

Most common adverse events leading to discontinuation: % of patients discontinuing		
Adverse Event	Exelon (N=3006)	Placebo (N= 983)
Nausea	6%	1%
Vomiting	3%	<1%
Anorexia	2%	<1%
Dizziness	2%	1%

Other significant AEs:

Nausea and vomiting: In the phase 3 studies, 35% of the patients on drug noted nausea at least once compared to 12% of patients on placebo. Nausea was more common in the younger age group, in females and in patients taking doses > 9 mg/day. The incidence of nausea did not appear to be related to baseline MMSE score or duration of dementia.

Weight loss: In the phase 3 studies, patients on drug lost weight whereas patients on placebo gained weight. 13% of patients had a $\geq 7\%$ change from baseline compared to 5% of patients on placebo. 27% of females in the high dose group had weight loss compared to 17% rate in males. The weight loss did not appear to be related to the severity of dementia but possibly related to the presence of GI symptoms. See the discussion on deaths for more information on weight loss.

GI bleeding: 5 of 3006 patients on drug had a GI bleed compared to 1 of 983 on placebo. 11 of 3006 had melena compared to 1/983 on placebo.

Syncope: 1.2% of patients on drug had a syncopal spell compared to 0.5% of patients on placebo. The majority occurred in patients 78 to 85 years.

Adverse events: The most common adverse events (incidence $\geq 5\%$) in the phase 3 studies that are of greater incidence in the drug group compared to placebo are summarized in the following table. The rates were highest for females treated with dose > 9 mg/day.

Most common adverse events		
Adverse event	Exelon N=1913	PBO N= 891
NAUSEA	34.1%	19.2 %
VOMITING	21.1 %	10.1%
DIZZINESS	18.2 %	12.5 %
DIARRHEA	15.4 %	12.6 %
HEADACHE	15.1 %	13.0 %
ANOREXIA	11.9 %	6.5 %
ABDOMINAL PAIN	10.7 %	6.4 %
AGITATION	8.6 %	8.4 %
INSOMNIA	8.2 %	7.2 %
FATIGUE	7.7 %	4.0 %
DYSPEPSIA	7.3 %	5.3 %
SOMNOLENCE	5.1 %	2.9 %

ECG: ECGs were evaluated in the phase 3 studies. 20 patients from the active treatment group discontinued for ECG events including bradycardia, tachycardia, atrial fibrillation, bundle branch blocks, first degree heart block, PVCs, and tachycardia. A patient in study 353 developed complete heart block with a pulse of 30 and symptomatic dizziness after 1 year of treatment. The patient's

baseline ECG demonstrated a right bundle branch block and a left anterior hemiblock. A pacemaker was inserted and the patient continued on treatment. In a group analysis, there was a greater percentage of patients with PR interval prolongation (from < 260 msec to > 260 msec) on drug compared to placebo. One patient with a baseline PR interval of 260 msec developed a PR interval of 360 msec 2 weeks after initiation of treatment. The PR interval returned to 260 msec after discontinuation of the drug.

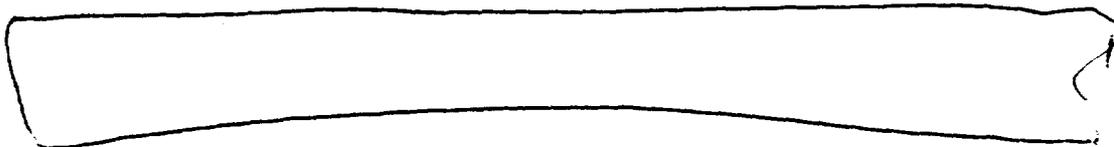
Vital signs: There were two patients discontinued from active treatment and none on placebo for hypertension. One occurred in a patient on drug for 11 weeks who had a temporary loss of consciousness, increased blood pressure and supraventricular arrhythmia and the other occurred in a patient 3 months and 4 months after treatment. Overall, no significant changes were noted for blood pressure, heart rate or temperature.

Labs: No clinically significant differences in the chemistry, hematology and/or urinalysis values were noted a comparison of the drug and placebo groups. The greatest difference was seen with the triglyceride levels which were reduced from baseline (-3.38) compared to patients on placebo (3.76). There were 9 patients who withdrew with abnormal labs. 5 had elevated LFTs, one had hyponatremia, one had a low platelet count, one had an increase in Alk Phos and one had an disorder of the spleen.

Long term safety: During the long term extension of the phase 3 studies, 7% of patients discontinued. 68% had adverse events that led to a decrease in dosage. 30% noted a decrease in weight. the most common AEs were nausea vomiting, dizziness, diarrhea, headache, anorexia, abdominal pain, accidental trauma, insomnia and agitation. The adverse events rates were higher in the older patients.

120 day safety update: The update was submitted on 8/27/97 with a cut off date of 3/31/97 for serious AEs. There was no change in the type of serious AEs and discontinuations from drop outs. An additional 7 deaths, 2 in patients on placebo, were included in the safety update. The frequency of serious AEs and AEs leading to discontinuation were increased as patients were exposed to drug in the long term extensions. The rates of common adverse events seen in the control trials were similar to those seen in the NDA submission.

Compliance:



**APPEARS THIS WAY
ON ORIGINAL**

Overall Conclusions:

The sponsor has provided adequate information to show that the drug is effective as a symptomatic treatment for Alzheimer's disease.

The efficacy appears to be dose related and confined to the highest doses studied, 10.5 to 12 mg/day.

In two of three studies evaluating doses of 1 to 4 mg/day, the treatment effect for both the ADAS-cog and CIBIC plus were not statistically distinguishable from placebo.

In the two studies evaluating the dose range of 6 to 12 mg/day, a statistically significant difference was noted in comparison with placebo suggesting the effective dose was somewhere between 6 and 12 mg/day.

In the fixed dose study, doses of 6 and 9 mg/day were significantly different from placebo for the ADAS-cog but not for the CIBIC plus. This would suggest that the effective dose is > 9 mg/day.

In a post hoc analysis of studies 303, 304 and 352, I looked at the difference in efficacy for three dose ranges; 1 to 4 mg/day, 6 to 9 mg/day and 10.5 to 12 mg/day. In all three studies, comparisons of the 10.5 to 12 mg/day group with placebo were associated with a p value of < 0.05 for both the ADAS-cog and CIBIC plus while comparisons between the placebo and other dose groups were associated with p values > 0.05 for the CIBIC plus.

The adverse effects of the drug also appear to be dose related. The most common side effects appear to be related to the cholinergic side effects. These effects interfere with the tolerability of the drug and worsen with increasing doses and more rapid titration. Some of the more common severe adverse events were nausea/vomiting, diarrhea and anorexia and weight loss also worsen with dose. Other events occurring at a higher frequency in drug group was prolongation of the PR interval.

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. While the mortality rates for patients on Exelon was higher than for patients on placebo, the number of deaths that this was based on was small (8 deaths). There were other factors in the data base that suggested a possible drug related increase in mortality including an increase in mortality for placebo patients when they were exposed to drug in the long term extension studies, an increase in mortality for patients more rapidly titrated, and an increase in mortality for patients titrated to higher doses of the drug in the long term extension. These findings while suggesting the possibility of increased mortality do not prove this point. The findings suggest that the increase in mortality is not an acute event and occurs after patients have been exposed to higher doses of the drug for longer periods of time.

A search for a clinical explanation for differences in mortality rates has not provided a reason for the drug to lead to an increase in mortality. The causes for death varied but most deaths were classified as sudden deaths. Dr. Oliva reviewed the cases of sudden death and found that all but 4 of the 17 patients with sudden death had significant cardiac conditions that could have contributed to the deaths. There was some evidence that raise the possibility of weight change being associated with the increase in dose and increase in mortality.

There are many difficulties in attempting to assess mortality in these studies. The use of dose titration and dose ranges rather than fixed dose makes it difficult to assess the drug relatedness of the effect on mortality. There is no clear clinical explanation for the deaths to be drug related. The population being studied is elderly and unlike a study involving a young population, deaths are expected to occur. Finding patients dying from an unexpected cause or finding a high incidence of

deaths from a particular cause would help to implicate the drug as causing these deaths. The causes of death in this study are those expected for elderly patients with AD. The methods used by Dr. Burkhart and Dr. Paccosin are helpful for detecting signals but do not provide the evidence necessary to show that the drug is causing patients to die. The method of comparing different dosage groups retrospectively without randomization can not eliminate other factors that may be contributing to the deaths. Finding a variable associated with increased doses could explain the deaths and could lead to a method of monitoring patients at increase risk.

Recommendations:

Alzheimer's disease is a serious condition with few options for treatment available. Currently, there are two drugs, Cognex and Aricept, approved for the symptomatic treatment of Alzheimer's disease. These drugs, like Exelon, presumably work by inhibiting cholinesterase. Like, Exelon, these drugs have been shown in efficacy studies in patients with mild to moderate AD to produce a relatively small change on the measures of cognitive performance and global functioning compared to patients on placebo. These drugs, like Exelon, have adverse events, consistent with its cholinergic properties.

Our review of the safety data shows a signal of increased mortality being associated with Exelon. The signal includes:

- a three fold increase in mortality in patients exposed to the drug compared to those treated with placebo in the phase 3 randomized controlled trials,
- a three fold increase in mortality in patients previously treated with Exelon in the randomized control trials who were exposed to high doses of the drug (> 9 mg/day) in the long term extension when compared to those exposed to lower doses (≤ 9 mg/day) and
- an eight fold increase mortality rate in placebo patients after being exposed to drug in the extension studies

This signal is not definitive. There were many factors making it difficult to clinically assess the cause of the differences in mortality seen in these studies. Use of dose titration and dose ranges rather than fixed doses makes it difficult to assess effects that are dose related. Incomplete information on the cause of death makes it difficult to accurately assign diagnoses. An elderly population where deaths are expected to occur makes it difficult to isolate those deaths that could be drug related.

Because of the potential risk of death without a demonstrated additional benefit to already marketed cholinesterase inhibitors, I cannot recommend that Exelon, the third cholinesterase inhibitor for the symptomatic treatment of Alzheimer's disease, be approved for marketing at this time. A recommendation of approval would be based on either being able to identify or monitor patients at risk, providing results from additional studies showing that mortality is not increased or demonstrating a substantial benefit of Exelon over already available treatments.

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Randy Levin, M.D.
Neurology Team Leader
rl/May 30, 1998

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: **July 2, 1998**

FROM: **Paul Leber, M.D.**
 Director,
 Division of Neuropharmacological Drug Products
 HFD-120

SUBJECT: **Not Approvable Action Recommendation:**
 NDA 20-823 Exelon(rivastigmine tartrate)

TO: **File NDA 20-823**
 &
 Robert Temple, M.D.
 Director, ODE1

This memorandum conveys, and explains the basis for, my recommendation that Novartis Pharmaceuticals Corporation's NDA 20-823 for Exelon (rivastigmine tartrate) capsules be declared not approvable.

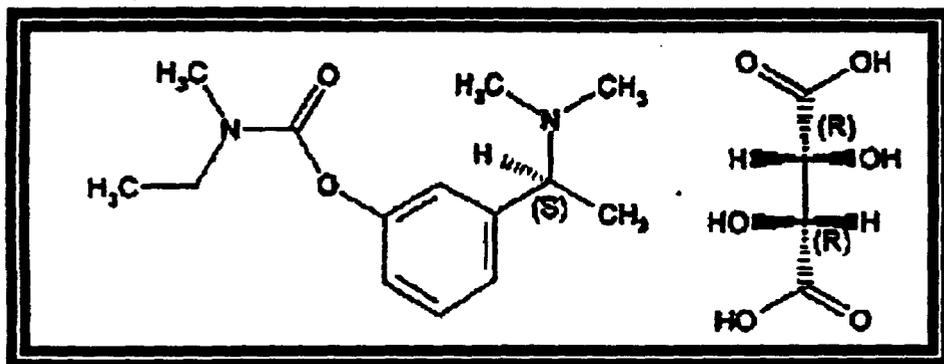
The NDA was submitted on 4/7/98; because of the submission of a major amendment on 3/9/98, the PDUFA goal date was extended to 7/7/98. Another major amendment was submitted on May 12, 1998, but policy does not permit any further change in the PDUFA goal date.

The Neurology Team Leader for the application was Dr. Randy Levin (memoranda of 1/23/98, and 6/16/98). The primary clinical effectiveness review was also conducted by Dr. Levin (11/30/97). The statistical consultative efficacy review was carried out by Dr. Hoberman (2/18/98). There are several clinical safety reviews. Dr. Armando Oliva, a neurologist, is the primary clinical safety reviewer assigned to the application (review documents dated 8/5/97, 3/10/98[joint effort with Drs. Racoosin and Feeney] and 5/28/98). Consultative reviews intended to assess what role, if any, Exelon exposure played in the deaths reported were conducted by Dr. Judith Racoosin (1/22/98) and Dr. Gregory Burkhart, the Division's Team Leader for Safety (documents of 2/6/98, 2/19/98, 3/9/98, 3/26/98, 5/28/98 and 6/12/98[metrifonate reference])

The pharmtox review was conducted by Dr. Rosloff; both he, and his team

leader, Dr. Fitzgerald, find the application approvable.

Drug substance and product



Rivastigmine hydrogen tartrate

(S)-Rivastigmine is a member of a class of carbamate esters that are substrates for acetylcholinesterase (AChase). Rivastigmine, like the best known example of the centrally active members of this drug class, physostigmine, readily penetrates the so-called blood brain barrier. Carbamate esters are effective inhibitors because they form very stable complexes with the AChase active site compared to acetylcholine (hours vs microseconds). The $t_{1/2}$ for hydrolysis and reactivation of the enzyme bound rivastigmine is more than 24 hours, for example.

Exelon is supplied as capsules of several strengths (3.0 mg, 4.5 mg and 6.0 mg). Labeling submitted with the NDA recommends that treatment be initiated at 3 mg a day (bid schedule), and titrated, over a period of weeks, tolerability of untoward effects permitting, to a maximum of 12 mg a day (bid dosing).

ADME

The information cited is derived from the review conducted by Dr. S Ibrahim (12/15/97, endorsed by Dr. Sahajwalla, 12/15/97); for the most part, the data is derived from small clinical studies and, as a result has

somewhat ~~limited~~ generalizability.

Although a mass balance study indicates that essentially all of an orally administered dose of 1 to 2.5 mg is absorbed by healthy volunteers, the absolute oral bioavailability of the parent is only 35%. Bioavailability, however, is affected by food which delays absorption but increases the total AUC.(30%)

Rivastigmine has a volume distribution of more than 5 L/kg; in vitro studies with human plasma find about 40% protein binding over the range of 1 to 400 ng/mL, which is said to cover the entire expected therapeutic plasma concentration range.

Metabolism of rivastigmine takes place in the gut wall, liver and plasma. There is a first pass effect that may be saturable. The primary degradation pathway proceeds via enzymatic decarbamylation to a phenolic metabolite (ZNS 114-666); this is subsequently conjugated (sulfate) and/or N-demethylated and then conjugated.

P450 enzymes are said, based on in vitro interaction studies, to have no important role on the elimination of rivastigmine and the latter has no effect on the metabolism of substrates via common CYP 450 systems.

By test of AUC, exposure to ZNS 114-666 is more than 6 fold that of rivastigmine; its pharmacologic activity has not been characterized, however. A logistic regression analysis, however, found a "significant" association between ZNS 114-666 and GI adverse events (Ibrahim p xiv)

Small studies in healthy male volunteers indicate that elimination of rivastigmine occurs entirely through the kidneys and only after it is converted to one or more of its metabolites. The elimination half-life is about 1.6 hours and said to be independent of dose (N.B. because of the stability of the enzyme-substrate complex, the biological effects of rivastigmine would be expected to persist longer than its elimination half-life would predict.

Age (> 60 yo vs young volunteers) is claimed to have a modest effect (30% reduction) on oral clearance.

The effects of Liver disease are not so clear--oral clearance was decreased by 60% in subjects with cirrhosis, but it is also asserted that the half-life does not differ among normals and hepatically impaired subjects.

Renal disease impairs elimination, but there are "no obvious correlations observed between GFR and any of the PK parameters of the drug."
(Ibrahim)

A study in Alzheimer's patients is said to show a reduction in clearance compared to normals, but the review does not make clear to what extent, if any, age was taken into account.

Effectiveness in Use

Dr. Levin's review of 11/30/97 and Dr. Hoberman's of 2/20/98 together provide a thorough review of the sponsor's 8 controlled trials, 4 of which are reasonably considered adequate and well controlled studies that can, by design and conduct, evaluate the effectiveness in use of an antimentia drug product. Among these 4 studies (B303, B304, B351 and B352), the firm identifies 2, **Studies B303** (26 week long, N of 722, 2 dose range vs. placebo parallel comparison) and **B352** (26 week long, N of 698 2 dose range vs. placebo parallel comparison) as "pivotal." and **Study B351** as **supportive**¹ of its claims.

¹ Although Study B351 detects statistically significant drug placebo differences in the change from baseline in ADAScog total scores (for patients randomized to 6 mg and 9 mg, but not 3 mg, daily doses of rivastigmine), there are no significant between group differences on the CIBIC plus. The study, therefore fails to provide evidence satisfying the dual outcome assessment criteria regularly used by the agency to weigh the evidence of efficacy of putative anti-dementia drug treatments. Accordingly, the study is, at best, supportive.

From another perspective, these results may be seen to support to Dr. Levin's view that rivastigmine is only reliably effective at doses above 9 mg a day. Admittedly, although I share his judgment, arguments of this kind are not especially compelling. The lack of statistical significance is a function of many factors, including, in particular, sample size. Accordingly, if the sponsor had elected to employ even more than 175 to 180 subjects per treatment arm that it did, it could

Risk Set 3: Case - patient #6
Potential controls - none available

Once a risk set was determined for each case based on observation days, potential controls were identified that matched the case on study number and origin of patient (domestic vs. foreign). Among the patients that matched the case, five controls were randomly selected. This same process was utilized for each case. Cases occurring later in time could function as controls for cases occurring earlier in time.

8.2.4.5 Covariate Collection

For each case and control, patient dosage data was extracted from the DAR data files provided by the sponsor. For studies 304, 305, 353, and 355, the DAR files from the 120 day safety update were used since they contained more complete data on the patients in those trials. The following dosage variables were determined: highest prescribed dose (HPD), highest actual dose (HAD), last prescribed dose (LPD), last actual dose (LAD), days since last dose change (DSLDC), cumulative actual dose (CAD), cumulative prescribed dose (CPD), difference between cumulative actual dose and cumulative prescribed dose (DIFF), cumulative dose at the last prescribed dose (CDLPD), cumulative dose at the last actual dose (CDLAD). Variables pertaining to HPD, LPD, and CAD were also calculated based on the patient's baseline weight (in kg) resulting in the variables HPD/kg, LPD/kg, and CAD/kg. The above variables were examined as continuous and categorical variables. Four categories were determined for each variable based on quartile distribution with the exception of HFD, HAD, LPD, and LAD. For the latter variables the categories were defined based on the approximate range of treatments in the RCTs (< 4 mg, 4-6 mg, 6.1-9mg, >9 mg). LPD, LPD/kg, HPD, and HPD/kg were also tested as continuous variables.

8.2.4.6 Analysis

Conditional logistic regression was used to perform conditional logistic regression to analyze the risk sets (a "matched analysis").

To rule out the possibility of the results being dependent on sampling, the analysis was repeated using a different set of 5 randomly selected controls for each case. For this analysis only the variables LPD and LPD/kg were collected.

8.2.4.7 Results

Table 11 summarizes the odds ratios by category for the variables LPDcat and LPDkgcat. The elevated risk of death associated with higher doses observed for these two variables with the first set of 120 controls are confirmed by the second set. When LPD and LPDkg were tested as continuous variables, the trend of elevated risk of death with higher Exelon doses was corroborated (p-values 0.063 and 0.005, respectively). The relationship between each of these variables and mortality was not confounded by age, gender, or baseline weight.

Both cases and controls were taking the last prescribed dose for a median of 50 days. There was no relationship between the number of days since last dose change and mortality. A trend towards elevated risk of mortality with increasing quartile of HPDkgcat (the categorical variable for HPD/kg) was also observed, but not for HPDcat or HADcat.

Variables related to cumulative exposure to Exelon (CPD, CAD, DIFF, CPDL, CADLD) showed no consistent relationship with mortality.

Table 11: Odds Ratios for Nested Case Control Study of Exelon Mortality

dose	LPDcat			quartiles	LPDkgcat		
	control set #1 (n=120) OR (95% CI)	control set #2 (n=120) OR (95% CI)	combined (n=240) OR (95% CI)		control set #1 (n=120) OR (95% CI)	control set #2 (n=120) OR (95% CI)	combined (n=240) OR (95% CI)
<4mg	1	1	1	1	1	1	1
4-6 mg	6.6 (0.7 - 62)	4.1 (0.5 - 36)	5.5 (0.6 - 49)	2	2 (0.3 - 13)	1.4 (0.3 - 7)	1.4 (0.3 - 7.2)
6.1-9 mg	5.4 (0.4-70)	5.5 (0.5 - 36)	5.3 (0.5 - 60)	3	3.9 (0.6 - 25)	2.9 (0.6 - 13)	3.5 (0.7 - 17)
>9 mg	11.5 (1.0 - 128.1)	8.1 (0.8-78)	9.8 (0.99 - 97)	4	6.0 (0.9 - 40)	4.8 (1.0 - 24)	4.7 (0.95 - 23)

(LPD= last prescribed dose, LPDkg= last prescribed dose per kg)

8.2.4.8 Discussion

This nested case control study of mortality in the Exelon NDA suggests that mortality is related to the patient's last prescribed dose, with patients receiving the highest doses having a ten-fold higher risk of mortality as compared with patients receiving the lowest doses. A dose-response relationship for mortality was still observed after controlling for baseline weight.

The confirmation of the dose-response relationship between Exelon dose and mortality with a second set of controls makes it unlikely that the result was due to sampling. One limitation of the study is the small number of controls matched to each patient. The small number of controls reduced the precision of the estimates.

Because patients were not randomized to final dose, it is possible that patients who were more likely to die received higher doses. However, without knowing a patient's comorbidities during their drug exposure (e.g. concurrent cardiovascular conditions, exposure to certain medications, drug-related weight loss), this explanation can not be proved or disproved.

At this point we will ask the sponsor to investigate this safety signal more thoroughly. There are additional deaths in the phase 3 studies which were not included in the data file from the sponsor which need to be included in any further study of mortality. Furthermore, the sponsor needs to evaluate covariates which may modify the relationship between Exelon dose and death, such as pre-existing cardiovascular disease, the use of cardiac medications, or substantial weight loss during drug treatment.

8.2.5 Summary

A total of 49 patients died during the Exelon clinical development program. The overall mortality rates in controlled clinical trials were 0.5% for Exelon and 0.2-0.3% for placebo. These are quite low for both groups and the differences seen are not statistically significant.

However, across all studies, and normalizing for exposure times, the Exelon treated group had a mortality rate of 30 per 1000 patient-years of exposures, compared to 5-7 per 1000 patient-years for placebo. Although many of the deaths cannot be reasonably attributed to the drug, others are less clear, I have identified and discussed 15 cases in which the drug may have played a role.

Results of the nested case control study performed by Dr. Judy Racoosin suggests that mortality risk in phase 3 trials was associated with the last dose of Exelon prescribed. Patients receiving high dose Exelon (>9-12mg) has a 10 fold risk of death compared with those receiving low dose (<4mg). This important safety signal requires further exploration by the sponsor using additional data available to them.

8.3 Serious Adverse Events

In all therapeutic studies (N=3886), 13% of patients reported at least one SAE (13% for both drug and placebo, Table 12). In Phase 3 controlled studies (N=2459), 15% of patients reported at least one SAE (14% drug vs. 16% placebo). A relationship between treatment group and incidence of SAE is not apparent. There were no differences in SAE incidence between males and females, with the exception of females exposed to >9-12 mg. In this subgroup, the incidence of SAE's was 19% vs. 15% for males in the same high dose group. There were no difference among races, although Caucasian and Asian placebo patients had higher SAE rates than those on drug.

Since the overall incidence of SAE's were comparable between Exelon and placebo treated patients, there is little signal to suggest that Exelon may be causing serious adverse events. I therefore limit the discussion of the individual serious adverse events to those seen in controlled phase 3 trials, and mention SAE's occurring in other trials when clinically relevant. A line listing of all serious adverse events in phase 2/3 trials is located in Appendix D, page 136.

Table 12: Patients with Serious Adverse Events, All Therapeutic Trials

Treatment	N	SAE	(%)
Placebo	983	124	13
Exelon	3006	389	13
Total	3886	511	13

FDA Table 13 lists the most common SAE's in phase 3 controlled trials (occurring with an incidence of $\geq 0.2\%$ in the Exelon treated patients). The most commonly reported SAE was Overdose. This is, in part, due to the methods employed in reporting overdoses. Any instance in which a patient took more study medication (even one more capsule) than was prescribed was considered and reported as an overdose. All known overdoses were reported as an SAE even though there may not have been any associated adverse events. Overdoses are discussed in more detail in section 8.14 "Overdose", page 93. All overdoses were small (10.5 mg or less) and clinically insignificant.

Table 13: SAE's in Phase 3 Controlled Trials

SAE	Total (N= 2450)	PBO N=74	(%)	Exelon N=1696	(%)
OVERDOSE	126	50	6.5	76	4.5
SYNCOPE	25	4	0.5	21	1.2
PROCEDURE NOS	25	8	1.0	17	1.0
SURGERY	24	9	1.2	15	0.9
CEREBROVASCULAR DISORDER	21	7	0.9	14	0.8
BONE FRACTURE	21	8	1.0	13	0.8
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
CONFUSION	10	3	0.4	7	0.4
FIBRILLATION ATRIAL	8	1	0.1	7	0.4
VOMITING	8	1	0.1	7	0.4
PNEUMONIA	10	4	0.5	6	0.4
GI HAEMORRHAGE	6	1	0.1	5	0.3
NAUSEA	5	0	0.0	5	0.3
SKIN NEOPLASM MALIGNANT	9	4	0.5	5	0.3
ABDOMINAL PAIN	4	0	0.0	4	0.2

BASAL CELL CARCINOMA	8	4	0.5	4	0.2
CARCINOMA	7	3	0.4	4	0.2
CARDIAC FAILURE	6	2	0.3	4	0.2
CONVULSIONS	6	2	0.3	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

Syncope occurred at a higher frequency in the Exelon group compared to placebo. (1.2% vs. 0.5%). All other SAE's were infrequent and/or occurred at an incidence similar to placebo. A brief discussion of the clinically significant SAE's is included below.

8.3.1 Syncope

There were 25 cases of syncope. As previously stated, syncope was more common with Exelon treatment, and it 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 the 76-85 years. 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 9-12 mg. The actual cause of syncope in these patients was not determined conclusively.

8.3.2 Other Cardiovascular Events

Myocardial Infarction rates were low and comparable in the two groups (0.5% for Exelon vs. 0.3% for placebo), however 8 patients (0.5%) on drug, vs. 0 patients on placebo reported angina. Atrial fibrillation was also higher in the Exelon group (0.4% vs. 0.1%) but numbers were small. Cardiac failure rates were comparable in the two groups (0.2% vs. 0.3%). The majority of patients with other cardiovascular SAE's were 66-75 years old. All but three patients had histories of cardiac disorders that reasonably explained the development of the SAE's.

8.3.3 Gastrointestinal Hemorrhage

Six patients (5 drug, 1 placebo) had gastrointestinal hemorrhage. The incidence of these events did not 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.

8.3.4 Cerebrovascular Disorders

These disorders include stroke, and intracranial hemorrhages. The incidences were comparable in the two treatment groups (0.8% for Exelon, vs. 0.9% for placebo). No relationship between incidence of these events and dose was evident for either sex. They tended to occur more frequently in 66-75 age group, and the 76-85 group had the second highest incidence.

8.3.5 SAE in Clinical Pharmacology Studies.

Only one SAE was reported in these studies, that of a subject hospitalized with a bout of bronchopneumonia. This was unlikely due to Exelon treatment.

8.3.6 Summary of SAE's

The incidence of SAE's in Exelon and placebo treated patients were the same, 13%. Overdoses were the most common SAE's reported. This is due to the methods employed in

reporting overdoses – all overdoses, no matter how small, were automatically reported as an SAE. All overdoses were small (10.5 mg or less) and clinically insignificant.

Syncope was the most common clinically significant SAE reported. It occurred with a higher frequency in the Exelon treated patients (1.2% vs. 0.5%). This may be related to the parasympathetic cardiovascular effects of the drug, but this explanation remains hypothetical.

In most cases, SAE's could be attributed to underlying medical conditions and not to Exelon administration.

8.4 Dropouts and "Other Significant Adverse Events"

8.4.1 Methods

Patients who discontinued early from clinical trials are grouped according to the maximum dose range achieved, with an emphasis on comparing all Exelon patients, and patients exposed to high doses (≥ 9 -12mg) vs. placebo. In other instances, patients are subdivided into dose groupings (placebo, ≤ 3 mg/day, >3 - 6 mg/day, >6 - 9 mg/day, >9 -12 mg/day). In the All Therapeutic Studies grouping, where data from the phase 3 placebo controlled studies and the extension studies have been combined, the maximum prescribed dose is that prescribed over a patient's total exposure.

The reasons for discontinuation were categorized as follows:

- adverse experiences
- death
- withdrawal of consent
- protocol violation
- treatment failure
- failure to return for visits
- other
- current medical conditions

All information on discontinuation is based on data from the End of Study CRF. All patients were assigned only one reason for discontinuation, multiple reasons were not permitted. The category "current medical condition" was used only in non-Japanese phase 2 studies. It does not occur anywhere else.

There were patients who were randomized but for whom there was no documentation of exposure to study medication. Because these patients had no safety or exposure data, they were excluded from the safety database. However, these patients were included in the disposition tables in the final study reports (FSR) as these tables were based on randomization. Thus, the ISS rate of completion are slightly higher than those in the individual FSR's since patients who failed to return for visits were excluded from the denominator in the ISS but included in the denominators for the FSR's.

The discontinuation category "death" only includes deaths that were actually the cause of discontinuation. Fatalities occurring after discontinuation from the study are not included here.

There were some patients who discontinued from a phase 3 controlled study, who subsequently returned to participate in an extension. These are discussed separately. Some of these patients later discontinued from the extension study; therefore, there are disposition data for two

endpoints. In order to prevent these patients from being counted twice, only the disposition data for the extension study are included in the tables, whereas placebo treated patients who discontinued from a core and an extension study would have their disposition data displayed twice, once in the placebo group for the core study, and once in the Exelon group for the extension.

Furthermore, patients who completed a phase 3 controlled study but decided not to enter in an extension are also discussed.

8.4.2 Overall Profile of Dropouts

Sponsor Table 14 and Table 15 show that, overall, more placebo-treated patients (85%) than Exelon-treated patients (74%) completed these studies. The numbers were similar in the phase 3 controlled trials (which comprised approximately 2/3 of the all therapeutics trials population). This means that 26% of all Exelon treated patients discontinued early, in contrast to 15% for placebo patients.

Table 14: Patient Disposition: All Therapeutic Studies

	Exelon (N=3006)	Placebo (N=983)	Total (N=3886)
Completed	2226 (74%)	832 (85%)	2958 (76%)
Discontinued Total	780 (26%)	151 (15%)	928 (24%)
Adverse Experience	469 (16%)	68 (7%)	536 (14%)
--Adverse Event	463 (15%)	67 (7%)	529 (14%)
--ECG	4 (<1%)	1 (<1%)	5 (<1%)
--Vital Signs	1 (<1%)	0	1 (<1%)
Death	8 (<1%)	0	8 (<1%)
Withdrawal of Consent	140 (5%)	29 (3%)	169 (4%)
Protocol Violation	26 (1%)	8 (1%)	34 (1%)
Treatment Failure	13 (<1%)	7 (1%)	20 (1%)
Failure to Return	36 (1%)	7 (1%)	42 (1%)
Other	83 (3%)	31 (3%)	113 (3%)
Current Medical Condition	5 (<1%)	1 (<1%)	6 (<1%)

Table 15: Patients who completed Studies

Study Groupings	Exelon (n%)	>9- 12mg/day (n%)	Placebo (n%)
All Therapeutic Studies	2226 (74%)	867 (85%)	832 (85%)
Phase 3 Controlled Studies	1246 (73%)	411 (86%)	637 (83%)
Phase 3 Controlled Studies - N. American	797 (69%)	177 (82%)	393 (80%)
Phase 3 Controlled Studies - Non- N. Am.	449 (82%)	234 (90%)	244 (89%)
Phase 3 Uncontrolled Extension Studies	244 (79%)	174 (82%)	NA
Phase 3 Uncontrolled Titration Studies	426 (76%)	238 (90%)	NA
Phase 2 Non- Japanese Studies	295 (74%)	NA	148 (89%)
Phase 2 Japanese Studies	212 (85%)	NA	47 (89%)

Sponsor Table 16 shows that Exelon treated patients discontinued therapy due to an adverse experience at a more than twice that of placebo treated patients (16% vs. 7%, respectively). Similar numbers were seen in the phase 3 controlled trials.

Table 16: Discontinuations due to Adverse Experiences

Study Group	Exelon (n%)	>9- 12 mg/ day (n%)	Placebo (n%)
All Therapeutic Studies	469 (16%)	91 (9%)	68 (7%)
Phase 3 Controlled Studies	296 (17%)	44 (9%)	60 (8%)
Phase 3 Controlled Studies - N. American	228 (20%)	26 (12%)	47 (10%)
Phase 3 Controlled Studies - Non- N. American	68 (12%)	18 (7%)	13 (5%)
Phase 3 Uncontrolled Extension Studies	34 (11%)	16 (8%)	NA
Phase 3 Uncontrolled Titration Studies	82 (15%)	13 (5%)	NA
Phase 2 Non- Japanese Studies	53 (13%)	-	6
Phase 2 Japanese Studies	13 (5%)	-	2

There were eight deaths which resulted in patient discontinuations in 3,886 patients. These are included and discussed in section 8.2, ("Deaths"), page 30.

Analysis of patients according to maximum prescribed dose showed that the percentages of patients in the >9-12 mg and placebo groups who completed the study were the same (85% for both), however this dose group is not a randomized sample. The incidence of AE's was 9% and 7%, respectively, suggesting that, if a patient was able to reach and tolerate a high dose, their risk of discontinuation was no greater than placebo.

Another analysis, comparing drop-out rates according to overlapping dose ranges, has the advantage of describing the drop out rate of the higher dose groups while including those who dropped out at lower doses. Table 17 groups patients into overlapping dose ranges (≤ 12 mg, ≤ 9 mg, ≤ 6 mg, ≤ 3 mg). This shows that there is a progressive, dose dependent increase in the cumulative incidence of discontinuations that extended from 4.8% in the ≤ 3 mg range to 25.9% in the ≤ 12 mg dose range in All Therapeutic Studies. A similar pattern occurs for AE associated drop-outs (Table 18).

Table 17: Discontinuations, by Overlapping Dose Ranges

	≤ 12 mg (%)	≤ 9 mg (%)	≤ 6 mg (%)	≤ 3 mg (%)	PBO (%)
All Therapeutic Studies	780 (25.9%)	621 (20.7%)	438 (14.6%)	145 (4.8%)	151 (15.4%)
Phase 3 Controlled Studies	450 (26.5%)	385 (22.7%)	260 (15.3%)	93 (5.5%)	126 (16.5%)
Phase 3 Controlled Studies - N. American	354 (30.8%)	316 (27.5%)	225 (19.5%)	82 (7.1%)	96 (19.6%)
Phase 3 Controlled Studies - Non-N. Am.	96 (17.6%)	69 (12.7%)	35 (6.4%)	11 (2.0%)	30 (10.9%)
Phase 3 Uncontrolled Extension Studies	66 (21.3%)	29 (9.4%)	20 (6.5%)	2 (0.6%)	NA
Phase 3 Uncontrolled Titration Studies	134 (24.0%)	106 (19.0%)	65 (11.6%)	18 (3.2%)	NA

Table 18: Discontinuations Due to Adverse Events, by Overlapping Dose Ranges

	≤ 12 mg (%)	≤ 9 mg (%)	≤ 6 mg (%)	≤ 3 mg (%)	PBO (%)
All Therapeutic Studies	469 (15.6%)	378 (12.6%)	251 (8.3%)	65 (2.2%)	68 (6.9%)
Phase 3 Controlled Studies	296 (17.5%)	252 (14.9%)	160 (9.4%)	44 (2.6%)	60 (7.9%)
Phase 3 Controlled Studies - N. American	228 (19.8%)	202 (17.5%)	136 (11.8%)	39 (3.4%)	47 (9.6%)
Phase 3 Controlled Studies - Non- N. American	68 (12.5%)	50 (9.2%)	24 (4.4%)	5 (0.9%)	13 (4.7%)

Phase 3 Uncontrolled Extension Studies	34 (11.0%)	18 (5.8%)	13 (4.2%)	2 (0.6%)	NA
Phase 3 Uncontrolled Titration Studies	83 (14.8%)	69 (12.3%)	42 (7.5%)	13 (2.3%)	NA

In the phase 3 controlled studies, 69% (1171) of the 1696 Exelon treated patients and 79% (603) of the 763 placebo treated patients entered the extension studies. Approximately 90% had completed the double-blind studies. Of the patients who had been discontinued from the double-blind studies, 11% of Exelon-treated and 15% of placebo-treated patients enrolled in open label extensions. For these previously discontinued patients, the most common reason given for dropping out of the double-blind study was "other." Examples of "other" reasons were "caregiver ill," "investigator feels caregiver is unreliable," and "primary care physician wants patient to try another drug." Adverse experiences accounted for discontinuation from the double-blind studies in 13% of Exelon patients and 10% of placebo patients.

Of the patients enrolled in phase 3 controlled trials, 685 patients chose not to enroll in an open label extension. Of these, 506 had discontinued the double-blind study (and were nonetheless offered enrollment in an extension study), and 179 had completed the controlled trial. For all patients who did not enter the extension studies, the most common reasons for non-participation were "caregiver/patient refusal" (29.6%), followed by "unknown" (23%), and "tolerability" (21%). Among patients who completed the controlled trial, the main reason not to enter an extension was "patient/caregiver refusal" (45% for both Exelon and placebo treated patients). "Unknown" reason was the second most common (Exelon 27%, placebo 23%). The incidence of "tolerability" problems was relatively low (6%, and 0%, respectively). In contrast, in patients who discontinued prematurely from the controlled trial, "tolerability" problems were much more common (Exelon 31%, placebo 14%), which may have had some influence on caregiver/patient refusal (23% vs. 27%).

Patients were considered to have completed the phase 3 extension trial if they completed open-label treatment for 26 weeks. As shown in Table 15, page 42, 79% completed an uncontrolled study, as opposed to 73% for all therapeutic studies overall, resulting in a lower discontinuation rate (21% vs. 27%). This is understandable, given the fact that patients who discontinued from controlled trials tended not to enroll in the extension, thereby enriching the extension population with patients less likely to drop out. Table 19 summarizes discontinuation rates in the phase 3 uncontrolled and controlled studies.

Table 19: Discontinuations in Phase 3 Uncontrolled and Controlled Studies

Disposition	Uncontrolled Extension Studies		Controlled Studies	
	Total ENA (%) n = 310	>9- 12 mg (%) n = 211	ENA (%) n = 1696	>9- 12 mg (%) n = 476
Completed	79	82	73	86
Discontinued (Total)	21	18	27	14
Adverse Experiences	11	8	17	9
Death	1	1	<1	<1
Withdrawal of Consent	6	5	4	2

8.4.2.1 Subgroup Analysis: Sex

A much higher percentage of women (32%) than men (19%) discontinued Exelon treatment in phase 3 controlled trials (Table 20). Rates of placebo discontinuations between the sexes were lower and comparable (15% male vs. 18% female). Rates of discontinuation from Exelon due to

adverse events were almost twice as higher in women than in men (21% vs. 12%), although AE discontinuation rates from placebo were 8% in both sexes.

Table 20: Discontinuations by Sex in Phase 3 Controlled Studies

Disposition	Males			Females		
	ENA (%) n = 711	>9- 12 mg (%) n = 218	PBO (%) n = 315	ENA (%) n = 985	>9- 12 mg (%) n = 258	PBO (%) n = 448
Completed	81	89	85	68	84	82
Discontinued (Total)	19	11	15	32	16	18
Adverse Experience	12	6	8	21	12	8
Death	<1	<1	0	<1	0	0
Withdrawal of Consent	3	<1	3	5	3	3

Analysis of overlapping dose ranges showed a progressive increase in the incidence of discontinuation and AE discontinuation in both genders, with females discontinuing at roughly twice the rate in all 4 dose ranges (Table 21).

Table 21: Discontinuations by Overlapping Dose Range and Sex

Disposition	≤12 mg		≤9 mg		≤6 mg		≤3 mg		PBO	
	N= 711	(%)	N= 315	(%)						
Males										
Did Not Discontinue	578	(81.3)	601	(84.5)	637	(89.6)	689	(96.9)	268	(85.1)
Discontinued (total)	133	(18.7)	110	(15.5)	74	(10.4)	22	(3.1)	47	(14.9)
Adverse Experience	85	(12.0)	71	(10.0)	50	(7.0)	11	(1.5)	26	(8.3)
-- Adverse Events **	84	(11.8)	70	(9.8)	49	(6.9)	11	(1.5)	26	(8.3)
-- ECG +	1	(0.1)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)
-- Laboratory +	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Death	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Withdrawal of Consent	21	(3.0)	20	(2.8)	13	(1.8)	4	(0.6)	8	(2.5)
Protocol Violation	6	(0.8)	5	(0.7)	2	(0.3)	2	(0.3)	3	(1.0)
Treatment Failure	6	(0.8)	4	(0.6)	3	(0.4)	1	(0.1)	0	(0.0)
Failure to Return for Visits	5	(0.7)	4	(0.6)	2	(0.3)	1	(0.1)	2	(0.6)
Other	9	(1.3)	6	(0.8)	4	(0.6)	3	(0.4)	8	(2.5)
Female										
Disposition	N= 985	(%)	N= 448	(%)						
Did Not Discontinue	668	(67.8)	710	(72.1)	799	(81.1)	914	(92.8)	369	(82.4)
Discontinued (total)	317	(32.2)	275	(27.9)	186	(18.9)	71	(7.2)	79	(17.6)
Adverse Experience	211	(21.4)	181	(18.4)	110	(11.2)	33	(3.4)	34	(7.6)
-- Adverse Events **	207	(21.0)	178	(18.1)	109	(11.1)	33	(3.4)	33	(7.4)
-- ECG +	3	(0.3)	2	(0.2)	1	(0.1)	0	(0.0)	1	(0.2)
-- Laboratory +	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)	0	(0.0)
Death	1	(0.1)	1	(0.1)	1	(0.1)	0	(0.0)	0	(0.0)
Withdrawal of Consent	53	(5.4)	46	(4.7)	34	(3.5)	16	(1.6)	13	(2.9)
Protocol Violation	9	(0.9)	8	(0.8)	8	(0.8)	5	(0.5)	5	(1.1)
Treatment Failure	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	7	(1.6)
Failure to Return for Visits	20	(2.0)	18	(1.8)	14	(1.4)	5	(0.5)	5	(1.1)
Other	23	(2.3)	21	(2.1)	19	(1.9)	12	(1.2)	15	(3.3)

The discontinuations due to adverse events is higher for females in all overlapping dose groups, but the difference is greater for ≤12mg and ≤9mg groups. This analysis suggests that females are more susceptible to the cholinergic effects of Exelon and that the threshold dose for intolerance is below 6 mg for females, while being higher for males.

8.4.2.2 Subgroup Analysis: Race

Caucasians constituted 94% of the phase 3 controlled trial population. Fewer blacks than Caucasians discontinued Exelon therapy (10% vs. 18%) but the incidence of AE discontinuations was the same (7%). The number of Orientals and other races in these trials were too small to permit valid comparisons.

8.4.2.3 Subgroup Analysis: Age

Discontinuations to Exelon treatment among the four age groups (≤ 65 yrs, 66-75, 76-85, ≥ 85 yrs) generally increased with increasing age (20%, 24%, 32%, 30%, Table 22), with the rate in the upper two groups being comparable. All rates were greater than placebo, and in the 76-85 year group, was more than twice placebo (32% vs. 15%). Discontinuations due to AE's ranged 15-20% among all age groups, and again were consistently higher than placebo.

Table 22: Discontinuations by Age in Phase 3 Controlled Trials

Disposition	≤ 65 years			66-75 years		
	ENA (%) n = 306	>9- 12mg (%) n = 113	PBO (%) n = 119	ENA (%) n = 680	>9- 12 mg (%) n = 219	PBO (%) n = 318
Completed	80	88	86	76	87	81
Discontinued (Total)	20	12	14	24	13	19
Adverse Experience	15	10	7	16	8	9
Death	0	0	0	<1	<1	0
Withdrawal of Consent	2	1	3	4	1	3

Disposition	76 - 85 Years			>85 Years		
	ENA (%) n = 650	>9- 12mg (%) n = 132	PBO (%) n = 300	ENA (%) n = 60	>9- 12 mg (%) n = 12	PBO (%) n = 26
Completed	68	83	85	70	100	81
Discontinued (Total)	32	17	15	30	0	19
Adverse Experience	20	11	7	18	0	12
Death	<1	0	0	0	0	0
Withdrawal of Consent	6	4	2	5	0	8

8.4.3 Conclusions

Overall discontinuation rates for all therapeutic studies were 26% for Exelon and 15% for placebo. Adverse dropouts were more than double in the Exelon treated patients (16% vs. 7%). This may have lead to significant unblinding of the treatment population. In particular, females discontinued at roughly twice the rate of males (32% vs. 19% for all reasons, and 21% vs. 12% for due to AE's). Older patients (≥ 76 years) tended to discontinue at a higher rate compared to younger patients, but adverse dropout rates were roughly the same across all ages (16-20%). Data on blacks were limited due to small numbers. They tended to discontinue less frequently than whites, but adverse dropout rates were the same. I discuss the topic of adverse dropouts in more detail in the next section.

8.4.4 Adverse Dropouts (ADO)

In all therapeutic studies, a total of 536 patients (14%) discontinued due to an adverse experience (Table 14: Patient Disposition: All Therapeutic Studies, page 42). ADO's were more common among Exelon patients compared to placebo (16% vs. 7%). Two percent (2%) withdrew due to a serious adverse event (3% for Exelon, 2% for placebo).

The most common AE's leading to discontinuation among Exelon patients were gastrointestinal in nature (8%, vs. 1% for placebo). These are listed in FDA Table 23. Nausea was the single

most common cause for an ADO, followed by vomiting, anorexia, diarrhea, and abdominal pain. When subtracting out the gastrointestinal adverse dropouts, the adverse dropout rate is 8% for Exelon vs. 6% for placebo. It appears that the differential drop-out rate is largely explained by significantly increased gastrointestinal related dropouts for Exelon treated patients.

Table 23: Gastrointestinal AE Dropouts, All Therapeutic Studies

	Exelon (N=3006)	Placebo (N=983)	Total (N=3886)
ALL GI DISORDERS	254 (8%)	10 (1%)	264 (7%)
Nausea	174 (6%)	5 (1%)	179 (5%)
Vomiting	92 (3%)	2 (<1%)	94 (2%)
Anorexia	50 (2%)	1 (<1%)	51 (1%)
Diarrhea	25 (1%)	1 (<1%)	26 (1%)
Abdominal Pain	31 (1%)	2 (<1%)	33 (1%)

The second most common category of AE dropouts was central and peripheral nervous system disorders (Exelon 4%, vs. placebo 1%). The two most common AE's in this category were dizziness (2% vs. 1%) and headache (1% vs. <1%). A complete listing of adverse dropouts is located in Appendix E, page 156. Very few patients (<1%) withdrew because of an abnormal biological finding (i.e., lab test, ECG, or vital sign).

8.4.5 Other Significant Adverse Events - Nausea and Vomiting

This section describes the two most frequently reported adverse events that occur upon treatment with Exelon, namely nausea and vomiting. These have been reported with other acetylcholinesterase inhibitors, and in standard medical practice may lead to a reduction in dose, administration of anti-emetic therapy, or discontinuation altogether.

8.4.5.1 Methods

Comparison of the incidence of nausea alone, and nausea with vomiting, were made between Exelon and placebo, and between high dose Exelon (>9-12mg) and placebo, with the understanding that the high dose group is not a randomized population, but rather consists of patients whose doses could be escalated to this range because of their tolerance of lower doses. Analysis is limited to the phase 3 controlled trials (B303, 304, 351, and 352). In addition, subgroup analyses by age, sex, and race are discussed.

8.4.5.2 Results - Nausea

Thirty-five percent (35%) of the 1696 Exelon treated patients in phase 3 controlled trials experienced at least one episode of nausea. By comparison, the incidence of nausea in the 763 placebo patients was 12% (Table 24). Single episodes (18%) and multiple episodes (17%) occurred with similar incidence in Exelon patients, whereas single episodes were more likely in placebo patients (9% single, vs. 3% multiple). Nausea was even more common in the high dose group (both single and multiple episodes).

Table 24: Nausea, Single and Multiple Episodes in Phase 3 Controlled Trials

	>9- 12 mg (N= 476) %	Total ENA (N= 1696) %	Placebo (N= 763) %
At Least One Episode of Nausea	44	35	12
Single Episode of Nausea	24	18	9
Multiple Episodes of Nausea	20	17	3

Nausea was more common in the ≤ 65 yr. age group (46%) compared with the three older age groups (66-75, 76-85, >85 , 31-33%). There was no significant difference in the incidence of nausea among the four age groups exposed to placebo (8-12%).

Nausea was more common in females than males exposed to Exelon (42% vs. 26%, respectively) and compared to placebo (females 14.5%, males: 8%).

There was an approximately three-fold increase in nausea among Caucasians on Exelon compared to placebo (36% vs. 11.3%). The low number of black patients precluded a definitive analysis, but the incidence of nausea appeared to be less than in the Caucasian population (24%) and was similar to the black placebo group (22%).

There was no systematic effect of duration of dementia or baseline MMSE on the incidence of nausea.

Nausea, in general, was reported with a higher incidence in the high dose group (>9 -12mg) compared to the total Exelon population or placebo among all demographic categories. A notable exception is that no black patient in the high dose group had nausea, but there were only 7 in that dose group (by contrast 44% Caucasians had nausea in this group).

During the titration phase (weeks 1-12), 31% of the Exelon patients experienced at least one episode of nausea, compared to 9% for placebo. Slightly more than half (55%) were single episodes. During the maintenance phase, a smaller percentage of Exelon patients (19%) experienced nausea, with the majority (79%) being a single episode. Overall, Exelon patients still experienced considerably more nausea compared to placebo throughout the trial, but it was more common during the titration phase. Males and females behaved similarly in both phases.

8.4.5.3 Results - Nausea and Vomiting

Nausea and vomiting (N&V) were analyzed together as a discrete event. For this analysis, multiple episodes of nausea and vomiting included cases with at least one episode of nausea and vomiting and multiple episodes of nausea or vomiting. N&V was more common in Exelon patients (17%) and, in particular, high dose Exelon (>9 -12 mg, 22%) compared to placebo (3%, Table 25).

Table 25: Nausea and Vomiting, in Phase 3 Controlled Trials

	>9- 12 mg (N= 476)	Total ENA (N= 1696)	Placebo (N= 763)
	%	%	%
At Least One AE	22	17	3
Single Episode of Nausea and Vomiting	6	5	2
Multiple Episodes of Nausea and Vomiting	16	12	1

In contrast to nausea alone, Exelon treated patients had a much greater incidence of multiple episodes of nausea and vomiting than single events (12% vs. 5%) and compared to placebo (1%). As with nausea alone, N&V incidence was highest in the ≤ 65 yr. group compared to the three older age groups (22% vs. 10-17%), whereas placebo patients among all age groups had low incidence (2-4%). More females reported N&V than males (20.4% vs. 11.4%) in the Exelon group. For placebo, the incidence was 4.5% in females and 1.6% in males. Females were also more likely to experience more episodes of N&V, with an incidence rate that was greater than males (15% vs. 7%) and greater than female placebo patients (2%).

During the titration phase, the incidence of N&V was higher in the high dose group (16%) which again outpaced the total Exelon group (13%). Both were substantially higher than placebo (2%). During the maintenance phase, the incidence leveled off in both high dose and total Exelon groups, which narrowed the margin between treatment and placebo (9%, 7%, and 2%, respectively).

8.4.6 Other Significant Adverse Event: Weight Loss

Weight loss is a common finding in patients with Alzheimer's Disease. Despite substantial care provided by family and/or health care workers, AD patients lose weight. The weight loss may be severe, and cachexia in advanced stages of the disease is not uncommon. The exact cause of the weight loss in AD patients is unknown, but a role for tumor necrosis factor (TNF) and nitrous oxide in the pathogenesis of weight decrease and an impact on mortality has been postulated. This section reviews the weight loss in more detail and explores the potential role of Exelon in this phenomenon.

8.4.6.1 Methods

A clinically notable weight loss was defined by the sponsor as a decrease of 7% from baseline weight. This is an arbitrary, though reasonable definition. Comparisons of the incidence of $\geq 7\%$ weight decrease were made between Exelon and placebo groups, and between high dose Exelon ($>9-12\text{mg/day}$) and placebo. Included in the high dose group are patients whose maximum prescribed dose, even for one day, was in this range. It is important to remember that this is not a randomly selected group, but rather includes patients who achieved this dose because of tolerance of lower doses.

In phase 3 controlled studies, weight was measured at screening, baseline, and at weeks 4, 8, 12, 16, 22, 26, and/or endpoint. The analyses presented were done on 2359 patients, not on the 2459 exposed to Exelon or placebo, since the weight for 100 patients (79 on Exelon, 21 on placebo) were either not recorded at baseline or not recorded post-baseline.

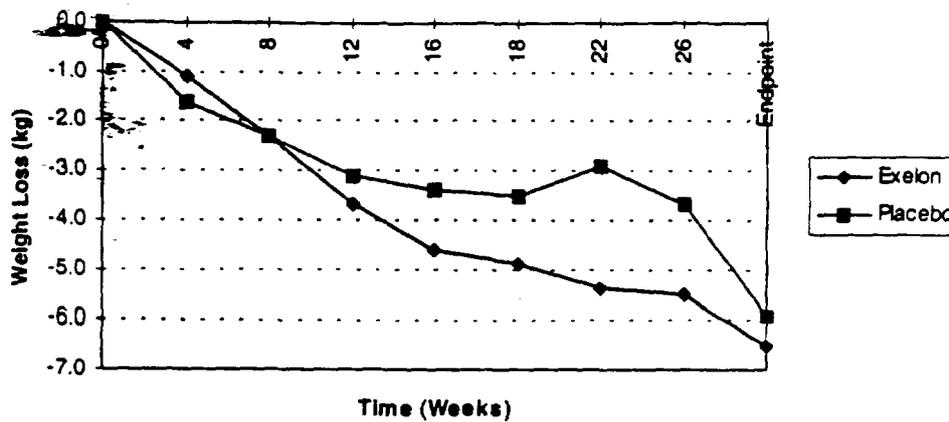
Notable weight decreases were analyzed by demographic variables (sex, race, age).

8.4.6.2 Results

In controlled 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, as previously defined as a $\geq 7\%$ change from baseline. Within this group, Exelon patients lost more weight (6.5 kg) at endpoint compared to their placebo counterparts (5.9 kg) (Figure 7).

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Figure 7: Notable^{*} Weight Loss over Time in Phase 3 Placebo Controlled Trials



^{*} defined as a $\geq 7\%$ loss in baseline weight

More Exelon treated females (15.3%) experienced clinically notable weight loss, compared to Exelon treated males (10.7%). The rates in the placebo group by sex were comparable (5.8% females vs. 4.9% males). Males on Exelon lost more weight than females (6.8 kg vs. 6.4 kg), compared with 6.9 kg and 5.3 kg, respectively, in placebo treated males and females. More females (27.2%) in the high dose Exelon group had notable weight loss than males (17.1%).

There was no systematic effect of age, race, duration of dementia, or baseline MMSE score on notable weight decrease in Exelon treated patients.

The sponsor used logistic regression analysis to study the relationship between the dichotomous response weight loss variable (the presence or absence of $\geq 7\%$ weight loss from baseline) and a set of explanatory variables such as gender, baseline weight, and gastrointestinal symptoms reported as AE's (nausea, vomiting, anorexia), and the interaction between these variables. Stepwise logistic regression was used to find the parsimonious model containing gender or baseline weight alone, and the interaction between gender and the selected gastrointestinal symptom.

In the stepwise procedure, none of the models included baseline weight or the interaction between gender and a given GI symptom alone as a predictor for $\geq 7\%$ weight decrease. From these models it is evident that females are at approximately 40% higher odds than males for experiencing notable weight decrease.

Subsequently, a model for $\geq 7\%$ weight decrease was fitted in which the predictor variable of interest was those patients who experienced at least one GI symptom, i.e., nausea, vomiting and anorexia. Neither gender, baseline weight, nor the interactions were predictive factors for $\geq 7\%$ weight decrease. Therefore, models with gender and a given GI symptom (although patients might have experienced multiple GI symptoms) predicted weight decrease; however, in models including the presence of any GI symptom, gender was no longer a predictor of $\geq 7\%$ weight decrease.

In summary, in phase 3 controlled study, Exelon treated patients tended to lose weight, and placebo patients tended to gain weight. Notable weight loss ($\geq 7\%$ from baseline) occurred more

often in Exelon patients (13%) than in placebo patients (5%). Women treated with Exelon were more at risk to lose weight compared to Exelon-treated men. The incidence of notable weight loss was not influenced by either age, race, or initial body weight. Finally, Exelon treated patients with notable weight loss also had a higher incidence of gastrointestinal related adverse events (nausea, vomiting, anorexia).

8.4.7 Other Significant Adverse Event: Orthostasis

At each vital signs measurement, patients had orthostatic blood pressures recorded (i.e., supine, standing x 1 minute, and standing x 3 minutes). Subjects were considered to exhibit an "orthostatic response" upon standing for three minutes if the following conditions were present at any visit: (1) a decrease in SBP \geq 20 mm Hg, or (2) a decrease in DBP \geq 10 mm Hg.

Patients who exhibited an orthostatic response did not necessarily have symptomatic orthostatic hypotension. In order to meet this criterion, a patient also had to have an associated adverse event, such as dizziness, lightheadedness, syncope, or accidental trauma. Data from the phase 3 controlled trials were analyzed for the incidence of orthostatic responses and associated adverse events.

Table 26 shows the incidences of orthostatic responses. Each orthostatic response was subdivided into whether the abnormality was present in systolic blood pressure, diastolic blood pressure, or both. The incidences in each Exelon treatment group were comparable to placebo, suggesting Exelon administration is not associated with an increased incidence of an orthostatic response.

Table 26: Orthostatic Responses, in Phase 3 Controlled Trials

	>9-12 mg (N = 476)	>6-9 mg (N = 295)	>3-6 mg (N = 680)	\leq 3 mg (N = 238)	Total Exelon (N = 1689)	Placebo (N = 760)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
O. R.	327 (69)	187 (63)	439 (64)	135 (57)	1088 (64)	536 (71)
SBP	124 (26)	67 (23)	163 (24)	59 (25)	413 (24)	193 (25)
DBP	110 (23)	59 (20)	156 (23)	37 (16)	362 (21)	187 (25)
SBP and DBP	93 (20)	61 (21)	120 (18)	39 (16)	313 (19)	156 (21)

The actual incidence of symptomatic orthostatic hypotension (as previously defined) is shown in Table 27 and Table 28. The tables show orthostatic responses that were associated with adverse events generally considered to co-exist with symptomatic orthostatic hypotension.

Table 27: Adverse Events Associated with Systolic O.R., in Phase 3 Controlled Trials

	>9- 12 mg (N = 217)	Total Exelon (N = 726)	Placebo (N = 349)
	n (%)	n (%)	n (%)
Postural Hypotension	0 (0)	0 (0)	0 (0)
Syncope	10 (5)	18 (2)	3 (1)
Dizziness	45 (21)	162 (22)	48 (14)
Accidental Trauma	22 (10)	78 (11)	26 (7)
Cerebrovascular Disorders	5 (2)	8 (1)	5 (1)

Table 28: Adverse Events Associated with Diastolic O.R., in Phase 3 Controlled Trials

	>9-12 mg	Total Exelon	Placebo
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	(N = 281) n (%)	(N = 902) n (%)	(N = 473) n (%)
Postural Hypotension	0 (0)	0 (0)	0 (0)
Syncope	13 (5)	27 (3)	4 (1)
Dizziness	55 (20)	179 (20)	55 (12)
Accidental Trauma	31 (11)	99 (11)	38 (8)
Cerebrovascular Disorders	6 (2)	7 (1)	5 (1)

The incidences of these adverse events were generally comparable in Exelon patients, high dose Exelon patients, and placebo. The one exception was in the "dizziness" category, where higher incidences in the Exelon treated patients with either systolic or diastolic orthostatic responses were seen.

8.4.8 Other Significant Adverse Events: "Evocative" Adverse Events

The sponsor defined "evocative adverse events" as those AE's which, by the nature of the elderly study population, were deemed clinically important, although not necessarily events that were serious or resulted in discontinuation. Included among these events were rash, cerebrovascular events, abnormal gait, hypokinesia, hyperkinesia, and accidental trauma. The analysis comes from data from the phase 3 controlled trials. As shown in Table 29, the incidence of these AE's were comparable in two treatment groups, suggesting there is no association between the administration of Exelon and the emergence of these events.

Table 29: "Evocative" Adverse Events in Phase 3 Controlled Trials

	Exelon (N=1696)		Placebo (N=763)	
	n	(%)	n	(%)
Accidental Trauma	155	(9)	66	(9)
Rash	49	(3)	22	(3)
Cerebrovascular Disorders	17	(1)	8	(1)
Gait Abnormality	25	(1)	4	(1)
Hyperkinesia	1	(< 1)	1	(< 1)
Hypokinesia	5	(< 1)	0	(0)

8.5 Adverse Events Incidence Tables

8.5.1 Approach to Eliciting and Analyzing Adverse Events

Adverse Events were elicited throughout the course of the clinical trials. If a patient had more than one occurrence of the same AE, the patient was counted only once in the incidence tables. If a patient had more than one occurrence of the same AE, and these AE's differed in severity ratings, then the most severe rating was chosen when performing the analyses of AE's by severity. Adverse events reported 48 hours after the last dose of study medication were not included in the sponsor analyses.

Worsened symptoms of AD may have been recorded as an AE (e.g., hallucinations, disorientation, memory loss). However, if a patient had a worsened symptom of AD, and the patient discontinued because of treatment failure, then the sponsor removed this symptom of AD from the AE list, since the symptom would be captured in the efficacy assessments. Three symptoms (agitation, depression, or delirium) were not removed because of the possibility that these may have been Exelon related AE's rather than a reflection of treatment failure.

Whenever a specific treatment-emergent syndrome or a disease entity had been diagnosed and entered as an AE by the investigator, all the reported associated symptoms and signs were removed from the AE list by the sponsor, and only the diagnosis remained as an AE.

Any medical intervention that did not require hospitalization and was recorded as an AE by the investigator, was removed from the AE list by the Sponsor and coded instead as a Current Medical Condition. Any medical intervention that required hospitalization remained on the AE list as a serious adverse event (SAE).

8.5.2 Adverse Events Categorization and Preferred Terms

Adverse Events were standardized for terminology and classification using the Sandoz Medical Terminology Thesaurus (SMTT), which is a modified version of the WHO Adverse Reaction Terminology Dictionary.

8.5.3 Selecting Key Adverse Events Tables

Adverse Events Incidence Tables were generated for various study groupings. Two groupings are presented in this review. The All Therapeutic Trials grouping gives AE incidences in all patients exposed to Exelon in phase 2 and 3 trials. In addition, I generated common AE incidence tables from the phase 3 controlled studies (303, 304, 351, 352), which allows comparison with placebo. This analysis was followed by a sponsor's comparison based on "dose breakout" whereby patients who received Exelon were assigned to one of four mutually exclusive dose categories (≤ 3 , $>3-6$, $>6-9$, $>9-12$ mg/d) based on the maximum daily dose prescribed. Because these groupings are composed of individual studies that employed various dosing regimens, the use of maximum prescribed dose does not allow for an unadulterated dose-response analysis in many cases.

8.5.4 Common and Drug-Related Side Effects

Of the 3886 patients in all of the therapeutic studies, 3172, or 82% reported one or more adverse event (Table 30). When analyzed by treatment, the incidence in the Exelon treated patients was 82%, compared with 72% for the placebo patients. The difference was accounted for mainly by the most commonly occurring AE's, which belong to the gastrointestinal system (Exelon: 57%, placebo: 31%).

Table 30: Common Adverse Events in All Therapeutic Studies

Body System/ Preferred Term	Exelon N = 3006		Placebo N = 983		Total N = 3886	
	n	(%)	n	(%)	n	(%)
At Least One Adverse Event	2464	(82)	708	(72)	3172	(82)
<u>CNS and PNS Disorders</u>	1093	(36)	234	(24)	1327	(34)
DIZZINESS	571	(19)	102	(10)	673	(17)
HEADACHE	456	(15)	115	(12)	571	(15)
<u>GASTRO- INTESTINAL DISORDERS</u>	1719	(57)	303	(31)	2022	(52)
NAUSEA	1147	(38)	103	(10)	1250	(32)
VOMITING	682	(23)	49	(5)	731	(19)
DIARRHEA	452	(15)	93	(9)	545	(14)
ABDOMINAL PAIN	317	(11)	62	(6)	379	(10)
ANOREXIA	344	(11)	25	(3)	369	(9)
<u>PSYCHIATRIC DISORDERS</u>	902	(30)	239	(24)	1141	(29)
AGITATION	242	(8)	66	(7)	308	(8)
INSOMNIA	232	(8)	55	(6)	287	(7)
CONFUSION	195	(6)	61	(6)	256	(7)

The most common AE's in the gastrointestinal system were nausea, vomiting, diarrhea, abdominal pain, and anorexia. In addition two of these 5 gastrointestinal events, two AE's from the Central and Peripheral Nervous System Disorders (i.e., dizziness and headache) also were more commonly reported among Exelon treated patients. Dizziness includes lightheadedness, giddiness, wooziness, and related terms.

Adverse events belonging to the Psychiatric Disorders body system (agitation, insomnia, confusion) also had higher incidences among Exelon treated patients. In other body systems, the incidence of AE's by treatment group were very similar for Exelon and Placebo.

In the phase 3 controlled trials, the sponsor used partial safety data for B304 (N used was 346). However, the safety dataset submitted contains data for all 678 patients enrolled in the trial. Therefore, I have recalculated phase 3 controlled trial adverse event incidence tables taking into account the entire B304 database.

The number of patients exposed in phase 3 controlled trials, using the complete B304 safety dataset (B303, B304, B351, B352) is shown in FDA Table 31. A total of 2,804 patients participated, of which 1913 were on Exelon, and 891 were on placebo. The numbers differ from those in sponsor Table 6, page 18 for the reason stated in the previous paragraph.

Table 31: Exposures in Phase 3 Controlled Trials (Complete B304 Safety Database)

Study	PBO	Exelon Total	Low (1-4mg)	High (6-12mg)		All Patients Total
B303	239	486	243	243		725
B352	235	464	231	233		699
B304	244	434	TID (2-12mg) 223	BID (2-12mg) 211		678
B351	173	529	3mg 175	6mg 176	9mg 178	702
TOTAL	891	1913				2804

Of the 2,804 patients, 2367 (84%) reported at least one AE (FDA Table 32). Similarly, more Exelon treated patients (86%) compared to placebo patients (82%) reported at least one AE. The 2367 patients who reported at least one AE reported a total of 13,838 adverse events, or 5.8 AE's per patient. Exelon patients reporting at least one AE on average experienced more AE's compared to placebo patients experiencing AE's (6.2 vs. 5.1).

Table 32: Incidence of AE's in Phase 3 Controlled Trials

	Total	At least 1 AE (%)	No AE (%)	Total AE's	AE's per Patient
Placebo	891	731 (82%)	160 (18%)	3721	5.1
Exelon	1913	1636 (86%)	277 (14%)	10117	6.2
All Pts	2804	2367 (84%)	437 (16%)	13838	5.8

FDA Table 33 lists the most common AE's reported in phase 3 controlled trials. It contains all AE's having an incidence of 5% or greater in the Exelon treated group. It excludes all AE's having a higher incidence in the placebo treated groups. It was derived directly from the

sponsor provided datasets on adverse events. I combined the data from the four controlled trials (B303, B304, B351, B352). I removed all patients who did not report an adverse event. Then, I summarized the table according to patient, adverse event, and treatment. This listed each patient only once. Finally, I summarized the new table according to AE. I added incidence columns by dividing the numerator by the total number exposed in each treatment group to obtain incidences.

Table 33: Most Common AE's in Phase 3 Controlled Trials

	Total (N=2804)	Exelon (N=1913)	(%)	PBO (N=891)	(%)
NAUSEA	824	653	34.1	171	19.2
VOMITING	494	404	21.1	90	10.1
DIZZINESS	459	348	18.2	111	12.5
DIARRHEA	407	295	15.4	112	12.6
HEADACHE	404	288	15.1	116	13.0
ANOREXIA	286	228	11.9	58	6.5
ABDOMINAL PAIN	261	204	10.7	57	6.4
AGITATION	239	164	8.6	75	8.4
INSOMNIA	220	156	8.2	64	7.2
FATIGUE	183	147	7.7	36	4.0
DYSPEPSIA	186	139	7.3	47	5.3
SOMNOLENCE	124	98	5.1	26	2.9

The most common AE's in phase 3 controlled trials are attributable to the gastrointestinal and central nervous system, and are similar to those encountered in all therapeutic studies (Table 30, page 53). Nausea, vomiting, diarrhea, anorexia, and abdominal pain accounted for most of the gastrointestinal related AE. Dizziness, headache, agitation, and insomnia were the most common CNS related effects, although many of them occurred with an incidence similar to placebo. A complete listing of all AE's reported is contained in Appendix F, page 161.

8.5.5 Additional Analyses and Explorations

8.5.5.1 High Dose (>9-12mg/day)

Using the sponsor's analysis, patients in the high dose group (>9-12mg) had an even higher overall incidence of AE's (90%). The total incidence of gastrointestinal related AE's in the Exelon group was 58%, compared with 34% in the placebo group. The treatment difference was even higher in the high dose group, with 65% reporting gastrointestinal related AE's.

8.5.5.2 Severity

Although a higher percentage of Exelon treated patients (and high dose Exelon) reported AE's compared to placebo, the incidence of severe AE's was similar among all three groups (15%, 14%, and 11% for Exelon, high dose Exelon, and placebo, respectively).

8.5.5.3 Gender

In all body systems, except for the gastrointestinal system, the incidences of AE's were very similar for males and females, irrespective of Exelon, high dose Exelon, or placebo ingestion. The incidence of the 5 most common gastrointestinal AE's were comparable in placebo patients, but females on Exelon had higher rates than males for nausea, vomiting, anorexia, and abdominal pain, but not for diarrhea. The rates were higher in the high dose groups.

Table 34: AE's by Sex, Phase 3 Controlled Trials

Body System Adverse Event	Males			Females		
	Exelon N= 711 n (%)	>9- 12 mg N= 218 n (%)	PBO N= 315 n (%)	Exelon N= 985 n (%)	> 9- 12 mg N= 258 n (%)	PBO N= 448 n (%)
At Least One AE	598 (84)	193 (89)	252 (80)	873 (89)	236 (91)	352 (79)
Gastrointestinal	347 (49)	123 (56)	100 (32)	636 (65)	185 (72)	158 (35)
Nausea	184 (26)	83 (38)	25 (8)	414 (42)	125 (48)	65 (15)
Vomiting	107 (15)	51 (23)	9 (3)	255 (26)	87 (34)	33 (7)
Diarrhea	115 (16)	44 (20)	40 (13)	156 (16)	53 (21)	45 (10)
Anorexia	65 (9)	33 (15)	7 (2)	144 (15)	47 (18)	15 (3)
Abdominal Pain	47 (7)	14 (6)	14 (4)	127 (13)	37 (14)	34 (8)

8.5.5.4 Race

The somewhat greater incidence of patients with at least one AE in the Exelon group, compared to placebo, was also evident for Caucasian patients (87% vs. 79%, n=2320), but not for Black patients (85% vs. 85%, n=94). However, the treatment effect observed for gastrointestinal events was still observed for both Caucasian and Black patients. Caucasian patients treated with Exelon appeared to have a greater incidence of gastrointestinal side effects than did Black patients (58% vs. 35%). The total number of patients of other races were too small to make any meaningful comparisons.

8.6 Laboratory Findings

This section focuses on the clinical laboratory abnormalities observed in the Phase 3 ENA studies.

8.6.1 Extent of Laboratory Testing During Development

The following laboratory examinations were performed on patients in the Exelon development program.

- **Hematology:** hemoglobin, hematocrit, erythrocyte count, platelet count, leukocyte count and differential (neutrophils, eosinophils, basophils, lymphocytes, monocytes, large unsustained cells) count.
- **Biochemistry:** serum glutamic oxaloacetic transaminase (SGOT/ASAT), serum glutamic pyruvic transaminase (SGPT/ALAT), gamma-glutamyl transpeptidase (g-GT), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), creatinine, uric acid, glucose, total cholesterol, triglycerides, sodium, potassium, calcium, inorganic phosphorous, chloride, bicarbonate, total protein and albumin.
- **Urinalysis:** specific gravity, pH, nitrite, protein, glucose, urobilinogen, bilirubin, ketone, leukocytes, casts and blood were to have been determined in midstream urine samples.

The schedule of these examinations varied depending on the duration of the study, but in the phase 3 controlled trials, testing was generally performed at screening, baseline, every 2 weeks during the initial 8-12 weeks of therapy, and then monthly until study conclusion.

In general, abnormal clinical laboratory findings of sufficient magnitude to be deemed clinically significant were repeated within 48 hours to rule out laboratory error. For persistent abnormalities which were considered to be drug related, repeat analyses were performed until the cause was determined, a return to pretreatment levels occurred, or the investigator no longer considered the abnormality to be of clinical significance.

8.6.2 Selection of Studies for Overall Drug-Control Comparisons

For this analysis, the Phase 3 controlled studies (B303, B304, B351, B352) have many advantages over other studies: appropriate doses over appropriate durations; double-blind, placebo-controlled studies, the use of central laboratories, and better database editing. Discussion of outliers in all studies are also presented.

8.6.3 Standard Analyses and Explorations of Laboratory Data

I reviewed laboratory data using two paradigms:

- mean change in values from baseline to endpoint (central tendencies)
- incidence of clinically notable abnormalities (outliers)

8.6.3.1 Analyses Focused on Measures of Central Tendencies

8.6.3.1.1 CLINICAL CHEMISTRY

No clinically significant differences were seen for any biochemistry variable between Exelon and placebo. Most notably, unlike tacrine, there are no clinically significant changes in liver function tests. Table 35 illustrates the mean changes from baseline of the chemistry lab parameters tested in phase 3 controlled trials.

Table 35: Clinical Chemistry Lab Values, Changes from Baseline, Phase 3 Controlled Trials

Variable (unit of measure)	n	Exelon		n	Placebo	
		Baseline Mean	Δ from Baseline		Baseline Mean	Δ from Baseline
Calcium (mg/ dL)	1673	9.3	-0.07	754	9.2	-0.07
Inorg. Phosph. (mg/ dL)	1671	3.5	0.04	753	3.6	-0.01
Urea (BUN) (mg/ dL)	1673	16.7	0.23	755	16.6	0.28
Uric Acid (mg/ dL)	1673	5.2	-0.09	755	5.1	-0.01
Glucose (mg/ dL)	1670	101.1	0.91	753	101.6	-0.81
Total Protein (g/ dL)	1673	7.0	-0.13	754	7.0	-0.09
Albumin (g/ dL)	1673	4.2	-0.08	754	4.2	-0.05
Total Bilirubin (mg/ dL)	1673	0.6	0.01	754	0.6	<0.01
Total Cholesterol (mg/ dL)	1673	226.5	-2.83	754	227.4	-1.26
Triglycerides (mg/ dL)	1672	157.1	-3.38	754	157.9	3.76
Alk. Phosphatase (IU/ L)	1672	83.7	-0.47	755	85.3	-1.42
SGOT (AST) (IU/ L)	1672	21.9	-0.35	755	22.1	0.21
SGPT (ALT) (IU/ L)	1673	21.1	-2.05	755	21.6	-0.74
Sodium (mEq/ L)	1668	139.9	0.11	755	139.9	0.28
Potassium (mEq/ L)	1668	4.3	0.01	754	4.3	0.03
Chloride (mEq/ L)	1668	103.6	0.33	755	103.6	0.56
Bicarbonate (mEq/ L)	1672	26.1	0.51	755	26.2	0.42
Creatinine (mg/ dL)	1673	1.1	0.02	754	1.1	0.02

The largest mean change from baseline for Exelon was for triglycerides, which is a very diet dependent lab value. All other changes were clinically not significant and were comparable for the Exelon and placebo groups. Subgroup analysis by age, dose (high vs. low), or center (US vs. non-US) also failed to reveal any clinically significant changes in chemistry mean values.

8.6.3.1.2 HEMATOLOGY

No differences are evident between Exelon in placebo treated patients in terms of hematological lab values (Table 36).

Table 36: Hematology Lab Values, Phase 3 Controlled Trials

Lab Value	n	Exelon		n	Placebo	
		Baseline Mean	Δ from Baseline		Baseline Mean	Δ from Baseline
Hemoglobin (g/ dL)	1673	13.8	-0.17	753	13.8	-0.15
Hematocrit (%)	1673	44.2	-1.34	753	43.9	-1.33
Red Blood Cells (10** 12/ L)	1673	4.5	-0.03	752	4.5	-0.01
Leukocytes (10** 9/ L)	1672	6.7	0.01	753	6.6	0.00
Neutrophils Total (%)	1668	62.9	0.40	752	62.9	0.64
Basophils (%)	1665	0.7	0.06	752	0.7	0.06
Eosinophils (%)	1668	1.8	0.07	752	1.9	0.03
Lymphocytes (%)	1668	27.0	-0.55	752	26.7	-0.55
Monocytes (%)	1668	6.9	0.07	752	7.0	-0.04
Platelet Count (10** 9/ L)	1672	235.9	4.1	752	233.5	3.3
Large Unstained Cells (%)	483	2.1	-0.15	241	2.0	-0.02

8.6.3.1.3 URINALYSIS

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 (section 8.6.3.2.3, page 60).

Table 37: Urinalysis Values, Phase 3 Controlled Trials

Variable	n	ENA		n	Placebo	
		Baseline mean	Δ from Baseline		Baseline mean	Δ from Baseline
Urine Specific Gravity	1662	1.0	<0.01	750	1.0	0.00
Urine pH	1662	5.7	-0.11	750	5.7	0.03
Urine Protein (mg/ dL)	870	2.3	0.73	391	2.3	-0.18
Urine Glucose (g/ dL)	1073	0.01	0.01	458	0.03	-0.01
Urine Leukocytes (/ hpf)	1070	2.2	-0.17	458	2.04	-0.26

8.6.3.2 Analyses Focused on Outliers

8.6.3.2.1 CLINICAL CHEMISTRY

Chemistry outliers were defined by the sponsor as those meeting laboratory criteria outlined in Table 38.

Table 38: Notable Clinical Chemistry Lab Values

Variable	Criterion Values	
	Standard Units	SI Units
SGOT	≥3 x upper limit of normal	≥3 x upper limit of normal
SGPT	≥3 x upper limit of normal	≥3 x upper limit of normal
Alk.Phosphatase	≥3 x upper limit of normal	≥3 x upper limit of normal
BUN*	≥30 mg/dL	≥10.7 μM
Creatinine	≥2 mg/dL	≥176.8 μM
Uric Acid male	≥10.5 mg/dL	≥624.6 μM
female	≥8.5 mg/dL	≥505.6 μM
Bilirubin (Total)	≥2 mg/dL	≥34.2μM
Cholesterol	≥330 mg/dL	≥8.53 mM
Triglycerides	≥340 mg/dL	≥3.89 mM

Glucose ^b	≥250 mg/dL or 45 mg/ dL	≥13.88 mM or 2.50 mM
Sodium ^b	<0.95 x lower limit of normal or >1.05 x upper limit of normal	
Potassium	<0.95 x lower limit of normal or >1.05 x upper limit of normal	
Chloride ^b	<0.95 x lower limit of normal or >1.05 x upper limit of normal	

^a in B303, B304, the criterion is stated as ≥40 mg/dl, however the FDA suggests a value of ≥30 mg/dl, which is used here.

^b Variable not included in the FDA "Supplementary Suggestions for Preparing an Integrated Summary of Safety" (1987)

This definition of outliers seems reasonable. Based on this definition, there were no significant differences seen among Exelon (high doses and all doses) and placebo (Table 39). Also, results from the phase 3 uncontrolled studies indicated no significant changes from baseline.

Table 39: Clinical Chemistry Outliers

Biochemistry Variable	Abnormal Result	Exelon >9-12 mg/ d (N= 476)		All Exelon Doses (N= 676)		Placebo (N= 757)	
		n	%	n	%	n	%
Urea (BUN)	High	27	6	116	7	43	6
Uric Acid	High	8	2	36	2	8	1
Total Bilirubin	High	4	1	14	1	12	2
Alkaline Phosphatase	High	2	<1	5	<1	1	<1
SGOT (AST)	High	1	<1	5	<1	3	<1
SGPT (ALT)	High	4	1	10	1	6	1
Creatinine	High	4	1	31	2	8	1

It is noteworthy that the incidence of outliers of ALT and AST were small and similar to placebo.

8.6.3.2.2 HEMATOLOGY

Table 40 lists the reference hematology lab values used to define outliers.

Table 40: Notable Hematology Lab Values

Variable		Criterion Values	
		Standard Units	SI Units
Hematocrit	male	≤37%	≤37%
	female	≤32%	≤32%
Hemoglobin	male	≤11.5 g/ dL	
	female	≤9.5 g/ dL	
Platelets		≤75,000/mm ³ or	≤75 x 10 ⁹ /L or
		≥700,000/ mm ³	≥700 x 10 ⁹ /L
Leukocytes		≤2,800/mm ³ or	≤2.8 x 10 ⁹ /L or
		≥16,000/mm ³	≥16 x 10 ⁹ /L
Eosinophils		≥10%	≥10%
Neutrophils		≤15%	≤15%

This definition is reasonable. Table 41 demonstrates that the incidence of clinical hematology outliers among the high dose Exelon, all doses Exelon, and placebo groups are very similar. There is no indication that Exelon treated patients have a higher incidence of significant hematology abnormalities.

Table 41: Hematology Outliers, Phase 3 Controlled Trials

Variable	Abnormal Result	Exelon	Exelon	Placebo
		>9- 12 mg/day (N= 476)	All Doses (N= 1677)	(N= 757)

		n	%	n	%	n	%
Hemoglobin	Low	12	3	51	3	22	3
Hematocrit	Low	36	8	87	5	42	6
Leukocytes	High	3	1	10	1	2	<1
	Low	4	1	24	1	12	2
Neutrophils Total	Low	0	0	2	<1	0	0
Eosinophils	High	8	2	26	2	17	2
Platelet Count	High	1	<1	3	<1	0	0
	Low	1	<1	4	<1	3	<1

8.6.3.2.3 URINALYSIS

The criteria used to identify urinalysis outliers are shown in Table 42.

Table 42: Notable Urinalysis Lab Values

Variable	Criterion Values
Protein (mg/ dL)	Increase of 2 or more units
Glucose (g/ dL)	Increase of 2 or more units
Casts*(cast/ Low Powered Field)	Increase of 2 or more units

Based on these criteria, Table 43 summarizes the incidence of urinalysis outliers in the phase 3 controlled trials. Comparison among three treatment groups, high dose Exelon, Exelon (all doses) and placebo reveals that the incidences are very similar among all groups.

Table 43: Urinalysis Outliers, Phase 3 Controlled Trials

Variable	Abnormal Result	Exelon >9- 12		Exelon All Doses		Placebo	
		mg/ day (N= 476)		(N= 1673)		(N= 755)	
		n	%	n	%	n	%
Urine Protein	High	19	4	46	3	25	3
Urine Glucose	High	26	5	61	4	27	4
U. Casts - Granular	High	8	2	41	2	11	1
U. Casts - Hyaline Text	High	26	5	137	8	59	8

8.6.3.3 Dropouts for Laboratory Abnormalities

As described in section 8.4.4 (Adverse Dropouts) on page 46, less than 1% of patients withdrew from clinical trials because of a biological finding abnormality (vitals signs, laboratory analysis, or ECG). In all therapeutic studies, there were a total of 9 patients who withdrew because of an abnormal laboratory value. Of these 9, seven (7) patients had an associated adverse event, and their withdrawals have already been included in section 8.4.4. The remaining two had isolated, asymptomatic laboratory abnormalities. Both were treated with Exelon. One was due to an elevation in liver enzymes, and the other was due to a low platelet count. All 9 patients are listed in Table 44, and the two patients with sole laboratory abnormality described above are highlighted in gray. This low number (n=2) of dropouts due to isolated laboratory abnormalities indicates that the use of Exelon does not result in an unusually high number of drop-outs due to laboratory abnormalities.

Table 44: Dropouts Due to Abnormal Laboratory Values, All Studies

Study	Patient Number	Age/ Sex/ Race	Dose	Days on Exelon	Abnormal Biological Finding
B103	050007*	85/ F/ CA	4 mg/ d	43	ADO: Increased alk. phosphatase

B103	260001	67/ F/ CA	4 mg/ d	56	ADO: Increased liver enzymes
B104	070013*	64/ M/ CA	12 mg/ d	28	SAE/ ADO: Hyponatremia
B104	08007*	79/ M/ CA	9 mg/ d	57	ADO: Hepatic function abnormal
B291	027002*	72/ F/ AS	4 mg/ d	78	ADO: Spleen disorder
B293	020011*	86/ F/ AS	1 mg/ d	15	ADO: Hepatocellular damage
B303	38006*	76/ F/ CA	7 mg/ d	44	SAE/ ADO: Hepatitis
B304	17004	72/ F/ CA	9 mg/ d	50	ADO: Low platelet count
B304	32005*	67/ F/ CA	placebo	NA	SAE/ ADO: Hepatic failure

8.7 ECG

Dr. Feeney reviewed the ECG and Vital Signs safety data. His review is contained in this section and in the following section (Section 8.8, Vital Signs, page 79).

Because of the cholinergic properties of Exelon, the possible effect of Exelon on cardiac conduction is of special interest. Two parameters of interest are heart rate and PR interval.

EKG heart rate and interval data were collected in the 2 primarily non-US controlled studies (B303 and B304) and the 2 US controlled studies (B351 and B352), as well as the 2 uncontrolled long-term extension studies (B305 and B353). In the 4 controlled trials, EKGs were recorded at baseline, 2 weeks, 4 weeks, 2 months, 3 months, 4 months, 4-1/2 months, 5-1/2 months, and 6-1/2 months. In the long-term extension studies, EKGs were recorded at 2, 4, and 6 weeks, and then every 6 weeks thereafter.

Additionally, Study 354 was an open-label 12-week pilot study which enrolled 15 patients. Study 355 was also an open-label study; the interim report provided summarized data on 544 patients treated for 14 weeks.

Study B351 is of interest because patients were assigned to placebo or 1 of 3 fixed-dose groups: 3mg/day, 6mg/day, or 9mg/day. There was no 12mg/day group in this study.

Study B303 had placebo and 2 dose groups: 1-4mg/day and 6-12mg/day. Study B304 had placebo and only 1 dose group: 2-12mg/day. Study B352 had placebo and 2 dose groups: 1-4mg/day and 6-12mg/day.

The randomized dose groups are obviously not easily poolable across studies. In the ISS, the sponsor has pooled the 4 controlled studies, assigning patients to 1 of 4 dose groups: ≤ 3 mg/day, ≤ 6 mg/day, ≤ 9 mg/day, or ≤ 12 mg/day. The assignment was based on the maximum prescribed dose for any given patient during the study.

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 primarily non-U.S. studies.

In the ISS, comparisons are presented for summary data (means, medians) for heart rate and interval data (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.]

Treatment-emergent abnormalities or worsening abnormalities for the controlled trials are also analyzed (Sponsor's Table 8.2.1.1).

Also presented in the ISS are shift tables showing maximum increases of given intervals of <15%, ≥15% to <25%, and ≥25% (Sponsor's Tables 8.4.1.1 and .2, 8.5.1.1 and .2, 8.6.1.1 and .2). Shift tables for sinus bradycardia are presented in Tables 8.7.1.1 and .2.

8.7.1 Results

Sponsor's ISS Table 8.1.1.2 (Table 45 below) summarizes the treatment emergent EKG interval changes for the 4 different dosing levels of drug and for placebo in the grouped controlled trials. There were no clinically significant differences noted between the placebo and Exelon groups, although for heart rate and PR interval, there appear to be suggestions of a drug effect (statistical comparisons for this grouped data were not provided by the sponsor in the ISS.)

Table 45: ECG Parameters in Phase 3 Controlled Studies

Integrated Summary of Safety: Theme 8 (Page 1 of 5)
 Table 8.1.1.2
 ECGs: ENA 713 (>9-12 mg/day, >6-9 mg/day, >3-6 mg/day, <=3 mg/day) and Placebo
 Change from Baseline to Endpoint
 Heart Rate (bpm)
 Phase III Controlled Studies

	Statistic	>9-12 mg	>6-9 mg	>3-6 mg	<=3 mg	Placebo
Baseline	N	475	295	679	220	753
	Mean	67.6	65.8	67.6	67.4	67.7
	SD	12.25	10.84	11.75	12.25	10.85
	Median	66.0	65.0	67.0	66.0	67.0
Endpoint	N	475	295	679	220	753
	Mean	65.7	65.0	67.3	67.2	68.5
	SD	11.73	9.52	11.82	11.50	11.92
	Median	64.0	64.0	66.0	66.0	67.0
Change	N	475	295	679	220	753
	Mean	-2.0	-0.8	-0.3	-0.2	0.7
	SD	10.49	10.12	10.02	9.45	10.33
	Median	-2.0	-1.0	0.0	0.0	0.0

Integrated Summary of Safety: Theme 8 (Page 2 of 5)
 Table 8.1.1.2

ECGs: ENA 713 (>9-12 mg/day, >6-9 mg/day, >3-6 mg/day, <=3 mg/day) and Placebo
 Change from Baseline to Endpoint
 PQ or PR Interval (msec)
 Phase III Controlled Studies

Statistic		>9-12	>6-9 mg	>3-6 mg	<=3 mg	Placebo
		mg				
Baseline	N	465	286	659	209	736
	Mean	162.4	166.7	162.0	163.8	163.0
	SD	25.82	29.05	27.55	24.96	25.29
	Median	160.0	162.5	160.0	162.0	160.5
Endpoint	N	465	286	659	209	736
	Mean	164.5	166.0	163.1	163.0	163.1
	SD	25.82	32.30	27.43	25.48	24.65
	Median	161.0	162.0	160.0	159.0	160.0
Change	N	465	286	659	209	736
	Mean	2.1	-0.6	1.1	-0.8	0.0
	SD	15.13	16.88	15.32	18.30	14.42
	Median	3.0	-2.0	1.0	-1.0	0.0

Integrated Summary of Safety: Theme 8 (Page 3 of 5)

Table 8.1.1.2

ECGs: ENA 713 (>9-12 mg/day, >6-9 mg/day, >3-6 mg/day, <=3 mg/day) and Placebo
 Change from Baseline to Endpoint
 QRS Duration (msec)
 Phase III Controlled Studies

Statistic		>9-12	>6-9 mg	>3-6 mg	<=3 mg	Placebo
		mg				
Baseline	N	475	295	678	220	753
	Mean	88.7	88.2	88.2	87.7	87.4
	SD	12.94	15.21	14.62	15.20	14.06
	Median	87.0	85.0	85.0	84.0	85.0
Endpoint	N	475	295	678	220	753
	Mean	88.6	88.3	88.6	88.2	87.9
	SD	13.08	14.71	14.65	16.21	14.04
	Median	87.0	86.0	86.0	85.5	85.5
Change	N	475	295	678	220	753
	Mean	-0.1	0.1	0.3	0.6	0.4
	SD	8.87	8.93	8.15	8.15	7.81
	Median	0.0	0.0	0.0	0.0	0.0

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Integrated Summary of Safety: Theme 8 (Page 4 of 5)

Table 8.1.1.2

ECGs: ENA 713 (>9-12 mg/day, >6-9 mg/day, >3-6 mg/day, <=3 mg/day) and Placebo
 Change from Baseline to Endpoint
 QT Interval (corrected) (msec)
 Phase III Controlled Studies

Statistic		>9-12 mg	>6-9 mg	>3-6 mg	<=3 mg	Placebo
Baseline	N	475	295	679	220	753
	Mean	405.7	408.2	407.9	411.0	408.0
	SD	26.83	26.82	27.98	27.52	25.89
	Median	404.0	408.0	407.0	412.0	408.0
Endpoint	N	475	295	679	220	753
	Mean	403.5	406.3	406.7	409.3	408.1
	SD	27.45	25.16	28.86	26.00	27.09
	Median	402.0	406.0	405.0	408.0	407.0
Change	N	475	295	679	220	753
	Mean	-2.2	-1.9	-1.2	-1.7	0.1
	SD	26.12	23.20	22.81	23.78	24.42
	Median	-4.0	-2.0	-1.0	-1.5	0.0

Sponsor's ISS Table 8.2.1.2 (Table 46 below) summarizes the treatment emergent abnormalities for the 4 different dosing levels of drug and for placebo in the grouped controlled trials. There were no significant differences noted between the placebo and Exelon groups. The most common abnormality reported was first degree block but the sponsor concludes that there is no evidence of a treatment difference on these analyses. The risk of first degree block was 6% for the placebo group, 9% for the highest dose group and the lowest dose group, with the other dose groups at 7% and 5%.

Individual studies were examined for similar changes in EKG intervals and EKG abnormalities. Study 303, did suggest an effect of Exelon on heart rate. In Study 303, mean decreases from baseline in pulse rate were statistically significantly greater in the 6-12 mg/day group than in the placebo group at most evaluations from Week 10 onward. The difference was on the order of 1-2 bpm. The sponsor noted that bradycardia was reported as an AE in 3 patients in Study 303 in the 6-12 mg/day group. In one of the cases, it contributed to discontinuation (Patient 24016) at a rate near 50 bpm. Another patient (Patient 02016 in the 1-4 mg/day group) also discontinued for bradycardia, a supine pulse of 42 bpm.

In Study 304, the mean decrease in pulse and the mean increase in PR interval were both statistically significantly different for drug vs. placebo at several timepoints, but the differences were very small.

Table 46: ECG Abnormalities in Phase 3 Controlled Trials

Integrated Summary of Safety: Theme 8
 Table 8.2.1.2
 ECGs: ENA 713 (>9-12 mg/day, >6-9 mg/day, >3-6 mg/day, <=3 mg/day) and Placebo
 Incidence of Newly Occurring or Worsening Abnormalities
 Phase III Controlled Studies

Preferred Term	>9-12 mg N = 476		>6-9 mg N = 295		>3-6 mg N = 679		<=3 mg N = 224		Placebo N = 756		Total N = 2430	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Patients with any abnormality	84 (18)	40 (14)	100 (15)	36 (16)	105 (14)	1365 (15)						
1ST DEGREE BLOCK	43 (9)	20 (7)	34 (5)	21 (9)	42 (6)	160 (7)						
APC	3 (1)	1 (<1)	7 (1)	2 (1)	6 (1)	19 (1)						
ARTIFICIAL PACEMAKER	1 (<1)	0 (0)	0 (0)	0 (0)	3 (<1)	4 (<1)						
ATRIAL FIBRILLATION	4 (1)	1 (<1)	4 (1)	3 (1)	4 (1)	16 (1)						
ATRIAL FLUTTER	1 (<1)	1 (<1)	1 (<1)	0 (0)	0 (0)	3 (<1)						
AV WENCKEBACH	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	2 (<1)						
ECTOPIC ATRIAL	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)						
INCOMPLETE RBBB	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)						
INFERIOR (2), 3, F	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)						
INTRAVENTRICULAR COND. DELAY	1 (<1)	0 (0)	1 (<1)	1 (<1)	1 (<1)	4 (<1)						
JUNCTIONAL	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	1 (<1)						
JUNCTIONAL RHYTHM	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	1 (<1)						
LEFT ANTERIOR HEMIBLOCK	0 (0)	1 (<1)	2 (<1)	0 (0)	1 (<1)	4 (<1)						
LEFT BUNDLE BRANCH BLOCK	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)						
LEFT POSTERIOR HEMIBLOCK	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)						
LEFT VENTRICULAR HYPERTROPHY	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)						
RIGHT BUNDLE BRANCH BLOCK	4 (1)	1 (<1)	1 (<1)	0 (0)	0 (0)	4 (1)						
ST SEGMENT DEPRESSED	2 (<1)	1 (<1)	5 (1)	1 (<1)	3 (<1)	12 (<1)						
T WAVES FLAT	3 (1)	0 (0)	6 (1)	1 (<1)	2 (<1)	12 (<1)						
T WAVES INVERTED	7 (1)	1 (<1)	10 (1)	2 (1)	7 (1)	27 (1)						
U WAVES ABNORMAL	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	2 (<1)						
VPC	27 (6)	13 (4)	45 (7)	8 (4)	43 (6)	136 (6)						

Discontinuations due to EKG abnormalities are not discussed in the EKG section of the ISS. Section 6.2.4 of the ISS, Adverse Dropouts, reports that across all studies, there were 20 dropouts among the drug groups (1%) for heart rate and rhythm disorders and 0 (0%) among the placebo patients. The majority of these discontinuations were >75 years of age. Sponsor's Table 6.2.4.4 (Table 47 below) lists the 10 discontinuations from the controlled trials, including one case of AV block and 2 cases of bradycardia.

Sponsor's Table 6.2.4.7 (Table 48, page 67) lists patients who were adverse dropouts because of abnormal ECG findings. Among these patients is a placebo patient with first degree block and a drug treated patient with AV block. The treated patient, number 2080 (although the CRF and patient narrative give the patient number as 0280), was an 81 year old male s/p coronary bypass surgery and previous M.I., who had a baseline PR interval of 260msec. Two weeks later, the PR was found to be 320msec and it appears that the patient was hospitalized. The next day the PR interval was 360msec and treatment was discontinued. The daily dose at time of discontinuation was 3.5mg/day (patient was assigned to the 9mg/day group and was being titrated upward by protocol). Four days after stopping study drug, the PR interval had returned to 260msec. According to the patient narrative submitted in the study report, the return to baseline value was thought to support a role of Exelon in prolonging the PR interval. The sponsor's outside cardiology consultant's summary follows on the next page and presents a less certain view.

Table 47: Adverse Dropouts due to Heart Rate and Rhythm Disorders

**Text Table 6.2.4.4:
 Individual Patients Who Were
 Adverse Dropouts Because of Heart Rate and Rhythm Disorders**

Study	Patient Number	Age/Sex/Race	ENA Dose	Days on ENA	ADO Description
B303	24016	78/F/CA	6 mg/d	67	ADO: Bradycardia Considered probably related by Investigator
	36008	70/F/CA	12 mg/d	76	SAE/ADO: Arrhythmia Considered unlikely related by Investigator
B304	03007	62/M/CA	5 mg/d	20	ADO: Palpitation Considered possibly related by Investigator
B351	02080	81/M/CA	3 mg/d	16	SAE/ADO: AV Block Considered possibly related by Investigator
	06024	81/F/CA	4 mg/d	43	ADO: Atrial fibrillation Considered possibly related by Investigator
	10067	85/F/CA	3.5 mg/d	44	ADO: Palpitation Considered definitely related by Investigator
	14021	76/M/CA	6 mg/d	115	SAE/ADO: Atrial fibrillation Considered not related by Investigator
E352	07031	82/M/CA	10.5 mg/d	73	ADO: Arrhythmia Considered possibly related by Investigator
	08009	80/F/CA	7 mg/d	29	ADO: Bradycardia Considered possibly related by Investigator
	20014	86/F/CA	3 mg/d	5	ADO: Tachycardia Considered possibly related by Investigator

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Table 48: ECG Associated Adverse Dropouts

**Text Table 6.2.4.7:
 Individual Patients Who Were Adverse Dropouts
 Because of Abnormal ECG Findings**

Study	Patient Number	Age/Sex/Race	ENA Dose	Days on ENA	Abnormal Biological Finding
B103	27009*	83/M/CA	4 mg/d	53	ADO: Atrial fibrillation
	36006*	70/M/CA	4 mg/d	15	ADO: Bradycardia
B105	01032*	82/F/BL	4 mg/d	14	ADO: Atrial fibrillation
B303	15002	66/M/CA	12 mg/d	121	ADO: Right bundle branch block, left anterior hemiblock
	24016*	78/F/CA	6 mg/d	67	ADO: Bradycardia
B304	01001	71/F/CA	9 mg/d	42	ADO: Left anterior hemiblock
	02012	78/M/CA	2 mg/d	16	ADO: Atrial fibrillation, PVCs, depressed ST segment, flat T waves
	18010	84/F/CA	12 mg/d	58	ADO: PVCs
	18014	70/F/CA	placebo	NA	ADO: Bradycardia, first degree block
E351	02080*	81/M/CA	3 mg/d	16	SAE/ADO: AV block
	06024*	81/F/CA	4 mg/d	43	ADO: Atrial fibrillation
	14021*	76/M/CA	6 mg/d	115	SAE/ADO: Atrial fibrillation
E352	14005	80/F/CA	6 mg/d	29	ADO: Bradycardia
	08009*	80/F/CA	7 mg/d	29	ADO: Bradycardia
	20014*	86/F/CA	3 mg/d	5	ADO: Tachycardia
E353	210013*	77/M/CA	8 mg/d	245	SAE/ADO: Bradycardia
E355	02106*	59/F/CA	3 mg/d	25	ADO: Tachycardia
	09107*	77/F/CA	3 mg/d	64	SAE/ADO: Cardiac arrest
	30108*	67/M/BL	9 mg/d	56	SAE/ADO: Myocardial ischemia

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Treatment Group: ENA 713 9 mg
Patient No. 02080 Narrative Classification: Significant ECG Abnormality

ECG Abnormality:
1. Baseline PR \leq 260 (224 msec) and treatment PR $>$ 280 (312 msec)

Demographics:
Age (yrs): 81 Race: Caucasian Sex: Male

Clinical Summary: This patient received 9 mg of ENA 713 from 9/7/95 through 9/22/95. All doses were taken per protocol. On the baseline visit (-6) and on visits 2, 2.1, and 3, right bundle branch block and first degree block were noted. On visits -6 and 3, VPC was also noted.

Relevant Ongoing Diagnoses: Diabetes, arthritis of back, grade IV/VI systolic murmur, benign prostate hypertrophy, and urinary incontinence. Myocardial infarction (1975 and 1989), bypass surgery (1975 and 1989).

Concomitant Medications/Therapies: Tylenol, Micronase, and Procardia.

Dr. Morganroth's assessment: This ECG abnormality on 9 mg of ENA 713 is of unknown cause.

Although not a discontinuation, Patient 3006 in Study 304 merits further discussion. This patient developed first degree AV block at week 12 of the study, but continued on drug through the end of the study. _____ notes that the patient received a pacemaker post-treatment, but _____ was unable to locate a narrative or further information beyond this.

Study: 3004
Treatment Group: ENA 713 TID
Patient No. 03006 Narrative Classification: Significant Cardiovascular Event

1. Atrioventricular block

Demographics:
Age (yrs): 67 Race: Caucasian Sex: Female

Clinical Summary: The patient was enrolled in the ENA 713 TID from 7/13/95 to 1/9/98. All doses were taken per protocol. During the maintenance phase on 10/5/95, the patient experienced atrioventricular block and this continued through the end of the study.

Relevant Ongoing Diagnoses: Hypothyroidism, left bundle branch block and vertigo.

Concomitant Medications/Therapies: Cod-liver oil, Regulin, Lintal (ibuprofen), paracetamol, thyroxine and pacemaker (post treatment).

Dr. Morganroth's assessment: This vascular event of atrioventricular block on ENA 713 TID is of unknown cause.

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Serious cardiac events, like discontinuations for EKG abnormalities, are not discussed in the EKG section of the ISS.

One serious AE that occurred in an open-label extension study, Study 353, is of note. After 1 year on Exelon, Patient 213002 developed complete heart block, a pulse of 30, dizziness, and required a pacemaker. The patient continued on Exelon after the pacemaker was placed.

The sponsor performed analyses by gender, race, and age without identifying any specific cardiac risk groups. However, note that for patients >85 years old, 37% had new or worsened EKG abnormalities during the controlled trials compared to 19% of placebo patients (Sponsor's Table 8.3.6.1); the risk of first degree block in the pooled controlled trials ranged from 8% in the placebo group to 42% in the lowest dose group; the risk was 10%, 27%, and 8% in the other dose groups, ascending from lower to highest dose group (Sponsor's Table 8.2.6.2, Table 49).

Table 49: ECG Abnormalities in Phase 3 Controlled Trial, Patients > 85 years old

Integrated Summary of Safety: Theme 8 (Page 3 of 3)
 Table 8.2.6.2
 ECGs: ENA 713 (>9-12 mg/day, >6-9 mg/day, >3-6 mg/day, <=3 mg/day) and Placebo
 Incidence of Newly Occurring or Worsening Abnormalities - Demographic Variable (Age)
 Phase III Controlled Studies

Preferred Term	> 85 (years)					
	>9-12 mg	>6-9 mg	>3-6 mg	<=3 mg	Placebo	Total
	N = 12	N = 15	N = 20	N = 12	N = 26	N = 85
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any abnormality	2 (17)	6 (40)	7 (35)	6 (50)	4 (15)	25 (29)
1ST DEGREE BLOCK	1 (8)	4 (27)	2 (10)	5 (42)	2 (8)	14 (16)
APC	1 (8)	0 (0)	0 (0)	1 (8)	0 (0)	2 (2)
ARTIFICIAL PACEMAKER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ATRIAL FIBRILLATION	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ATRIAL FLUTTER	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AV WENCKEBACH	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	1 (1)
ECTOPIC ATRIAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
INCOMPLETE RBBB	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
INFERIOR (2), 3, F	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
INTRAVENTRICULAR COND. DELAY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
JUNCTIONAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
JUNCTIONAL RHYTHM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LEFT ANTERIOR HEMIBLOCK	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LEFT BUNDLE BRANCH BLOCK	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LEFT POSTERIOR HEMIBLOCK	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LEFT VENTRICULAR HYPERTROPHY	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
RIGHT BUNDLE BRANCH BLOCK	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	1 (1)
ST SEGMENT DEPRESSED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
T WAVES FLAT	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	1 (1)
T WAVES INVERTED	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
U WAVES ABNORMAL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
VPC	0 (0)	2 (13)	5 (25)	0 (0)	1 (4)	8 (9)

Controlled Studies - B303, B304, B351, and B352

Analyses by drug-drug and drug-disease interactions were not presented.

Within the individual study reports are presented shift tables with numbers of patients shifting from relatively normal values to arbitrarily defined "abnormal" values. The shift tables are not presented this way for the pooled data in the ISS. The tables for PR interval are reproduced below for 3 of the 4 controlled trials.

Table 50: PR Interval Abnormalities in Studies B303, B351, B352

SD2 EMA 713 Study No. B303
 Table 3
 Shift Analysis of Number and Percent of Patients Whose PR Intervals Changed
 From ≤ 260 to > 260 , or > 260 to ≤ 260

	POST BASELINE PR INTERVAL											
	6-12mg				1-4mg				PBO			
	≤ 260		> 260		≤ 260		> 260		≤ 260		> 260	
	N	%	N	%	N	%	N	%	N	%	N	%
BASELINE PR INTERVAL												
≤ 260	235	100.00	0	0	227	99.56	0	0	226	99.56	0	0
> 260	0	0	0	0	0	0	1	0.44	1	0.44	0	0

SD2 EMA 713 Study No. B351
 Table 3
 Shift Analysis of Number and Percent of Patients Whose PR Intervals Changed
 From ≤ 260 to > 260 , or > 260 to ≤ 260

	POST BASELINE PR INTERVAL															
	9 mg			6 mg			3 mg			PBO						
	≤ 260		> 260	≤ 260		> 260	≤ 260		> 260	≤ 260		> 260				
	N	%	N	%	N	%	N	%	N	%	N	%				
BASELINE PR INTERVAL																
≤ 260	163	96.45	3	1.78	162	95.86	6	3.55	156	98.73	1	0.63	166	99.40	0	0
> 260	0	0	3	1.78	0	0	1	0.59	1	0.63	0	0	0	0	1	0.60

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 Table 6
 Number and Percent of Patients with PR Intervals ≤ 260 at Baseline and > 260 at Post Baseline
 Pairwise Comparisons Between Treatment Groups

Statistic					Chi-Square Comparisons					
	9 MG	6 MG	3 MG	PBO	9 MG VS PBO	6 MG VS PBO	3 MG VS PBO	9 MG VS 6 MG	9 MG VS 3 MG	6 MG VS 3 MG
Total Pts.	163	169	158	167						
N	3	6	1	0	0.248	0.030 *	0.486	0.502	0.624	0.122
%	1.8	3.6	0.6	0						

BEST POSSIBLE COPY