CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-823

CHEMISTRY REVIEW(S)

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL SAFETY REVIEW OF NDA

Brand Name:	**Exelon**
Generic Name:	**rivastigmine tartrate**
Sponsor:	**Novartis**
Indication:	**dementia of Alzheimer's type**
NDA Number:	**20-823**
Original Receipt Date:	**4/7/97**
Clinical Reviewers:	**Armando Oliva, M.D.** **Judy Racoosin, M.D.** **John Feeney, M.D.**
Review Author:	**Armando Oliva, M.D.**
Review Completed:	**3/10/98**

Table of Contents

Table of Figures

Table of Tables

1. Review Sources

This is the safety review for Exelon tablets. The sources used for the review are outlined in Table 1.

Table 1: NDA Materials used in Review

Source	Submission Date	Material
section2.pdf	4/7/97	NDA summary
iss.pdf	4/7/97	Integrated Summary of Safety
study reports (pdf format)	4/7/97	Study reports for B303, 304, 351, 352, 303, 353
CRF's of all deaths	4/7/97	Case Report Forms (electronic format) of all deaths
General Correspondence	8/21/97	analyses of efficacy and safety excluding Borison and Diamond centers
120 Day Safety Update	8/27/97	electronic submission, also containing final safety report for B304

2. Background

2.1 Indication

Exelon's proposed indication is for the treatment of mild to moderately severe dementia of the Alzheimer's type.

2.2 Important Information from pharmacologically related agents

Exelon is a centrally active pseudo-irreversible inhibitor of acetylcholinesterase. Therefore, it has a similar mechanism of action as tacrine (Cognex®) and can be expected to produce similar cholinergic-mediated adverse effects.

2.3 Administrative History

End of Phase 2 Meeting	9/19/94
Pre-NDA Meeting	11/25/96

Sandoz submitted the proposed end of phase 3 program on 6/22/94 and the end of phase 2 meeting was held the following September 19th. The following agreements were reached.

- The size of the safety database would include approximately 2000 patients exposed to the drug as well as a few hundred patients with greater than 6 months exposure
- Patients enrolled must meet DSM-IV criteria for dementia, and NINCDS-ARDA criteria for probable Alzheimer's Disease
- Study duration should by 26 weeks of double-blind treatment and an open label follow-up treatment.
- Inclusion of patients who discontinued treatment (retrieved dropout population). Patients who discontinued from the double-blind studies were asked to return for all scheduled efficacy evaluations, and if they complied were eligible for open label treatment

In a letter dated 3/2/95, the Division requested that Sandoz modify the procedure that the rater used when rating the patient's global performance using the CIBIC+ scale to insure that the examiner did not have access to any previous post-baseline CIBIC+ data. This was approved for all four controlled studies (B352, B303, B351, and B304). However 4 centers in study B303 (24, 28, 29, and 42) did not fully comply. Therefore 36 patients had ratings performed with

raters who were not blinded to previous CIBIC+ findings. Because of the risk of bias, an analysis was conducted that excluded the data for these 36 patients.

In conversations dated 3/14/96 and 3/15/96 between Robbin Nighswander and Rob Kowalski, a basic NDA submission strategy was outlined:

- Proof of efficacy will be based on the results from two completed trials, with safety established on data from approximately 2000 patients and 300 non-patient volunteers.
- The long term safety will be established in over 100 patients treated for one year and several hundred treated for six months or longer.
- Safety assessment will include drug-drug interactions and assessment of safety in very old patients (>85 yrs) and in those with significant illnesses (cardiovascular, respiratory).
- Evaluation of an improved titration rate and agreement for inclusion in the labeling.
- No statistical penalty for performing an interim safety analysis on ongoing pivotal studies, provided the sponsor takes appropriate measures to ensure that no bias is introduced.
- A plan for reporting safety data was determined.

The pre-NDA meeting was held on 11/25/96. The FDA agreed on the filing strategy, the ISS and ISE plans. In addition, the FDA requested that Sandoz provide specific information on patients receiving treatment at high doses 9-12 mg) including numbers exposed, the duration of treatment, and any relevant safety issues.

2.4 Proposed Labeling

I briefly review the pertinent sections of the sponsor's proposed labeling here. A more comprehensive review is located in section 9, Labeling Review, page 116.

2.4.1 Indications and Usage

2.4.3 Warnings

- incidence of

2.4.4 Precautions

- Exelon has the ability to interfere with anticholinergic medications.
- A synergistic effect may be expected when used with succinylcholine or other cholinergic agents.

[redacted]

[redacted]

[redacted]

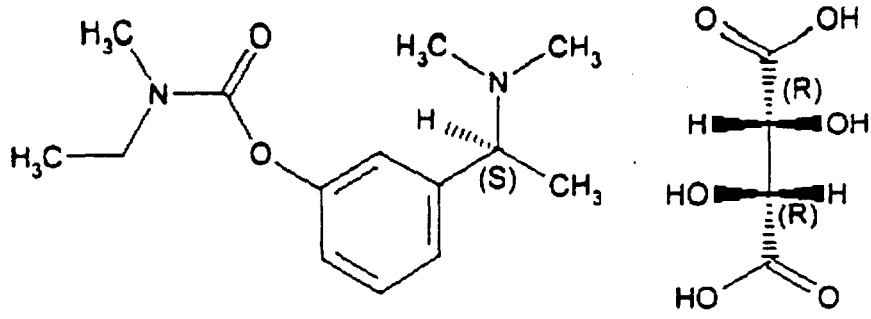
2.5 Foreign Marketing

Exelon is not marketed outside the United States.

3. Chemistry, Manufacturing and Controls

Generic Name: **rivastigmine tartrate**
Chemical Name: **(S)-N-Ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate, hydrogen-(2R,3R)-tartrate**
Alternative Name: **ENA 713**
Molecular Formula: **$C_{14}H_{22}N_2O_2 \cdot C_4H_6O_6 = C_{18}H_{26}N_2O_8$**
Molecular Weight: **250.3 + 150.1 = 400.4**
Appearance: **white or off-white, finely crystalline powder**

Figure 1: Chemical Structure - Rivastigmine hydrogen tartrate



After storage at 50 °C and 60 °C in tight packaging, no change of quality is observed. These results confirm the supportive development data that SDZ ENA 713 is considered to be a thermally stable substance.

After exposure to light [redacted], no change of quality is observed. These results confirm the supportive development data that SDZ ENA 713 is not sensitive to light and consequently, no special protection from light is necessary.

Under humidity levels above 55% relative humidity, it absorbs moisture, turning into a liquid. Therefore the protection from humidity is necessary. The results of the long term stability testing, as well as accelerated and stress testing of pilot batches of the drug substance confirm the supportive data results. Results of long term stability or re-control of the stock of three development batches show that no change of quality occurs after 5 years of storage. Therefore the same re-test periods of 5 years and storage instructions are assigned for the pilot batches.

4. Animal Pharmacology

4.1 Pharmacology

Carbamate inhibitors (like physostigmine and rivastigmine) mimic acetylcholine (ACh) as a substrate for acetylcholinesterase (AChE) by forming a carbamoylated instead of an acylated complex with the enzyme. The hydrolysis and reactivation of carbamoylated AChE is considerably longer ($T_{1/2}$ is 2 hours for physostigmine and >24 hours for rivastigmine). Sequestration of AChE in its carbamoylated form precludes further enzyme-catalyzed hydrolysis of ACh for an extended period of time. This is the basis for the "pseudo-irreversible inhibition" of AChE. The mechanism of AChE inhibition by tacrine is completely different, comprising both competitive and non-competitive inhibition.

Rivastigmine is metabolized primarily by its target enzyme, cholinesterases, to the reaction product 226-90. This compound itself exhibits AChE (mainly competitive) inhibition at higher concentrations *in vitro*.

Rivastigmine has no affinity for muscarinic receptors nor for α- and β-adrenergic, dopaminergic, serotonergic, or opioid binding sites as demonstrated *in vitro* using rat brain membranes.

4.2 Toxicology

4.2.1 Single Dose Toxicity

The oral LD_{50} in mice, rats, and dogs was 9-15 mg/kg, 13-22 mg/kg, and 2-8 mg/kg, respectively. Clinical signs included decreased locomotor activity, loss of righting reflex, ataxia, immobility, twitching, tremors, vomiting, gasping, labored and shallow breathing, tachypnea, hypersalivation.

4.2.2 Multidose Toxicity / Carcinogenicity

In an 8 week dose range finding study in mice (0-10 mg/kg/day), treatment related mortality occurred at 10 mg/kg/day. Dose dependent clinical signs were consistent with excessive cholinergic stimulation. Mean body weights were decreased at 5 mg/kg/day by 5-15%. Mean food consumption was decreased at 4 and 5 mg/kg/day. There were no treatment related macroscopic or microscopic findings or organ weights.

In a 13 week oral mouse toxicity study (0-120 mg/kg/day), reduced body weights and food consumption were observed. One high dose male was found dead prior necropsy at week 14. Cholinergic mediated effects were seen. No treatment related macroscopic findings or effects on organ weights were seen.

The mouse carcinogenicity study was negative.

The sponsor conducted a 15 day, 4-, 13-, 26-, and 52-week oral studies, a 17 day i.v. study, and an oral (gavage) carcinogenicity study in rats. Doses ranged up to 9.6 mg/kg/day. In general, cholinergic effects were seen, as well as decreased body weights and food consumption (generally dose-dependent). 6 deaths in the 26 week study were seen: 5 were deemed related to venipuncture or dosing procedure, the cause for the sixth death was unknown. Microscopic findings in the naturally dying animals during the year-long study disclosed pulmonary edema, congestion, bronchopneumonia, and aspiration pneumonia. Very subtle and not dose-related bile duct proliferation was observed in a few sacrificed animals at the end of the treatment phase.

The rat carcinogenicity study, increased cysts in the adrenal cortex of females was noted at 1.8 mg/kg/day. Pituitary neoplasia (adenoma and carcinoma) was observed in all groups, including controls, and was considered to be a spontaneous tumor in this species.

The sponsor conducted one 2-week, two 4-week, one 26-week, and one 52-week toxicity study in dogs. Dose ranged 0-4 mg/kg/day. Cholinergic effects, decreased body weight were seen. Blood in feces and rectal bleeding was seen at the higher doses. There was no effect on hematology, Potassium was slightly elevated in one high dose animal and was felt to be due to excessive vomiting and diarrhea. No ECG or ophthalmoscopic effects were seen. Multifocal granulation with hemorrhage in the serosa of the small and large intestine of one high dose 26-week dog was seen, correlating with macroscopic findings. Two dogs in the 52-week study died after the first week. The first dog (2.5/2.1 mg/kg/day) died from intussusception from intestinal hypermotility. The cause of death of the second was unknown. A third dog in the same study died at day 241 with macroscopic and microscopic findings of lymphoid depletion of the spleen, thymus, and lymph nodes, and hemorrhage of the heart, intestine (with granulation), and lymph

nodes. Probable cause of death was cardiac hemorrhage. One tonic-clonic convulsion was seen in a 0.6 mg/kg/day male at week 39, approximately 4 hours post-dose. A high dose (2.5/2.1 mg/kg/day) female had convulsions on two separate occasions (week 37 and 46).

The sponsor conducted a 2 week oral range-finding study in monkeys. Doses up to 10 mg/kg/day were used. Cholinergic effects, and decreased body weight were seen. There was no mortality.

Six genotoxicity tests were performed. One was weakly positive (Chinese hamster cells chromosome aberration model). The *in vivo* studies were negative. Embryofetal and teratogenic effects were not observed at doses up to 4 mg/kg/day in rats and rabbits.

5. Clinical Data Sources

5.1 Primary Data Sources

5.1.1 Demographics

5.1.1.1 All Studies

A total of 3,591 patients and normal subjects were exposed to Exelon in the clinical development program. A complete listing of the Clinical Pharmacology (Phase I) Studies is listed in Appendix A, page 128. A complete listing of the Patient Treatment Studies (Phases 2 and 3) is located in Table 6, page 18.

5.1.1.2 Clinical Pharmacology

There were 585 subjects participated in phase I (clinical pharmacology) studies. Four hundred forty-four (444) were male and the remaining 139 were female, resulting in a male to female ratio of 3:1. Seventy-six percent (76%, n=445) were Caucasian, 2% were black (n=11) and 3% (n=20) were Asian-Oriental. More complete demographic information is contained in Appendix A, page 128.

5.1.1.3 Patient Treatment Trials

The sponsor provided demographic datasets for all the phase 3 trials, and the US/European phase 2 trials (103, 104, 105). Using these datasets, I have calculated the follow demographic summary statistics.

The mean age of the patients was 72.8 (S.D. ±8.3, range 41-95). The median age was 74. Forty-two percent (42%) of the patients were male and 58% were female. The vast majority of patients (>94%) were white. Four percent (4%) were black, and 0.05% were oriental. The remaining 1.5% were classified as "other."

In the four phase 3 placebo-controlled trials (B303, B304, B351, B352), 2,472 received treatment (1707 with Exelon, and 765 with placebo). Pertinent demographic data for this important population is shown in Table 2, and is very similar to the overall patient treatment trial population described above.

This controlled trial study population had a mean age of 73 years. Fifty-eight percent (58%) were female and 42% were male, and the vast majority (94%) were white. Grouping by treatment group (Exelon vs. placebo) shows no substantial differences in the main three demographic parameters of age, sex, and race between the treatment groups.

Table 2: Demographics for Phase 3 Controlled Trials (B303, B304, B351, B352)

		PBO n=765	Exelon n=1707	Total N=2472
Age (yrs)	mean	73.2	73	73.1
	SD	7.9	8.2	8.1
	median	74	74	74
	min	45	41	41
	max	90	95	95
Sex	male	319	710	1029
	%	41.7	41.6	41.6
	female	446	997	1443
	%	58.3	58.4	58.4
Race	white	727	1605	2332
	%	95.0	94.0	94.3
	black	27	68	95
	%	3.5	4.0	3.8
	oriental	4	6	10
	%	0.5	0.4	0.4
	other	7	28	35
	%	0.9	1.6	1.4

5.1.2 Extent of Exposures

5.1.2.1 Methods

Exposure data for the total population is presented for all clinical pharmacology (Phase 1) and therapeutic (Phase 2 and Phase 3) studies. For the therapeutic studies, exposure by dose group is also presented. The design of these studies required patients to be titrated with study drug and then receive either a fixed dose or fixed range of Exelon. Due to these differences in study design, the exposure by dose information is presented based on non-overlapping dose ranges for mean, modal, and maximum dose, and by demographic variables (age, sex, and race).

The calculations of mean, modal, and maximum dose were based on the information recorded in the Drug Administration Record during each study. These data may represent estimates in cases where the records maintained by the patient were inconsistent with the amount of drug returned. These types of errors were insignificant in the calculation of the overall dose for a patient.

A small number of patients (0.1% of the population) were treated in more than one study or were re-entered under a different patient number in the same study. These patients were counted each time they were entered in a study. This procedure was used because of the extreme difficulty in trying to eliminate the double counting programmatically and because the effect of this double counting is minimal. There was a total of 18 patients which were counted twice (Appendix B; page 134). Two (2) were in the phase 3 program. The remaining 16 were in phase 2 studies. All other patients were counted only once.

5.1.2.2 Study Groupings

The study groupings were chosen to provide exposure information that would be useful in the interpretation of the safety data in subsequent sections (sponsor Table 3).

Table 3: Study Groupings

Groupings	Dose Breakout
All Studies	ENA (Total)
All Therapeutic Studies	ENA (Total) vs. ENA (by Dose)
All Phase 3 Studies	ENA (Total) vs. ENA (by Dose)
Phase 3 Controlled Studies	ENA (Total) vs. ENA (by Dose)
Phase 3 Controlled Studies - N. Am vs Non- N. Am	ENA (Total) vs. ENA (by Dose)
Phase 2 Studies	ENA (Total) vs. ENA (by Dose)
Phase 2 Japanese Studies	ENA (Total)

5.1.2.3 All Studies

Of the 3,591 patients and subjects in the Exelon clinical development program, 2,424 (67%) were treated for 12 or more weeks, 1,249 (35%) were treated for 26 or more weeks, and 220 (6%) were treated for 52 or more weeks. These exposures satisfy ICH guidelines for long term exposure. A summary table of exposures by mean daily dose and duration is shown in sponsor Table 4 (ISS, Text Table 3.5.1, page 3.16). A complete table of duration of exposures by study grouping is located in Appendix C, page 135.

Table 4: Cumulative Duration of Exposure, All Treatment Studies, By Treatment Dose

Mean Daily Dose mg/ day	Exposure (Weeks)											
	Any Exp. n (%)	≥1 n (%)	≥2 n (%)	≥4 n (%)	≥12 n (%)	≥26 n (%)	≥38 n (%)	≥52 n (%)	≥65 n (%)	≥78 n (%)	≥91 n (%)	≥104
≤3	535 (100)	514 (96)	485 (91)	451 (84)	378 (71)	128 (24)	6 (1)	4 (1)	0	0	0	0
>3 - 6	1266 (100)	1265 (100)	1244 (98)	1178 (93)	971 (77)	513 (41)	91 (7)	74 (6)	43 (3)	40 (3)	39 (3)	30 (2)
>6 - 9	586 (100)	586 (100)	586 (100)	584 (100)	456 (78)	248 (42)	47 (8)	33 (6)	0	0	0	0
>9 - 12	619 (100)	619 (100)	619 (100)	619 (100)	619 (100)	360 (58)	142 (23)	109 (18)	39 (6)	34 (5)	33 (5)	13 (2)
Total	3006 (100)	2984 (99)	2934 (98)	2832 (94)	2424 (81)	1249 (42)	286 (10)	220 (7)	82 (3)	74 (2)	72 (2)	43 (1)

5.2 Secondary Data Sources

5.2.1 Other Studies

No other studies are included in the NDA.

5.2.2 Post-marketing Experience

Exelon is not marketed outside the United States.

5.2.3 Literature

To the best of my ability to find one, a literature review section is not contained in the NDA.

5.3 Adequacy of Human Experience

Three-thousand five hundred ninety-one (3,591) patients have been exposed to Exelon in the clinical development program. Two thirds of these (67%) were treated for 12 or more weeks, 1,249 (35%) were treated for 26 or more weeks, and 220 (6%) were treated for 52 or more weeks. In my opinion, the human exposure to the drug is quite robust and the long term safety database easily exceeds ICH guidelines.

6. Human Pharmacokinetics

6.1 Background and Methods

Rivastigmine is a pseudo-irreversible inhibitor of acetylcholinesterase (AChE). It mimics acetylcholine as a substrate for AChE. Normally, acetylcholine is hydrolyzed and the enzyme is acetylated. The hydrolysis of AChE results in reactivation of the enzyme. Both events occur within a very short period.

In the case of rivastigmine, the drug is hydrolyzed and the enzyme is carbamoylated. However, hydrolysis and reactivation of the carbamoylated AChE occurs much more slowly. The slower regeneration of the enzyme activity compared to the hydrolysis of rivastigmine results in a time dependent divergence of PK and PD post-dose.

A total of 20 studies contain significant PK information. The pharmacokinetics of rivastigmine were studied in healthy young subjects, healthy elderly subjects, in subjects with renal impairment, hepatic impairment, in patients with normal pressure hydrocephalus, and in patients with mild to moderate Alzheimer's Disease. The actual studies in these populations are listed in FDA Table 5.

Table 5: Clinical PK Studies

Population	Study
healthy young subjects (open label)	A101, A102, B151, P106, W104, W361, W362, W363, W365
healthy young subjects (controlled)	W101, W251, W253
healthy elderly subjects	A103, W101
renal impairment	W253
hepatic impairment	W251
normal pressure hydrocephalus	A107
Alzheimer's Disease	B103, B104, B351, B352, B353, W252

The concentrations of rivastigmine and it's primary metabolite ZNS 114-666 were measured in plasma, urine, and cerebrospinal fluid (not all studies) using gas chromatography coupled with mass spectrometry. Further information on drug disposition was obtained by administering ^{14}C labeled rivastigmine and monitoring total radioactivity, parent drug, and metabolites (including ZNS 114-666) in biological fluids and excreta. The protein binding of the drug and the drug's interaction with oxidative metabolizing enzymes and potential interferences by concomitantly administered drugs were determined *in vitro* and *ex vivo* in selected studies. Cholinesterase activity in plasma, red blood cells, and cerebrospinal fluid was determined colorimetrically.

6.2 Absorption and Bioavailability

Rivastigmine is rapidly absorbed with T_{max} 0.8-1.2 hours. Absorption is nearly complete (>96% of administered dose) but bioavailability is lowered by pre-systemic biotransformation (oral/i.v. AUC ratio = 35.5%). Rivastigmine AUC increases more than proportionally with oral dose,

about 2 to 2.5 fold greater than expected for healthy subjects in the dose range 1 - 2.5 mg and for AD patients in the dose range 1.5 - 6 mg bid.

Intersubject variability is greater than intrasubject variability (60% vs. 23%). Inter-individual differences in body size significantly contribute to variability of bioavailability, with a small AD patient (40 kg) projected to show up to 3 fold and 2 fold greater AUC for rivastigmine and ZNS 114-666, respectively compared to a large patient of 90 kg.

6.3 Distribution

Rivastigmine is weakly plasma protein bound (36-48%). The blood/plasma ratio is 0.8 - 0.9 with 40-50% of drug being associated with red blood cells, independent of concentration. The volume of distribution for rivastigmine is 1.8-2.7 L/kg.

6.4 Metabolism

Rivastigmine is rapidly and extensively metabolized prior to elimination, principally via cholinesterase mediated hydrolysis of the carbamate moiety, to the phenolic metabolite (ZNS 114-666) which itself may experience N-demethylation and/or conjugation. The phenolic metabolite shows dose-proportional bioavailability, as opposed to the parent which shows greater than proportional increase of AUC with dose (see section 6.2). The drug does not inhibit the metabolism of typical cytochrome P450 isoenzyme substrates.

The phenolic metabolic product ZNS 114-666 shows no appreciable inhibition of acetylcholinesterase *in vitro* (< 10% activity of parent).

6.5 Elimination

The $T_{1/2}$ of rivastigmine is 0.76 ± 0.24 hours after 1 mg and 0.95 ± 0.35 hours after a 3 mg oral dose, representing principally bioconversion to its phenolic metabolite, which shows an apparent $T_{1/2}$ of appearance of 0.8 hours and declines with an apparent $T_{1/2}$ of 2.7 ± 0.39 hours.

The plasma clearance of rivastigmine is 133 L/h after 0.2 mg i.v., 70 L/h after 2.7 mg i.v. and is similar to the plasma perfusion rate of the liver, a major site of cholinesterase activity. There is no relevant accumulation of rivastigmine or ZNS 114-666 with chronic drug treatment. Steady state condition should be reached by the second drug dose.

Greater than 90% is eliminated in the urine and <1% in feces. There is no retention of drug.

6.6 Special Populations

The AUC of rivastigmine increased 58% (1 mg p.o.) and 70% (2.5 mg p.o.) in healthy elderly subjects (mean age 67 yrs) compared to body surface area matched young subjects (mean age 29). Exposures to the phenolic metabolite is similar. In AD patients, there are age related increases by 31-50% in the phenolic metabolite but there is no change in rivastigmine AUC (age range 50-92 years).

In hepatic impairment, reduced biotransformation is evidenced by a 2.3 fold higher rivastigmine AUC and 0.8 fold lower phenolic metabolite compared to age and gender matched healthy controls.

Reduced clearance compared to healthy controls is evidenced by a 2.6 fold higher rivastigmine and 1.6 fold higher ZNS 114-666 AUC in patients with moderate renal impairment (GFR 10-50 mL/min).

The relationship of dose with bioavailability in renal and hepatic impairment is not appreciably different from the relationship observed in healthy subjects. In AD patients, the plasma concentrations of drug and phenolic metabolite are generally higher than those encountered in healthy subjects, but there is no evidence of accumulation of drug.

6.7 Drug-Drug Interactions

Co-administration of rivastigmine with digoxin, warfarin, diazepam, or fluoxetine has no effect on the PK of either drug.

6.8 Conclusions

- Absorption of rivastigmine is complete and rapid, with T_{max} 0.8-1.2 hours.
- Bioavailability is reduced by first-pass metabolism, to 35.5% after a 3 mg dose. The AUC increases greater than proportionally with dose in all populations studied. Intersubject variability of bioavailability is about two to three fold greater than the intrasubject variability.
- Rivastigmine is completely metabolized, principally by the target cholinesterase enzyme, prior to elimination, which occurs exclusively via the urine (>90% drug and all metabolites within 24 hours). Elimination is rapid, with $T_{1/2}$ for parent drug of 0.8-1 hr and $T_{1/2}$ for metabolites of 3.5-3.9 hours.
- Food delays T_{max} to 1.4-1.6 hours and increases AUC by 20-31%.
- There is no evidence for drug accumulation in multiple PK studies.
- Elimination of drug is somewhat slower in healthy elderly compared to healthy young subjects and drug exposure is moderately increased. In AD, only small age related increases in metabolite (ZNS 114-666) are observed and there is no change in rivastigmine AUC.
- Decreased metabolism of the parent drug to the phenolic metabolite appears likely in subjects with liver dysfunction, and decreased elimination of parent drug and the phenolic metabolite appears to occur with renal disease. The observed differences compared to control subjects should be accommodated by the recommended dose titration scheme and do not necessitate specific dosing recommendations for these populations.
- No significant PK interactions occur between single doses of rivastigmine and digoxin (at steady state), warfarin, diazepam, or fluoxetine. The PD effects of digoxin and warfarin are not altered by rivastigmine.

7. Review of Clinical Studies

7.1 Clinical Pharmacology

7.1.1 Summary

A total of 30 clinical pharmacology studies were performed. The majority of these deal with the pharmacokinetics, pharmacodynamics, and safety and tolerability of orally administered rivastigmine given as a capsule. Nineteen (19) of these were PK studies on the service capsule formulation of rivastigmine. Three (3) studies addressed only pharmacodynamic effects of the drug. Seven (7) studies utilized alternative formulations (a slow-release capsule and a transdermal patch), and one (1) assessed the safety and tolerability of rivastigmine given intravenously.

The primary objective of most clinical pharmacology studies was assessment of the PK of oral rivastigmine. Safety data were reported for all clinical pharmacology studies. Of the studies using the service capsule, eight (8) of them evaluated single dose and multiple dose

pharmacokinetics, dose-dependence of PK, food interaction, absolute bioavailability, intrasubject variability, and bioequivalence of dosage forms in young non-patient volunteers.

Since most patients with AD are over 60 years old, several studies were conducted in elderly subjects. Three (3) studies addressed single dose PK and dose-dependency of PK in elderly non patient volunteers compared to the young. One study (B102) evaluated PK parameters in elderly patients with AD.

In order to elucidate the mechanism of action in man, 7 studies examined PD effects and PK/PD relationships. Two (2) studies were performed in subjects with liver or renal impairment. Four (4) drug interaction studies were also performed (digoxin, warfarin, diazepam, and fluoxetine). These drugs were chosen on the basis of their narrow margins of safety and/or frequency as concomitant medications in the target population. Seven (7) studies used alternative formulation: 2 used a slow-release capsule, and 5 evaluated a transdermal delivery system.

More complete descriptions of these studies are located in Appendix A, page 128.
These studies demonstrated that single and multiple oral doses up to 3 mg were safe and well tolerated in all groups, including patients with AD. Exceptions to be noted were that 2 mg was considered the maximum tolerated single oral dose in elderly men in Japanese Study ENA/AD-VD/P-1A and in elderly men and women in Study A103. Side effects reflect peripheral cholinergic activation. Single i.v. doses up to 2.7 mg were also safe and well tolerated (Study W104).

The pharmacokinetic data gathered from these studies are summarized in Section 6, Human Pharmacokinetics, beginning on page 15.

7.2 Clinical Trials

7.2.1 Background

A total of 14 studies comprise the Exelon phase 2 and phase 3 programs. Eight of these were controlled , and six were uncontrolled. In addition, there were 2 controlled extensions, 3 uncontrolled extensions, and 2 small European compassionate use programs These are shown in Table 6.

Table 6: Exposures in Phase 2 and Phase 3 Clinical Studies

Study No.	Location	N (PBO)	N (Exelon)
Phase 2 Controlled			
B103	EUR, CAN	133	269
B104	EUR, CAN	24	90
B105	US	10	40
OR1/ALZ/PH2L/01	JAP	53	117 [116][a]
Extension			
B103-E-01	EUR, CAN	50[b]	119[b]
B103-E-04	EUR, CAN	27[b]	64[b]
Sub-Total		**220**	**516 [515][a]**
Phase 3 Controlled			
B303	EUR, CAN, US	239	486 [484][a]
B304	EUR, S. AFR, AUSTR	117	229 [228][a]
B351	US	173	529 [522][a]
B352	US	235	464 [462][a]

Sub-Total		**764**	**1708 [1696][a]**
Total Controlled		**984**	**2224 [2211][a]**
Phase 2 Uncontrolled			
AD/EP-II	JAP		71
AD/VD-II	JAP		62
Extension			
B103-E06	EUR, CAN		43[c]
B104-E01	EUR, CAN		49[c]
B104-E02	EUR, CAN		41[a]
Compassionate Use			
B901	EUR		20[c]
B902	EUR		12[c]
Sub-Total			**133**
Phase 3 Uncontrolled			
Extension			
B305	EUR, CAN, S. AFR, AUSTR		99[c] [34][d]
B353	US		211[c] [69][d]
Titration			
B354	US		15
B355	EUR, US, AUSTR		548 [544][a]
Sub-Total			**666 [662][a]**
Total Uncontrolled			**799 [795][a]**
TOTAL – ALL PHASE 2/3 Studies		**984**	**3023 [3006][a]**

[a] [ ] patients who received study medication, and different from the number randomized or enrolled
[b] patients who participated in previous controlled studies are not counted in the total unless they previously received placebo
[c] Exelon patients who participated in controlled studies are not recounted in the uncontrolled studies total
[d] placebo patients who participated in controlled studies and are counted in Exelon total

7.2.2 Phase 2 Studies

7.2.2.1 Background

Four controlled Phase 2 clinical studies were conducted in 736 patients (B103, B104, B105, OR1/ALZ/PH2L/01). A total of 516 were randomized to Exelon and 515 actually received the drug. Two hundred twenty (220) received placebo (Table 6). These studies were primarily dose ranging, dose frequency and maximum tolerated dose trials. Whereas the phase I program established safety and tolerability up to 6 mg/day, the phase 2 program expanded the dosing range and evaluated doses of 2-12 mg/day. In addition, evidence of efficacy was also sought. All four were randomized, double blind, placebo controlled trials.

Two additional double blind extensions of B103 (E-01 and E-04) extended double blind treatment for an additional 8 weeks. These patients were then eligible to enter open label treatment.

Seven uncontrolled Phase 2 studies were conducted, involving a total of 225 patients, including 92 patients who had been previously exposed to Exelon in double blind studies. Therefore, 133 additional patients were enrolled. The uncontrolled Phase 2 studies included two tolerability studies in Japanese AD and vascular dementia patients (AD/EP-II and VD/EP-II), three open label extension studies (B103-E-06, B104-E-01, B104-E-02), and two compassionate need studies (B901 and B902).

7.2.2.2 Study B103

This study evaluated the efficacy and tolerability of Exelon administered at doses of 4 mg/day or 6 mg/day (administered twice daily) for 3 months, followed by a two week washout period. A

total of 402 patients were randomized: 133 to the 6 mg/d group, 136 to the 4 mg/d group, and 133 to placebo. Eighty-nine percent (89%, or 357 patients) completed the three months of treatment and 86% (346) completed the two week washout period.

Exelon was initiated at 1 mg bid, which was then titrated to the target dose level over a period of 1 week (2 mg bid) or 3 weeks (3 mg bid) using a fixed dose escalation schedule.

7.2.2.2.1 SAFETY

There was a higher incidence of AE's in the 3 mg bid group (77%) than the 2 mg bid (63%) and placebo (53%) groups. In addition, both treatment groups had a higher incidence of deaths (2%, 2%, 0% for 3 mg bid, 2 mg bid, placebo, respectively), SAE's (7%, 4%, 2%), and AE related discontinuations (13%, 13%, 4%). Treatment emergent lab abnormalities, including liver function tests, were infrequent in all treatment groups. The most frequently occurring AE were nausea (31%, 17%, 6%), vomiting (18%, 10%, 3%), diarrhea (12%, 7%, 2%), and abdominal pain (7%, 6%, 5%).

7.2.2.2.2 EFFICACY

At week 13, there was a statistical difference between the 3 mg bid group compared with placebo for the primary efficacy variable (CGIC) using the valid patient population (not the intent-to-treat population). The high dose group also showed evidence of efficacy in some secondary measures.

7.2.2.3 Studies B103-E-01 and E-04

B103-E-01 was the 3 month double blind extension to B103 (total exposure was 6 months). All patients who completed B103 and benefited from treatment without significant safety problems were eligible to participate. A total of 169 patients (119 received Exelon, 50 received placebo) entered the study and 157 patients completed.

B103-E-04 provided for an additional 6 months of double blind treatment (total exposure was one year). A total of 91 patients (64 received Exelon, and 27 received placebo) entered the study and 88 patients completed. Only these patients who completed E-04 were eligible to continue on open label treatment under B103-E-06.

7.2.2.3.1 SAFETY

Gastrointestinal AE's were significantly greater in patients receiving 3 mg bid than placebo. Headaches and dizziness in the 2 mg bid group was increased compared to placebo. Nine (9) patients discontinued due to adverse events compared to none in the placebo group (3 in the 3 mg bid group, and 6 in the 2 mg bid group).

7.2.2.4 Study B104

This was an 18 week study that investigated the maximum tolerated dose (MTD) of Exelon. The doses were titrated to the maximum tolerated level over 10 weeks and then maintained at that level (6, 9, or 12 mg/d) for up to 8 weeks. The study enrolled 114 patients (45 randomized to bid, 45 to tid, and 24 to placebo). Seventy five percent (75%, or n=85) completed the study.

7.2.2.4.1 SAFETY

A higher incidence of AE's occurred in the bid group (91%) and tid group (80%) than in the placebo group (54%). Most common AE's were nausea, vomiting, dizziness, and headaches, and were more common in both Exelon groups. Also, 22% discontinued because of an adverse event (31% - bid, 22% - tid, 4% - placebo). Serious adverse events were 9% in the bid group, 18% in the tid group, and 4% in the placebo group. During the maintenance phase, the maximum dose of 12 mg/d was tolerated by 60% of the tid group compared with 46% of the bid

group. Nausea and vomiting were the most frequent dose-limiting AE's. Antiemetics were permitted and seemed effective at relieving these symptoms. Liver toxicity was not a concern.

7.2.2.4.2 EFFICACY

No definite evidence of efficacy was present in the intent-to-treat population. In the valid patient population, a larger proportion of patients in the bid group (but not the tid group) showed significantly more improvement (57% vs. 16%) with respect to the CIBIC+ (primary variable) and NOSGER (secondary variable) evaluations.

7.2.2.5 Study B105

This was a 10 week trial (9 weeks of active treatment, 1 week placebo washout). It investigated the maximum tolerated bid and tid doses of Exelon in AD patients. The doses were titrated to a maximum tolerated level of 12 mg/day given bid or tid over an 8-9 week period. Fifty (50) patients enrolled (20 bid, 20 tid, and 10 placebo) and 45 completed the study. This study also investigated the effectiveness of withholding up to three consecutive doses as a means of increasing tolerability of dose escalation during times of poor tolerance.

7.2.2.5.1 SAFETY

Gastrointestinal AE's were more common in both Exelon groups. The incidence of nausea was 55%, 40%, 10% for bid, tid, and placebo, respectively. Discontinuations due to adverse events were 5%, 10%, and 10%, respectively. No deaths occurred and one SAE was reported in the bid group (elevated liver enzymes). The majority (at least 90%) of patients in both bid and tid groups tolerated 12 mg/day, thus the MTD was not defined in this study. Comparison of bid and tid revealed no large differences in tolerability between the two groups.

7.2.2.5.2 EFFICACY

No evidence of efficacy was found in terms of the CIBIC+ and MMSE. However, this was a short trial with small numbers.

7.2.2.6 Study OR1/ALZ/PH2L/01

This was a Japanese study designed to determine the optimal dose of Exelon in patients with AD. The study enrolled 170 patients into three treatment groups: 2 mg bid (58 patients), 1 mg bid (59 patients) or placebo (53 patients). A total of 165 patients completed the 12 week study. One Exelon patient did not receive study drug.

7.2.2.6.1 SAFETY

Nausea and vomiting were more common in the 2 mg bid group. There was no obvious difference between Exelon and placebo in the incidence of other AE's, ECG abnormalities, or laboratory findings.

7.2.2.6.2 EFFICACY

For all primary outcome measures, there was no difference observed between Exelon and placebo.

7.2.2.7 Study B103-E-06

This was a 1 year open label extension for patients who had received Exelon during B103 and the two double blind extensions B103-E-01 and E-04. Patients who had previously received placebo were not eligible. A total of 43 patients entered the study and 37 completed (total Exelon exposures was 2 years). In general, Exelon was well tolerated and psychometric testing suggested that patients who continued in the study remained relatively stable.

7.2.2.8 Study B104-E-01

B104-E-01 was an open label extension of B104 designed to allow the long term (additional 34 weeks) treatment of patients with AD. All patients who had participated in the double blind B104 trial were eligible to participate. Patients who had received placebo during B104 were withdrawn from E-01 after the code was broken. Patients continued the same dose of study drug (6, 9, or 12 mg/d give bid or tid). A total of 63 patients entered the initial double blind portion, 23 bid group, 26 tid group, and 14 placebo. Once the code for B104 was broken 22 in the bid group, and 24 in the tid group continued therapy.

7.2.2.8.1 SAFETY

The adverse events nausea, vomiting, headache, and dizziness were reported more frequently in the Exelon treatment groups than the placebo group during the eight weeks of double blind extension. The long term treatment was well tolerated.

7.2.2.8.2 EFFICACY

After the double blind treatment period, there was no difference in CIBIC+ scores. However 50-60% of Exelon patients compared with only 20% receiving placebo showed improvement compared to baseline.

7.2.2.9 Study B104-E-02

This was an extension of B104-E-01 and allowed for the continued treatment of patients for a second year (additional 52 weeks). A total of 41 patients entered and 32 patients completed the study. Patients were given the option to participate in a compassionate need study (B902) upon completion.

7.2.2.9.1 SAFETY

Results showed that Exelon in doses up to 12 mg/d administered either bid or tid was generally well tolerated for up to 2 years and resulted in no unexpected safety problems.

7.2.2.9.2 EFFICACY

The CIBIC+ showed no change or minimal worsening.

7.2.2.10 Studies B901 and B902

B901 was a compassionate need study designed for patients who completed B103-E01/04/06 (24 months of Exelon) and B902 was a compassionate need study for patients who completed B104-E01/02 (also 24 months of Exelon). A total of 20 patients entered B901 and 12 entered B902. They were treated with Exelon at a total daily doses between 4 and 12 mg administered bid or tid for an additional 2 years.

7.2.2.10.1 SAFETY

Long-term therapy has generally been well tolerated. These studies are ongoing.

7.2.2.11 Studies AD/EP-II and EP/VD-II

These Japanese studies were early Phase 2 open label trials that evaluated the safety, efficacy of Exelon in patients with AD and vascular dementia (VD), respectively. Both were identical, 2 step, open label, 12 week design. In Step 1, patients received Exelon 0.5 mg bid for 4 weeks then, based on efficacy and safety, either 0.5 mg bid or 1 mg bid for the next 8 weeks. In Step 2, based on tolerability, patients could advance to 1 mg bid for 4 weeks, 1.0 mg bid for 4 weeks and then 1.0 or 1.5 mg bid for 8 weeks. These dosages were based on findings in previous Japanese studies suggesting the maximum tolerated dose was 2.0 mg in the elderly.

7.2.2.11.1 SAFETY

No particular safety concerns were raised. The 1.5 mg bid dose was well tolerated.

7.2.2.11.2 EFFICACY

Both were small and uncontrolled, therefore no efficacy conclusions could be drawn. Improvement in 24% of AD and 15% of VD patients was observed in global efficacy assessment.

7.2.3 Phase 3 Studies

7.2.3.1 Background

Data from the Phase 2 studies B104 and B105 demonstrated the tolerability of Exelon in doses up to and including 12 mg/day. These studies also demonstrated that dose limiting AE's might be managed by various strategies including administration with food, withholding doses during periods of intolerance (B105), and administration of antiemetics for relief of drug-induced nausea or vomiting (B104). Preliminary, but not conclusive, evidence of efficacy was observed in B103 and B104. The evidence was not conclusive possibly because of too few subjects (B104 N=114), too low of a maximum dose used (B103, maximum 6 mg/day), or too short a duration of treatment (B103, B104, B104; 13, 18, and 9 weeks, respectively). In these earlier studies, the most common AE's reported were nausea, vomiting, dizziness, and headaches. As a result of these findings, Phase 3 studies were initiated to assess the safety and efficacy of Exelon in AD patients in doses up to 12 mg/day.

The Phase 3 clinical program for Exelon was initiated on 12/94 and included eight clinical studies, 4 controlled (B303, B304, B351, B352) and 4 uncontrolled (B305, B353, B354, B355) trials. They are listed in Table 6, page 18.

The four controlled studies were each double blind, 6 month, placebo controlled safety and efficacy studies in patients with mild to moderate Alzheimer's Disease. These studies were conducted in Europe, the United States, Canada, South Africa, and Australia. All were conducted under the US IND. Two studies (B351, B352) were conducted exclusively in US centers. The remaining two studies (B303, B304) were multi-center, multinational trials. Because B304 was started late, only the unblinded safety data are provided in the NDA. No efficacy data was presented at the time of the submission.

Of the four uncontrolled trials, B353 was a 26 week open label extension for patients in B351 and B352 and five US centers in B303. Study B305 was also a 26 week open label extension for patients in non-US B303 centers, and B304. These studies were later amended to allow continued treatment with Exelon for up to 2.5 years. B354 (US Pilot) and B355 (multinational) were conducted to assess the tolerability of and patient compliance with a higher starting dose and faster rate of dose titration than used in previous studies.

The complete study reports for three of the four controlled trials (B303, B351, B352) and for one of the uncontrolled trials (B353) are included in the NDA. Interim safety results are included for the remaining four studies (B304, B305, B353, and B355). B304 is completed in the field, whereas B305, B353, and B355 are ongoing at the time of the submission.

7.2.3.2 Controlled Studies

The four phase 3 controlled studies (B303, B304, B351, B352) each were 26 week, randomized, double blind, placebo controlled, multicenter studies in patients with mild to moderate probable Alzheimer's Disease. They included a total of 2,472 patients. Of these, 1708 were randomized to Exelon treatment and 1696 actually received the drug. Seven hundred sixty four (764) were randomized to placebo.

B304 is an interim safety report and a final safety report is due as part of the 120 day safety update. The remaining three complete study reports are included in the NDA.

7.2.3.3 Uncontrolled Studies

Studies B305 and B353 were designed to provide 26 weeks open-label treatment for patients from the controlled studies. These protocols were subsequently amended to provide an additional two years of treatment. Only patients who entered these studies before 10/31/95 are included in the interim safety reports. A total of 310 patients from these studies are included in the analyzable database for the NDA including 197 who have a full 52 weeks of exposure.

Studies B354 and B355 were designed to study the tolerability of a faster titration rate than that used in the controlled trials. B354 was a single center, open label, 12 week pilot study in 15 patients to assess a higher starting dose, 1.5 mg bid, and a faster rate of titration (3 mg/day weekly increase). This is in comparison to the previous titration schedule used in the controlled trials: 0.5 - 1 mg bid, and 1-1.5 mg/day weekly increase. B355 is a larger, multicenter 26 week open label study using the more rapid titration schedule.

7.2.3.4 Patient Selection

The phase 3 trials enrolled male and female outpatients, at least 50 years of age, who fulfilled DSM-IV criteria for Alzheimer's type dementia and the NINCDS-ARDA criteria for a diagnosis of probable AD. They had to have an MMSE score between 10-26 (inclusive). The phase 3 trials included many patients with evidence of significant co-morbidities, such as cardiac, pulmonary, and endocrinologic diseases, as well as very old (>85 years of age) patients. They were excluded if they had evidence of severe progressive illness, including severe chronic pulmonary disease, cardiovascular, hepatic, renal, psychiatric, or neurological disorders other than AD.

7.2.3.5 Prior and Concomitant Medication

Almost no restrictions were placed on the use of concomitant medications. Those that are known to influence the assessment of safety and efficacy were not allowed: psychotropics, beta blocker used for psychiatric indications, anticholinergics (including non-prescription drugs), health food supplements that are acetylcholine precursors (*e.g.* lecithin, choline, memory enhancers).

Studies B351, B352, and B354 allowed the occasional use of chloral hydrate to induce sleep or control severe agitation. Studies B303 and B304 allowed for the occasional short-term use of chloral hydrate, short-acting benzodiazepines (*e.g.*, temazepam) and the antipsychotic haloperidol. There were restrictions on the number of days these drugs could be used successively or preceding a baseline or efficacy evaluation. In addition, in B303, B304, and B305, patients who had been taking a benzodiazepine daily were permitted to continue taking the lowest possible dose of the drug throughout the study period.

B353 and B305 relaxed the constraints and allowed the use of psychotropic medication, except for depot neuroleptics and lithium. Psychotropic medications were also allowed in the rapid titration study, B355, but not allowed 3 days before an efficacy rating.

7.2.3.6 Dosage and Administration

In the four phase 3 controlled studies, patients were titrated up to a maintenance dose ranging from 1-12 mg/day over 7 to 12 weeks. Dose decreases were not permitted during this period. During the maintenance phase (weeks 13-26), dose adjustments (increases or decreases) were

permitted in all studies except B351, which evaluated 3 fixed doses (3 mg, 6 mg, and 9 mg/day) and placebo. B352 and B303 evaluated flexible dosing of two non-overlapping dose ranges, 1-4 mg/day and 6-12 mg/day, and placebo. B304 assessed a dose range of 2-12 mg/day administered either bid or tid. Strategies for improving patient tolerability included administering study medication with food, dose interruption up to three consecutive doses/wk, and use of an anti-emetic.

At the conclusion of the 26 week double blind treatment period, patients were offered the opportunity to participate in one of the open-label long term extensions.

7.2.3.7 Efficacy Assessment

Efficacy was assessed at weeks 12, 18, and 26. Key efficacy measures included the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), and the Clinician Interview Based Impression of Change plus caregiver information (CIBIC+) for evaluation of global functioning, and the Progressive Deterioration Scale (PDS) to assess effect on activities of daily living (ADL's).

The number of patients with a clinically significant response, *i.e.*, ≥4 point change on ADAS-cog, 10% improvement from baseline on the PDS, and improvement on the CIBIC+, was evaluated.

Other measures used was the ADAS-cogA, which included an attention item from the non-cognitive portion of the ADAS. A tertiary measure, the Caregiver Assessment Scale (CAS) assessed impact on the caregiver (this was not analyzed in the NDA submission). Furthermore the mini-mental status examination (MMSE) and the Global Deterioration Scale (GDS) were used to assess the severity of the patient's illness.

For evaluation of efficacy, the classical intent to treat (ITT), traditional last observation carried forward (LOCF), traditional observed cases (OC), retrieved drop-out data (RDO), and observed cases plus retrieved drop-outs (OC+RDO) analyses were performed.

Primary statistical tests used in the analysis of efficacy in the Phase 3 studies included analyses of variance (ANOVA: ADAS-cog, CIBIC+, GDS), analyses of covariance (ANCOVA: ADAS-cogA, PDS, MMSE), categorical analyses (ADAS-cog, CIBIC+, PDS), and linear and non-linear regression models, including logistic regression.

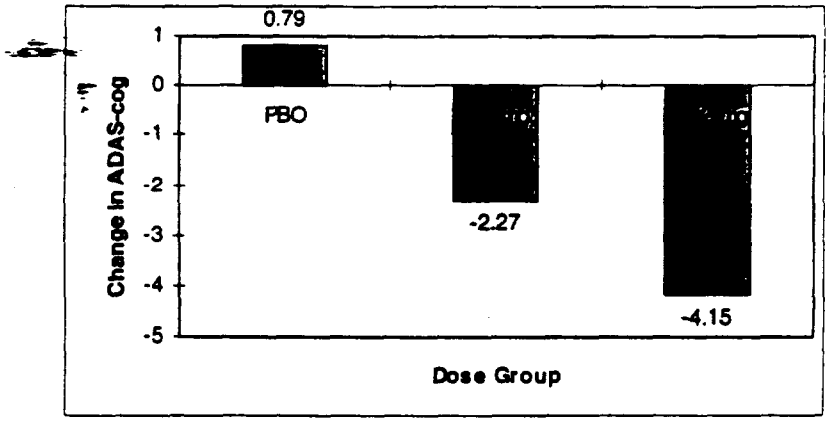
7.2.3.8 Study B352 - Controlled U.S. Study

In study B352, 699 patients were randomized to three treatment groups, Exelon 6-12 mg/day (3-6 mg bid), Exelon 1-4 mg/day (0.5-2 mg bid), or placebo. Patients had a mean age of 75 years with a mean MMSE and GDS of 19.7 and 4.0 (30% rated ≥5), respectively.

7.2.3.8.1 EFFICACY

Overall, Exelon treated patients performed better than placebo, particularly the high dose group. The change in ADAS-cog scores in patients who completed 26 weeks were significantly different and better from placebo (+0.79, -2.27, -4.15 for 6-12 mg, 1-4 mg, and placebo, respectively, Figure 2). The high dose group actually improved slightly from baseline. A significant change from baseline was also seen in CIBIC+ (both high and low dose) and PDS (high dose). The proportion of clinically meaningful responders was significantly different from placebo for the ADAS-cog, CIBIC+ (both groups), and PDS (high dose).

Figure 2: Study B352 - Change in ADAS-cog Scores in Patients who Completed Study

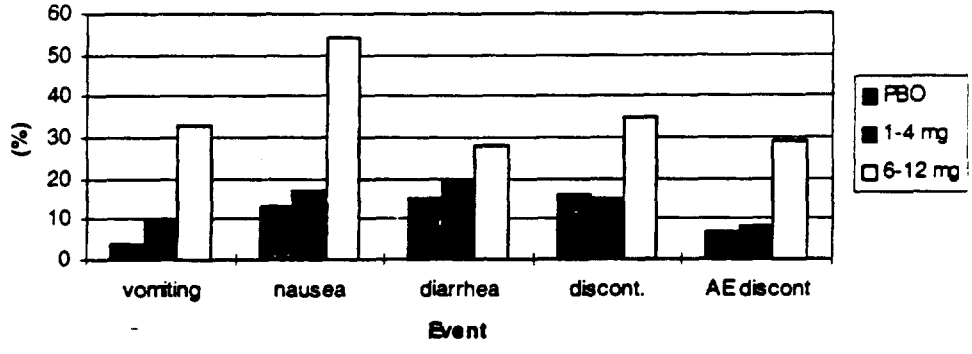


7.2.3.8.2 SAFETY

A significantly higher percentage of patients in the 6-12 mg group than in the 1-4 mg or placebo groups reported adverse events. The incidence of vomiting, anorexia, nausea, diarrhea, flatulence, dyspepsia, and dizziness all occurred higher in the 6-12 mg group. Discontinuations and adverse event related discontinuations were also higher in the 6-12 mg group (Figure 3). Discontinuations tended to occur during the forced titration phase (74%).

Two patient deaths were reported, one in the 6-12 mg groups (on study drug) and one in the 1-4 mg group (three months after the last dose of study drug). These are discussed in more detail in section 8.2, page 30. There was no difference among treatment groups in the incidence of serious adverse events (12%, 11%, 15%, for 6-12 mg, 1-4 mg, and placebo, respectively).

Figure 3: B352: Adverse Events and Discontinuations



7.2.3.9 Study B303 - Global Study

This study was similar to B352. It randomized 725 patients to three treatment groups: Exelon 6-12 mg/day (3-6 mg bid), Exelon 1-4 mg/day (0.5-2 mg bid), or placebo. The mean age of the patients was 72, with mean MMSE scores of 19.9 and mean GDS scores of 4.1 (32% ≥ 5).

7.2.3.9.1 EFFICACY

At week 26, improvement in ADAS-cog scores was significantly greater in the 6-12 mg group than placebo in the intent-to-treat, LOCF, and OC populations. Furthermore, a significantly greater percentage of 6-12 mg patients than placebo demonstrated a 4 point or greater

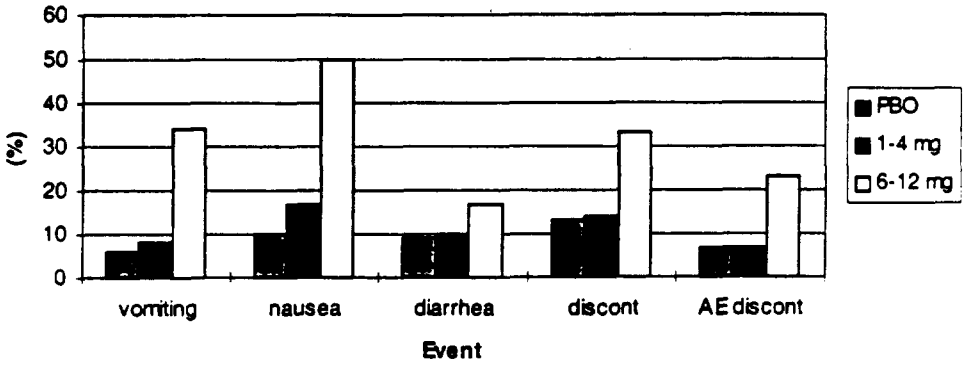
improvement in the ADAS-cog in all populations (24% vs. 16% in the intent-to-treat population). Also at week 26, the mean CIBIC+ score was higher in the 6-12 mg group compared with placebo, and a significantly higher proportion of patients in both high and low dose groups dose groups had CIBIC+ ratings of improvement. The mean change from baseline score for the PDS in the 6-12 mg LOCF population was significant when compared with placebo.

7.2.3.9.2 SAFETY

Significantly more patients in the high dose (6-12 mg/day) group than in the low dose (1-4 mg/day) or placebo groups reported adverse events, particularly gastrointestinal effects. Patients in the high dose treatment group had a higher incidence of AE's (Figure 4). As in B352, the majority of the adverse event-related discontinuations occurred during the forced titration phase (64%) during which dose reductions were not allowed, even at times of intolerance.

Two patients in the high dose group died. These are discussed in more detail in section 8.2, page 30.

Figure 4: B303: Adverse Events and Discontinuations



The incidence of serious adverse events were similar among all three groups (18%, 17%, 20%, for high dose, low dose, and placebo, respectively).

7.2.3.10 Study B351 - US Fixed Dose Study

In tnis study, 751 patients were randomized to one of four treatment groups: 3 mg/day, 6 mg/day, 9 mg/day, or placebo. It was conducted at 14 US centers. The mean age was 74 years, mean MMSE score was 20 and mean GDS scores were 3.8.

7.2.3.10.1 EFFICACY

Significant differences from placebo were seen in ADAS-cog score in the 9 mg and 6 mg groups (intent-to-treat, LOCF, and OC). No differences compared with placebo were demonstrated in the CIBIC+, PDS, and GDS..

7.2.3.10.2 SAFETY

Significantly more patients in the 9 and 6 mg groups than in the 3 mg and placebo groups reported AE's during the study. Nausea, vomiting, abdominal pain, and anorexia were the most commonly reported AE's and tended to be dose dependent. No differences in cardiovascular AE's were detected between treatment groups.

Five patients died (1 - 9 mg, 1 - 6 mg, 2 - 3 mg, 1 - placebo). These are discussed in more detail in section 8.2, page 30. Discontinuations were higher in the in the 9 mg (49%) and 6 mg

(37%) groups compared to placebo (26%). Seventy-four percent (74%) of the discontinuations occurred during the titration phase in which dose decreases were not allowed even at times of intolerance. AE associated discontinuations were higher in the 9 mg (34%) and 6 mg (21%) vs. 3 mg (10%), and placebo (12%). There was no difference in SAE incidence rates (12%, 14%, 11%, 9%, for 9, 6, 3 mg, and placebo, respectively).

7.2.3.11 Study B304 - Global Study

This study was deigned to assess the efficacy and safety of the individual highest well-tolerated doses (2-12 mg/day) given either bid or tid. The interim safety report contains safety data for patients with a cut-off date of 10/31/95. For this interim report, 346 patients have been enrolled. Of these, 111 received rivastigmine tid, 118 received bid dosing, and 117 received placebo. Mean age was 70.5; 99% were Caucasian; and 56% were female.

7.2.3.11.1 SAFETY

There was one death in the placebo group (pulmonary embolus). Eighty-five percent (85%) completed 26 weeks of treatment. Discontinuations were 15% and 7% discontinued for adverse events. SAE's were similar in the three groups (19%, 15%, 17%, for tid, bid, and placebo, respectively). Most common AE's were similar to previous studies (nausea, vomiting, diarrhea, anorexia, headache, dizziness). No clinically meaningful changes in vital signs, ECG's, or laboratory parameters were seen.

7.2.3.12 Study B353 - Interim Safety Report

This was the six months open label extensions for patients who successfully completed studies B351, B352, and B303 (US centers only). A total of 211 patients enrolled as of 10/31/95 and had taken at least one dose. Seventy-four percent (74%) complete 26 weeks of open label treatment (total exposure = 1 year). Mean age was 75 years; 90% were Caucasian, and 52% were female.

Three patients died. These are discussed in more detail in section 8.2, page 30. Twenty-six percent (26%) discontinued, and 12% discontinued due to adverse events. A total of 94% reported at least one AE. Most common AE's were nausea (44%), vomiting (26%), dizziness (23%), anorexia (20%) and diarrhea (18%). No other safety concerns were evident regarding vital signs, physical exams, ECG, or labs except for weight loss (22%).

The protocol was amended to allow for an additional 2 years of treatment.

7.2.3.13 Study B305 - Interim Safety Report

B305 was the 6 month open label extension study for patients who successfully completed B303 (non-US centers). A total of 99 patients enrolled. Eighty-eight percent (88%) completed 26 weeks of open label treatment. The mean age was 70 years; 99% were Caucasian and 55% were female.

Two patients died (neither attributable to medication). Twelve percent (12%) discontinued and 8% discontinued because of adverse events. Overall 80% reported at least one AE. Most common AE's were similar to previous studies: nausea, vomiting, agitation, confusion, headaches, and dizziness. No other safety concerns were evident regarding vital signs, physical exams, ECG's, or laboratory tests.

The protocol (like B353) was amended to allow for an additional 2 years of treatment.

7.2.3.14 Study B354

This 12 week US open label pilot study was designed to explore the safety and tolerability of a higher starting dose and faster titration schedule. Fifteen (15) patients were enrolled. The starting dose was 15 mg bid and the titration rate was 3 mg/week. The study is completed in the field and analysis is ongoing at the time of the NDA submission.

7.2.3.15 Study B355 - Interim Safety Report

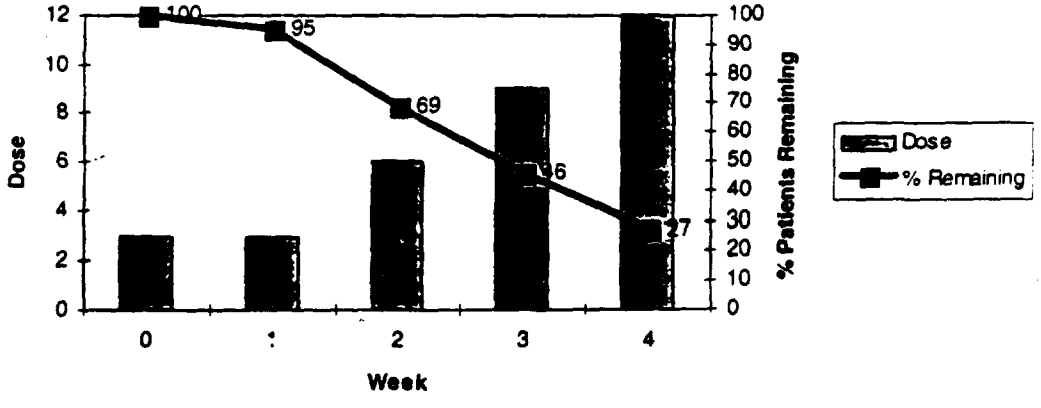
This global study assessed the tolerability and safety of a 3 mg initial dose and titration by 3 mg/wk up to 12 mg/day (beginning at week 4). It compared it to titration rates of 1-1.5 mg and 2 mg/wk used in the phase 3 controlled trials. This 26 week (interim report through week 14), open label study enrolled 548 patients, 544 of whom took Exelon. The mean age was 74 years. The number of patients remaining at week 14 was 420 patients (77%).

The proportion of patients tolerating the 3 mg/wk accelerated titration schedule was 95% at week 1(3 mg/d), 69% at week 2 (6 mg/d), 46% at week 3 (9 mg/d) and 27% at week 4 (12 mg/d) (Figure 5). It is clear that this accelerated titration schedule was not well tolerated.

At week 14, 92% had reported at least one AE. Most common AE's were nausea (56%), vomiting (32%), dizziness (22%), diarrhea (16%), and headache (16%).

There were 3 patient deaths. Fifteen percent had experienced an SAE. Nine percent (9%) had weight loss.

Figure 5: Study B355 - Tolerability of Accelerated Titration Schedule, by Week and Daily Dose



8. Integrated Review of Safety

8.1 Background and Methodology

The safety populations consists of all patients who:

- entered a study
- took study medication, and
- had any safety data for analysis

The safety data analyzed includes adverse events, physical examination, vital signs, ECG's, and laboratory evaluations (drugs of abuse, liver function tests, chemistry, hematology,

urinalysis). In the phase 3 trials, patients were evaluated at baseline, then weekly for the first 12 weeks, and every other week for the remainder of the study (weeks 13-26). All patients who received at least one dose of study medication and had a subsequent safety evaluation were included in the safety database.

8.2 Deaths

I first reviewed all deaths by reviewing the "Deaths" section in the ISS (Section 6.22, page 6.2.18). Then, I reviewed all CRF's submitted for each death, and finally, Dr. Judy Racoosin, performed a more detailed analysis of deaths in the Exelon NDA. Her review is incorporated into this section.

A death was included in the safety database if a patient died during a study or within 30 days after the last dose of study drug was given. The cut-off date for inclusion of data in the NDA database was 7/31/96. However, any data available concerning patient deaths that occurred up to and including 12/31/96 have also been included.

A total of 49 patient deaths occurred as of December 31, 1996. Patient narratives were available for every case but one, but in this case, pertinent information from the death could be obtained from the CRF. In other cases, the CRF lacked information regarding the death, particularly in deaths that occurred after the study was completed but before the 30 day cutoff limit. In these cases, the patient narratives were more informative. Thirty-one (31) deaths had occurred as of the NDA cutoff date of July 31, 1996. These 31 deaths form the basis of the mortality analysis, since we have reasonably accurate exposure data for all patients in the NDA up until this date and calculation of mortality rates based on patient-years is possible. The additional 18 deaths in the subsequent months provide additional useful qualitative information. Table 7 lists demographic characteristics of patients who died.

Table 7: Deaths during Exelon Clinical Development through 12/31/96

Parameter	7/31/96	12/31/96
Males	16	22
Females	15	27
Mean ± SD Age (years)	77.26 ± 5.78	77.12 ± 6.37
Minimum Age (years)		
Maximum Age (years)		
Mean ± SD Days on ENA	137.9 ± 113.08	171.3 ± 122.27
Minimum Days on ENA		
Maximum Days on ENA		
Mean ± SD ENA Dose (mg/d)	7.3 ± 3.75	8.0 ± 3.78
Minimum ENA Dose (mg/d)		
Maximum ENA Dose (mg/d)		

An additional 9 deaths have occurred in patients after the 30 day post-study cutoff date. The earliest death recorded occurred 42 days after the last dose (range 42-390). The causes of death were varied (cancer, stroke, MI, malnutrition) and I could find no specific pattern attributable to drug in these 9 "late" deaths.

A more detailed discussion of individual deaths is located in section 8.2.3, page 32.

8.2.1 Mortality Risk in Controlled Clinical Trials

My first mortality risk analysis focused on data from the controlled clinical trials. It is in these studies where mortality risk between drug and placebo can be most easily compared, since the duration of exposures to both drug and placebo were similar. One flaw in the analysis is that it

does not take into account differences in drop-out rates between drug and placebo. In the case of Exelon, where the drop-out rate was higher in the active treatment groups, this will tend to decrease the overall duration of exposure in the Exelon treated groups compared to the duration of exposure in the placebo group. The potential effect is to decrease the perceived mortality rate in the Exelon group than what might have otherwise been seen had patients remained in the study longer since there was relatively less time for death to occur on drug. Nonetheless, the analysis is useful if there is a substantial difference in mortality rates.

In all controlled clinical trials, 984 patients took placebo and 2224 patients took Exelon (Table 6, page 18). Of the 49 deaths that occurred overall, 14 occurred in controlled clinical trials (phase 2 and 3 combined), 34 occurred in open label trials, and 1 occurred in an ongoing Phase I patient trial (FDA Table 8).

Table 8: Distribution of Deaths by Study Type

		Treatment Assignment		
Study Type	**Deaths**	**Unknown**	**Placebo**	**Exelon**
1 - Clin Pharm	1	0	0	1
2 - Controlled	6	0	1	5
3 - Controlled	8	1*	1	6
Open Label	34	0	0	34
All Studies	**49**	**1***	**2**	**46**

represents a death from study B304, which is still blinded at the time of submission

Of the 14 deaths occurring in phase 2 or 3 controlled trials, 11 took Exelon, 2 took placebo, and 1 treatment assignment was still not known at the time of the submission. Assuming this patient took placebo (which would favor the drug), then the mortality risk for the drug and placebo are: 0.5% (11/2224) and 0.3% (3/984), respectively. If, on the other hand, the patient took Exelon, then the mortality rates are 0.5% (12/2224) and 0.2% (2/986). These numbers are very small and make it difficult to draw meaningful conclusions about mortality risk other than they are quite low for both groups. Using Fisher's Exact Test for both scenarios described above, then the difference in mortality risks is not statistically significant, p=0.25 and p=0.57, respectively.

8.2.2 Mortality Rates and Drug Exposures

It is not meaningful to compare mortality risk in all patients (including those in long-term extensions) who were exposed to drug vs. placebo since duration of exposures to drug in the long-term open label trials are much longer (some are greater than 2 years) compared to duration of placebo exposures in the controlled trials (6 months). The risk of dying on drug is greater since duration of exposure is longer during which time death from many causes can occur. Therefore, it is useful to calculate mortality rates in these two groups according to total duration of drug exposures (in patient-years). Even this analysis is flawed, because patients exposed to drug for 2 years are different than those exposed to placebo for six months. By necessity, patients exposed to drug for 2 years are older, and more likely to have more concomitant illnesses, and therefore are expected to have a higher background mortality risk.

Estimation of total drug exposure in patient-years is possible using the data in Table 4: Cumulative Duration of Exposure, All Treatment Studies, By Treatment Dose, page 14, which is directly taken from the ISS (Text Table 3.5.1, page 3.16). First, I determined how many patients were exposed to a specific mean daily dose for a specific interval. Then I multiplied the number of patients in that interval by the mean duration of the interval (this assumes a constant drop-out rate in that interval). For example, the average patient in the ≥2-4 week interval would be exposed for 3 weeks. Therefore, the average patient in these cells would contribute an average

of 3 patient-weeks to the total. The results of these calculations are shown in Table 9, page 32. Note that since mean daily dose is used, then by definition this is constant throughout exposure and patients are not switching from row to row. Note that for the last column (≥104 weeks), it is impossible to censor patients to any time longer than 104 since it is not known what the upper limit of exposure duration is in this group. Therefore, a conservative figure of 104 weeks is used. This tends to minimize duration of exposure in this group, and in the total overall. Therefore, the total Exelon exposure in patient-years should be taken as an estimate and very well will likely be higher than the total presented here, since total patient exposures are generally underestimated by this analysis.

Table 9: Exposures, All Patient Treatment Studies, by Dose and Duration (in pt-wks)

Daily Dose mg/ day	Any Exp. (Wks)	<1	≥1-2	≥2-4	≥4-12	≥12-26	≥26-38	≥38-52	≥52-65	≥65-78	≥78-91	≥91-104	≥104	Total
≤3	535	10.5	43.5	102	511	4750	4148	90	234	0	0	0	0	10424
>3 - 6	1266	0.5	31.5	198	1449	8702	14348	765	1813.5	214.5	84.5	877.5	3120	32870
>6 - 9	586	0	0	6	896	3952	6834	630	1930.5	0	0	0	0	14834.5
>9 - 12	619	0	0	0	0	4921	7412	1485	4095	357.5	84.5	1950	1352	22276
Total	**3006**	**11**	**75**	**306**	**2856**	**22325**	**32742**	**2970**	**8073**	**572**	**169**	**2827.5**	**4472**	**80404.5**

From Table 9, a total of 80,404.5 patient-weeks of exposures has been achieved. Dividing by 52 gives a total exposure of 1546 patient-years (across all dose ranges).

The mortality rate for Exelon treated patients is therefore 30 per 1000 patient-years (46 or 47/1546 x 1000). The sponsor has analyzed the total exposure to placebo to be 434 patient-years. This gives a placebo mortality rate of 5-7 per 1000 patient-years (2 or 3/434 x 1000). Although this suggests a 4-6 fold higher mortality in the Exelon group, it does not take into account the causes of death seen and the likelihood that the deaths may have been related to drug. This is addressed in section 8.2.3 below.

By comparison, the sponsor reports that the total exposure to tacrine in its development program was 1855 patient-years and 51 deaths occurred, for a mortality rate of 28 deaths per 1000 patient-years. I note that it is impossible to compare these numbers since they were obtained from different studies, with different populations.

8.2.3 Individual Deaths

Table 10 lists each individual death reported. I have reviewed the information contained in the case report forms and the patient narratives supplied by the sponsor for each patient. In most cases (34 of 49), the cause of the death is doubtfully related to study medication. The causes of death in this group are quite varied and include accidental, suicide, infection, stroke, and cancer. The remaining 15 patients comprise cases which, in my opinion, the drug may have played a role. These are reviewed in more detail below. Generally, these cases involve sudden death, or cases for which a clear cause was not apparent on first inspection. These are highlighted in gray in Table 10.

Table 10: Individual Deaths

	Patient	Age	Sex	Dose (mg/day)	Duration of Rx (days)	Cause
1	B103 033 004	80	M	6	102	pneumonia & pyelonephritis
2	B103 035 007	85	F	4	52	pneumonia

3	B103 005 002	71	M	4	161	MVA
4	B104 100001	72	M	PBO	?	? PE after aortofem bypass
5	ADEPII 220-01	79	M	3	75	sudden death
6	VDEP[redacted]13	67	F	3	85	intracerebral hemorrhage
7	B129 UK	83	F	8	53	aspiration pneumonia
8	B303 009 004	67	M	5	20	sudden death, heart failure
9	B303 034 018	75	M	12	102	sudden death in sleep
10	B304 409 003	70	F	?	?	GI hemorrhage
11	B304 411 001	79	F	PBO	?	broken leg, pneumonia, PE
12	B305 302 004	80	M	8	126	hip fracture, sepsis, death
13	B305 304 001	73	M	12	246	sudden death
14	B305 312 016	83	M	12	348	hip fracture ?bleeding anticoag
15	B305 329 008	83	F	8	23	sudden death (asystole)
16	B305 342 006	73	M	12	141	sudden death
17	B305 411 003	76	F	6	424	pneumonia
18	B305 413 010	76	F	12	232	colon cancer
19	B305 413 013	78	M	12	394	malignant thymoma
20	B305 425 004	85	M	12	204	sudden death
21	B305 431 015	85	M	2	33	septicemia
22	B351 103 011	83	M	1	10	prostate cancer
23	B351 105 003	77	M	4	40	stroke 3/14/95
24	B351 111 013	76	M	3	99	MVA
25	B352 015 039	83	F	6	25	poss MI (sudden death)
26	B353 105 021	68	F	2	369	arrythmia asystole (sudden death)
27	B353 106 045	78	F	12	322	diverticulitis
28	B353 111 049	75	F	12	207	respiratory failure
29	B353 203 003	83	F	10	364	pancreatic cancer
30	B353 203 025	80	F	12	276	MI
31	B353 204 022	80	F	4	31	metastatic brain cancer
32	B353 204 042	82	F	12	427	stroke
33	B353 206 021	78	M	4	112	septicemia diverticulitis
34	B353 207 028	73	F	12	258	cardiac arrest (sudden death)
35	B353 209 022	75	M	10	220	MI (? sudden death)
36	B353 213 004	88	M	12	304	pneumonia
37	B353 213 019	69	F	12	218	lung cancer
38	B353 215 011	70	F	12	175	acute heart failure
39	B353 220 009	73	M	10	354	cardiac arrests, coma p colectomy
40	B355 007 116	86	F	6	70	sudden death
41	B355 010 117	57	M	12	171	suicide (gun shot to the head)
42	B355 015 108	76	F	3	186	MI (? Sudden death)
43	B355 016 104	73	F	9	240	MVA
44	B355 018 102	75	F	9	141	poss stroke
45	B355 024 116	70	F	3	94	stroke
46	B355 028 101	75	F	3	7	pelvic cancer
47	B355 028 105	85	F	12	195	post op wound infection
48	B355 028 121	86	F	9	20	metastatic colon cancer
49	B355 028 126	85	M	6	200	pneumonia

Of the 15 cases highlighted in gray and described below, 8 had a history or past medical history suggestive or indicative of underlying cardiac disease and their death could reasonably be attributed to a primary cardiac etiology. Two others had severe underlying medical conditions which likely contributed to their death. One patient died suddenly 26 days after the last dose of medication, therefore the timing of the death makes it unlikely related to study drug. The remaining 4 patients had unexplained sudden death (nos. 1, 5, 7, and 11, below) without any prior history of cardiac disease.

8.2.3.1 AD/EP-2 220-01

79 year old Japanese male with only past medical history of "neurogenic bladder, sleep disturbance, and constipation" was taking neostigmine 3 mg/day. On the 75th day of treatment, around 4:15 PM, he suddenly collapsed and experienced a cardiac arrest. Immediate emergency resuscitative efforts including CPR, intravenous drugs, and mechanical ventilation were unsuccessful.

ECG showed ventricular tachycardia, ventricular fibrillation, and cardiac arrest. Electrical defibrillation was attempted several times. Death was pronounced at 5:23 PM.

8.2.3.2 B303 309 004

67 year old male with a history of "cardiac insufficiency" began taking rivastigmine on 4/11/95. He took a total of 20 days of medication. The last dose taken was 5 mg/d. He required hospitalization for deteriorating physical condition, anorexia, anemia, weight loss and cardiac insufficiency on 4/25/95. Study medication was stopped. His condition improved clinically but on 5/12/95, he suddenly died (12 days after his last dose), presumably from a cardiac event. No autopsy was performed.

8.2.3.3 B303 334 018

76 year old male with a history of diabetes mellitus, no history of cardiac disease and a "sleep disorder" was taking rivastigmine 12 mg/d. On day 103 of the study, his wife found him dead in his bed. Cause of death in the CRF is stated as "cardiac failure during sleep" or "sleep apnea". One day prior to death, he complained of neck and shoulder pain induced by exercise. It's possible this represented pre-infarction angina.

8.2.3.4 B305 304 001

73 year old male with a history of CHF following an MI underwent surgical resection of a prostate adenoma. Four weeks later he developed severe dyspnea which progressed to ventricular fibrillation, asystole and death. At the time of death he had received 246 days of rivastigmine treatment. The last dose was 12 mg/d on the day prior to his death. The death was attributed to "pulmonary edema." In fact, it appears he experienced a sudden cardiac death.

8.2.3.5 B305 329 008

84 year old female with a history of hypertension collapsed and died of a sudden cardiac arrest at 52 weeks of therapy, 12 hours after her last dose (8 mg/d). No autopsy was performed. The exact cause of death is unknown and presumed to be cardiac.

8.2.3.6 B305 342 006

83 year old male with a 10 year history of angina pectoris and abnormal ECG's at baseline (ST changes and extra-systoles) died suddenly while taking a walk. No resuscitation was attempted. At the time of death, he had been on rivastigmine for 141 days. His last dose was 12 mg/d.

8.2.3.7 B305 425 004

85 year old male was found dead within two hours after going to bed following dinner and the last dose of study medication. No autopsy was performed. A cardiac death was presumed. Another possible cause was a rupture of a previously documented abdominal aortic aneurysm. He was on his 204th day of treatment and the last dose taken was 12 mg/d.

8.2.3.8 B351 103 011

83 year old male died at week 2, on 3 mg/d. He withdrew from the study due to moderate nausea, vomiting, and anorexia. He was diagnosed with metastatic prostate cancer the next day. He died in the hospital four days after discontinuation of study drug from metastatic prostate cancer.

8.2.3.9 B352 215 039

83 year old female with no previous cardiac history (but had an abnormal ECG at baseline consistent with previous and persistent myocardial disease) entered the study on 10/13/95. She died suddenly at home on 11/11/95, 25 days into the course of therapy. The last dose taken was 6 mg/d. No autopsy was performed. The death certificate lists the cause of death as "cardiac arrest probably due to accute (sic) MI".

8.2.3.10 B353 105 021

At week 54, 2 mg/d. 68 year old female was hospitalized for total right knee replacement surgery and was discharged on the study. At week 78, the caregiver withdrew consent and she was seen for an early termination visit. The patient died of a cardiac arrhythmia 26 days after termination.

8.2.3.11 B353 207 028

At week 63, 12 mg/d. 73 year old female collapsed in an unresponsive state and was determined to be in cardiac arrest when paramedics arrived. She was hospitalized on a pacemaker and artificial life support. At the family's request, artificial life support was stopped and patient went into asystole and died. The cause of death was cardiac arrest secondary to myocardial infarction.

8.2.3.12 B353 209 022

At week 57, 10 mg/d. 77 year old male with a long-standing history of cardiac disease including CAD, previous MI, experienced severe chest pain and admitted with an acute anterolateral MI. At week 58, 10 mg/d, he was discontinued from the study due to this event. Nine days later, he died presumably from another MI.

8.2.3.13 B353 215 011

70 year old female with no prior cardiac history developed ECG changes 10 weeks into treatment with rivastigmine indicative of myocardial ischemia and infarction. The ECG abnormalities persisted while the patient remained in the study. She experienced mental and physical deterioration during the remainder of the study including a 17 lb weight loss however most of the weight loss (10 lbs) occurred while she was taking placebo in study B352. At week 52, 12 mg/d drug was held because she was not eating, too weak to get out of bed. At week 53, 11 days after last dose of study drug, she died in her sleep. Cause of death was listed as acute heart failure due to terminal Alzheimer's Disease.

8.2.3.14 B355 007 116

86 year old female with a history of atherosclerotic cardiovascular disease, and breast cancer entered the study on 3/28/96. She achieved a final dose of 6 mg/d. ECG's during the study were normal except for a sinus bradycardia at screening. On 6/6/96, 70 days into therapy, she was found dead on the bathroom floor. Cause of death was presumed to be cardiac.

8.2.3.15 B355 015 108

At week 27, 3 mg/d. 76 year old female was taken to the ER because of chest pain, dizziness, syncope, and nausea. While in the hospital, she became dyspneic requiring intubation. She soon developed completed cardiac arrest unresponsive to CPR and expired.

The next section details a case-control study to investigate Exelon mortality further.

8.2.4 Case-Control Mortality Analysis

After discussion of the increased Exelon mortality rate with the safety team, Dr. Judy Racoosin performed a nested case control study on Exelon associated mortality to see if a dose-response relationship between Exelon dose and death could be identified. The details of this study are contained in this section.

8.2.4.1 Introduction

During the initial review of mortality in the Exelon NDA, Dr. Armando Oliva identified that the mortality rate in the Exelon-treated group exceeded that in the placebo-treated group in the phase 2/3 trials by six-fold. Dr. Oliva's estimate of the person-time exposure to Exelon of 1546 person-years (over all dose ranges) was based on the data in text table 3.5.1 of the ISS, "Cumulative Duration of Exposure: ENA 713 Mean Daily Dose, All Therapeutic Studies". Using this estimate, the mortality rate for Exelon treated patients was 30 per 1000 person-years (46/1546 x 1000). In comparison, the mortality rate in placebo patients based on the sponsor's estimate of 434 person-years placebo exposure was 5 per 1000 person-years.

Because the estimate of person-time exposure to Exelon was based on summary data, I used the "DAR" data files for studies 303, 351, and 352 provided by the sponsor to calculate a more exact person-time estimate. Using these estimates and the deaths occurring in these studies, the mortality rate in the Exelon-treated group was 10.1 deaths per 1000 person-years (6/592.3) vs. 0 deaths per 1000 person-years (0/286.1) for the placebo-treated patients. Furthermore, in studies 303 and 352, the two studies utilizing a high-dose range up to 12 mg, there were 3

deaths in the high dose group and none in the low-dose or placebo groups. These suggestions of excess mortality in the Exelon-treated group led us to examine the mortality data further. Capitalizing on the titration design of randomized controlled trials and extensions, we aimed to determine whether there was a dose-response relationship between Exelon dose and death.

8.2.4.2 Methods

Study Cohort

The study utilized a data file provided by the sponsor submitted September 18, 1997. This data file contained the following information for all patients exposed to Exelon during the randomized controlled trials (RCT) and/or extension (EXT) trials: demographic data; identification numbers of RCT and EXT trials with the corresponding number of days the patient was in each portion; whether the patient died during a trial, and if so, the number of days between the patient's last medication dose and their death. Thirty-one deaths were included in this file. Two deaths occurred during phase 2 trials. Since we did not have daily dosing information for all phase 2 patients in the data files provided by the sponsor we excluded all phase 2 patients from the analysis.

8.2.4.3 Case Definition

The safety team defined a case in the study as a death occurring in a phase 3 trial within 30 days of the last dose of medication. Five phase 3 deaths occurred greater than 30 days after the last dose of medication and were thus excluded from the analysis. Therefore our study included 24 cases.

8.2.4.4 Control Selection

For each case, the time to death was determined by calculating the number of observation days between initiation of the RCT and the day of death. The number of observation days was the sum of the number of days in the RCT, the number of days in the EXT (if applicable), and the number of days between the last dose and the death date (by definition, between 0 and 30). For all the other patients, observation days was the sum of the number of days in the RCT, the number of days in the EXT (if applicable), and 30 additional days of observation (to balance for the 30 potential days to death for the cases). All cases and potential controls were sorted by number of observation days to determine which patients could serve as controls for the cases when being matched on failure time (see Figure 6).

*Figure 6: **Sampling Procedure for Nested Case Control Study of Exelon Mortality***

```
Patient 1  ----------D (84)
Patient 2  ----------C (28)
Patient 3  ----------C (56)
Patient 4  ----------C (112)
Patient 5  --------C (21)
Patient 6  ----------D (126)
Patient 7  ----------C(70)
Patient 8  ------D (14)
Patient 9  ----------C (42)
Patient 10----------C (98)
```

C= censored; D= death; (#)= days of observation

Risk Set 1: **Case - patient #8**
Potential controls - patients #1,2,3,4,5,6,7,9,10

Risk Set 2: **Case - patient #1**
Potential controls - patients #4,6,10

ENAB353 213 0002	353	6	4	OVERDOSE	OVERDOSE	1
ENAB353 213 0002	353	6	6	THIRD DEGREE HEART BLOCK	HEART BLOCK	2
ENAB353 213 0004	353	12	12	ACUTE RENAL INSUFFICIENCY	RENAL FAILURE ACUTE	6
ENAB353 213 0004	353	12	6	DEHYDRATION	DEHYDRATION	17
ENAB353 213 0004	353	12	12	ELEVATED LIVER ENZYMES	HEPATIC ENZYMES INCREASED	6
ENAB353 213 0004	353	12	12	PNEUMONIA	PNEUMONIA	6
ENAB353 213 0004	353	12	6	VARICELLA ZOSTER	HERPES ZOSTER	17
ENAB353 215 0005	353	8	8	OVERDOSE	OVERDOSE	1
ENAB353 216 0005	353	.	.	SURGICAL REMOVAL OF PLATE AND SCREW (L) HIP	SURGERY	1
ENAB353 219 0005	353	2	2	OVERDOSE	OVERDOSE	1
ENAB353 220 0008	353	10	10	COUMADIN TOXICITY	DRUG-DRUG INTERACTION (NO SYMPTOM SPECIFIED)	4
ENAB353 220 0009	353	.	.	CARDIAC ARREST	CARDIAC ARREST	4
ENAB353 220 0009	353	10	10	LOWER GI BLEEDING DUE TO DIVERTICULOSIS	HAEMORRHAGE RECTUM	1
ENAB353 220 0009	353	.	.	SEPSIS	SEPSIS	5
ENAB353 221 0002	353	6	6	OVERDOSE	OVERDOSE	1
ENAB355 001 0113	355	.	.	LEFT UPPER QUADRANT PAIN	ABDOMINAL PAIN	1
ENAB355 002 0118	355	.	.	OVERDOSE	OVERDOSE	6
ENAB355 002 0120	355	6	6	OVERDOSE	OVERDOSE	1
ENAB355 002 0121	355	.	.	OVERDOSE	OVERDOSE	7
ENAB355 004 0114	355	12	0	R KNEE REPLACEMENT	SURGERY	1
ENAB355 006 0105	355	.	.	SIGMOID VOLVULUS	GASTRO-INTESTINAL DISORDER NOS	.
ENAB355 006 0108	355	9	9	FRACTURED CHEEKBONE SECONDARY TO FALL	BONE FRACTURE	.
ENAB355 006 0108	355	9	9	FRACTURED HANDS SECONDARY TO FALL	BONE FRACTURE	.
ENAB355 006 0109	355	6	6	OVERDOSE	OVERDOSE	1
ENAB355 006 0110	355	6	3	STUDY MED OD	OVERDOSE	1
ENAB355 007 0101	355	9	4.5	POSTURAL HYPOTENSION	HYPOTENSION POSTURAL	1
ENAB355 007 0104	355	.	.	INTRACEREBRAL HEMORRHAGE	CEREBRAL HAEMORRHAGE	1
ENAB355 007 0107	355	3	3	LEFT HIP FRACTURE SECONDARY TO FALL	BONE FRACTURE	3
ENAB355 007 0116	355	6	6	PROBABLE CARDIAC EVENT	CARDIOVASCULAR DISORDERS NOS	1
ENAB355 007 0120	355	.	.	OVERDOSE	OVERDOSE	1
ENAB355 008 0101	355	.	.	OVERDOSE	OVERDOSE	1
ENAB355 009 0104	355	12	12	AGITATION	AGITATION	6
ENAB355 009 0105	355	9	9	POSSIBLE BOWEL OBSTRUCTION	INTESTINAL OBSTRUCTION	47
ENAB355 009 0107	355	9	9	ASYSTOLE	CARDIAC ARREST	1
ENAB355 010 0113	355	.	.	FALL-R HIP FX	BONE FRACTURE	.
ENAB355 011 0102	355	.	.	BOWEL OBSTRUCTION	INTESTINAL OBSTRUCTION	2
ENAB355 011 0105	355	6	6	OVERDOSE	OVERDOSE	1
ENAB355 011 0105	355	9	9	OVERDOSE	OVERDOSE	1
ENAB355 011 0108	355	12	12	SYNCOPE	SYNCOPE	1
ENAB355 012 0120	355	9	9	POST CAROTID ANGIOGRAM	PROCEDURE NOS	2

ENAB355 013 0114	355	3	3	OVERDOSE	OVERDOSE	1
ENAB355 014 0103	355	9	9	1 EXTRA DOSE PM	OVERDOSE	1
ENAB355 014 0106	355	3	1.5	OVERDOSE STUDY MEDICATION	OVERDOSE	1
ENAB355 015 0114	355		.	HOSPITALIZATION FOR DEHYDRATION	DEHYDRATION	16
ENAB355 015 0114	355	.	.	METASTIC COLON CARCINOMA	COLON CARCINOMA	.
ENAB355 016 0120	355	3	3	PNEUMOTHORAX SECONDARY TO MVA	PNEUMOTHORAX	12
ENAB355 016 0120	355	3	3	RIB FRACTURE SECONDARY TO MVA	BONE FRACTURE	12
ENAB355 016 0130	355	3	3	DISLOCATION OF R SHOULDER SECONDARY TO MVA	JOINT DISLOCATION	1
ENAB355 016 0140	355	.	.	MALIGNANT MELANOMA(RIGHT FOREARM)	MELANOMA MALIGNANT	45
ENAB355 017 0101	355	6	6	SEIZURE	CONVULSIONS	1
ENAB355 017 0110	355	.	.	AGITATION	AGITATION	.
ENAB355 017 0111	355	3	1.5	OVERDOSE,STUDY MEDICATION	OVERDOSE	7
ENAB355 019 0107	355	9	9	CHF	CARDIAC FAILURE	20
ENAB355 019 0110	355	12	12	COMBATIVE	AGGRESSIVE REACTION	1
ENAB355 019 0110	355	12	12	AGITATION	AGITATION	1
ENAB355 019 0111	355	12	12	OVERDOSE	OVERDOSE	1
ENAB355 019 0113	355	12	0	COLON POLYPS	POLYP COLORECTAL	1
ENAB355 019 0113	355	12	12	OVERDOSE	OVERDOSE	1
ENAB355 019 0116	355	9	9	GASTROENTERITIS	GASTROENTERITIS	.
ENAB355 019 0116	355	9	9	DEHYDRATION	DEHYDRATION	4
ENAB355 021 0104	355	12	12	DIGESTIVE BLEEDING	GI HAEMORRHAGE	4
ENAB355 022 0105	355	6	6	OVERDOSE	OVERDOSE	1
ENAB355 023 0101	355	9	9	PNEUMOPATHY	PULMONARY DISORDER	8
ENAB355 023 0101	355	6	6	WRIST FRACTURE SECONDARY TO FALL	BONE FRACTURE	32
ENAB355 023 0101	355	12	12	RIGHT HUMERUS FRACTURE SECONDARY TO FALL	BONE FRACTURE	.
ENAB355 023 0101	355	.	.	LEFT FEMUR FRACTURE	BONE FRACTURE	.
ENAB355 024 0108	355	9	9	FRACTURE OF 3 BODIES OF THE VERTEBRAE	BONE FRACTURE	.
ENAB355 024 0116	355	9	9	LEFT CEREBRAL INFARCT	CEREBROVASCULAR DISORDER	4
ENAB355 024 0116	355	9	9	DOG BITE	ACCIDENTAL TRAUMA	28
ENAB355 024 0120	355	6	6	NECK PAIN	BACK PAIN	7
ENAB355 025 0102	355	12	12	BRONCHOSPASM	BRONCHOSPASM	3
ENAB355 025 0104	355	12	12	CONFUSION	CONFUSION	1
ENAB355 025 0104	355	12	12	WEAKNESS	ASTHENIA	1
ENAB355 025 0104	355	12	12	CHEST PAIN	CHEST PAIN	1
ENAB355 025 0109	355	12	12	ACUTE GASTRITIS	GASTRITIS	1
ENAB355 025 0109	355	12	12	ANTEROSEPTAL MYOCARDIAL INFARCH	MYOCARDIAL INFARCTION	.
ENAB355 025 0113	355	3	3	OVERDOSE	OVERDOSE	1
ENAB355 026 0105	355	6	6	OVERDOSE	OVERDOSE	1
ENAB355 027 0102	355	9	9	FRACTURED R CLAVICLE	BONE FRACTURE	48

				SECONDARY TO FALL		
ENAB355 027 0105	355	3	3	CONFUSION	CONFUSION	2
ENAB355 027 0106	355	3	3	PARANOIA	PARANOID REACTION	2
ENAB355 027 0109	355	6	6	RESPITE CARE	PROCEDURE NOS	.
ENAB355 027 0109	355	3	3	OVERDOSE OF EXTRA STUDY TABLET	OVERDOSE	1
ENAB355 028 0101	355	3	3	PELVIC MALIGNANCY OUTCOME FATAL	CARCINOMA	.
ENAB355 028 0103	355	6	6	FOUND UNCONCIOUS	COMA	1
ENAB355 028 0109	355	6	6	RESPITE CARE	PROCEDURE NOS	12
ENAB355 028 0121	355	9	9	DIARRHOEA	DIARRHOEA	.
ENAB355 028 0121	355	9	9	CHEST INFECTION	INFECTION	.
ENAB355 028 0126	355	3	3	AGRESSIVE BEHAVIOUR	AGGRESSIVE REACTION	97
ENAB355 028 0126	355	6	6	RECTAL BLEEDING	HAEMORRHOIDS	3
ENAB355 029 0102	355	9	9	RESPITE CARE	PROCEDURE NOS	15
ENAB355 029 0111	355	3	3	HYPOTENSION	HYPOTENSION	1
ENAB355 029 0112	355	.	.	PRESUMED OVERDOSE	OVERDOSE	2
ENAB355 029 0115	355	6	6	RESPITE CARE	PROCEDURE NOS	.
ENAB355 030 0108	355	9	9	MYOCARDIAL ISCHAEMIA(ECG FINDING)	MYOCARDIAL ISCHAEMIA	.

Appendix E - Adverse Events Associated Dropouts

Table 105: Adverse Events Associated with Dropouts, All Therapeutic Trials

	Exelon N = 3006	Placebo N = 983	Total N = 3886
Body System/			
Preferred Term	n (%)	n (%)	n (%)
At Least One Adverse Event	458 (15)	67 (7)	524 (13)
AUTONOMIC NERVOUS SYSTEM DISORDERS	22 (1)	0 (0)	22 (1)
SWEATING INCREASED	12 (<1)	0 (0)	12 (<1)
SYNCOPE	9 (<1)	0 (0)	9 (<1)
MOUTH DRY	2 (<1)	0 (0)	2 (<1)
SKIN COLD CLAMMY	1 (<1)	0 (0)	1 (<1)
PALLOR	1 (<1)	0 (0)	1 (<1)
BODY AS A WHOLE - GENERAL DISORDERS	90 (3)	7 (1)	97 (2)
FATIGUE	21 (1)	3 (<1)	24 (1)
ASTHENIA	24 (1)	0 (0)	24 (1)
MALAISE	18 (1)	1 (<1)	19 (<1)
OVERDOSE	1 (<1)	1 (<1)	2 (<1)
WEIGHT DECREASE	20 (1)	0 (0)	20 (1)
INFLUENZA-LIKE SYMPTOMS	1 (<1)	0 (0)	1 (<1)
CHEST PAIN	4 (<1)	0 (0)	4 (<1)
RIGORS	1 (<1)	1 (<1)	2 (<1)
FEVER	1 (<1)	0 (0)	1 (<1)
HOT FLUSHES	1 (<1)	0 (0)	1 (<1)
PROCEDURE NOS	0 (0)	1 (<1)	1 (<1)
ALLERGY	1 (<1)	0 (0)	1 (<1)
FEELING COLD	1 (<1)	0 (0)	1 (<1)
SURGERY	1 (<1)	0 (0)	1 (<1)
PAIN	1 (<1)	0 (0)	1 (<1)
DEATH	1 (<1)	0 (0)	1 (<1)
HYPOTHERMIA	1 (<1)	0 (0)	1 (<1)
SYNCOPE	1 (<1)	0 (0)	1 (<1)
CARDIOVASCULAR DISORDERS, GENERAL	25 (1)	4 (<1)	29 (1)
HYPERTENSION	13 (<1)	2 (<1)	15 (<1)
HYPOTENSION	5 (<1)	1 (<1)	6 (<1)
CHEST PAIN	2 (<1)	1 (<1)	3 (<1)
HYPOTENSION POSTURAL	2 (<1)	0 (0)	2 (<1)
CARDIAC FAILURE	2 (<1)	0 (0)	2 (<1)
CARDIAC FAILURE RIGHT	1 (<1)	0 (0)	1 (<1)
CENTRAL AND PERIPHERAL NERVOUS SYST. DISORDERS	110 (4)	12 (1)	121 (3)
DIZZINESS	53 (2)	5 (1)	58 (1)
HEADACHE	22 (1)	3 (<1)	24 (1)
SOMNOLENCE	10 (<1)	0 (0)	10 (<1)
TREMOR	9 (<1)	0 (0)	9 (<1)

VERTIGO	6 (<1)	0 (0)	6 (<1)
ATAXIA	3 (<1)	1 (<1)	4 (<1)
GAIT ABNORMAL	5 (<1)	0 (0)	5 (<1)
PARAESTHESIA	1 (<1)	1 (<1)	2 (<1)
MUSCLE CONTRACTIONS INVOLUNTARY	2 (<1)	0 (0)	2 (<1)
HYPOAESTHESIA	2 (<1)	0 (0)	2 (<1)
CONVULSIONS	6 (<1)	2 (<1)	8 (<1)
DYSPHONIA	1 (<1)	0 (0)	1 (<1)
NEURALGIA	1 (<1)	1 (<1)	2 (<1)
HYPERTONIA	1 (<1)	0 (0)	1 (<1)
SPEECH DISORDER	1 (<1)	0 (0)	1 (<1)
COMA	1 (<1)	0 (0)	1 (<1)
HYPERKINESIA	1 (<1)	1 (<1)	2 (<1)
PARESIS	1 (<1)	1 (<1)	2 (<1)
SPASM GENERALIZED	1 (<1)	0 (0)	1 (<1)
STUPOR	1 (<1)	0 (0)	1 (<1)
PARALYSIS SPASTIC	1 (<1)	0 (0)	1 (<1)
GASTRO-INTESTINAL SYSTEM DISORDERS	254 (8)	10 (1)	264 (7)
NAUSEA	174 (6)	5 (1)	179 (5)
VOMITING	92 (3)	2 (<1)	94 (2)
DIARRHOEA	25 (1)	1 (<1)	26 (1)
ABDOMINAL PAIN	31 (1)	2 (<1)	33 (1)
ANOREXIA	50 (2)	1 (<1)	51 (1)
DYSPEPSIA	6 (<1)	1 (<1)	7 (<1)
CONSTIPATION	4 (<1)	0 (0)	4 (<1)
FLATULENCE	5 (<1)	1 (<1)	6 (<1)
ERUCTATION	1 (<1)	0 (0)	1 (<1)
FAECAL INCONTINENCE	2 (<1)	0 (0)	2 (<1)
GASTRITIS	2 (<1)	0 (0)	2 (<1)
GASTROENTERITIS	1 (<1)	0 (0)	1 (<1)
SALIVA INCREASED	4 (<1)	0 (0)	4 (<1)
GASTRO-INTESTINAL DISORDER NOS	1 (<1)	0 (0)	1 (<1)
DIVERTICULITIS	2 (<1)	0 (0)	2 (<1)
INTESTINAL OBSTRUCTION	3 (<1)	0 (0)	3 (<1)
POLYP COLORECTAL	1 (<1)	0 (0)	1 (<1)
GASTRIC ULCER	1 (<1)	0 (0)	1 (<1)
COLITIS	1 (<1)	0 (0)	1 (<1)
DUODENAL ULCER	1 (<1)	0 (0)	1 (<1)
HEARING AND VESTIBULAR DISORDERS	2 (<1)	1 (<1)	3 (<1)
TINNITUS	2 (<1)	1 (<1)	3 (<1)
HEART RATE AND RHYTHM DISORDERS	20 (1)	0 (0)	20 (1)
PALPITATION	4 (<1)	0 (0)	4 (<1)
BRADYCARDIA	5 (<1)	0 (0)	5 (<1)
FIBRILLATION ATRIAL	4 (<1)	0 (0)	4 (<1)
TACHYCARDIA	2 (<1)	0 (0)	2 (<1)
ARRHYTHMIA	3 (<1)	0 (0)	3 (<1)
AV BLOCK	1 (<1)	0 (0)	1 (<1)
CARDIAC ARREST	1 (<1)	0 (0)	1 (<1)
LIVER AND BILIARY SYSTEM DISORDERS	4 (<1)	1 (<1)	5 (<1)
HEPATIC FUNCTION ABNORMAL	1 (<1)	0 (0)	1 (<1)

HEPATITIS	1 (<1)	0 (0)	1 (<1)
HEPATOCELLULAR DAMAGE	1 (<1)	0 (0)	1 (<1)
CHOLECYSTITIS	1 (<1)	0 (0)	1 (<1)
HEPATIC FAILURE	0 (0)	1 (<1)	1 (<1)
METABOLIC AND NUTRITIONAL DISORDERS	7 (<1)	0 (0)	7 (<1)
DEHYDRATION	4 (<1)	0 (0)	4 (<1)
HYPONATRAEMIA	1 (<1)	0 (0)	1 (<1)
CACHEXIA	1 (<1)	0 (0)	1 (<1)
PHOSPHATASE ALKALINE INCREASED	1 (<1)	0 (0)	1 (<1)
MUSCULO-SKELETAL SYSTEM DISORDERS	15 (<1)	6 (1)	21 (1)
BACK PAIN	2 (<1)	2 (<1)	4 (<1)
ARTHRALGIA	3 (<1)	0 (0)	3 (<1)
PAIN	2 (<1)	0 (0)	2 (<1)
BONE FRACTURE	3 (<1)	3 (<1)	6 (<1)
MYALGIA	1 (<1)	0 (0)	1 (<1)
CRAMPS LEGS	2 (<1)	1 (<1)	3 (<1)
PAIN LEG(S)	1 (<1)	0 (0)	1 (<1)
CRAMPS	0 (0)	1 (<1)	1 (<1)
SURGERY	1 (<1)	0 (0)	1 (<1)
BURSITIS	1 (<1)	0 (0)	1 (<1)
MYO-, ENDO-, PERICARDIAL AND VALVE DISORDERS	13 (<1)	1 (<1)	14 (<1)
ANGINA PECTORIS	8 (<1)	0 (0)	8 (<1)
MYOCARDIAL INFARCTION	4 (<1)	1 (<1)	5 (<1)
MYOCARDIAL ISCHAEMIA	1 (<1)	0 (0)	1 (<1)
CORONARY ARTERY DISORDER	1 (<1)	0 (0)	1 (<1)
NEOPLASMS	5 (<1)	4 (<1)	9 (<1)
CARCINOMA	3 (<1)	2 (<1)	5 (<1)
BREAST NEOPLASM MALIGNANT FEMALE	0 (0)	1 (<1)	1 (<1)
COLON CARCINOMA	2 (<1)	0 (0)	2 (<1)
LYMPHOMA MALIGNANT	0 (0)	1 (<1)	1 (<1)
PSYCHIATRIC DISORDERS	111 (4)	26 (3)	137 (4)
AGITATION	25 (1)	9 (1)	34 (1)
INSOMNIA	19 (1)	2 (<1)	21 (1)
CONFUSION	20 (1)	7 (1)	27 (1)
DEPRESSION	23 (1)	5 (1)	28 (1)
ANXIETY	8 (<1)	3 (<1)	11 (<1)
NERVOUSNESS	11 (<1)	1 (<1)	12 (<1)
HALLUCINATION	10 (<1)	1 (<1)	11 (<1)
AGGRESSIVE REACTION	11 (<1)	2 (<1)	13 (<1)
DELUSION	3 (<1)	2 (<1)	5 (<1)
PARONIRIA	3 (<1)	0 (0)	3 (<1)
PARANOID REACTION	3 (<1)	3 (<1)	6 (<1)
BEHAVIOURAL DISTURBANCE	2 (<1)	1 (<1)	3 (<1)
SOMNOLENCE	1 (<1)	0 (0)	1 (<1)
EMOTIONAL LABILITY	2 (<1)	0 (0)	2 (<1)
SUICIDAL IDEATION	1 (<1)	0 (0)	1 (<1)
AMNESIA	0 (0)	1 (<1)	1 (<1)
APATHY	1 (<1)	0 (0)	1 (<1)
DELIRIUM	0 (0)	1 (<1)	1 (<1)