found only minor deficiencies, none preventing approval. The deficiencies were sent to the sponsor. Following review of the responses, there are no issues pending.

The drug is supplied as ——, 1.5, 3, 4.5 and 6 mg immediate release capsules. It is stable but hygroscopic requiring that it be protected from humidity.

Nonclinical toxicology

Conclusions: Dr. Rosloff and Dr. Fitzgerald have reviewed the nonclinical toxicology and conclude that there are no issues preventing approval.

The sponsor submitted adequately conducted toxicity studies including 6 month and 1 year studies in rats and dogs, 2 year carcinogenicity studies in mice and rats and standard reproduction and genotoxicity batteries.

Dose related signs consistent with cholinesterase inhibition was seen in both the rat and dog studies. The most consistent effect was seen in the GI tract. In the 6 month and 1 year dog study, the high dose dogs had serosal lesions in the large intestine consisting of nodules, hemorrhage, granulation tissue, etc. Similar lesions were also seen in the 2 week iv study. These lesions may be related to the pharmacological activity of the drug because a similar lesion was seen with —— preclinical studies. Other GI lesions included intussusception, mucosal congestion and/or hemorrhage in the large and small intestine. No drug effects were seen on the heart rate, EKG or ophthalmoscopic exam. Carcinogenicity studies showed a borderline/equivocal increase in mammary adenocarcinomas. The incidence of these lesions were similar to that seen in historical controls. There was no increase in hyperplasia and adenomas. There was no drug effect seen on

mammary gland tumors in the rat studies. Based on this and other information, the lesions were not thought to be significant.

Biopharm

Conclusion: Dr. Safaa Ibrahim and Dr. Sahajwalla reviewed the biopharm portion of the submission and found it acceptable. They recommended changes to the sponsor's draft labeling. The biopharm reviewers found the dissolution methodology and specifications acceptable. Analytical methodology was also acceptable. There are no outstanding issues.

Pharmacokinetics was investigated in healthy young and elderly subjects up to doses of 3 mg, the maximum dose tolerated. In patients, pharmacokinetics was investigated to doses up to 6 mg bid following dose titration. The findings from these studies is summarized in the following table.

Summary of the PK results	
Absorption	almost completely absorbed (97% of radioactivity found in the urine
Tmax	1 hour
bioavailability	35% of oral 3 mg dose compared to 1 mg iv dose 104% of single 3 mg dose compared to an oral solution
bioequivalence	capsule used in the clinical studies are the capsules to be marketed
food effect	decrease absorption, delayed Tmax and decreased Cmax by 30% and increased mean AUC by 30% (in all efficacy studies, drug given with food).
Volume of distribution	Mean volume of distribution is 5/1 L/kg.
CSF	CSF peak concentrations in 1 to 4 hours with mean AUC ratio of CSF/plasma 40% following 1 to 6 mg bid.
Protein binding	40%
Metabolism	major pathway is direct cholinesterase mediated decarbamylation to the phenolic metabolite ZNS 114-666 which is conjugated with sulfate
Cytochrome P450	minimal role
Metabolite	ZNS 114-666 pharmacological activity unknown
Elimination	elimination almost exclusively via the urine. No parent drug in the urine (40% sulfate metabolite)
t1/2	1 to 2.5 hours, dose independent
clearance	1.8 L/min following 6 mg bid
Dose proportionality	linear kinetics up to 3 mg bid. Nonlinear kinetics from 3 to 6 mg bid (double dose leads to 4 fold increase in AUC)
Accumulation	none expected with multiple dosing
Age/race/gender	no effect found in population PK analyses (no effect found for age in studies)
Nicotine	23% increase in oral clearance
Hepatic disease	60% decrease in clearance with similar half life, no accumulation expected
Renal disease	There were higher concentrations in patients with moderate renal insufficiency while no changes were noted in patients with severe renal impairment. The reason for the differences were not clear. The sponsor is going to repeat the study.
Alzheimer's disease	30% longer half-life and 30% lower clearance in patients compared to healthy subjects
other diseases	from population PK, there were no effects on the oral clearance for patients with arthritis, diabetes, dyspepsia and hypertension.
Drug interactions in vitro	no effects on substrates for P450 isoenzymes, there were no effects on the haldol, fluxotenine, thioridazine, amitriptyline and nortriptyline on decarbamylation
Drug interactions in vivo	no interaction with the following drugs digoxin, warfarin, diazepam, fluoxetine
Drug interactions population PK	no interaction with population PK data ($n \geq 70$) for the following drugs: antacids, antihypertensives, calcium channel blockers, NSAID, estrogens

Efficacy:

Conclusion: I reviewed the efficacy data from this NDA. Dr. Hoberman was the statistical consultant. We both concluded that the sponsor provided sufficient evidence to allow the drug to be approved as a symptomatic treatment for Alzheimer's disease.

For the assessment of a drug for the treatment of Alzheimer's disease, the division has relied on the demonstration of a statistically significant difference in a measure of cognition such as the ADAS-cog as well as an independent assessment of the patient's function that would detect a clinically evident improvement. In my opinion, a reason for the inclusion of the assessment of functioning is to base efficacy, at least in part, on clinically relevant improvements. This "clinically relevant" change was supposed to be based on a clinician's assessment of the patient from information obtained from an interview with the patient and possibly the patient's caregiver.

In three adequate and well controlled studies (B303, B304 and B352), the sponsor demonstrated a statistically significant difference in the ADAS-cog and an global assessment in favor of the drug over placebo. In one additional study (B351), a statistically significant difference was demonstrated in the ADAS-cog but not on the global assessment.

It is debatable whether the global assessment used in the pivotal Exelon trials validly provided an independent assessment of a clinically relevant improvement of the patient. For the pivotal studies, the sponsor used the results of a structured interview with the patient and caregiver for assessment of the clinically evident improvements. The structured portions of this "global" assessment differs from those used for the assessment of Cognex and Aricept. The clinician performed three different scales to assess improvement. One was an assessment of cognitive functioning. Another was an assessment of functioning in activities and the third was an assessment of the behavior of the patient. This assessment appears to be a composite score of these three assessments rather than a impression of clinically relevant changes. The assessment of cognitive functioning is similar to the ADAS-cog. If the changes seen in the global were related only to changes on the cognitive assessment, then it would not be independent of the ADAS-cog assessment. When I analyzed the global assessment, the statistically significant changes were not only in the cognitive assessment but were also in the assessment of functioning suggesting that an independent clinically evident change was seen thus fulfilling the purpose of the clinical assessment.

The efficacy of the drug is dose related but the dose or dose range at which the drug is effective is more difficult to determine. In the two studies (B103 and B351) evaluating fixed doses of the drug (3, 4, 6 and 9 mg/day), the drug was not statistically superior to placebo for both the measure of cognition and global assessment. In the three studies demonstrating statistically significant changes for both the ADAS-cog and CIBIC plus, the patients were randomized to dose ranges (2 to 12 mg/day in one study, 1 to 4 mg/day and 6 to 12 mg/day in two studies). Patients receiving lower doses of the drug ($\leq$ 4 mg/day) were not consistently statistically superior to placebo for both the measure of cognition (ADAS-cog or MMSE) and global assessment (CGIC or CIBIC plus). Because the fixed doses studies did not demonstrate improvement of the 6 and 9 mg/day dose, the only "effective" dose may be doses > 9 mg/day.

Efficacy overview:

The efficacy of Exelon was evaluated in 5 adequate and well controlled studies. One of these studies, Study B103, was a phase 2, 13 week, randomized, placebo controlled, dose ranging study evaluating doses of 4 and 6 mg/day. I will not discuss this study further except to say that

patients were titrated over one week to 4 mg/day or over two weeks to 6 mg/day, outcome was assessed with the Mini Mental Status Exam (MMSE) and Clinical Global Impression of Change (CGIC) and no significant differences were seen between groups.

The other four studies were 26 week, randomized, double blind, placebo controlled studies. Patients with probable Alzheimer's disease (AD) as defined by the NINCDS criteria were enrolled. Patients had mild to moderate severity as defined by MMSE scores ranging from 10 to 26. The mean age of patients participating in Exelon trials was 73 years with a range of 41 to 95 years. Approximately 59% of patients were women. The racial distribution was white 94%, black 4% and other races 2%.

During the first 3 months of the study, patients were titrated to their maintenance dose to improve tolerance. Essentially, patients were started on doses of 1 to 2 mg/day given bid given as two equal, divided doses. Doses were advanced weekly by 0.5 to 1 mg/day based on tolerance to the drug. The titration took 9 and 12 weeks depending on the patient's tolerance to the drug. In two studies, B303 and 352, patients were titrated to dose ranges, 1 to 4 mg/day and 6 to 12 mg/day. In one study, B351, patients were titrated to fixed doses of 3, 6 or 9 mg/day. In the final study, B304, patients were titrated to doses ranging from 2 to 12 mg/day.

In each study, the effectiveness of treatment with Exelon was evaluated using a dual outcome assessment strategy. The ability of Exelon to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher. The patients recruited as participants in each study had mean scores on the Alzheimer's Disease Assessment Scale (ADAS-cog) of approximately 22 units, with a range from 1 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggest that they gain 6 to 12 units a year on the ADAS-cog. However, lesser degrees of change are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in Exelon trials was approximately 5 units per year.

The ability of Exelon to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC plus. The CIBIC plus is not a single instrument and is not a standardized instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC plus reflect clinical experience from the trial or trials in which it was used and can not be compared directly with the results of CIBIC plus evaluations from other clinical trials. The CIBIC plus used in Exelon trials was a structured instrument that was intended to examine three major areas of patient function: Cognitive, Behavioral and Activities of Daily Living. The CIBIC-plus was scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved", to a score of 4, indicating "no change" to a score of 7, indicating marked worsening". The CIBIC-plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

Fixed dose study (351):

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 26 weeks of the study. After 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon treated patients

compared to the patients on placebo were 0.5, 1.6 and 1.8 units for the 3, 6 and 9 mg/day treatments, respectively. The differences for the 6 and 9 mg/day group were statistically significant. While the treatment effect size may appear to be slightly greater for the 9 mg/day treatment, there was no statistically significant difference between the active treatments.

Figure 1: ADAS-cog change from baseline over 26 weeks.
X axis is duration in weeks. Y axis is the ADAS-cog change score.
The dose groups are from top to bottom at week 12, placebo , 6 mg/day, 3 mg/day and 9 mg/day.

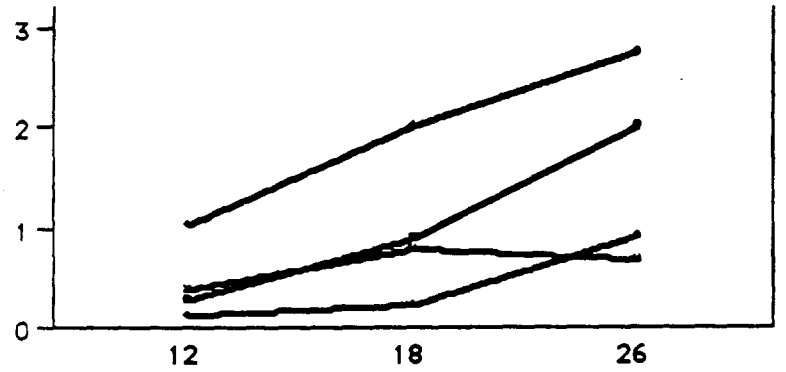
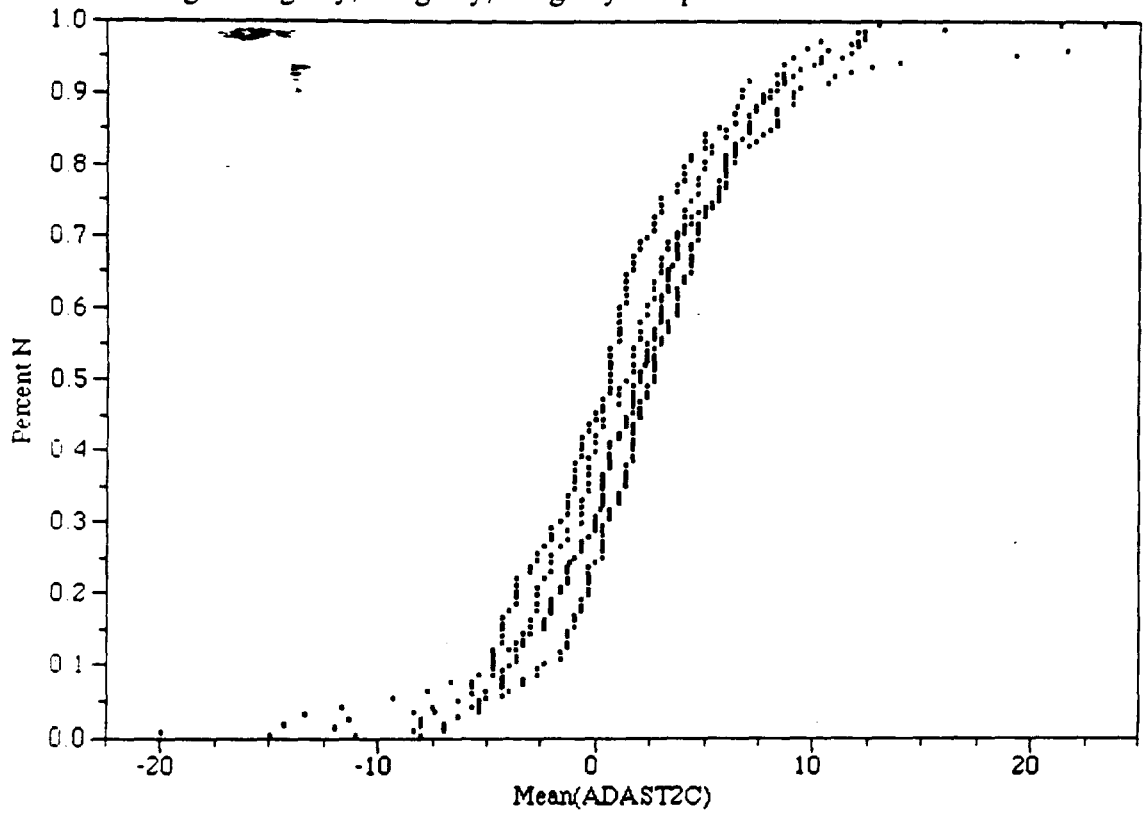


Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table. The curves demonstrate that both patients assigned to placebo and Exelon have a wide range of responses, but that the active treatment groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

Figure 2: Cumulative percentage of patients with ADAS-cog change score
From left to right 9 mg/day, 6 mg/day, 3 mg/day and placebo.



Effects on the CIBIC-plus: Figure 3 is a histogram of the frequency distribution of CIBIC-plus scores attained by patients assigned to each of the treatment groups who completed 26 weeks of treatment. The mean drug-placebo differences for these groups of patients were 0.0, 0.0 units and 0.2 units for 3 mg/day, 6 mg/day and 9 mg/day of Exelon, respectively. These differences were not statistically significant.

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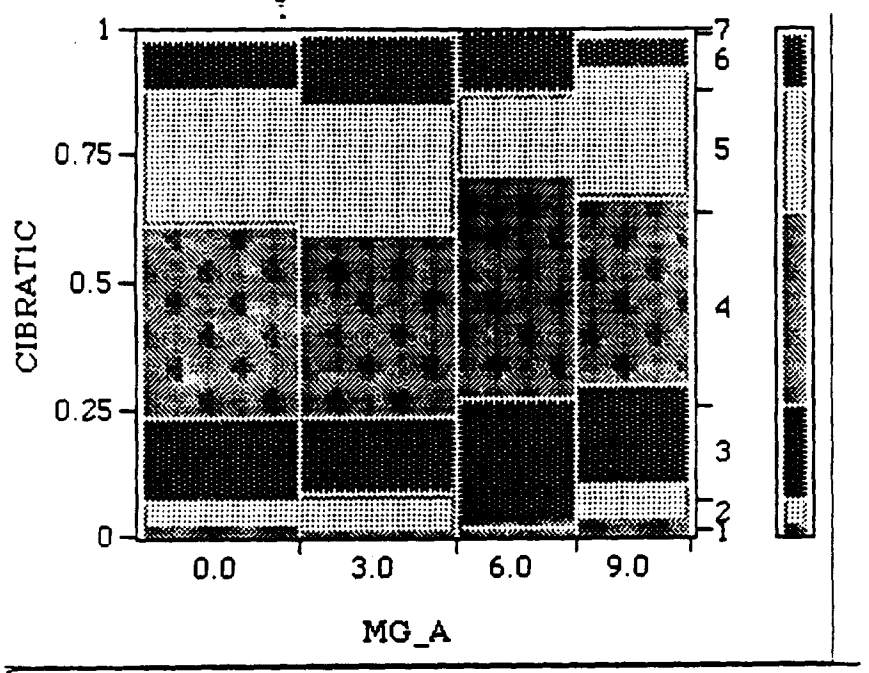
Figure 3: Histogram of frequency distribution of CIBIC plus scores in patients who completed 26 weeks of treatment. The Crosstabs table show the percentage of patients in each group that receiving the specific numeric rating



Crosstabs

MG_A

CIBRATIC Col %	0.0	3.0	6.0	9.0
1	1.59	0.00	1.03	2.22
2	5.56	8.73	2.06	7.78
3	16.67	15.08	24.74	20.00
4	37.30	35.71	43.30	36.67
5	26.98	25.40	16.49	25.56
6	10.32	14.29	12.37	6.67
7	1.59	0.79	0.00	1.11

Dose range studies (303, 352 and 304):

Effects on the ADAS-cog: Figure 4 a-c illustrates the time course for the change from baseline in ADAS-cog scores for the three dose ranges studied over the 26 weeks of studies 303, 304 and 352. After 26 weeks of treatment, the mean differences in the ADAS-cog change scores for the Exelon treated patients compared to the patients on placebo are summarized in the table 1.

Table 1: Mean difference in ADAS-cog/CIBIC plus score in Exelon treated patients compared to placebo treated patients at week 26 (*p value < 0.05)

	Study 303		Study 304		study 352	
	ADAS-cog	CIBIC+	ADAS-cog	CIBIC+	ADAS-cog	CIBIC+
1 to 4 mg/day	0.2	0.14	n/a	n/a	1.9*	0.18*
6 to 12 mg/day	2.6*	0.41*	n/a	n/a	4.9*	0.21*
2 to 12 mg/day	n/a	n/a	2.7*	0.43*	n/a	n/a

Figure 4a: ADAS-cog change from baseline over 26 weeks for studies 303 and 352 combined.
X axis is duration in weeks. Y axis is the ADAS-cog change score.
The dose groups are from top to bottom at week 12: placebo , 1 to 4 mg/day, 6 to 12 mg/day

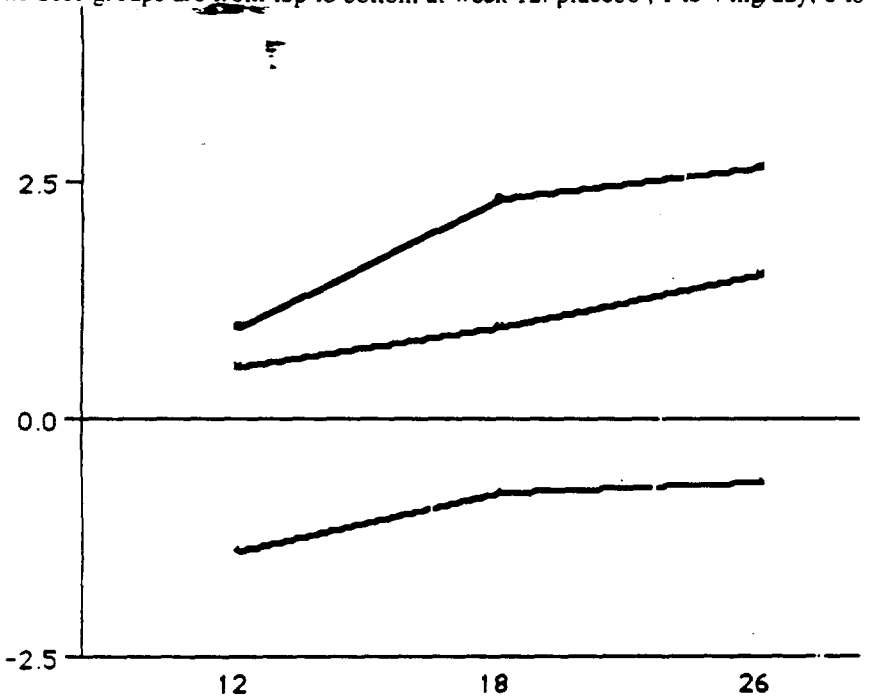


Figure 4b: ADAS-cog change from baseline over 26 weeks for study 304.
X axis is duration in weeks. Y axis is the ADAS-cog change score.
The dose groups are from top to bottom at week 12: placebo , 2 to 12 mg/day

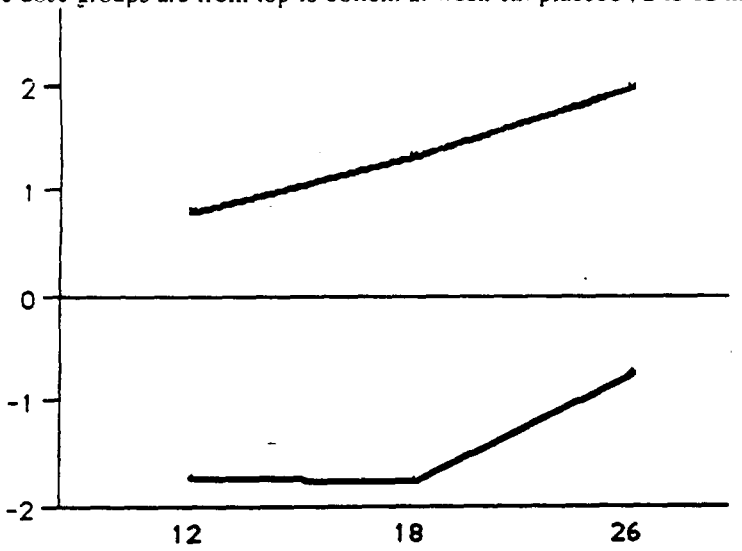


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Figure 4c: ADAS-cog change from baseline over 26 weeks for studies 303, 304 and 352 combined. The dose ranges were chosen retrospectively for illustrative purposes.
X axis is duration in weeks. Y axis is the ADAS-cog change score.
The dose groups are from top to bottom at week 12: placebo , 1 to 4 mg/day, 5 to 9 mg/day, 10.5 to 12 mg/day

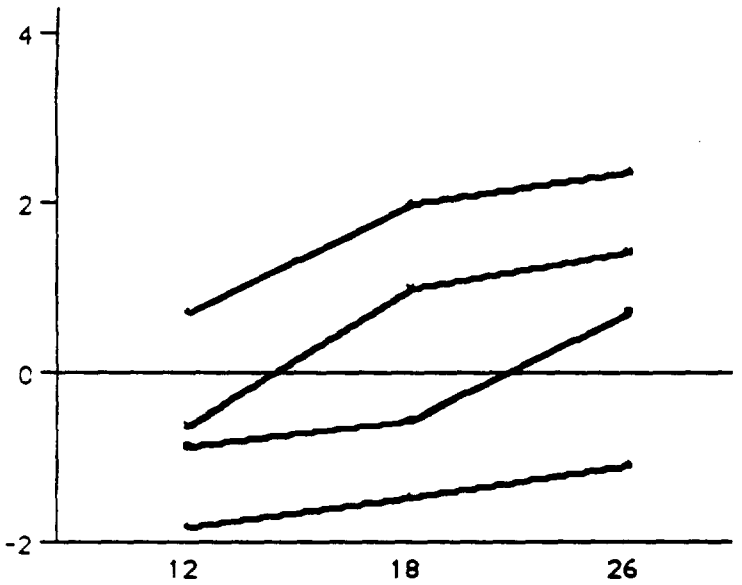

Figure 5a-c illustrates the cumulative percentages of patients from each treatment group who had attained the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table. The curves demonstrate that both patients assigned to placebo and Exelon have a wide range of responses, but that the active treatment groups are more likely to show the greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

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Figure 5a: Cumulative percentage of patients with ADAS-cog change score for studies 303 and 352
x axis change in ADAS-cog from baseline, y axis cumulative probability
From left to right 6 to 12 mg/day, 1 to 4 mg/day and placebo.

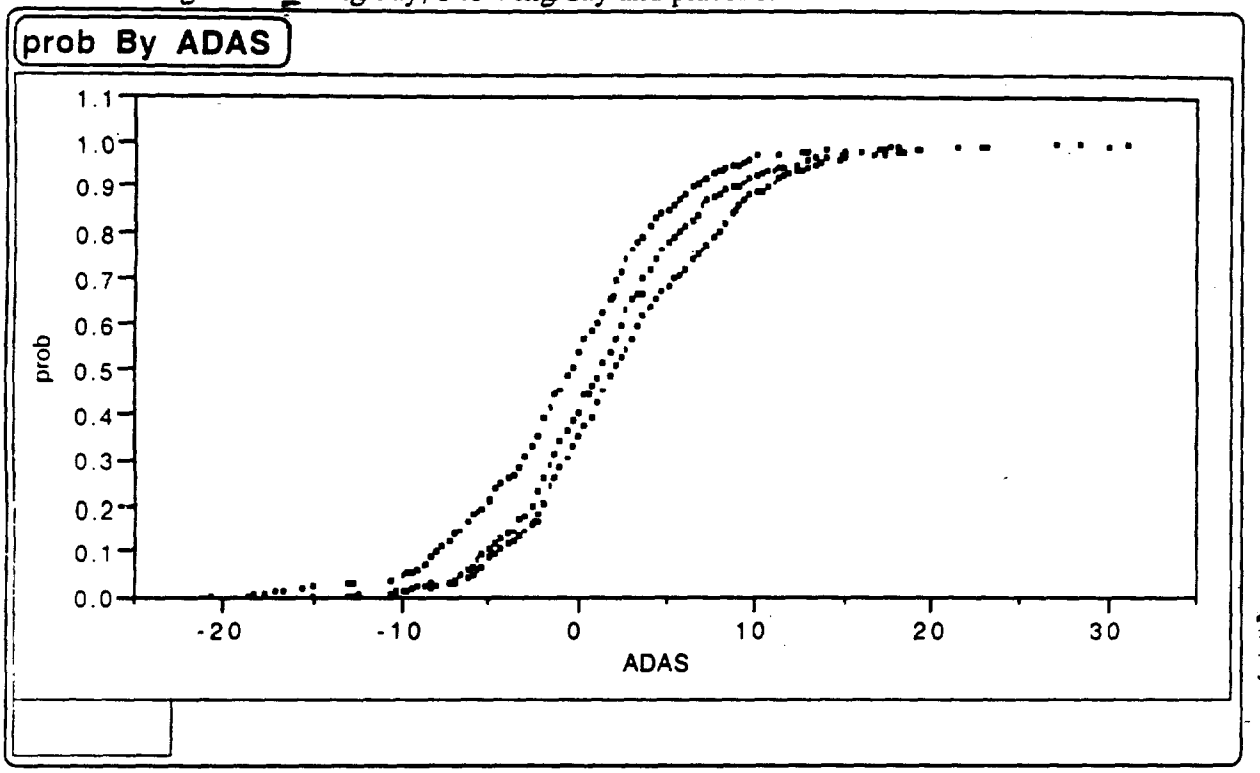

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Figure 5b: Cumulative percentage of patients with ADAS-cog change score in study 304
x axis change in ADAS-cog from baseline, y axis cumulative probability
From left to right 2 to 12 mg/day and placebo.

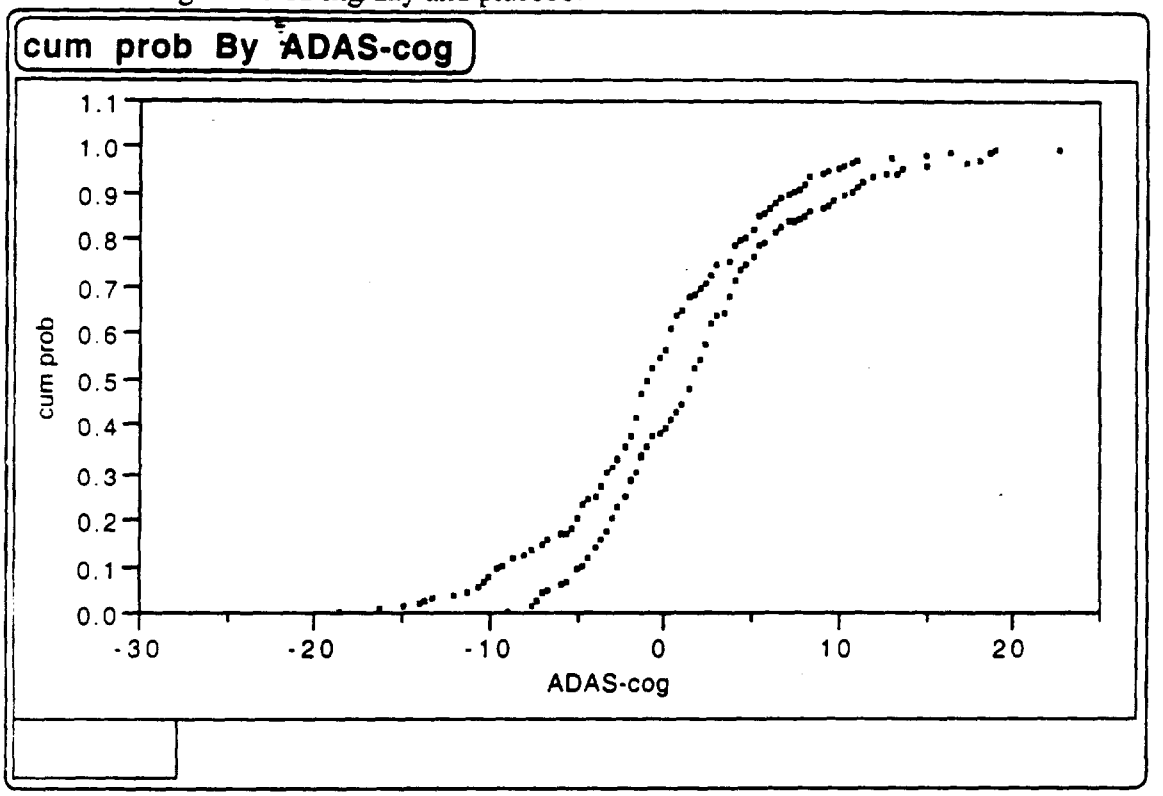

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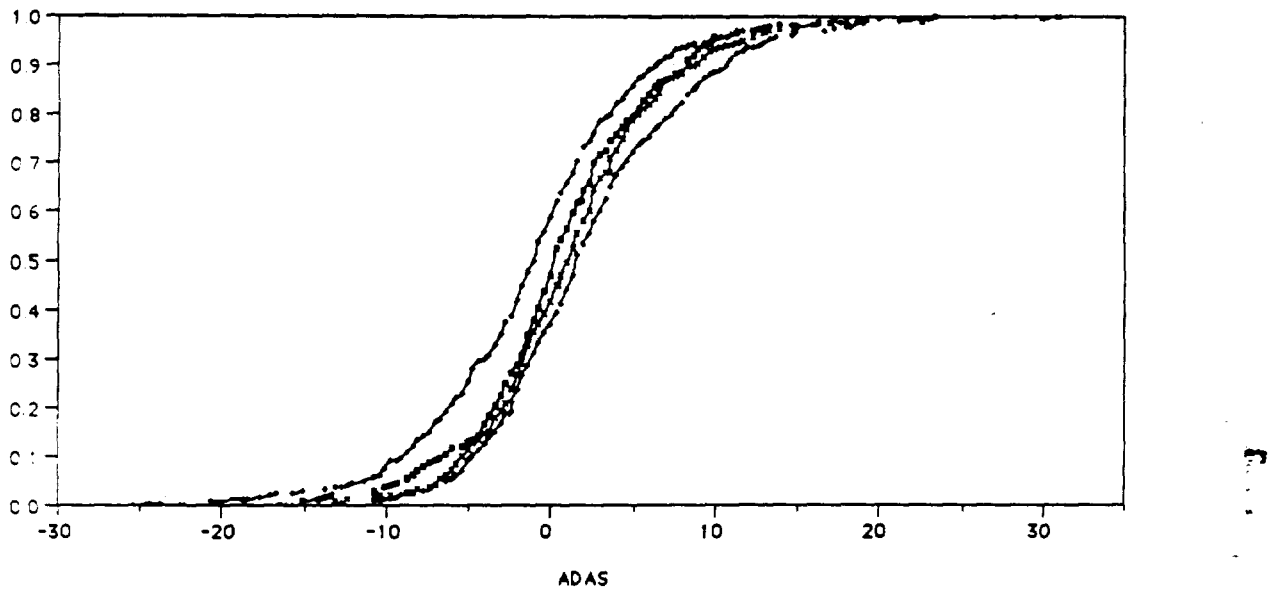
Figure 5c: Cumulative percentage of patients in studies 303, 304 and 352 with ADAS-cog change score. The dose groups, 10.5 to 12 mg/day (12 mg/day), 5 to 9 mg/day (9 mg/day) and 1 to 4 mg/day (4 mg/day) were defined retrospectively for illustrative purposes.
x axis change in ADAS-cog from baseline, y axis cumulative probability
From left to right 10.5 to 12 mg/day, 5 to 9 mg/day, 1 to 4 mg/day and placebo.



Effects on the CIBIC-plus: Figure 3a-c is a histogram of the frequency distribution of CIBIC-plus scores attained by patients assigned to each of the treatment groups who completed 26 weeks of treatment. The mean drug-placebo differences for these groups in each study is summarized in Table 1. The Crosstabs table show the percentage of patients in each group that receiving the specific numeric rating.

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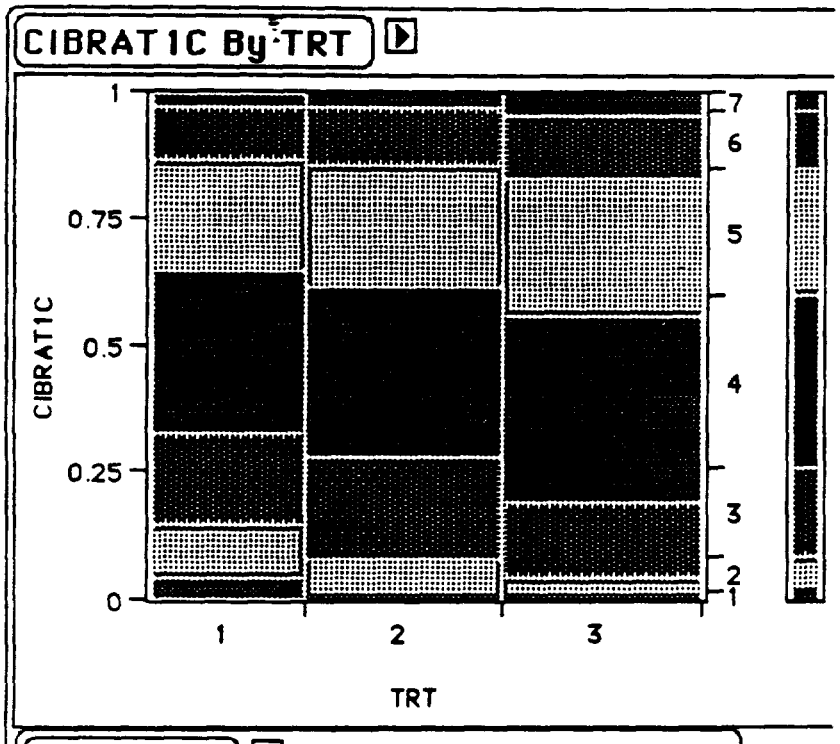
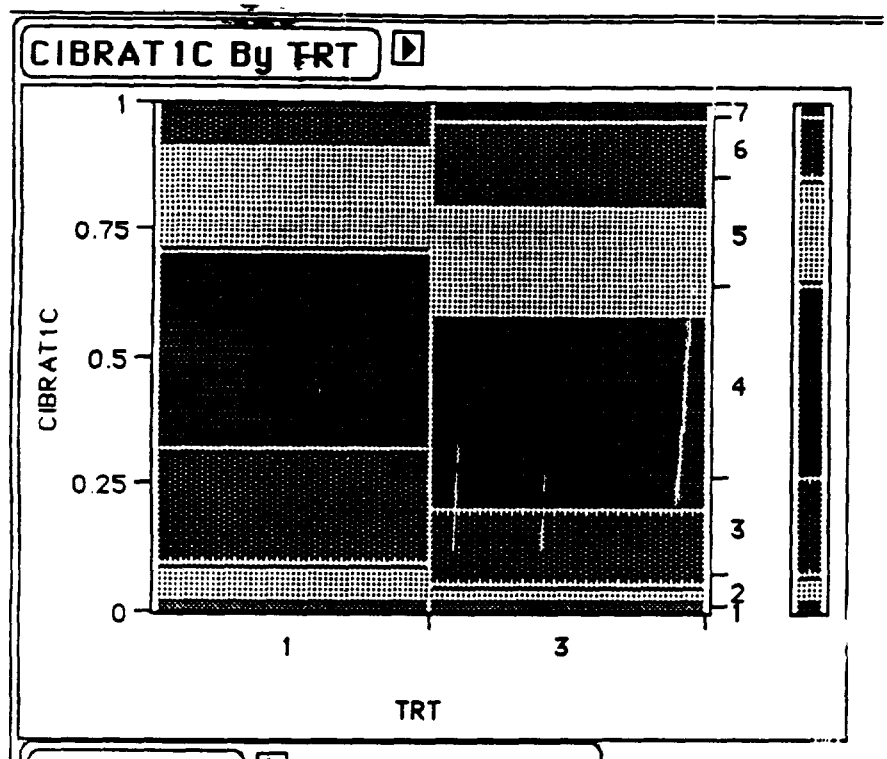
Figure 3a: CIBIC plus frequency distribution for studies 303 and 352 combined.
Treatment 1 = 6 to 12 mg/day, treatment 2 = 1 to 4 mg/day, and treatment 3 = placebo.



Crosstabs

CIBRAT1C	TRT 1	2	3
Col %			
1	4.28	0.76	0.51
2	10.86	7.61	3.79
3	17.76	19.54	14.90
4	31.91	33.76	36.62
5	21.71	23.86	27.02
6	10.86	11.68	12.63
7	2.63	2.79	4.55

Figure 3b: CIBIC plus frequency distribution for study 304.
Treatment 1 = 2 to 12 mg/day given bid and treatment 3 = placebo.



Crosstabs

TRT

CIBRAT1C	Col %	1	3
	1	1.12	1.12
	2	8.43	4.47
	3	23.03	14.53
	4	38.20	38.55
	5	20.79	21.23
	6	7.30	16.76
	7	1.12	3.35

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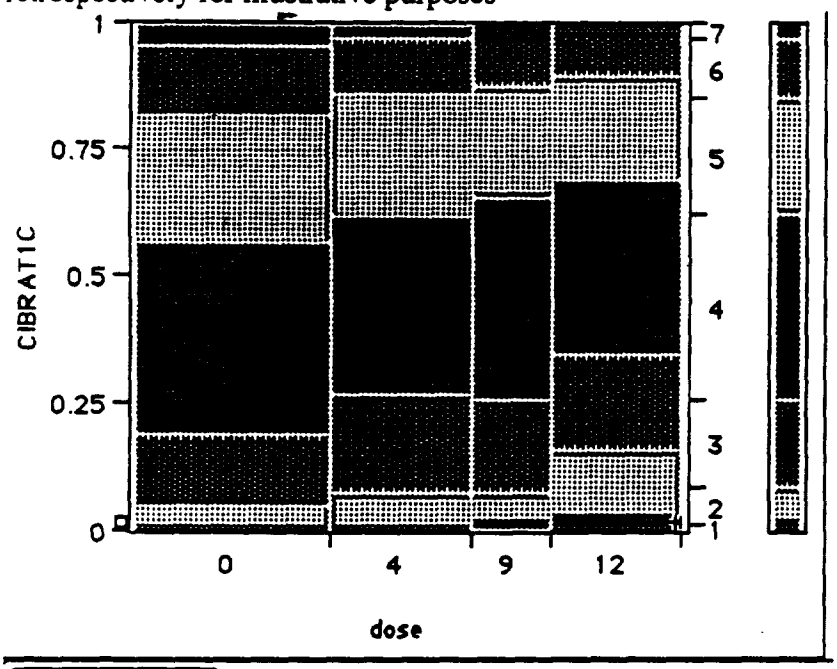
Figure 3c: CIBIC plus frequency distribution for studies 303, 304 and 352 combined. The dose groups 0=placebo, 4= 1 to 4 mg/day, 9 = 6 to 9 mg/day and 12 = > 9 mg/day were chosen retrospectively for illustrative purposes



Crosstabs

dose

CIBRATIC Col %	0	4	9	12
1	0.70	0.73	3.04	2.34
2	4.04	7.04	4.78	13.54
3	14.59	19.42	18.26	19.01
4	37.26	34.47	39.57	34.11
5	25.13	24.51	21.74	20.83
6	14.06	10.92	10.00	8.85
7	4.22	2.91	2.61	1.30

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Safety:

Conclusions: The safety data was primarily evaluated by Dr. Armando Oliva. Dr. Judy Racoosin and Dr. Greg Burkhart evaluated patient deaths and Dr. John Fenney evaluated ECG findings.

Dr. Oliva recommended against approval based on an increased in mortality seen in the controlled clinical trials and extension studies. Other safety issues found during the evaluation did not preclude approval.

Dr. Burkhart noted the following pieces of evidence that Exelon may be associated with increased mortality. First, the mortality rate in the RCT was about 3 fold higher in the drug group compared to placebo. There was some indication that deaths were occurring early in the RCT but this was not seen in the titration studies or in the extension studies. Second, there was an 8 fold increase in mortality when placebo patients entered the extension study. Third, for patients already exposed to drug in the RCT, there is a three fold increase mortality rate for those patients titrated to higher dose compared to those who stay on lower doses. While Dr. Burkhart notes that there was no clear clinical reason found to explain these findings it is difficult to dismiss them based on the possibility of the chance occurrence of only 1 death in the placebo group in the RCT. Dr. Burkhart recommends a large randomized study comparing the mortality rates of Aricept and Exelon. He also suggests that possible further evaluation of the deaths to provide a possible clinical explanation of the deaths including the possibility of weight change as a factor may also be helpful.

Safety overview:

The safety information provided in the NDA and safety update included serious AEs that occurred up to 3/31/97. A separate submission regarding deaths was provided May 13, 1998 and included an update for all deaths up to June 30, 1997.

Review sources: Dr. Oliva reviewed the safety data presented in section 2, the integrated summary of safety and the CRFs for patients who died. He also reviewed an analysis of the safety update sent 8/27/97. The cut off date for inclusion of safety data in the NDA was 7/31/96. The cut off date for deaths and serious events was 12/31/96. For the safety update submitted on 8/27/97, the cut off date was 3/31/97 for serious AEs. He also reviewed a separate report evaluating mortality with a cut off date of 6/30/97.

The NDA included 30 phase 1 studies evaluating pharmacology and pharmacokinetics. Twenty two studies evaluated the capsule formulation proposed for marketing. One study evaluated the PK of the iv formulation (72 subjects), five studies evaluated a transdermal formulation (292 subjects) and two studies evaluated an extended release formulation (40 subjects). Of the subjects in the phase 1 studies, 585 were exposed to the drug. Forty five subjects exposed to the drug for one week or more. The maximum exposure was for about 4 weeks in 11 AD patients. Healthy subjects were exposed to doses up to 4 mg/day and patients were exposed to doses up to 12 mg/day.

The 14 phase 2/3 trials are summarized in the following table.

Phase 2/3 studies				
Study	**Objective**	**location**	**N on placebo**	**N on Exelon**
B103	Tolerability/Dose finding	Europe/Canada	133	269
B104	Tolerability/Dose finding	Europe/Canada	24	90
B105	Tolerability/Dose finding	US	10	40
OR1	Tolerability/Dose finding	Japan	53	117
EP-11	Tolerability	Japan	0	71
VD-11	Tolerability	Japan	0	62
B901	Compassionate use	Europe	0	20
B902	Compassionate use	Europe	0	12
B354	Titration regimen	US	0	15
B355	Titration regimen	Eur/US/Australia	0	548
B303	Efficacy/safety	Eur/Can/US	239	486
B304	Efficacy/safety	Eur/S.Africa/Australia	117	229
B351	Efficacy/safety	US	173	529
B352	Efficacy/safety	US	235	464
Total			**984**	**2952**

Exposure: The sponsor provided an adequate size database to assess safety for the dose range proposed (up to 12 mg/day). This is based on ICH guidance that suggests 1500 patients exposed to drug with 300 to 600 exposed for 6 months or more and 100 exposed for 1 year or more. The following table summarizes the human exposure to the drug. The exact duration of exposure for each possible dose of drug was difficult to calculate because in the multidose studies, patients were titrated to either a fixed dose or to a dose range based on tolerability. To calculate exposure by dose, the mean daily dose for the patients was used and the dose exposure was divided into dose ranges.

Cumulative number of patients exposed to drug: Mean Daily dose (mg/day) by number of weeks						
Mean dose	Any	≤ 4	≤ 12	≤ 26	≤ 52	≤ 104
≤3 mg/day	535	451	378	128	4	0
>3 - 6 mg/day	1266	1178	971	513	74	30
>6 - 9 mg/day	586	584	456	248	33	0
>9 - 12 mg/day	619	619	619	360	109	13
Any dose	3006	2832	2424	1249	220	43

The cumulative number of patients exposed to any dose is summarized in the following table.

Cumulative number of patients exposed to any dose of drug in weeks						
Grouping	Any	= 4	= 12	= 26	= 52	=104
Phase 1 Total	585	11	0	0	0	0
Phase 1 Japanese	20	0	0	0	0	0
Phase 1 other	565	11	0	0	0	0
Phase 2 Total	648	609	503	157	95	43
Phase 2 Japanese	249	235	205	0	0	0
Phase 2 other	399	374	298	157	95	43
Phase 3 Total	2358	2223	1921	1092	125	0
Phase 3 Controlled	1696	1626	1388	989	0	0
Phase 3 Uncontrolled	869	799	711	197	0	0
Phase 2 + 3 Total	3006	2832	2424	1249	220	43
All Studies Total	3591	2863	2424	1249	220	43

Deaths:

In the randomized controlled trials, there was a three fold increase in the mortality rates for patients treated with Exelon compared to those treated with placebo. This increase in mortality was based on a small number of deaths. In the phase 3 placebo controlled studies, 7 of approximately 1700 patients died on drug (0.4%) and 1 of 850 patient died (0.1%) while on placebo. Since these patients died from a variety of causes common for this population, it was difficult to explain the finding and a chance occurrence was possible. The causes of all deaths will discussed later.

The deaths are summarized in the following table:

Summary of deaths in the 6 month phase 3 placebo controlled trials			
Study	Treatment group	Number of patients dying/enrolled	time to death
303	Placebo	0/238	n/a
	1 to 4 mg	0/242	n/a
	6 to 12 mg	2/242	30 and 103 days
304	Placebo	1/117	160 days
	2 to 12 mg	1/229	118 days
351	Placebo	0/171	n/a
	3 mg	2/175	14 and 99 days
	6 mg	1/176	47 days
	9 mg	0/177	none
352	Placebo	0/234	n/a
	1 to 4 mg	0/233	n/a
	6 to 12 mg	1/231	24 days

This finding differed from data seen with Aricept where the mortality rates in the controlled clinical trials were lower in the active group when compared to placebo. The mortality rate for all patients assigned to Exelon (deaths, approximate person time) was 8.6 (7, 811) compared to 2.9 (1, 350) for placebo. In the original NDA for Aricept, the studies were 3 and 6 months in duration. There

were 3 deaths from the 355 patients treated with placebo and 1 death in the 747 patients treated with drug. Mortality rates in person time were not calculated. In a more recently completed 6 month study, patients were randomized equally between doses of 0, 5 and 10 mg. There were 3 deaths in the 544 patients treated with Aricept. The drop out rate in this study was less than 20%. I estimated the mortality rate to be 12 to 14. There were two deaths in the 274 patients treated with placebo. I estimated the mortality rate to be around 16.

Because of this signal, additional analyses were performed. Dr. Racoosin performed a nested case control study of mortality with data from the phase 3 studies (phase 2 studies were not included because the necessary data was not available). All deaths that occurred within 30 days of the last dose of drug were included. For each of the 24 deaths, 5 other patients in the trial at risk were randomly selected as controls. Dr. Racoosin compared the mortality based on the doses received by the patients and the doses received based on dose and weight of the patient. When the last prescribed dose and last prescribed dose by weight were compared, there appeared to be an increase in the risk for death with higher doses. This finding was not confounded by age, gender or baseline weight. This was not found when comparing the highest prescribed dose (there was a trend for the highest prescribed dose by weight), highest actual dose or the cumulative dose. The results are summarized in the following table:

Odds ratio for nested case control study of mortality		
	last prescribed dose n=240 (95% confidence interval)	last prescribed dose/kg n=240 (95% confidence interval)
< 4 mg	1	1
4 to 6 mg/day	5.5 (0.6 - 49)	1.4 (0.3 - 7.2)
> 6 to 9 mg/day	5.3 (0.5 - 60)	3.5 (0.7 - 17)
> 9 mg/day	9.8 (0.99 - 97)	4.7 (0.95 - 23)

Because the signal for excessive deaths was in the high dose group and most of the experience with the high dose group was collected during the extension phase, we asked the sponsor to extend the mortality data base to June 30, 1997 to obtain more data about the long term experience with the drug. The sponsor provided the analyses and data sets in a submission received 5/13/98. This submission was reviewed by both Dr. Oliva and Dr. Burkhart. The analysis of this data confirmed that the vast amount of experience with the higher doses came from the extension part of the randomized controlled trials (RCT). Over 75% of the person time for the high dose was from the extension phase.

Evaluation of the safety data from the long term extension studies provided more evidence suggesting a drug related increase in mortality. There was an increase in mortality rates for the patients on placebo in the RCT after they were exposed to drug and there was an increase in mortality rates for patients titrated to higher doses of the drug in the long term extension. This information is summarized in the following table:

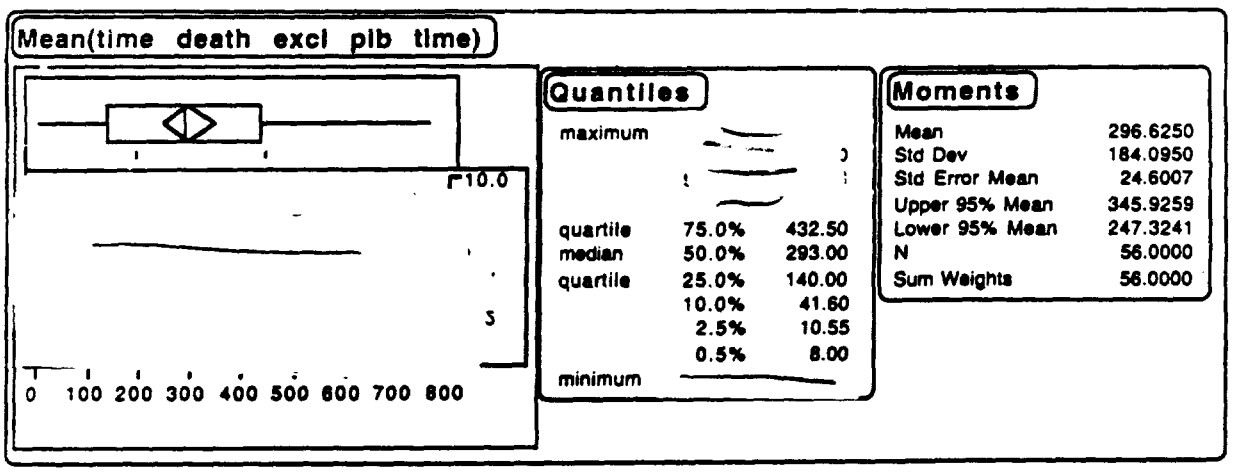
Mortality rates for patients in the long term extension trials			
Group	patient years	deaths	mortality rate per 1000 patient years
all patients - dose = 9 mg/day	997	12	12
- dose > 9 mg/day	991	23	23
patients on drug in the RCT - dose = 9 mg/day	628	5	8
- dose > 9 mg/day	719	17	23
patients on placebo in RCT - dose = 9 mg/day	370	7	19
- dose > 9 mg/day	272	6	22

When the sponsor analyzed the data, they concluded that the mortality was more dependent on time of exposure than on dose. They divided the mortality rates in duration of exposure to < 100 days and > 100 days and found that the mortality rate was greater in the time period of > 100 days. Since no deaths occurred in the first 60 days of the extension study, Dr. Burkhart divided time after the 60 days and found no increase in mortality over time of the extension study. The sponsor compared the mortality rates for patients assigned to = 4 mg with those treated with > 4 mg and found no difference. Dr. Burkhart compared the mortality rates for patients treated with doses of = 9 mg and > 9 mg and found a difference in mortality rates.

The sponsor argued that the mortality rates was unusually low for the placebo group and that this may explain the difference in the groups. Comparing the mortality rate of the placebo patients in the Exelon trial with the rates seen with Aricept, this may be true. It is possible that the placebo patients enrolled were healthier than those in the active group because of a failure in randomization. If this were true, then it would be expected that when the placebo patients were enrolled in the extension trial, they would have a lower mortality rate compared to patients in the active treatment group but the mortality rates for the placebo patients were the same or higher than the patients enrolled from the active treatment group (see the table on mortality rates above). If the placebo patients were healthier, the increase in mortality seen in the extension portion of the study could be related to drug exposure. The low rate in the placebo group could also be related to a chance occurrence rather than a problem with randomization. With the relatively small number of deaths reported, it would be difficult to determine if this were true.

These findings suggest that if the drug was associated with mortality in a dose related fashion, it was not occurring early in the course of exposure to the drug. The effect did not appear to be an acute effect from an increase in dosage but rather an effect from long term exposure to the drug at higher doses. This was supported by the findings in the titration study 355. In this study, patients were titrated more aggressively to higher doses. If the effect of the drug was more of an acute effect, an increase in mortality early in the titration would be expected. This was not the case as most of the deaths in the titration study were seen well after titration.

The data base showed that many of the deaths occurred later in the course of treatment. The mean time to death was almost 300 days. The following figure summarizes the time to death excluding time when the patients were on placebo during the double blind portion of the study.



The findings up to this point suggest that there may be an increase in mortality rate in patients exposed to high doses (> 9 mg/day) for longer periods of time. The mechanism could be related to events that occurred with time such as drug accumulation and chronic effects of adverse events such as weight loss. Since patients may develop other medical problems over time, a drug

interaction or interaction with intercurrent medical problems might not be seen until patients were on drug for a longer period of time.

To look for a clinical explanation for the increase in mortality, Dr. Oliva evaluated the causes of deaths. There were difficulties in evaluating the causes of death. Many times the exact cause of death was not known and many deaths were reported as "sudden deaths" without additional information given. The causes of deaths were those frequently found in this population of patients. Of the 57 deaths reported, 25 were classified as either sudden deaths or cardiac related deaths. In his review of the cases of sudden death, Dr. Oliva found that all but 4 had significant known cardiac conditions that could have contributed to the deaths. Other major causes were cancer (9), pneumonia (7), sepsis (5) and stroke (5). Dr. Oliva also evaluated the causes of death that occurred early in the course of exposure. 7 deaths occurred within 90 days of the patient entering the study. 3 were "caused" by cancer, 1 was related to a stroke and 3 were designated as sudden death. All of these patients were on doses of 1 to 9 mg of the drug at the time of death. This would explain why the mortality rates was lower in the RCT compared to the extension phase.

Evaluation of the safety data base found that there were problems with the tolerability of the drug. Tolerance to the drug appeared to be dose related and females appeared to be less tolerant to the drug. As with other drugs in this class, Exelon use was associated with nausea, vomiting and/or diarrhea in a significant number of patients with a higher incidence in patients exposed to higher doses. Most commonly the events responded to a decrease in dose but could be sufficiently severe to lead to discontinuation of treatment. Of patients exposed to drug, 6% discontinued because of nausea. Possibly related to the GI complaints, drug use was also associated with anorexia and weight loss, which in some patients was also sufficiently severe to lead to discontinuation (2% of patients on drug discontinued for anorexia).

Dr. Oliva evaluated the association of weight loss on the patients who died. In these analyses, he used the last available weight for the patients. Many times these weights were obtained weeks before the patient died. He found that patients who were on higher doses during the extension study and died had the highest percentage of weight change (a mean of about 6% loss from baseline). One possible explanation is that patients who die are going to lose weight prior to death but the data showed that patients who died on the lower doses did not have the weight change (1.5% loss) seen with the higher dose (6% loss). A second possibility is that time confound the findings since AD patients may lose weight over time. The patients who survived had a mean loss of about 1.5%. A third possibility is that patients who are on higher doses have weight loss since this is a reported adverse event with the drug and it appears to be dose related. The patients on high dose who survive had an mean weight loss of about 1.5%.

The clinical importance of this finding is not clear. It is possible that the weight loss led to a higher exposure to the drug. A higher exposure can lead to a greater incidence of various adverse events which could contribute to an increase in mortality. Serious adverse events and other abnormalities occurring at higher rates in patients on drug included syncope, orthostatic hypotension, and GI bleeding. PR prolongation was also seen. Weight loss could also be associated with an increase susceptibility to variety of adverse events which could explain why there were a variety of adverse events seen.

The tolerance to the drug also appeared to be related to the rate of the dose titration. In studies 351, 352 and 303, the starting dose was 1.5 to 2 mg/day and patients were titrated based on their tolerance to the maximum dose over 9 weeks. The maximum dose was 12 mg/day in studies 352 and 303 and 9 mg/day in study 351. After 14 weeks, about 60% of patients were able to achieve the highest dose. Fewer patients were able to achieve 12 mg/day in study 355 which employed a more rapid titration schedule. Patients were started on 3 mg/day with the dose increased by 3 mg/day each week. The results are summarized in the following table.

Ability to tolerate high doses with different titration regimens			
	Study 355	**Study 352**	**Study 351**
Max dose	12 mg/day	12 mg/day	9 mg/day
Starting dose	3 mg/day	2 mg	1.5 mg
Time to maximum dose	4 weeks	9 weeks	9 weeks
% on max dose after titration	27%	45%	57%
% on max dose after 14 weeks	24%	60%	60%
% on max dose after 26 weeks	n/a	55%	52%

There was an increase in mortality seen with in the faster titration study. The sponsor noted that the patients in this study were sicker than in the other studies though the evidence for this was not presented. The mean weight loss in the patients who died was higher than for patients who survived.

Serious Adverse events: In all of the studies, 13% of the patients assigned to placebo or drug reported at least one serious adverse event. The most common serious AE was overdose. This may be an artifact of the definition of overdose which included any patient taking even a single capsule more than directed. The serious AEs with a higher incidence in the active group compared to placebo are summarized in the following table.

Serious AEs occurring at a higher frequency in the active group compare to placebo					
SAE	Total	PBO		Exelon	
	(N= 2450)	N= 74	%	N= 1696	%
SYNCOPE	25	4	0.5	21	1.2
MYOCARDIAL INFARCTION	11	2	0.3	9	0.5
ACCIDENTAL TRAUMA	11	3	0.4	8	0.5
AGGRESSIVE REACTION	8	0	0.0	8	0.5
AGITATION	10	2	0.3	8	0.5
ANGINA PECTORIS	8	0	0.0	8	0.5
FIBRILLATION ATRIAL	8	1	0.1	7	0.4
VOMITING	8	1	0.1	7	0.4
GI HEMORRHAGE	6	1	0.1	5	0.3
NAUSEA	5	0	0.0	5	0.3
ABDOMINAL PAIN	4	0	0.0	4	0.2
MALAISE	4	0	0.0	4	0.2
CHEST PAIN	4	1	0.1	3	0.2
DEHYDRATION	3	0	0.0	3	0.2

Discontinuations: In all studies, the discontinuation rate was higher for patients on drug (26%) compare to placebo (15%). Most of the discontinuations were related to intolerance to the drug. The percentage of patients discontinuing for adverse events was higher for patients on drug (16%) compared to placebo (7%).

The rates increased with dose. Females were more likely to drop out for adverse events (21%) compared to males (12%). The common causes for discontinuations (> 1%) that were more common in the active group compared to placebo are summarized in the following table.