CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-823

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

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BIOPHARMACEUTICS

NDA 20-823
Exelon™
(Rivastigmine Tartrate) Capsules
), 1.5 mg, 3.0 mg, 4.5 mg, & 6.0 mg
Classification: 1S

Date	Document	Tab
12/15/97	Biopharm. Review # 1, S. Ibraham, Ph.D.	P
7/7/98	NOT APPROVABLE Letter to Firm	
5/12/99	APPROVABLE Letter to Firm	
1/19/00	Biopharm. Review # 2, S. Al-Habet, Ph.D.	Q
3/22/00	Biopharm. Review # 3, S. Al-Habet, Ph.D.	R

RECEIVED DEC 15 1997 DEC 15 1997

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-823

Submission Dates: April 7,1997
July 11, 1997
August 27, 1997
October 29, 1997

Generic Name, Strength(s), and Formulation: **Rivastigmine Tartrate (ENA 713) — 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg (As Free Base), Immediate-Release, Hard-Gelatin Capsules for Oral Administration.**

Brand Name: **EXELON™**

Sponsor: Novartis Pharmaceuticals Co
East Hanover, NJ

Reviewer: Safaa Ibrahim, Ph.D.

Type of Submission: Review of Original NDA

EXELON™ (rivastigmine tartrate, EN A 713) is an acetyl-cholinesterase inhibitor of the carbamate type. It is being proposed for the treatment of mild to moderately severe dementia associated with Alzheimer's disease.

The sponsor is proposing to market EXELON™ as [redacted]. 1.5, 3.0, 4.5, and 6 mg (as free base) immediate-release, hard-gelatin capsules for oral administration.

The proposed starting dose is 1.5 mg b.i.d, with maintenance doses of 3-6 mg b.i.d, and the maximum dose of 6 mg b.i.d.

EXELON™ will be manufactured by Novartis Pharma AG, Basel, Switzerland.

COMMENTS:

(To the Medical Reviewer):

1. The effect of food on the absorption of ENA 713 was evaluated at lower doses (viz., 1 mg and 2.5 mg) in healthy subjects. Food delayed Tmax by 1.5 hours and decreased Cmax and increased AUC by 30 %. Due to nonlinear pharmacokinetics of ENA 713, this effect of food on drug absorption after 1 mg and 2.5 mg doses can not be extrapolated to the highest 6 mg dose. The effect of food may be more pronounced at doses higher than 2.5 mg.

2. The renal impairment study (No.W253) showed that moderately renally impaired patients had higher plasma concentrations of ENA 713 than normals in contrast to severely renally impaired patients who had plasma levels comparable to those in normals. There is no tangible explanation for this discrepancy and therefore, the results of this study are considered inconclusive.

(To be Sent to the Firm):

3. The proposed dissolution methodology and specification for **all** strengths of rivastigmine tartrate capsules [redacted] 1.5 mg, 3.0 mg, 4.5 mg, and 6 mg) as outlined below, are acceptable:

Apparatus:	USP Apparatus 2 (Rotating Paddle)
Speed of Rotation:	50 rpm
Medium:	500 mL of water at 37 ± 0.5 °C
Specification:	[redacted]

4. The sponsor is requested to incorporate OCPB's pharmacokinetic labeling as outlined in Appendix A.

RECOMMENDATION:

The NDA # 20-823 submitted for EXELON™ capsules has been found to be acceptable provided that the sponsor incorporates OCPB's pharmacokinetic labeling as outlined in Appendix A. Please forward the above Recommendation and Comments 3 and 4 to the firm. Comments 1 and 2 are to the Medical Reviewer.

Table of Contents

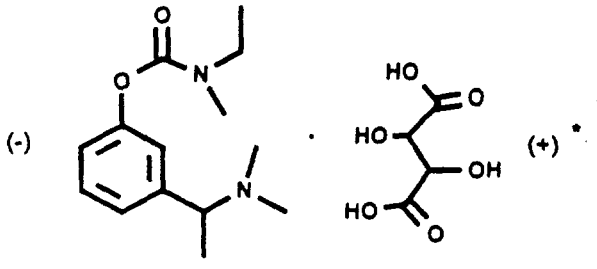
BACKGROUND:

EXELON™ (rivastigmine tartrate, ENA 713) is an acetyl-cholinesterase inhibitor of the carbamate type.

PHYSICO-CHEMICAL PROPERTIES:

ENA 713 is a white to off-white, fine crystalline, hygroscopic powder. It is highly soluble in water (>1 g/mL). The partition coefficient in n-octanol/phosphate buffer solution, pH 7 is 3.0.

STRUCTURAL FORMULA:



* The optical rotation of the base is (-); the optical rotation of the (+) hta salt is (+)

CHEMICAL FORMULA:

ENA 713 is chemically known as (S)-N-ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate hydrogen-(2R,3R)-tartrate. Conversion of the chiral center of the molecule under *in vivo* conditions is unlikely. It has an empirical formula of $C_{14}H_{22}N_2O_2 \bullet C_4H_6O_6$ and a molecular weight of 400 (hydrogen tartrate salt) and 250 (free base).

INDICATION AND USAGE:

EXELON™ is being proposed for the treatment of mild to moderately severe dementia associated with Alzheimer's disease.

HOW IT IS SUPPLIED:

EXELON™ will be supplied as hard-gelatin capsules containing rivastigmine tartrate, equivalent to [redacted] 1.5, 3.0, 4.5, and 6 mg of rivastigmine base for oral administration.

PROPOSED DOSAGE AND ADMINISTRATION (FIRM'S):

The recommended starting dose of EXELON™ is 1.5 mg BID. After a minimum of two weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and then to 6 mg BID are to be based on tolerability to the current dose. The maximum dose is 6 mg BID (12 mg/day).

MANUFACTURER AND MANUFACTURING SITE:

EXELON™ will be manufactured by Novartis Pharma AG, Basel, Switzerland.

APPEARS THIS WAY
ON ORIGINAL

SUMMARY OF BIOAVAILABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics (PKs) of ENA 713 were determined in young and elderly volunteers up to single 3 mg and 2.5 mg oral doses, respectively, because of lack of tolerability to the higher doses of the drug. In Alzheimer's patients, PKs of ENA 713 were determined up to 6 mg b.i.d with titration.

ABSORPTION/BIOAVAILABILITY

Absorption: Based on the results from mass balance study in healthy volunteers (n=6, dose=1 mg or 2.5 mg), ENA 713 is rapidly (Tmax =1 hour) and completely (97 % radioactivity recovered in urine) absorbed (Study No. B151).

Absolute Bioavailability: Mean±SD absolute bioavailability of ENA 713 is 35.5±13 % following single 3 mg oral and 1 mg intravenous doses to 12 healthy subjects (Study No. W361).

Relative Bioavailability: Mean±SD relative bioavailability (F_{rel}) of ENA 713 from capsule compared to an oral solution in nine Alzheimer's patients is 125±49 % after a single 3 mg dose and 104±21 % after a single 6 mg dose. However, dropping one patient with a F_{rel} value of 242 % brings the mean to 109±23 % following the 3 mg dose (Studies No. B353). Relative bioavailability was also determined after a single 3 mg dose in 10 healthy volunteers (Study No. W251) and averaged 105±14 %.

BIOEQUIVALENCE

No bioequivalence studies were required to be conducted since the final to-be-marketed capsules ([redacted], 1.5, 3.0, 4.5, and 6 mg) were identical in composition to those used in the clinical trials.

FOOD EFFECT

In a single-dose, 4-way crossover study (Study No. W101) involving two separate doses, 1.0 mg and 2.5 mg given under fed and fasting conditions (n=24 healthy subjects), food was found to decrease the rate of absorption of END 713. Food delayed mean time to Cmax (Tmax) by 1.5 hours, lowered mean Cmax by 30 % and increased mean area under

plasma concentration/time curve ($AUC_{0-\infty}$) by 30 %. The effect of food has not been studied following the highest recommended dose (i.e. 6 mg), however, in clinical trials patients were instructed to take the drug with food if tolerability (especially nausea, vomiting, and diarrhea) was a problem.

DISTRIBUTION

In Vivo: ENA 713 is widely distributed throughout the body with a mean apparent volume of distribution of 5.1 ± 2.8 L/kg (416 L) in 10 healthy subjects following a single 3 mg oral dose (Study No. W251). ENA 713 penetrates the blood brain barrier reaching CSF peak concentrations in 1-4 hours. Mean $AUC_{0\text{-}12hr}$ ratio of CSF/plasma averaged 40 ± 0.5 % following 1-6 mg b.i.d. doses in patients (Study No. W252).

In Vitro: ENA 713 is about 40 % bound to human plasma proteins at concentrations ranging from 1-400 ng/mL which covers the therapeutic concentration range of the drug. ENA 713 distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1-400 ng/mL.

METABOLISM

An *in vitro* study (Study No. 303-302) of ENA 713 with human liver, small intestine, and plasma revealed that ENA 713 is extensively metabolized in liver (1.15 μmol/kg), small intestine (0.26 μmol/kg), and to lesser extent in plasma (0.006 μmol/kg). The major pathway of biotransformation is the direct cholinesterase-mediated decarbamylation of ENA 713 to the phenolic metabolite, ZNS 114-666 (See Figure 1). Results also indicate that saturable first-pass metabolism exists with ZNS 114-666 formation being 80 % and 60 % at 10 μM and 50 μM incubations, respectively. ZNS 114-666 is subsequently conjugated with sulfate or, to lesser extent, N-demethylated followed by conjugation with sulfate. Cytochrome P450 system plays a minimal role in the metabolism of ENA 713. The exposure to ZNS 114-666 (as measured by AUC) is about 7-fold higher than that to parent drug (Study No. B151). However, the pharmacological activity of ZNS 114-666 is unknown.

ELIMINATION

Mass-Balance: Following single 1 mg and 2.5 mg oral doses of ^{14}C-ENA 713 to healthy male volunteers (n=6/dose), excretion appears to be exclusively via the renal pathway. Total radioactivity recovered is 97 % in urine and 0.4 % in feces over 120 hours. No parent drug is detected in urine, indicating that ENA 713 is completely metabolized before being excreted. At both dose levels, the sulfate metabolite is the major component excreted in urine and represents about 40 % of a dose. ZNS 114-666 represents 1 % of dose following the 1 mg dose and 7% of dose following the 2.5 mg dose (Study No. B151).

Clearance and Half-life: Mean oral clearance is 3.5±1.4 L/min following 1 mg b.i.d dosing (n=3 patients) and 1.8±0.6 L/min following 6 mg b.i.d dosing (n=3 patients) (Study No. W252). ENA 713 is rapidly eliminated with a mean elimination half-life ($t_{1/2}$) of 1.6±0.1 hours at 6 mg b.i.d in patients (n=3). The half-life ($t_{1/2}$) remained relatively constant across doses and ranged from 1-2.5 hours (Study No. W252).

DOSE-PROPORTIONALITY

In patients with Alzheimer's disease (n=3/dose), ENA 713 exhibits linear kinetics over the dosing range of 1mg to 3 mg b.i.d. At higher doses of 3-6 mg b.i.d, ENA 713 tends to display nonlinear kinetics; doubling the dose from 3 to 6 mg b.i.d resulted in 4-fold increase in $AUC_{0\text{-}12hr}$ (Study No. W252).

Population PK analysis (Studies No. B351 and B352) revealed that ENA 713 displays nonlinear kinetics over the doses of 1.5 mg to 6 mg b.i.d. In medium size (70 kg, 175 cm), nonsmoking male patients with severe Alzheimer's disease, AUC and Cmax increased 10-fold as dose increased 4-fold (1.5 mg to 6 mg).

Nonlinearity is more pronounced in young volunteers (n=24), elderly volunteers (n=24), hepatically impaired patients (n=10), and renally impaired patients (n=16) compared to patients with Alzheimer's disease. In young and elderly volunteers, $AUC_{0-\infty}$ increased 5-fold when dose increased from 1 mg to 2.5 mg (Study No. W101). In hepatically and renally impaired patients, $AUC_{0-\infty}$ increased 9-fold as dose increased from 1 mg to 3 mg (Studies No. W251 and W253, respectively). This nonlinearity may be attributed to saturable esterase metabolism in liver and small intestine.

MULTIPLE-DOSE

ENA 713 has a short half-life ($t_{1/2}$ ~ 2 hours) and its steady state plasma levels are expected to reach within 1 day of dosing. Accumulation of the drug is not expected upon b.i.d dosing.

SPECIAL POPULATIONS

AGE: Following a single 2.5 mg oral dose to elderly volunteers (> 60 years of age, n= 24) and younger volunteers (n=24), mean oral clearance of ENA 713 was 7 L/min and 10 L/min, respectively (Study No. W101). Elderly subjects have a 30 % lower clearance than younger subjects. No dosage adjustment is necessary in elderly patients, since the dose of the drug is individually titrated to tolerability, and further, safety and efficacy studies have been conducted in elderly population. In addition, population PK analysis (Studies No. B351 and B352) showed that age has no effect on the oral clearance of ENA 713 (n=625 patients, age =50-92 years).

GENDER AND RACE: No formal PK study has been conducted to examine the effect of gender or race on the pharmacokinetics of ENA 713. However, population PK analysis indicated that gender (n=277 males and 348 females) and race (n=575 Caucasians, 34 Blacks, 4 Orientals, 12 Others) has no effect on the oral clearance of ENA 713.

NICOTINE USE: Population PK analysis showed that nicotine use increases the oral clearance of ENA 713 by 23 % (n=75 Smokers and 549 Nonsmokers).

HEPATIC DISEASE: Following a single 3 mg dose (Study No. W251), mean oral clearance of ENA 713 is 60 % lower in hepatically impaired patients (n=10, biopsy-proven liver cirrhosis) than in healthy subjects (n=10); 1.2 L/min vs 3.1 L/min. Variability (cv) in clearance was high (cv=50-70 %). The half-life of ENA 713 was similar in hepatically impaired patients and healthy volunteers. Accumulation upon twice a day dosing is not expected in hepatically impaired patients. Dosage adjustment is not necessary in hepatically impaired patients as the dose of the drug is individually titrated to tolerability.

RENAL DISEASE: Following a single 3 mg dose (Study No. W253), mean oral clearance of ENA 713 is 64 % lower in moderately impaired renal patients (n=8, GFR=10 - 50 mL/min*) than in healthy subjects (n=10, GFR≥60 mL/min); CL/F=1.7 L/min (cv=

45 %) and 4.8 L/min (cv=80 %), respectively. In severely impaired renal patients (n=8, GFR < 10 mL/min), oral clearance values were within the normal values. Two subjects in severe group (#4 and #8) with GFR values of 0.0 mL/min were found to have very low clearance values, 0.77 L/min and 0.96 L/min, respectively; which is about 80 % lower than in normal subjects (4.8 L/min). Mean oral clearance in the severe group is about 35 % higher than in the healthy group, CL/F = 6.5 L/min (cv=89%) and 4.8 L/min (cv=80 %), respectively. [*GFR was determined by ^{99m}TC-DTPA]

In this study, it is noted that two subjects (#5 and #6) with GFR values of 11.7 and 11.5 mL/min were included in the severe group, which according to the definition in the protocol should be considered and analyzed in the moderate group. At the reviewer's request (October 3, 1997), the sponsor reanalyzed the data after removing these two subjects from the severe group and placing them in the moderate group. Similar results were obtained, that is:

Mean oral clearance of ENA 713 is 54 % lower in moderately impaired renal patients (n=12, GFR=10-50 mL/min) than in healthy subjects (n=10, GFR ≥ 60 mL/min); CL/F = 2.2 L/min (cv= 64 %) and 4.8 L/min (cv=80 %), respectively. Mean oral clearance in the severely impaired renal patients (n=8, GFR < 10 mL/min) is 6.9 L/min (cv=90%), which about 43 % higher than in healthy subjects (n=10, GFR ≥ 60 mL/min); CL/F = 6.9 L/min (cv=90 %) and 4.8 L/min (cv=80 %), respectively.

The moderate renal group had a decreased clearance and an increased Cmax while the severe group had virtually no change. At the reviewer request (Submission dated October 28, 1997), the sponsor provided an explanation, suggesting large intersubject variability and relatively small number of patients studied may be responsible for this discrepancy. The study results are inconclusive due to this discrepancy.

No obvious correlations were observed between GFR and any of the PK parameters of the drug. Dosage adjustment may not be necessary in renally impaired patients as the dose of ENA 713 is individually titrated to tolerability.

ALZHEIMER'S DISEASE: A cross-study comparison (Studies No. B353 and W251) showed that patients with Alzheimer's disease clear ENA 713 slower than healthy subjects. Following a single 3 mg dose, mean CL/F is 2.2±1.0 L/min in patients (n=9) and 3.1± 1.9 L/min in healthy subjects (n=10) (about 30 % lower). Mean Half-life is 2.1± 1.1 hours in patients and 1.6±0.7 hours in healthy subjects (about 30 % longer in patients). Mean apparent volume of distribution is comparable; 382±205 L and 416±

257 L in patients and healthy subjects, respectively. Dose-nonlinearity is less pronounced in patients than in healthy subjects (see DOSE PROPORTIONALITY).

Population PK analysis showed that oral clearance values in patients with moderate (n=335) and severe (n=14) Alzheimer's disease decreased by 13 % and 30 %, respectively, compared to the basic mean population clearance estimate value (i.e. with no covariates). Mean (SE) population clearance estimate value is 0.51 (0.09) L/min.

OTHER DISEASES:

Population PK analysis with a data base of 625 patients indicated that arthritis (n=186), diabetes mellitus (n=36), dyspepsia (n=46), hypertension (n=201), neoplasms (n=2) have no effect on the oral clearance of ENA 713.

DRUG INTERACTIONS

In Vitro Interaction Studies (Study No. 303-343): *In vitro* enzymatic studies revealed that:

(a) ENA 713 had no inhibitory effect on substrates of cytochrome P450 for the major isoenzymes such as CYP 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4. ENA 713 is therefore unlikely to influence the metabolism of the majority of drugs which are metabolized by cytochrome P450 system.

(b) Potentially coadministered drugs, such as haloperidol, fluoxetine, thioridazine, amitriptyline, nortriptyline, and diazepam, as well as the enantiomers of the phenyl metabolite of ENA 713, ZNS 114-666, have no effect on ENA 713 decarbamylation, the major pathway of drug biotransformation.

(c) Drugs that inhibit butyrylcholinesterase, such as thioridazine, amitriptyline, and nortriptyline, have no effect on ENA 713 decarbamylation in human liver.

In Vivo Interaction Studies:

Digoxin: Coadministration of ENA 713 (3 mg single dose) with digoxin (1 mg loading dose and 0.25 mg QD) did not alter the steady-state pharmacokinetics of digoxin in 12 healthy subjects (Study No. W361). The combination of ENA 713+digoxin was not different from placebo+digoxin in the pharmacodynamic variables (viz., heart rate, PR intervals, systolic and diastolic pressure, and pulse rate). Digoxin also did not alter the

pharmacokinetics of ENA 713.

Warfarin: Concomitant administration of ENA 713 (3 mg single dose) with warfarin (30 mg single dose) did not alter the pharmacokinetics of racemic warfarin or its enantiomers in 12 healthy subjects (Study No. W362). Coadministration of ENA 713 did not alter the prothrombin complex activity of warfarin. Mean change from baseline in the prothrombin complex activity of warfarin was 38.5±9.8 % after warfarin+ENA 713 administration and 41.25±9.6 % after warfarin alone administration. Warfarin also did not alter the pharmacokinetics of ENA 713.

Diazepam: A single 3 mg dose of ENA 713 administered in combination with 2 mg diazepam did not have any effect on the pharmacokinetics of either diazepam or its metabolite, nordiazepam in 12 healthy subjects (Study No. W363). Diazepam also did not alter the pharmacokinetics of ENA 713.

Fluoxetine: Administration of a single 3 mg dose of ENA 713 did not alter the pharmacokinetics of either fluoxetine or its metabolite, norfluoxetine (40 mg single-dose fluoxetine) in 12 healthy subjects (Study No. W365). Fluoxetine also did not alter the pharmacokinetics of ENA 713.

In addition, population PK analysis with a data base of 625 patients showed that the pharmacokinetics of ENA 713 were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), non-steroidal anti-inflammatory drugs (n=79), estrogens (n=70), analgesics (n=177), antianginals (n=35), benzodiazepines (n=2), and antihistamines (n=15).

PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONSHIP

Study No. W252:

ENA 713 inhibits the **AChE** and **BChE** activities in **CSF** over the dosing range of 1-6 mg b.i.d (n=3 patients/dose). Inhibition was observed within 1 hour and was maintained over the 12-hour dosing interval. Mean maximum inhibition ranged from 20 % at 1 mg b.i.d to 60 % at 6 mg b.i.d (n=3 patients/dose). Inhibition of **BChE** activity in **plasma** is lower than that in **CSF**; mean maximum decrease in BChE activity ranged from 7 % at 1 mg b.i.d to 35 % at 6 mg b.i.d (n=3 patients/dose).

$AUC_{0\text{-}12hr}$ of **AChE** activity in **CSF** is linearly correlated with $AUC_{0\text{-}12hr}$ of ZNS 114-666 in **plasma** ($p < 0.0001$, n=3) and with $AUC_{0\text{-}12hr}$ of ZNS 114-666 in **CSF** ($p < 0.0001$, n=3). $AUC_{0\text{-}12hr}$ of **BChE** activity in **plasma** is linearly correlated with $AUC_{0\text{-}12hr}$ of ZNS 114-666 in **plasma** (p=0.0018, n=3) and with $AUC_{0\text{-}12hr}$ of ZNS 114-666 in **CSF** (p=0.027, n=3).

Cmax of **AChE** activity in **CSF** is linearly correlated with Cmax of ZNS 114-666 in **plasma** (p=0.0104, n=3). **Cmax of BChE** activity in **plasma** is linearly correlated with Cmax of ZNS 114-666 in **plasma** (p=0.0078, n=3).

Studies No. B351 and B352:

Linear regression analysis (n=625) of relationships between efficacy measures (viz., ADAS, CIBIC, and PDS) and exposure at Weeks 12, 18, and 26 showed that a significant relationship exists between ADAS at Week 12 and dose-normalized $AUC_{0\text{-}12h}$ and Cmax of ZNS 114-666 ($p > 0.05$). However, significant relationship was not shown when the $AUC_{0\text{-}12h}$ and Cmax were not dose-normalized; which is a more relevant analysis. No significant relationships between efficacy measures and exposure to drug or its metabolite was found at Weeks 18 and 26.

Logistic regression analysis (n=625) showed that a significant relationship between ZNS 114-666 exposure and the incidence of gastrointestinal adverse events ($p > 0.05$). During the titration phase, the incidence of anorexia and diarrhea were significantly and directly related to ZNS 114-666 $AUC_{0\text{-}12h}$ and Cmax, while nausea and vomiting were directly related Cmax of ZNS 114-666. During the maintenance phase, anorexia, diarrhea, and nausea did not change, while vomiting was directly related to $AUC_{0\text{-}12h}$ and Cmax of ZNS 114-666. Clinically notable weight loss of more than 7 % after Day 84 was associated with the $AUC_{0\text{-}12h}$ and Cmax of ZNS 114-666 during the maintenance phase but not during the titration phase. The significant PK/PD relationship with ZNS 114-666 indicates that this metabolite may be a better surrogate for the exposure of the parent drug.

FORMULATION

The sponsor is proposing to market rivastigmine tartrate as ———————, 1.5 mg, 3 mg, 4.5 mg, and 6 mg (as free base) immediate-release, hard-gelatin capsules for oral administration. Capsules are not compositionally proportional. The composition of

different capsule strengths is shown in **APPENDIX II**. Clinical capsules were identical in composition to those proposed for marketing and therefore, no links between clinical and to-be-marketed formulations are needed to be established.

IN VITRO DISSOLUTION

ENA 713 is a highly soluble drug. Its permeability is not known. Dissolution of the drug substance is independent of pH over the physiological pH range of 1-7. Water was selected as a dissolution medium for ENA 713 capsules. Dissolution testing was performed using the USP Apparatus 2 (rotating paddle) at a speed of 50 rpm in 500 mL of water at 37 ± 0.5 °C. [redacted], were submitted for the to-be-marketed as well as stability capsules.

Dissolution of rivastigmine tartrate in water was fast; mean % dissolved was more than 90 % in 30 minutes (See also **APPENDIX III**). However, some individual capsules, especially those of stability batches showed dissolution rate as low as 76 % in 30 minutes. The sponsor proposes a specification of [redacted].

The Agency agrees on the firm's dissolution methodology and specification for all strengths of rivastigmine tartrate capsules ([redacted] 1.5 mg, 3.0 mg, 4.5 mg, and 6 mg) as outlined below:

Apparatus:	USP Apparatus 2 (Rotating Paddle)
Speed of Rotation:	50 rpm
Medium:	500 mL of water at 37 ± 0.5 °C
Specification:	[redacted]

ANALYTICAL METHODOLOGY

In the studies submitted, the sponsor utilized a gas chromatography with mass spectrometric detection (GC/MS) method to measure plasma concentrations of ENA 713. The method is adequately validated. Details of the method are shown in **APPENDIX IV**.

[redacted]

/S/

Safaa S. Ibrahim, Ph.D.
Division of Pharmaceutical Evaluation I

ClinPharm/Biopharm Briefing on: November 26, 1997 (Attendees: Drs.: Malinowski, Chen, Lazor, Mehta, Baweja, Miller, Sahajwalla, Ibrahim, Tammara, Levin, Fitzgerald, Rosloff)

RD/FT initialed by C. Sahajwalla, Ph.D. /S/

cc: NDA # 20-823 (Orig.), HFD-120, HFD-860 (Ibrahim, Sahajwalla, Malinowski), HFD-19 (FOI), and Drug files (Barbara Murphy, CDR).

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Table 6. All-cause and SUD mortality (per 1000 PYs) In the rivastigmine NDA using the findings from the FDA team					
Study Type	PYs	Deaths within 30	Kane NIP deaths	FDA NIP Deaths	FDA SUDs
RCTs					
Placebo	396	0.3 (1)	0	0.3 (1)	0
> 0- <10 mg	646	7.7 (5)	3.1 (2)	6.2 (4)	1.5 (1)
10&12 mg	165	6.1 (1)	6.1 (1)	6.1 (1)	6.1 (1)
RR (95% CI)		1.1* (0.1,8.8)	3.2* (0.3,34.9)	1.3* (0.1,10.8)	6.3* (0.4,101.1)
RCT Extensions					
<10 mg	996	12.1 (12)	2.0 (2)	6.0 (6)	2.0 (2)
10&12 mg	991	23.2 (23)	17.2 (17)	15.1 (15)	7.1 (7)
RR (95% CI)		1.9 (0.96,3.9)	8.5 (2.0,37.0)	2.5 (0.97,6.5)	3.5 (0.7, 16.9)
Titration Studies					
<10 mg	301	36.9 (12)	19.9 (6)	26.6 (8)	10.0 (3)
10&12 mg	135	14.8 (2)	7.4 (1)	7.4 (1)	0
RR (95% CI)		0.4 (0.1, 1.7)	0.4 (0.04,3.1)	0.3 (0.0, 2.2)	
All Studies					
Placebo	396	0.3 (1)	0.0 (0)	0.3 (1)	0.0 (0)
<10 mg	1943	14.9 (29)	5.1 (10)	9.3 (18)	3.1 (6)
10&12 mg	1290	20.1 (26)	14.7 (19)	13.2 (17)	6.2 (8)
RR (95% CI)		1.6* (0.9,2.7)	3.4* (1.6,7.4)	1.6* (0.8, 3.1)	2.4* (0.8,7.0)

*10 & 12 mg compared to < 10 mg including placebo
NIP, not implausible; PYs, person-years; RCTs, randomized controlled trials

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ON ORIGINAL

Table 7. Mortality rates by current dose in the RCT extension dataset for deaths considered implausible by FDA reviewers and deaths meeting their SUD criteria

		FDA NIP Deaths		FDA SUDs	
Dose	PYRs	Counts	Rate	Counts	Rate
2	134	1	7.5	0	0
4	221	0	0	0	0
6	355	2	5.6	1	2.8
8	285	3	10.5	1	3.5
10	231	2	8.7	2	8.7
12	760	13	17.1	5	6.6
<10	996	6	6.0	2	2.0
10 & 12	991	15	15.1	7	7.1

Rates are deaths per 1000 person years (PYRs)
NIP, not-implausible; SUDs, sudden unexplained deaths

Table 8. Mortality Rates (per 1000 PYs) in the RCT Extension dataset by Time Since Study Entry

TSSE	Deaths 30	Deaths 7		FDA NIP	FDA SUDs
Days 0-60	3 (1)	3 (1)	3 (1)	0 (0)	0 (0)
Days 61-180	18 (10)	14 (8)	9 (5)	12 (7)	2 (1)
Days 181-365	25 (17)	8 (6)	12 (8)	13 (9)	4 (3)
Days 365+	16 (7)	12 (5)	12 (5)	12 (5)	12 (5)

NIP, not-implausible; SUDs, sudden unexplained deaths; TSSE, time since study entry

Table 9. Mortality rates (per 1000 PYs) in the RCT extension dataset by time since study entry

			FDA NIP Deaths		FDA SUDs	
TSSE		PYs	N	Rate	N	Rate
Days 0-60						
	<10	237	0	0	0	0
	10 & 12	81	0	0	0	0
Days 61-180						
	<10	260	2	7.7	0	0
	10 & 12	302	5	16.5	1	3.3
Days 181-365						
	<10	315	4	12.7	2	6.3
	10 & 12	367	5	13.6	1	2.7
Days 365 +						
	<10	184	0	0	0	0
	10 & 12	240	5	20.8	5	20.8

PYs, person-years; NIP, not-implausible; SUDs, sudden unexplained deaths; TSSE, time since study entry

Appendix 2: Donepezil Mortality

Table 1. Mortality rate (per 1000 PYs) in study 303 using time at each dose			
Dose	**PYRs**	**Deaths within 30 days of LPD**	**Deaths within 7 days of LPD**
5 mg	163	18.4 (3)	18.4 (3)
10 mg	1109	27.0 (30)	18.0 (20)
Rate Ratio		1.5 (0.5,4.8)	1.0 (0.3,3.3)

Table 2. Mortality rates (per 1000 PYs) within 30 days of LPD by time since entering the extension.		
Time Period	**5 mg Dose**	**10 mg Dose**
0-60	11.3 (1 in 88 PYs)	39.7 (4 in 101)
60-180	52.1 (1 in 19 PYs)	15.8 (3 in 189)
180-365	45.4 (1 in 22 PYs)	7.5 (2 in 265)
365-730	(0 in 28 PYs)	34.9 (15 in 430)
730+	(0 in 6 PYs)	48.4 (6 in 124)

Table 3. Mortality rates (per 1000 PYs) across all phase 3 open-label experience.			
Dose	**PYRs**	**Deaths within 30**	**Deaths within 7**
<10 mg	411	19.4 (8)	14.6 (6)
10 mg	1421	25.3 (36)	18.3 (26)
Rate Ratio		1.3 (0.6,2.8)	1.3 (0.5,3.0)

Table 4. Mortality Rates (per 1000 PYs) for Deaths classified as not-implausible or SUDs by the FDA across all phase 3 open-label experience with donepezil.			
Dose	**PYRs**	**FDA NI Deaths**	**FDA SUDs**
<10 mg	373	9.7 (4)	4.9 (2)
10 mg	1421	12.0 (17)	4.2 (6)
Rate Ratio		1.1 (0.4,3.2)	0.8 (0.2, 3.4)

NI, not implausible

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Appendix 3: Selected Tables and Figures from Novartis's response to the NA letter

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Post-text Table 5.5.1:
Exelon June 30, 1997 Mortality Data
Summary of Nested Case Control Analyses Conducted for All Deaths

GROUP	Data Used	Variable	DF	Parameter Estimate	Std Err	Chi-Sq	P-Value	Relative Risk	LL	UL	WOC	WC
All Phase III	All Data	-2 LN L	6			5.372	0.497				640.243	634.87
All Phase III	All Data	Placebo	1	-1.25983	1.1589	1.18176	0.277	0.284	0.029	2.75		
All Phase III	All Data	>2 - 4 mg	1	-0.64651	0.72022	0.80579	0.3694	0.524	0.128	2.149		
All Phase III	All Data	>4 - 6 mg	1	-0.1592	0.63619	0.06262	0.8024	0.853	0.245	2.967		
All Phase III	All Data	>6 - 8 mg	1	-0.88241	0.80048	1.21518	0.2703	0.414	0.086	1.987		
All Phase III	All Data	>8 - 10 mg	1	0.15554	0.66303	0.05503	0.8145	1.168	0.319	4.285		
All Phase III	All Data	>10 - 12 mg	1	-0.11919	0.61746	0.03726	0.8469	0.888	0.265	2.977		
All Phase III	All Data	-2 LN L	4			1.593	0.81				640.243	638.649
All Phase III	All Data	Placebo	1	-0.86913	1.13102	0.59052	0.4422	0.419	0.046	3.848		
All Phase III	All Data	4 - 6 mg	1	0.17115	0.53184	0.10356	0.7476	1.187	0.418	3.365		
All Phase III	All Data	>6 - 9 mg	1	0.13633	0.57661	0.05552	0.8137	1.146	0.369	3.562		
All Phase III	All Data	>9 - 12 mg	1	0.31336	0.51697	0.36741	0.5444	1.368	0.497	3.768		
All Phase III	All Data	-2 LN L	4			1.801	0.772				640.243	638.442
All Phase III	All Data	Placebo	1	-0.86058	1.10676	0.60461	0.4368	0.423	0.048	3.701		
All Phase III	All Data	>4 - 6 mg	1	0.25891	0.46485	0.31021	0.5775	1.296	0.521	3.222		
All Phase III	All Data	>6 - 9 mg	1	0.15464	0.50299	0.09451	0.7585	1.167	0.436	3.128		
All Phase III	All Data	>9 - 12 mg	1	0.32878	0.41767	0.61965	0.4312	1.389	0.613	3.16		
All Phase III	All Data	-2 LN L	2			1.116	0.572				640.243	639.126
All Phase III	All Data	Placebo	1	-0.98294	1.09786	0.8016	0.3706	0.374	0.044	3.218		
All Phase III	All Data	6 - 12 mg	1	0.05586	0.36399	0.02355	0.878	1.057	0.518	2.158		
All Phase III	All Data	-2 LN L	2			1.486	0.475				640.243	638.756
All Phase III	All Data	Placebo	1	-0.96971	1.08407	0.80013	0.3711	0.379	0.045	3.174		
All Phase III	All Data	>9 - 12 mg	1	0.17979	0.28649	0.3938	0.5303	1.197	0.683	2.099		
All Phase III	All Data	-2 LN L	2			1.312	0.519				640.243	638.931
All Phase III	All Data	Placebo	1	-1.08269	1.09254	0.98205	0.3217	0.339	0.04	2.882		
All Phase III	All Data	>0 - <4 mg	1	-0.22285	0.48749	0.20897	0.6476	0.8	0.308	2.081		
All Phase III	All Data	-2 LN L	2			1.611	0.446				640.243	638.631
All Phase III	All Data	Placebo	1	-1.12366	1.09285	1.05716	0.3039	0.325	0.038	2.768		
All Phase III	All Data	>0 - 4 mg	1	-0.27295	0.38979	0.49036	0.4838	0.761	0.356	1.634		
All Phase III	All Data	-2 LN L	1			0.921	0.337				640.243	639.321
All Phase III	All Data	Prescribed Dose	1	0.039476	0.04153	0.90358	0.3418	1.04	0.959	1.128		
All Phase III	All Data	-2 LN L	2			11.394	0.003				640.214	628.82
All Phase III	All Data	Dose/10 kg (TD)	1	0.4538	0.24377	3.4657	0.0627	1.574	0.976	2.539		

Covariates identified with (TD) are time-dependent.
Wald Chi-sq used for Parameter Estimates.
Likelihood-ratio test used for overall model (difference between -2 ln likelihood for model fit with no covariates vs model with the given covariates).

Post-text Table 5.5.1:
Exelon June 30, 1997 Mortality Data
Summary of Nested Case Control Analyses Conducted for All Deaths

GROUP	Data Used	Variable	DF	Parameter Estimate	Std Err	Chi-Sq	P-Value	Relative Risk	LL	UL	WOC	WC
EXT	All Data	-2 LN L	1	.	.	0.004	0.952	.	.	.	409.404	409.401
EXT	All Data	>0 - 4 mg	1	-0.029097	0.48524	0.0036	0.9522	0.971	0.375	2.514	.	.
EXT	All Data	-2 LN L	1	.	.	1.152	0.283	.	.	.	409.404	408.252
EXT	All Data	Prescribed Dose	1	0.058935	0.05611	1.10312	0.2936	1.061	0.95	1.184	.	.
EXT	All Data	-2 LN L	2	.	.	11.877	0.002	.	.	.	409.404	397.528
EXT	All Data	Dose/10 kg (TD)	1	0.55254	0.32025	2.9767	0.0845	1.738	0.928	3.255	.	.
EXT	All Data	Weight (TD)	1	-0.02996	0.01544	3.7627	0.0524	0.97	0.942	1	.	.
EXT	All Data	-2 LN L	2	.	.	7.556	0.022	.	.	.	408.161	400.605
EXT	All Data	Dose/10 kg	1	0.45098	0.32686	1.90361	0.1677	1.57	0.827	2.979	.	.
EXT	All Data	Bsl Weight	1	-0.02479	0.01498	2.74512	0.0976	0.976	0.947	1.005	.	.
EXT	All Data	-2 LN L	1	.	.	0.076	0.783	.	.	.	409.404	409.329
EXT	All Data	Cum Dose (1000 mg)	1	-0.004108	0.01491	0.07597	0.783	0.996	0.967	1.025	.	.
EXT	All Data	-2 LN L	6	.	.	5.059	0.536	.	.	.	409.404	404.345
EXT	All Data	>2 - 4 mg	1	-1.08912	0.91521	1.41614	0.234	0.337	0.056	2.023	.	.
EXT	All Data	>4 - 6 mg	1	-1.01521	0.76541	1.7592	0.1847	0.362	0.081	1.624	.	.
EXT	All Data	>6 - 8 mg	1	-1.06134	0.8188	1.68017	0.1949	0.346	0.07	1.722	.	.
EXT	All Data	>8 - 10 mg	1	-0.38783	0.73413	0.27909	0.5973	0.679	0.161	2.861	.	.
EXT	All Data	>10 - 12 mg	1	-0.26953	0.62838	0.18399	0.668	0.764	0.223	2.617	.	.
EXT	All Data	Prev Exp to Exelon (vs Pbo)	1	-0.22711	0.35271	0.41461	0.5196	0.797	0.399	1.591	.	.
EXT	All Data	-2 LN L	4	.	.	4.997	0.287	.	.	.	409.404	404.408
EXT	All Data	4 - 6 mg	1	-1.04045	0.70857	2.15611	0.142	0.353	0.088	1.417	.	.
EXT	All Data	>6 - 9 mg	1	-1.06134	0.8188	1.68016	0.1949	0.346	0.07	1.722	.	.
EXT	All Data	>9 - 12 mg	1	-0.29718	0.61801	0.23123	0.6306	0.743	0.221	2.495	.	.
EXT	All Data	Prev Exp to Exelon (vs Pbo)	1	-0.22748	0.35262	0.41617	0.5189	0.797	0.399	1.59	.	.
EXT	All Data	-2 LN L	4	.	.	3.553	0.469	.	.	.	409.404	405.852
EXT	All Data	>4 - 6 mg	1	-0.43585	0.67307	0.41933	0.5173	0.647	0.173	2.419	.	.
EXT	All Data	>6 - 9 mg	1	-0.48055	0.73216	0.43079	0.5116	0.618	0.147	2.597	.	.
EXT	All Data	>9 - 12 mg	1	0.28289	0.4984	0.32216	0.5703	1.327	0.5	3.524	.	.
EXT	All Data	Prev Exp to Exelon (vs Pbo)	1	-0.22944	0.35254	0.42354	0.5152	0.795	0.398	1.587	.	.
EXT	exc304	-2 LN L	1	.	.	0.011	0.916	.	.	.	324.277	324.266
EXT	exc304	Placebo	0	0								
EXT	exc304	6 - 12 mg	1	-0.0573	0.5422	0.01117	0.9158	0.944	0.326	2.733	.	.

Covariates identified with (TD) are time-dependent.
Wald Chi-sq used for Parameter Estimates.
Likelihood st used for overall model (difference between -2 ln likelihood for model fit with no covari model with the given covariates)

Post-text Table 7.2.1:
Exelon June 30, 1997 Mortality Data
Summary of Nested Case Control Analyses Conducted for Deaths WI 7 Days (Kane)

GROUP	Data Used	Variable	DF	Parameter Estimate	Std Err	Chi-Sq	P-Value	Relative Risk	LL	UL	WOC	WC
All Phase III	All Data	-2 LN L	6	.	.	6.179	0.403	.	.	.	381.575	375.396
All Phase III	All Data	Placebo	1	-14.8527	1311	0.00013	0.991	0	0	.	.	.
All Phase III	All Data	>2 - 4 mg	1	-0.6196	1	0.38542	0.5347	0.538	0.076	3.808	.	.
All Phase III	All Data	>4 - 6 mg	1	-0.275	0.94	0.08522	0.7703	0.76	0.12	4.814	.	.
All Phase III	All Data	>6 - 8 mg	1	-0.3300	1.12	0.08761	0.7672	0.718	0.08	6.426	.	.
All Phase III	All Data	>8 - 10 mg	1	0.1347	0.98	0.01894	0.8905	1.144	0.168	7.792	.	.
All Phase III	All Data	>10 - 12 mg	1	0.3814	0.9	0.17904	0.6722	1.464	0.25	8.569	.	.
All Phase III	All Data	-2 LN L	4	.	.	4.857	0.302	.	.	.	381.575	376.718
All Phase III	All Data	Placebo	1	-15.5836	2129	0.00005	0.9942	0	0	.	.	.
All Phase III	All Data	4 - 6 mg	1	-0.1055	0.72	0.0213	0.884	0.9	0.218	3.71	.	.
All Phase III	All Data	>6 - 9 mg	1	0.3585	0.76	0.22052	0.6386	1.431	0.321	6.39	.	.
All Phase III	All Data	>9 - 12 mg	1	0.5974	0.68	0.78132	0.3767	1.817	0.483	6.835	.	.
All Phase III	All Data	-2 LN L	4	.	.	4.897	0.298	.	.	.	381.575	376.678
All Phase III	All Data	Placebo	1	-15.487	2132	0.00005	0.9942	0	0	.	.	.
All Phase III	All Data	>4 - 6 mg	1	0.1655	0.67	0.06085	0.8055	1.18	0.316	4.404	.	.
All Phase III	All Data	>6 - 9 mg	1	0.525	0.69	0.5807	0.446	1.69	0.438	6.523	.	.
All Phase III	All Data	>9 - 12 mg	1	0.7658	0.58	1.74437	0.1866	2.151	0.69	6.701	.	.
All Phase III	All Data	-2 LN L	2	.	.	3.515	0.172	.	.	.	381.575	378.061
All Phase III	All Data	Placebo	1	-15.4434	2138	0.00005	0.9942	0	0	.	.	.
All Phase III	All Data	6 - 12 mg	1	0.5839	0.55	1.11102	0.2919	1.793	0.605	5.31	.	.
All Phase III	All Data	-2 LN L	2	.	.	4.284	0.117	.	.	.	381.575	377.292
All Phase III	All Data	Placebo	1	-15.5668	2125	0.00005	0.9942	0	0	.	.	.
All Phase III	All Data	>9 - 12 mg	1	0.5273	0.37	2.00123	0.1572	1.694	0.816	3.518	.	.
All Phase III	All Data	-2 LN L	2	.	.	2.49	0.287	.	.	.	381.575	379.085
All Phase III	All Data	Placebo	1	-15.7732	2120	0.00006	0.9941	0	0	.	.	.
All Phase III	All Data	>0 - <4 mg	1	-0.3026	0.64	0.22539	0.635	0.739	0.212	2.577	.	.
All Phase III	All Data	-2 LN L	2	.	.	3.403	0.182	.	.	.	381.575	378.173
All Phase III	All Data	Placebo	1	-15.9886	2136	0.00006	0.994	0	0	.	.	.
All Phase III	All Data	>0 - 4 mg	1	-0.5543	0.55	1.01748	0.3131	0.574	0.196	1.687	.	.
All Phase III	All Data	-2 LN L	1	.	.	3.657	0.055	.	.	.	381.575	377.918
All Phase III	All Data	Prescribed Dose	1	0.10776	0.0584	3.40536	0.065	1.114	0.993	1.249	.	.
All Phase III	All Data	-2 LN L	2	.	.	11.987	0.002	.	.	.	381.572	369.586
All Phase III	All Data	Dose/10 kg (TD)	1	0.8894	0.33804	6.9224	0.0085	2.434	1.255	4.721	.	.

Covariates identified with (TD) are time-dependent.
Wald Chi-sc 'or Parameter Estimates.
Likelihood- used for overall model (difference between -2 ln likelihood for model fit with no covari odel with the given covariates).

Exelon June 30, 1997 Mortality Data

Summary of Nested Case Control Analyses Conducted for Deaths WI 7 Days (Kane)

GROUP	Data Used	Variable	DF	Parameter Estimate	Std Err	Chi-Sq	P-Value	Relative Risk	LL	UL	WOC	WC
RCT	All Data	Placebo	1	-30.8166	3367	0.00008	0.9927	0	0	.	.	.
RCT	All Data	>0 - 4 mg	1	-16.5041	2528	0.00004	0.9948	0	0	.	.	.
RCT	All Data	-2 LN L	1	.	.	4.095	0.043	.	.	.	38.527	34.432
RCT	All Data	Prescribed Dose	1	0.48592	0.35233	1.90215	0.1678	1.626	0.815	3.243	.	.
RCT	All Data	-2 LN L	2	.	.	2.712	0.257	.	.	.	38.524	35.812
RCT	All Data	Dose/10 kg (TD)	1	1.97872	1.38721	2.03463	0.1538	7.233	0.477	109.683	.	.
RCT	All Data	Weight (TD)	1	0.02611	0.04498	0.33883	0.5617	1.026	0.94	1.121	.	.
RCT	All Data	-2 LN L	2	.	.	2.701	0.259	.	.	.	38.437	35.736
RCT	All Data	Dose/10 kg	1	1.98601	1.39952	2.01374	0.1559	7.286	0.469	113.184	.	.
RCT	All Data	Bsl Weight	1	0.0291	0.04443	0.42685	0.5126	1.03	0.944	1.123	.	.
RCT	All Data	-2 LN L	1	.	.	3.966	0.046	.	.	.	38.527	34.561
RCT	All Data	Cum Dose (1000 mg)	1	1.78895	1.87206	0.91316	0.3393	5.983	0.153	234.652	.	.
EXT	All Data	-2 LN L	5	.	.	6.636	0.249	.	.	.	230.081	223.445
EXT	All Data	>2 - 4 mg	1	-0.71952	1.41715	0.25778	0.6116	0.487	0.03	7.831	.	.
EXT	All Data	>4 - 6 mg	1	-1.41099	1.4156	0.9935	0.3189	0.244	0.015	3.91	.	.
EXT	All Data	>6 - 8 mg	1	-0.46641	1.22667	0.14457	0.7038	0.627	0.057	6.944	.	.
EXT	All Data	>8 - 10 mg	1	-0.36927	1.22746	0.0905	0.7635	0.691	0.062	7.664	.	.
EXT	All Data	>10 - 12 mg	1	0.42731	1.04203	0.16816	0.6818	1.533	0.199	11.818	.	.
EXT	All Data	-2 LN L	3	.	.	5.119	0.163	.	.	.	230.081	224.962
EXT	All Data	4 - 6 mg	1	-1.12332	1.2262	0.83923	0.3596	0.325	0.029	3.597	.	.
EXT	All Data	>6 - 9 mg	1	-0.464	1.22666	0.14308	0.7052	0.629	0.057	6.96	.	.
EXT	All Data	>9 - 12 mg	1	0.26998	1.03531	0.068	0.7943	1.31	0.172	9.986	.	.
EXT	All Data	-2 LN L	3	.	.	5.097	0.164	.	.	.	230.081	224.985
EXT	All Data	>4 - 6 mg	1	-0.96331	1.22666	0.64631	0.4214	0.373	0.034	4.13	.	.
EXT	All Data	>6 - 9 mg	1	-0.04056	1.00169	0.00164	0.9677	0.96	0.135	6.84	.	.
EXT	All Data	>9 - 12 mg	1	0.69269	0.75641	0.83862	0.3598	1.999	0.454	8.804	.	.
EXT	All Data	-2 LN L	1	.	.	0.286	0.592	.	.	.	230.081	229.795
EXT	All Data	6 - 12 mg	1	0.38091	0.74834	0.25909	0.6107	1.464	0.338	6.345	.	.
EXT	All Data	-2 LN L	1	.	.	4.212	0.04	.	.	.	230.081	225.869
EXT	All Data	>9 - 12 mg	1	0.99587	0.51877	3.68511	0.0549	2.707	0.979	7.483	.	.
EXT	All Data	-2 LN L	1	.	.	0.008	0.928	.	.	.	230.081	230.073
EXT	All Data	>0 - <4 mg	1	0.093293	1.02791	0.00824	0.9277	1.098	0.146	8.231	.	.

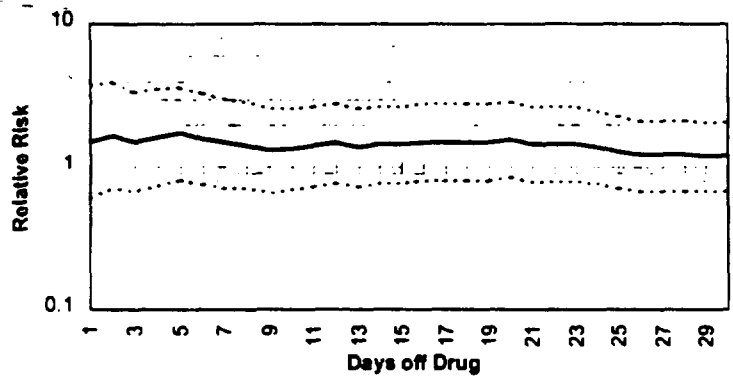
Covariates identified with (TD) are time-dependent.

Wald Chi-sr 'or Parameter Estimates.

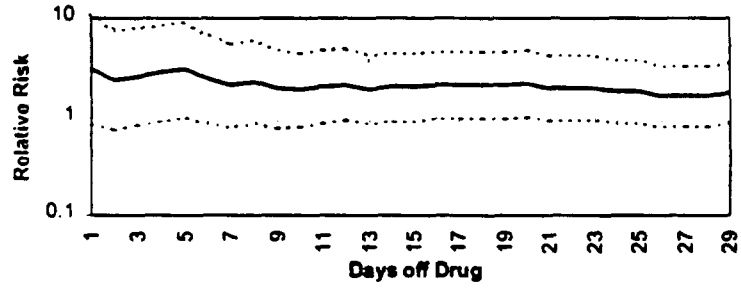
Likelihood- used for overall model (difference between -2 ln likelihood for model fit with no covari. lodel with the given covariates).

Figure 7.3 **Days off drug > 9 mg vs <=9 mg (All Phase 3, EXT, TITR)**

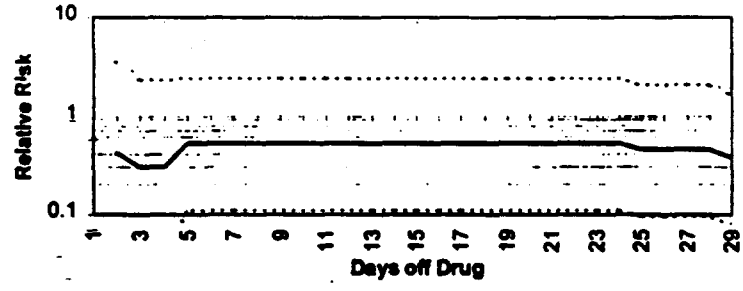
All Phase III: >9 mg versus <=9 mg



Extension Studies: >9 mg versus <=9 mg



Titration Studies: >9 mg versus <=9 mg



Appendix 4. Drs. Boehm, Feeney and Freiman reviews of implausibility and SUDs for rivastigmine and donepezil

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages regarding draft labeling

COMPLETED FEB 0 8 2000

FEB 7 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-823

Submission Dates:
October 21, 1999

Generic Name:	Rivastigmine Tartrate Oral Capsule (ENA 713)
Brand Name:	EXELON®
Indication (s)	Alzheimer's disease
Sponsor:	Novartis
Type of Submission:	Pre-Approval Safety Update Package
Reviewer:	Sayed Al-Habet, Ph.D.
Date of Review:	January 19, 2000

SYNOPSIS:

Novartis Pharmaceuticals has submitted for review a pre-approval safety update package. The most relevant information to the Office of Clinical Pharmacology and Biopharmaceutics are: 1) liver impairment study (Attachment 1) and absolute bioavailability study (Attachment 2).

Background/Discussion:

1) In the current label of the original NDA the clearance of the drug was reduced by 60% in liver impairment patients compared to healthy subjects. The study was conducted at a single 3 mg oral dose. In the current submission, the sponsor has conducted a multiple dose study at 6 mg bid oral dose in liver impairment patients and healthy subjects (study # W368); the dose of 6 mg bid was shown to be effective in clinical trails. The results of this study indicate that the mean oral clearance was reduced by 65% (46% to 70%) in liver impairment patients compared to control (see Comment below). In addition, in cirrhotic patients, the mean oral clearance was 25% lower after morning 6 mg dose than after evening dose (32 L/h vs 40 L/h). This small difference does not appear to be of clinical significance.

2) The mean absolute bioavailability of rivastigmine at an oral dose of 6 mg and an IV dose of 2 mg is about 72% ranging from 22-118%. The previous study (#W361) of the original NDA was 35% at an oral dose of 3 mg and an IV dose of 1 mg. The reason for this discrepancy is not clear, but could possibly be due to the non-linear PK of the drug. In

this case, the best estimate of the absolute bioavailability for this drug would be at the same oral and IV dose (e.g., 3 mg). The 6 mg IV dose may be too high to be given to humans.

Labelling/Comment (Comment to the Clinical Division) :

For the multiple dosing hepatic impairment study, the sponsor is requested to add the following statement to the current label:

RECOMMENDATION:

Please incorporate the contents of the above Labelling Comment to the current labelling for Exelon Oral Capsule.

Reviewed by:

/S/

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D. /S/ 11/2000.

cc: NDA # 20-823 (Orig.), HFD-120, HFD-860 (Al-Habet, Baweja, Mehta), Drug files (Biopharm File, CDR).

Attachment 1

1. Clinical Pharmacology Summary Report SDZ ENA 713 W368

Study title: A multiple dose study employing titration to evaluate the pharmacokinetics of SDZ ENA 713 capsules at an oral 6 mg (single and bid) dose in subjects with liver cirrhosis compared to a control group of healthy volunteers.

Investigator(s): Kenneth Lasseter, MD, Clinical Pharmacology Associates, Miami, FL, USA

Report authors: Mr. C. McDonald, Dr. M. Hossain (Clinical Pharmacology, Novartis, E. Hanover, NJ, USA), Dr. E. Singer (Drug Metabolism and Pharmacokinetics, Novartis, Basel, Switzerland) and Dr. J. Lee (Medical Information Processing and Statistics, Novartis, E. Hanover, NJ, USA)

Publication(s): None

Study period: first subject dosed 19-Jun-98 last subject completed 17-Sep-98

Objectives:

Primary: To determine if the pharmacokinetic parameters of SDZ ENA 713 (ENA 713; rivastigmine) and its phenolic metabolite NAP 226-90 at the 6 mg single dose are altered in subjects with liver cirrhosis compared to healthy control subjects.

Secondary: To evaluate if the pharmacokinetic parameters of rivastigmine and NAP 226-90 at the 3 mg bid and 6 mg bid doses are altered in subjects with liver cirrhosis compared to healthy control subjects.

To evaluate the safety and tolerability of rivastigmine at the 6 mg dose in subjects with liver cirrhosis compared to healthy control subjects.

To compare pharmacokinetic parameters of rivastigmine and NAP 226-90 between the morning and the evening medication cycle at steady state bid dosing.

Design: This was a single center, open-label, parallel-group, 22-day titration trial, using doses up to 6 mg bid.

Number of subjects: Enrolled: 21 total; Completed: 20 (10 in each Group I and II) - one subject in Group I (#0009) discontinued prematurely after completing only the 3 mg single dose and 3 mg b.i.d. dosing treatments.

Criteria for inclusion:

Group I: Ten (10) subjects, 21-70 years of age with biopsy proven liver cirrhosis, a Child-Pugh score of 5-12, normal renal function, and free of encephalopathy or moderate to severe ascites.

Group II: Ten (10) age, gender and weight matched healthy subjects.

Investigational drug:

[redacted]

Duration of treatment: 22 day titration, 7 different dose regimens of rivastigmine.

3 mg q.d., 3 mg b.i.d., 4 mg b.i.d., 5 mg b.i.d., 5 mg q.d., 6 mg q.d. and 6 mg b.i.d.

Criteria for evaluation:

Table 2-5.: Comparison between cirrhotic and healthy groups for ENA713 pharmacokinetics from 6 mg bid dosing (morning)

ENA713 STUDY W368 6 mg, bid dosing (a.m.)					
PARAMETER	ARITHMETIC MEAN + SD GEOMETRIC MEAN (RANGE)		% DIFFERENCE	p-value	(90% C.I.)
	Cirrhotic group (N =10)	Healthy group (N =10)			
AUC(0-12) (ng.hr/mL)	215.75 + 92.38 199.74	83.38 + 44.84 73.41	158.77 172.10	<.01*	(1.88 3.93)
Cmax (ng/mL)	37.38 + 12.91 35.80	24.70 + 12.76 21.91	51.32 63.39	0.02*	(1.18 2.27)
Tmax § (hr)	1.50 + 0.41 1.50	1.05 + 0.28 1.00	42.86 50.00	0.03*	
T-HALF (hr)	3.35 + 1.79 2.99	1.83 + 0.23 1.81	83.42 64.87	0.01*	(1.25 2.17)
CL/F (L/h)	32.32 + 12.68 30.05	92.23 + 46.33 81.70	-64.96 -63.21	<.01*	(0.25 0.53)
M/P ratio	0.21 + 0.12 0.18	0.71 + 0.43 0.61	-70.06 -70.48	<.01*	(0.18 0.47)
Accumu. index	1.47 + 0.16 1.46	1.32 + 0.33 1.28	11.41 14.11	0.16	(0.97 1.34)

NOTE: § MEDIAN IS PROVIDED FOR TMAX INSTEAD OF GEOMETRIC MEAN. P-VALUE WAS OBTAINED FROM WILCOXON'S RANK SUM TEST.
FOR p-value, * = STATISTICALLY SIGNIFICANT (p<=0.05) DIFFERENCE BETWEEN TREATMENT MEANS.

Table 2-6.: Comparison between cirrhotic and healthy groups for ENA713 pharmacokinetics from 6 mg bid dosing (evening)

ENA713 STUDY W368 6 mg, bid dosing (p.m.)					
PARAMETER	ARITHMETIC MEAN + SD GEOMETRIC MEAN (RANGE)		% DIFFERENCE	p-value	(90% C.I.)
	Cirrhotic group (N = 9)	Healthy group (N =10)			
AUC(0-12) (ng.hr/mL)	173.89 + 78.48 159.81	83.91 + 60.28 67.42	107.23 137.03	0.01*	(1.49 3.78)
Cmax (ng/mL)	25.50 + 7.02 24.53	20.71 + 19.46 15.78	23.15 55.43	0.11	(0.99 2.45)
Tmax # (hr)	2.78 + 1.18 2.00	1.90 + 0.88 2.00	46.21 0.00	0.16	
T-HALF (hr)	4.17 + 2.65 3.58	2.01 + 0.42 1.97	107.78 81.67	0.01*	(1.30 2.53)
CL/F (L/h)	40.65 + 16.62 37.56	108.09 + 65.03 89.03	-62.40 -57.81	0.01*	(0.26 0.67)
M/P ratio	0.22 + 0.13 0.19	0.74 + 0.43 0.63	-70.07 -70.45	<.01*	(0.18 0.49)

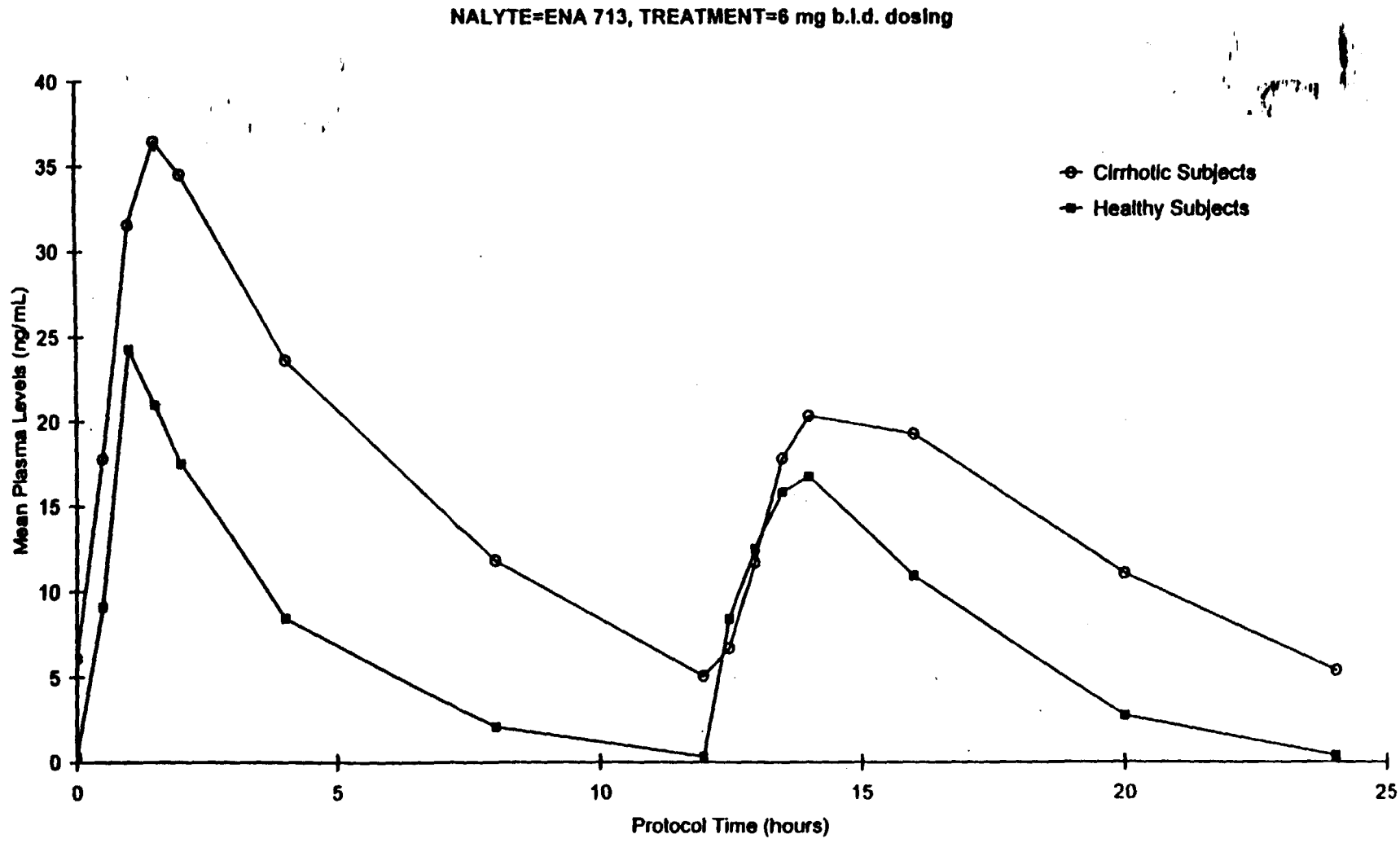
NOTE:# MEDIAN IS PROVIDED FOR TMAX INSTEAD OF GEOMETRIC MEAN. P-VALUE WAS OBTAINED FROM WILCOXON'S RANK SUM TEST.
FOR p-value; * = STATISTICALLY SIGNIFICANT (p<=0.05) DIFFERENCE BETWEEN TREATMENT MEANS.

Table 2-13.: Comparison of 6 mg evening versus morning dose for ENA713 pharmacokinetics of cirrhotic subjects

	ENA713 STUDY W368 6 mg, bid dosing				
PARAMETER	ARITHMETIC MEAN + SD GEOMETRIC MEAN (RANGE)		% DIFFERENCE	p-value	(90% C.I.)
AUC(0-12) (ng.hr/mL)	Evening dose (N = 9) 173.89 + 78.48 159.81	Morning dose (N =10) 215.75 + 92.38 199.74	-19.40 -19.99	<.01*	(0.73 0.86)
Cmax (ng/mL)	25.50 + 7.02 24.53	37.38 + 12.91 35.80	-31.78 -31.48	0.01*	(0.53 0.84)
Tmax # (hr)	2.78 + 1.18 2.00	1.50 + 0.41 1.50	85.20 33.33	0.03*	
T-HALF (hr)	4.17 + 2.65 3.58	3.35 + 1.79 2.99	24.38 19.48	<.01*	(1.13 1.33)
CL/F (L/h)	40.65 + 16.62 37.56	32.32 + 12.68 30.05	25.77 24.98	<.01*	(1.17 1.36)
M/P ratio	0.22 + 0.13 0.19	0.21 + 0.12 0.18	3.77 3.05	0.14	(0.99 1.13)

NOTE:# MEDIAN IS PROVIDED FOR TMAX INSTEAD OF GEOMETRIC MEAN. P-VALUE WAS OBTAINED FROM WILCOXON'S SIGNED RANK TEST.
FOR p-value, * = STATISTICALLY SIGNIFICANT (p<=0.05) DIFFERENCE BETWEEN TREATMENT MEANS.

Figure 4.1.4.: Mean plasma concentration time profile of rivastigmine following 6 mg b.i.d. oral dosing (n=10)



Attachment 2

Clinical Pharmacology Summary Report Exelon® W370

Study title: An absolute bioavailability study comparing a single dose of 6 mg SDZ ENA 713 capsule with a single 2 mg SDZ ENA 713 intravenous infusion in patients with probable Alzheimer's disease

Co-Investigator(s): Jameel Hourani, D.O. and Parvaneh P. Zolnouni, M.D., California Clinical Trials, Beverly Hills, CA, USA

Report authors: Mr. C. McDonald, Dr. M. Hossain (Clinical Pharmacology, Novartis, E. Hanover, NJ, USA), Ms. F. Pommier (Drug Metabolism and Pharmacokinetics, Novartis, Rueil-Malmaison, France) and Dr. J. Lee (Medical Information Processing and Statistics, Novartis, E. Hanover, NJ, USA)

Publication(s): None

Study period: first subject dosed 14-Aug-98 last subject completed 22-Sep-98

Objective: To assess the bioavailability of a single 6 mg SDZ ENA 713 (ENA 713) capsules dose compared to a single 2.0 mg ENA 713 i.v. infusion in patients with probable Alzheimer's disease currently participating in ENA 713 Studies B356 or B357.

Design: This was a single center, open-label, randomized order, two-way crossover trial using 6 mg Exelon® capsules & 2 mg ENA 713 i.v. solution.

Number of subjects: Planned: 12 (for at least 8 evaluable) Entered and completed: 11

Criteria for inclusion: Twelve male and female (non-child-bearing potential) outpatients between 50 and 86 years of age that were currently participating in ENA 713 Studies B356 or B357; patients had to have no medical conditions that would put them at an increased risk for participation in the study. Only medications required for coexistent medical conditions or to treat newly occurring adverse events were administered during the study.

Investigational drug:

Duration of treatment: Two single doses 3 days apart and 5 days total participation.

Single doses: a 6 mg capsule administered P.O. and a 2 mg i.v. infusion administered over 60 minutes

Criteria for evaluation:

Safety and tolerability: Physical exam, vital signs and safety laboratory evaluations

Pharmacokinetics: Plasma samples for determination of ENA 713 (rivastigmine) and its metabolite NAP 226-90 were obtained before and at 0.5, 0.75, 1, 1.5, 2, 4, 6, 8 and 12 hours after capsule administration or at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, and 12 hours after i.v. administration. Rivastigmine and its metabolite NAP 226-90 were determined in plasma using a GC/MS method at a limit of quantitation . for both compounds. Concentrations of rivastigmine and NAP 226-90 in plasma were used to determine: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, λ_z, and M/P ratio (calculated as $AUC_{0-\infty}$ of NAP 226-90 divided by $AUC_{0-\infty}$ of rivastigmine); and for rivastigmine only, to determine CL and V_z (both after i.v. only), and F_{abs}. The subjects' pharmacokinetic profiles were analyzed by standard non-compartmental methods using the pharmacokinetic software (version 1.5, Scientific Consulting Inc., Cary, NC).

Table 1: Pharmacokinetic parameters of rivastigmine following a single oral and intravenous administration of rivastigmine

	Arithmetic Mean ± SD Coefficient of Variation (CV%) (Range)	
Parameter	**2 mg Intravenous** **N = 11**	**6 mg Oral** **N = 11**
AUC_{0-t} (ng.h/mL)	35.69 ±19.88 55.7	69.79 ±28.05 40.2
$AUC_{0-\infty}$ (ng.h/mL)	37.13 ± 19.78 53.3	71.24 ± 28.17 39.5
C_{max} (ng/mL)	16.32 ± 6.84 41.9	25.62 ± 9.60 37.5
T_{max} (h)	1.28 ±0.92 72.0	1.18 ± 0.96 82.0
$T_{1/2}$ (h)	1.39 ±0.37 26.7	1.71 ± 0.23 13.2
CL (L/h)	62.61±19.68 31.4	
V_z (L)	124.05±49.58 40.0	
F_{abs} (%)		71.7 ±0.34 47.7

Following single oral administration of a 6 mg capsule and a single i.v. infusion of a 2 mg dose of rivastigmine, the average time to peak plasma concentrations of NAP 226-90 ranged from hours and the average terminal elimination half-life ranged from hours for both the treatments (Table 2). The intersubject variability (coefficient of variation, CV) of all the pharmacokinetic parameters except T_{max} and M/P ratio for NAP 226-90 ranged from . Following i.v. administration, the $AUC_{0-\infty}$ ratio of NAP 226-90 to rivastigmine averaged 0.53 (range: , whereas the ratio averaged 1.35 (range: after oral administration. This suggests that more NAP 226-90 is formed following oral administration presumably due to presystemic metabolism.

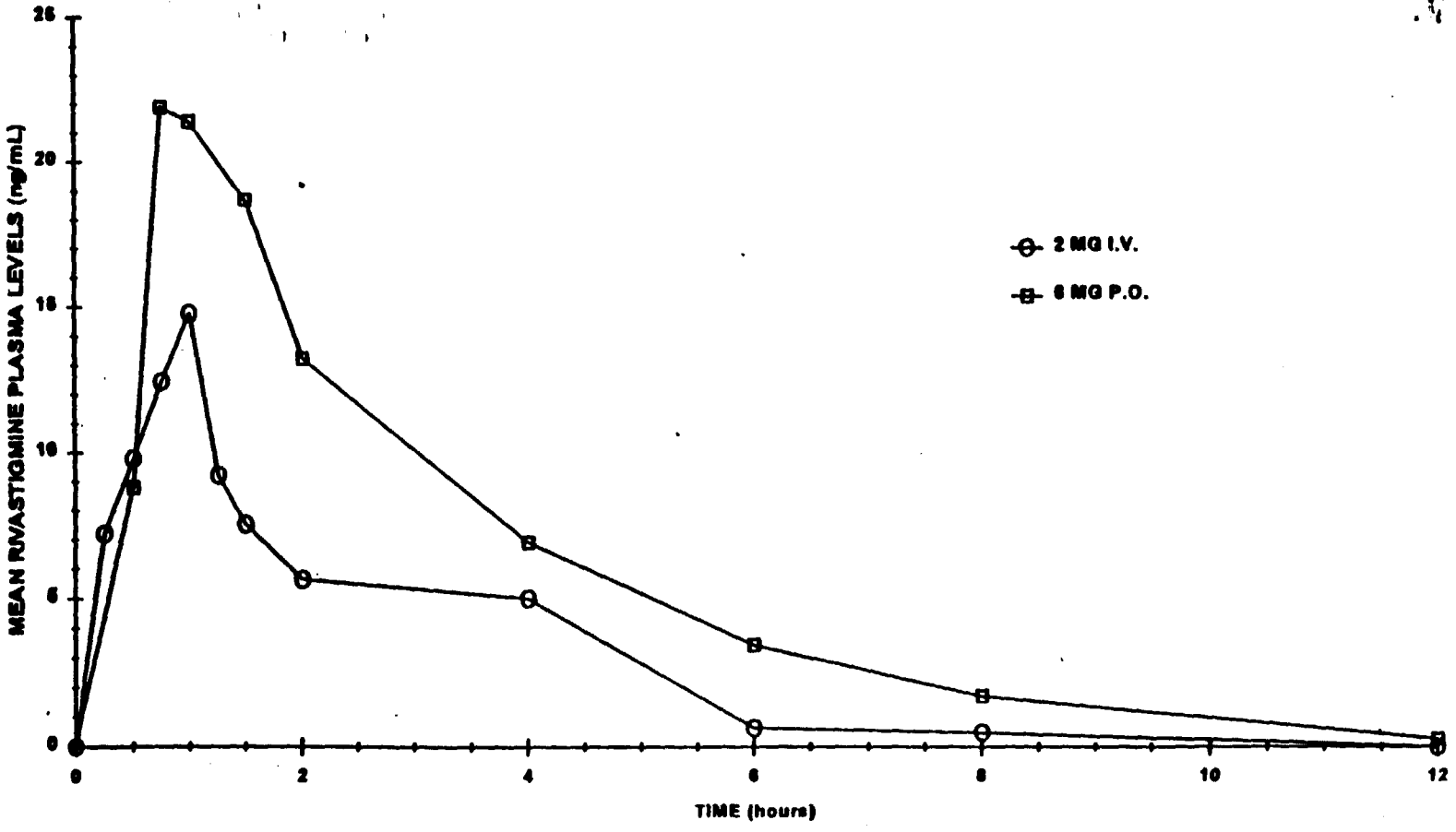
Table 2: **Pharmacokinetic parameters of NAP 226-90 following a single oral and intravenous administration of rivastigmine**

	Arithmetic Mean ± SD Coefficient of Variation (CV%) (Range)	
Parameter	**2 mg Intravenous** **N = 11**	**6 mg Oral** **N = 11**
AUC_{0-t} (ng.h/mL)	15.94 ± 5.96 37.4	67.27 ± 31.85 47.3
$AUC_{0-\infty}$ (ng.h/mL)	17.87 ± 6.93 38.8	77.42 ± 37.87 48.9
C_{max} (ng/mL)	2.67 ± 0.57 21.5	11.59 ± 4.23 36.4
T_{max} (h)	1.89 ± 1.01 53.5	1.64 ± 0.89 54.3
$T_{1/2}$ (h)	3.22 ± 0.43 13.3	3.64 ± 0.51 14.1
$M_{AUC0-\infty}$ / $P_{AUC0-\infty}$ (ratio)	0.53 ± 0.15 28.5	1.35 ± 1.03 76.5

Conclusions: The mean absolute bioavailability of rivastigmine following oral administration of a 6 mg capsule was 71.7% compared to a 2 mg i.v. infusion dose of rivastigmine when normalized for dose. Single oral 6 mg capsule doses and 60 min i.v. infusions of 2 mg/5 mL of ENA 713 administered to 11 patients with probable Alzheimer's disease were safe and well tolerated. This was evidenced by the absence of any significant effects on vital signs measurements and did not appear to cause clinically relevant changes in hematology, or serum chemistry parameters.

Status: First Interpretable Results; pharmacokinetic results are final; safety results are preliminary.

Figure 4.1. **Mean plasma concentration-time profile of rivastigmine following single oral administration of 2 mg I.V. and 6 mg P.O. dose**



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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-823

Submission Dates:
October 21, 1999
February 22, 2000

Generic Name:	Rivastigmine Tartrate Oral Capsule (ENA 713)
Brand Name:	EXELON®
Indication (s)	Alzheimer's disease
Sponsor:	Novartis
Type of Submission:	Pre-Approval Safety Update Package/Review Amendment
Reviewer:	Sayed Al-Habet, Ph.D.
Date of Review:	March 22, 2000

SYNOPSIS:

In OCPB review dated February 7, 2000 the following statement/comment was forwarded to the Clinical Division to be incorporated in Labelling relevant to PK data of Exelon on hepatic impairment patients:

The sponsor stratified the data on hepatically impaired patients into mild (n=7), moderate (n=3) and severe (n=1) groupings (February 22, 2000 submission). Mean oral clearance for the mild and moderate group was about 65% lower than the normal group. The subject with severe hepatic impairment dropped out from the study.

Based on this new information that was submitted by the sponsor on February 22, 2000 the above statement should be replaced with the following statement:

RECOMMENDATION:

Please incorporate the contents of the above modified Labelling Comment to the current labelling for Exelon Oral Capsule.

Reviewed by: /S/ March 23, 2000

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D. /S/

cc: NDA # 20-823 (Orig.), HFD-120, HFD-860 (Al-Habet, Baweja, Mehta), Drug files (Biopharm File, CDR).

APPEARS THIS WAY
ON ORIGINAL