MULTIPLE DOSE STUDIES:

Study 1101: A Phase I multiple application study of Exelon in Japanese young healthy male subjects

Objectives:

Primary Objective

- To evaluate the safety/tolerability of multiple applications of ENA713 patches 5, 7.5 and 10 cm2 in Japanese healthy male volunteers
- To evaluate the pharmacokinetics of ENA713 and its metabolite, NAP226-90, at the steady state

Secondary Objectives

- To evaluate the pharmacodynamics of multiple ENA713 patch applications on plasma BuChE activities
- To investigate the potential of multiple ENA713 patch applications to induce skin irritation
- To check the adhesion of ENA713 patch

The study design is as follows:

Study Design	single center, randomized, placebo-controlled, single blind, 3-period, 3-dose ascending study
Site and Analytical Site	[redacted] b(4)
Study Population	N= 24 healthy Japanese subjects 18 on active, 6 on placebo) Age: 21-32 years (mean age 24.8 years) Gender: 24 males Weight: 55.4-72.8 kg (mean 62.1 kg) Race: all Japanese
Treatment Group	3 treatment periods (Day 1 to 15), a postdose follow-up period (Day 16 to 17) and a study completion evaluation (Day 23). Treatment 1: 5 cm^2 patch or placebo on Days 1-5 Treatment 2: 7.5 cm^2 patch or placebo on Days 6-10 Treatment 3: 10 cm^2 patch or placebo on Days 11-15 Each subsequent dose was given upon evaluation of safety in the previous treatment group.

	Study medication	**Total dose loaded onto patches**	**Batch number**
	ENA713 Patch 5 cm^2	9 mg	J03050
	ENA713 Patch 7.5 cm^2	13.5 mg	J03051
	ENA713 Patch 10 cm^2	18 mg	J03052
	ENA713 Patch 5 cm^2 Placebo	-	J03053
	ENA713 Patch 7.5 cm^2 Placebo	-	J03054
	ENA713 Patch 10 cm^2 Placebo	-	J03055
Dosage and Administration	Each Patch applied for 24 hours on the upper scapular region of the back Diet: breakfast, 1000 hours; lunch, 1300 hours; and dinner, 1800 hours) and be completed within 30 minutes. Bathing: subjects must shower only within 1 hour before patch removal. Bathing times should be about 15 minutes Washout: No washout between two treatments		
Sampling: Blood	For rivastigmine and its metabolite, NAP 226-90: Day 1, 5, 6, 10, 11: pre-patch application, 3, 6, 8, 12, 16 hours post-patch application Day 2 to 4, 7 to 9, 12 to 14: pre-patch application, 12 hours post-patch application Day 15: pre-patch application, 3, 6, 8, 12, 16 hours post-patch application, 24, 26, 28, 32, 36, 40 hours post-patch application (Day 16), 48 hours post-patch application (Day 17)		
Urine	Day 1, 5, 6, 10, 11: pre-patch application (Day 1 only), and during time intervals 0-4, 4-8, 8-12, 12-24 hours post-patch application Day 15: During time intervals 0-4, 4-8, 8-12, 12-24 hours post-patch application, 24-36 hours post-patch application (Day 16), 36-48 hours post-patch application (Day 17)		
Feces	none		
Analysis	GC/MS method Lower Limits of Quantitation Rivastigmine — Plasma 0.2 ng/mL — Urine 5 ng/mL		

	NAP 226-90 0.2 ng/mL 5 ng/mL Plasma: Linear Range: 0.2-25 ng/ml in plasma for both moeities Quality control concentrations: 0.4, 5 and 25 ng/ml Inter-day precision: < 10.31% CV for both moieties Inter-day accuracy: within -4.5 to 2.4% both moieties Urine: Linear Range: 5-2500 ng/ml in plasma for both moeities Quality control concentrations: 5, 15, 40, 100, 450 and 1000 ng/ml Inter-day precision: < 7.72% CV for both moieties Inter-day accuracy: within -4 to 2% both moieties
PK Assessment	AUC0-24, AUC0-24norm, AUC0-last, AUC0-last norm, Cmax, Cmaxnorm, Tmax, t1/2 , Ae, Cl/F, CLr, R (accumulation)
Safety Assessment	Physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, hematology), and adverse event monitoring
PGx Assessment	none
PD Assessment	BChE determination: Day 1, 5, 6, 10, 11: pre-patch application, 3, 6, 8, 12, 16 hours post-patch application Day 15: pre-patch application, 3, 6, 8, 12, 16 hours post-patch application, 24, 26, 28, 32, 36, 40 hours post-patch application (Day 16), 48 hours post-patch application (Day 17) Parameters: AUE, Emax, Tmax, t To characterize the relationship between plasma concentrations versus inhibitory effect of ENA713, pertinent concentration-effect data were plotted and assessed by Emax model to estimate values of EC50 and Emax as follows: E=[(Emax*C)/(EC50+C)]
Other Assessment	Patch adhesion assessment Subjects were allowed to take a shower 1 hour prior to the removal of the study drug during the treatment period and adhesion was assessed before and after the shower. Skin irritation assessment: 24 hours after patch application, at patch removal

Pharmacokinetic Results:

The mean delivered rate of loaded dose were similar between the patch sizes 5, 7.5 and 10 cm^2 with the range of 45.3 to 49.7%.

Table: Amount of ENA713 remaining in the patch or delivered after a 24-hr Application

Patch size (loaded dose)	Day	Loaded drug in unused patch* (mg/patch)	Residual amount (mg)	Delivered amount** (mg)	% of delivered amount*** (%)
5 cm^2	Day 1	8.80 ± 0.149	4.81 ± 0.646	3.99 ± 0.646	45.3 ± 7.34
(9 mg)	Day 5		4.78 ± 0.911	4.02 ± 0.911	45.7 ± 10.3
7.5 cm^2	Day 6	14.33 ± 0.192	7.62 ± 1.15	6.71 ± 1.15	46.8 ± 8.02
(13.5 mg)	Day 10		7.20 ± 1.07	7.13 ± 1.07	49.7 ± 7.48
10 cm^2	Day 11	18.53 ± 0.148	9.67 ± 1.41	8.86 ± 1.41	47.8 ± 7.61
(18 mg)	Day 15		9.78 ± 1.39	8.75 ± 1.39	47.2 ± 7.48

Values are Mean ± SD.

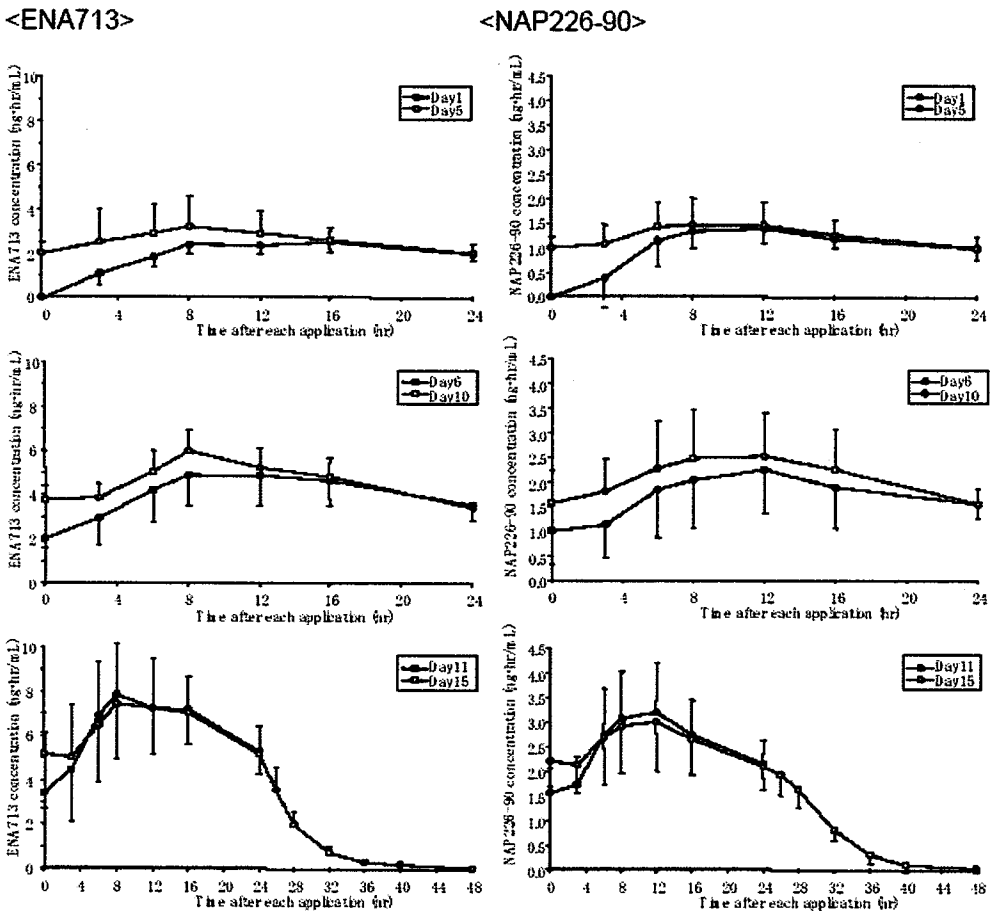
*: 4 sheets of unused patches were measured in each patch size.

**: Delivered amount (mg) = Drug load of unused patch (mg) - residual amount (mg)

***: % of delivered amount (%) = delivered amount (mg) / drug load of unused patch (mg) x 100

Plasma concentration vs. time profiles of ENA713 and NAP226-90 on the first day (Day 1, 6, and 11) and the last day (Day 5, 10, and 15) in each patch size were graphed in the following Figure and PK parameters are summarized in below:

Figure: Mean +/- SD plasma ENA713 and its metabolite NAP226-90 concentration vs. time profile following ENA713 patch multiple application



Mean ± SD ENA713 (left) and NAP226-90 (right) concentration profiles at ENA713 patches of 5 cm^2 (*upper*), 7.5 cm^2 (*middle*), 10 cm^2 (*lower*) in Japanese healthy subjects.

Table: Pharmacokinetic parameters of plasma ENA713 (upper) and its metabolite NAP226-90 (lower)

<ENA713>

Patch size	5cm²		7.5cm²		10cm²	
Day	Day 1	Day 5	Day 6	Day 10	Day 11	Day 15
(Number of patches)*	(1st)	(5th)	(1st)	(5th)	(1st)	(5th)
C_{trough} (ng/mL)	1.96 ± 0.29	2.01 ± 0.41	3.54 ± 0.67	3.41 ± 0.72	5.27 ± 1.01	5.18 ± 1.26
C_{max} (ng/mL)	2.68 ± 0.33	3.39 ± 1.44	5.29 ± 1.43	6.35 ± 1.97	8.59 ± 2.73	8.27 ± 2.31
t_{max} (h)	16.0 (8.0 - 24.0)	8.0 (0.0 - 24.0)	12.0 (6.0 - 16.0)	8.0 (0.0 - 16.0)	10.0 (6.0 - 16.0)	8.0 (0.0 - 16.0)
AUC_{0-24} (ng*h/mL)	47.8 ± 7.1	62.9 ± 18.7	98.7 ± 23.7	111.3 ± 30.8	152.6 ± 39.8	153.3 ± 41.5
$t_{1/2}$ (h)	-	-	-	-	-	3.30 ± 0.59
CL/F_{App} (L/h)	-	151.2 ± 42.3	-	138.1 ± 37.4	-	129.9 ± 37.6
CL/F (L/h)	-	65.6 ± 10.9	-	66.5 ± 11.6	-	60.6 ± 18.9
R_A (C_{trough})	1.02 ± 0.13		0.96 ± 0.12		0.98 ± 0.14	
(C_{max})	1.28 ± 0.59		1.20 ± 0.18		0.99 ± 0.17	
(AUC_{0-24})	1.34 ± 0.47		1.13 ± 0.14		1.02 ± 0.17	

Values are mean ± SD, except t_{max} which are median (range).
*: Number of repeated applications in each patch size

<NAP226-90>

Patch size	5cm²		7.5cm²		10cm²	
Day	Day 1	Day 5	Day 6	Day 10	Day 11	Day 15
(Number of patches)*	(1st)	(5th)	(1st)	(5th)	(1st)	(5th)
C_{trough} (ng/mL)	0.98 ± 0.23	1.00 ± 0.22	1.56 ± 0.32	1.56 ± 0.29	2.15 ± 0.35	2.09 ± 0.46
C_{max} (ng/mL)	1.56 ± 0.50	1.60 ± 0.53	2.25 ± 0.61	2.77 ± 0.98	3.27 ± 1.07	3.19 ± 0.95
t_{max} (h)	12.0 (3.0 - 24.0)	8.0 (0.0 - 16.0)	12.0 (8.0 - 16.0)	10.0 (3.0 - 16.0)	12.0 (6.0 - 16.0)	10.0 (0.0 - 26.0)
AUC_{0-24} (ng*h/mL)	24.6 ± 5.3	30.2 ± 8.0	42.0 ± 10.9	50.7 ± 15.9	61.2 ± 17.8	61.4 ± 16.7
$t_{1/2}$ (h)	-	-	-	-	-	4.21±1.43
R_A (C_{trough})	1.05 ± 0.23		1.02 ± 0.17		0.97 ± 0.16	
(C_{max})	1.09 ± 0.42		1.23 ± 0.22		1.01 ± 0.25	
(AUC_{0-24h})	1.26 ± 0.32		1.21 ± 0.18		1.03 ± 0.23	

Values are mean ± SD, except t_{max} which are median (range).
*: Number of repeated applications in each patch size

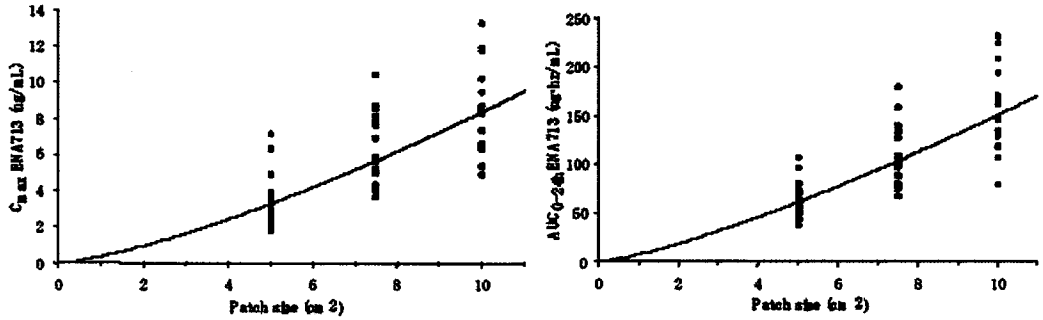
The mean accumulation ratio (R_A) of C_{trough} of ENA713 were 1.02, 0.96 and 0.98, and those of NAP226-90 were 1.05, 1.02 and 0.97 for the each of three patch sizes, respectively. R_A on AUC_{0-24} of ENA713 were 1.34, 1.13 and 1.02, and those of NAP226-90 were 1.26, 1.21 and 1.02 for the each patch, respectively. Plasma ENA713 and NAP226-90 indicated no apparent accumulation after 5-day multiple applications in either patch size.

The C_{max} and AUC_{0-24} values for ENA713 increased slightly in excess of

patch-size ratio with lower limit of 90% confidence interval (CI) slightly greater than one. However, as for NAP226-90, the exposure increased with patch-size proportionally over the investigated patch sizes.

Figure: Relationship between patch size and C_{max} and AUC_{0-24} on the last day of each patch size period

<ENA713>



<NAP226-90>

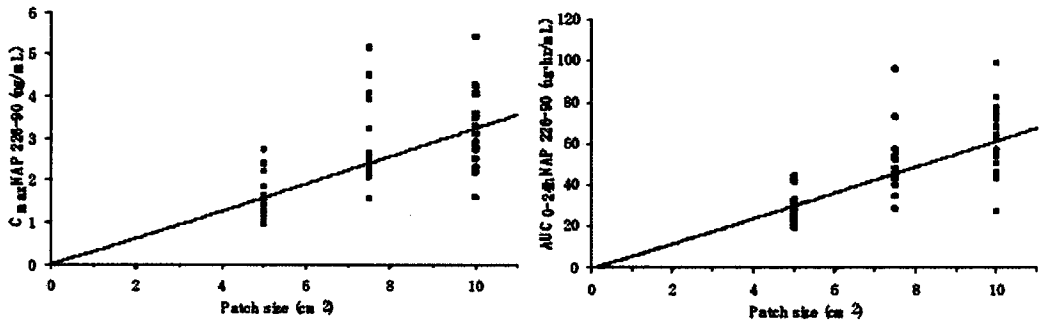


Table: Dose-exposure regressions: ENA713 and NAP226-90

Compound	Parameter	Regression equation	(90%CI, ln transformed)
ENA713	$C_{max,b}$	$C_{max} = 0.646 \times (dose)^{1.35}$	(1.09, 1.62)
	AUC_{0-24}	$AUC_{0-24} = 2.41 \times (dose)^{1.30}$	(1.08, 1.52)
NAP226-90	$C_{max,b}$	$C_{max} = 0.595 \times (dose)^{1.03}$	(0.77, 1.28)
	AUC_{0-24}	$AUC_{0-24} = 2.13 \times (dose)^{1.03}$	(0.81, 1.26)

Urinary Excretion of rivastigmine and NAP226-90:

Mean urinary excretion ratio and CL_r of ENA713 and NAP226-90 on the first day are almost constant over the patch size range of 5 to 10 cm_2, and did not change after 5-day repeated applications of ENA713 in either patch size. These results suggest that urinary excretion of ENA713 and NAP226-90 were linear in the range of tested patch sizes and repeated applications have no influence on the elimination of both compounds into urine. The mean CLr values of ENA713 were ranged from 3.6 to 4.2 L/h, which were less than

10% of total plasma clearance. Urinary excretion of unchanged ENA713 was low, indicating that ENA713 is extensively metabolized in the body.

Table: Mean urinary excretion ratio and CL_r of ENA713 and NAP226-90

Analyte	PK parameters	5 cm^2		7.5 cm^2		10 cm^2	
		Day 1	Day 5	Day 6	Day 10	Day 11	Day 15
ENA713	% of applied dose	2.0 ± 0.9	2.5 ± 0.9	2.5 ± 0.9	2.6 ± 0.5	2.9 ± 1.3	3.4 ± 1.0
	% of delivered amount	4.3 ± 1.9	5.5 ± 1.7	5.4 ± 1.7	5.0 ± 1.0	6.0 ± 2.2	7.4 ± 2.1
	CL_r (L/h)	3.6 ± 1.6	3.6 ± 1.3	3.8 ± 1.4	3.6 ± 0.9	3.6 ± 1.3	4.2 ± 0.9
NAP226-90	% of applied dose	8.5 ± 2.8	11.7 ± 2.7	9.4 ± 2.9	11.1 ± 2.8	11.2 ± 4.3	12.0 ± 3.4
	% of delivered amount	19.1 ± 7.2	26.0 ± 5.0	20.2 ± 4.9	22.4 ± 4.4	23.0 ± 6.4	25.3 ± 5.4
	CL_r (L/h)	20.5 ± 7.5	23.0 ± 4.3	21.4 ± 4.5	21.3 ± 3.9	22.6 ± 5.6	24.5 ± 5.5

Values are Mean ± SD

Pharmacodynamics:

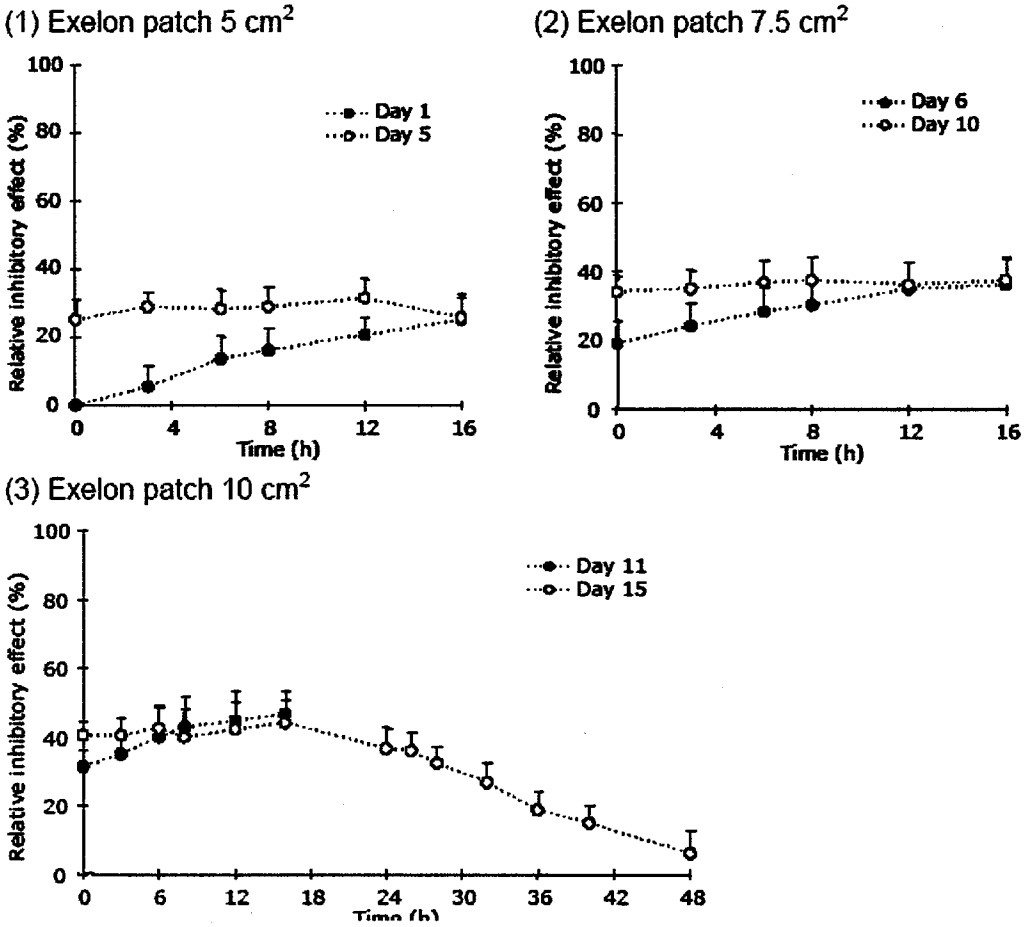
Inhibitory effects of ENA713 on BuChE activity were observed after the first application of the lowest ENA713 patch 5 cm^2. Inhibitory effects of ENA713 increased with the increasing doses.
On the fifth day of 5-day multiple applications of each patch, Day 5, 10 and 15, inhibitory effect of ENA713 on plasma BuChE activity remained almost the same level. The mean E_{max} were 32.2, 39.5, and 45.8%, and $AUE_{0\text{-}16}$ were 460, 581, and 666%*h with each patch size 5, 7.5, and 10 cm^2, respectively. After 24 hours from the removal following the last 24-hour application of 10 cm^2 patch on Day 15, the mean BuChE inhibitory effect gradually decreased to 6.2%.

Table: BuChE inhibitory response parameters of ENA713

Patch size	5 cm^2		7.5 cm^2		10 cm^2	
	Day 1	Day 5	Day 6	Day 10	Day 11	Day 15
t_{max} (h)	16.0	12.0	16.0	8.0	16.0	12.0
	(12.0 - 16.0)	(0 - 12.0)	(12.0 - 16.0)	(0.0 - 16.0)	(8.0 - 16.0)	(0.0 - 16.0)
E_{max} (%)	25.3 ± 6.5	32.2 ± 5.1	36.9 ± 7.7	39.5 ± 6.6	47.5 ± 7.0	45.8 ± 6.1
$AUE_{0\text{-}16}$ (%*h)	231 ± 81	460 ± 84	476 ± 111	581 ± 95	654 ± 116	666 ± 102

t_{max} is median (range). E_{max} and $AUE_{0\text{-}16}$ are mean ± SD.

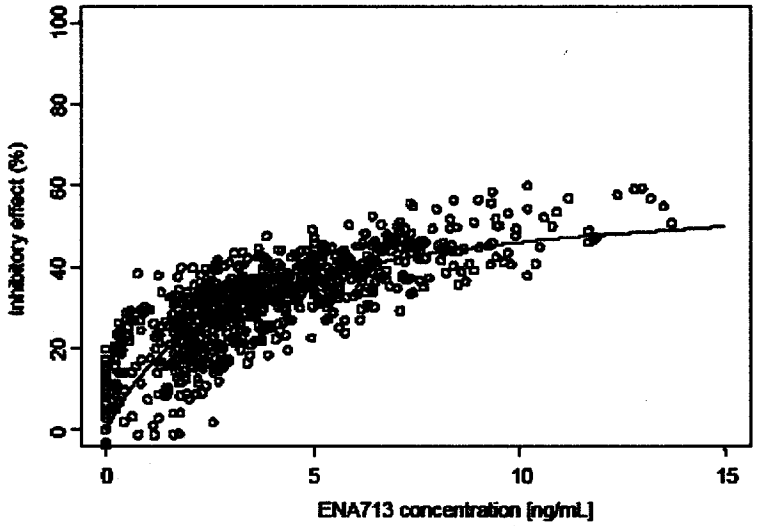
Figure: Inhibitory effect of ENA713 on BuChE activity-time profiles during multiple applications of ENA713 patches 5, 7.5, and 10 cm2



Relationship between Pharmacokinetics and Pharmacodynamics

The relationship between plasma concentrations of ENA713 and the inhibitory effects on BuChE activity is shown in the following Figure with the E_{max} model fit. The inhibitory effect increased with increase of ENA713 concentrations in plasma and adequately described by E_{max} model. In this model analysis, the concentration yielding the half maximal inhibitory effect (EC_{50}) and the maximal inhibition (E_{max}) were estimated as 2.99 ± 0.22 ng/mL and 59.8 ± 1.8% (mean ± SD), respectively.

Figure: Relationship of plasma concentrations of ENA713 and inhibitory effect on BuChE activity



Adhesion:

Overall adhesion of ENA713 patches was good. Adhesion scores were generally evaluated with '>90%' or '100%' in most of the subjects. Some subjects experienced the scores of '75- 90%' or less after Day 8 in ENA713 group. The number of subjects with the less scores was increased in the later treatment period. In placebo group, only one subject experienced '50- 74%' once, and the rest of the subjects were evaluated with the scores of '100%'. There were no remarkable difference between the scores evaluated before and after the shower.

Conclusions:

- The mean delivered rate of loaded dose after 24-hour application was similar throughout the treatment period regardless of the ENA713 doses and ranged from 45.3 to 49.7%.
- The C_{max} and AUC_{0-24} values of ENA713 after 5-day multiple applications increased in a slightly overproportional manner with increasing doses of ENA713 patches ranged from 5 to 10 cm^2. Those of NAP226-90 increased with patch-size proportionally.
- No apparent accumulation of plasma ENA713 and its metabolite NAP226-90 concentration were observed for each 5-day multiple application of ENA713 patch 5, 7.5 and 10 cm^2.
- Urinary excretion ratios and CL_r of ENA713 and its metabolite NAP226-90 were almost constant during repeated applications of ENA713 patch regardless of patch sizes tested.

- Low amount of ENA713 was excreted unchanged in urine, suggesting that ENA713 is extensively metabolized in the body.
- Inhibitory effect of ENA713 on BuChE activity reached steady state by the fifth day of repeated application with tested patch sizes.
- Inhibitory effect on BuChE at steady state increased with increasing doses with the maximal inhibition of 45.8% with ENA713 10 cm^2 patch.

MULTIPLE DOSE STUDIES IN PATIENTS:

Study 2331: ***An open-label, parallel group, dose proportionality study evaluating ENA713 5 cm^2, 10 cm^2, 15 cm^2, and 20 cm^2 (FMI) transdermal patches and 1.5 mg, 3 mg, 4.5 mg, and 6 mg b.i.d. capsules at steady state in patients with mild-to-moderate Alzheimer's disease***

Objectives:

Primary Objective

- To explore the dose-pharmacokinetic exposure relationship of rivastigmine and its metabolite NAP 226-90 following administrations of 5 cm^2, 10 cm^2, 15 cm^2, and 20 cm^2 (FMI) transdermal patches in patients **with mild-to-moderate Alzheimer's** disease
- To explore the dose-pharmacokinetic exposure relationship of rivastigmine and its metabolite NAP 226-90 following b.i.d. administrations of 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules in patients with **mild-to-moderate Alzheimer's disease**
- To compare the bioavailability of rivastigmine and its metabolite NAP226-90 following once daily patch with b.i.d administrations of Exelon capsules

Secondary Objectives

- To evaluate potential changes with time in rivastigmine and its metabolite pharmacokinetics following patch application
- To evaluate the safety and tolerability of once daily administrations of 5 cm^2, 10 cm^2, 15 cm^2, and 20 cm^2 (FMI) transdermal patches and bid administrations of 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules in patients with mild-to-moderate **Alzheimer's disease**
- To evaluate the effects of multiple doses of either 5 cm^2, 10 cm^2, 15 cm^2, and 20 cm^2 (FMI) transdermal patches or b.i.d administrations of 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules on butyryl cholinesterase (BuChE) activity in patients with **Alzheimer's disease**

The study design is as follows:

Study Design	single center, open label, parallel group, four-periods, ascending dose study.
Site and Analytical Site	[redacted] b(4)
Study Population	N= 51 randomized, 30 patients completed (13 on TDS and 17 on capsule): 16 discontinued due to AEs and 4 due to other reasons Age: 53-84 years (mean age 71 years) Gender: 37 males , 14 females Weight: 47-110 kg (mean 75.8 kg) Race: 33 Caucasians. 5 Black and 13 others
Treatment Group	Daily administration of patches (QD) and capsules (BID) for 14 days.

	Outpatient after first dose Treatment 1: 5 cm^2 patch QD or 1.5 mg capsule BID for 14 days Treatment 2: 10 cm^2 patch QD or 3 mg capsule BID for 14 days Treatment 3: 15 cm^2 patch QD or 4.5 mg capsule BID for 14 days (changed to 3 day in amendment #2) Treatment 4: 20 cm^2 patch QD or 6 mg capsule BID for 14 days (changed to 3 day in amendment #2) Each subsequent dose was given upon evaluation on safety in the previous treatment group. Exelon® (rivastigmine) oral capsule: 1.5 mg, 3 mg, 4.5 mg, and 6 mg capsules Batch #: X308-1202, X313-1202, X309-1202, X310-1202, respectively. Batch # (re-supply): X308-1202, X313-1202, X309-1202, X310-1202, respectively. Exelon Patch FMI (rivastigmine transdermal system): 5 cm^2 (9 mg), 10 cm^2 (18 mg), 15 cm^2 (27 mg), and 20 cm^2 (36 mg) transdermal patches Batch #: 8-22061-02, 8-22063-02, 8-22064-02, 8-22065-02, respectively. Batch # (re-supply): 8-22050-03, 8-22051-03, 8-22052-03, 8-22053-03, respectively.
Dosage and Administration	Each Patch applied for 24 hours on upper back (above the scapula or over the upper half of the scapula). Consecutive patches were applied to a new site on the upper back. Alternate side of the upper back was allowed to be used. Diet: For patients randomized to the capsule treatment, dose administration occurred with breakfast and dinner meals, approximately at 0800 and 2000 hrs, respectively. For patients randomized to the patch treatment, dose was administered at the time of the breakfast meal approximately at 0800 hr. Washout: No washout between two treatments
Sampling: Blood	For rivastigmine and its metabolite, NAP 226-90: For treatment with transdermal patches Day 13: Predose (prior to the morning patch application) Day 14: Predose, and 0.5, 1, 1.5, 2, 3, 6, 8, 12, 16, and 24 hrs post last patch application of each titration period. Following the very last patch application (Period 4), plasma samplings were extended with additional samples taken at 26, 28, 32, 36, and 40 hrs.

	For treatment with capsules Day 14: Predose, and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.5, 12.75, 13, 13.5, 14, 15, 16, 18, 20, 22, and 24 hrs post morning dose on the last day of each period. Following the very last dose (Period 4), plasma samplings were extended with additional samples taken 27, 30, and 36 hrs post morning dose on the last day of treatment. Protocol (amendment #2 was generated to modify the study design, more specifically, the visiting schedule of the study. The changes in the visiting schedule were made under the assumption that a steady state concentration of rivastigmine is reached by the 3rd day after initial dosing. Briefly, patients would continue to undergo the same 14 days treatment period for Periods 1 to 3, however, PK sampling for Period 3 was moved from Day 13 (trough concentration for patch patients only) and Day 14 to Day 2 (trough concentration for patch patients only) and Day 3, respectively. Patients then returned to the study clinic on Day 1 of Period 4 after 14 days of Period 3 treatment and began the treatments for Period 4. PK sampling for Period 4 then began on Day 2 (trough concentration for patch patients only) and continued till Day 4 of Period 4. After undergoing end of study evaluation assessments in the morning of Day 5 of Period 4, patients then were discharged from the study clinic.
Urine	none
Feces	none
Analysis	LC/MS/MS method Lower Limits of Quantitation Plasma — Urine Rivastigmine — 0.2 ng/mL — NA NAP 226-90 — 0.2 ng/mL — NA Plasma: Linear Range: 0.2-30 ng/ml in plasma for both moeities Quality control concentrations: 0.4, 7.5 and 25 ng/ml Inter-day precision: < 7.6% CV for both moieties Inter-day accuracy: within -3.6 to 3% both moieties
PK Assessment	AUC0-24, AUC0-last, Cmax, Cav, Cmin, Tmax, t1/2 , FI
Safety Assessment	Physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, hematology), and adverse event monitoring
PGx Assessment	none
PD Assessment	BChE determination: For treatment with transdermal patches **Day 13— pre-patch application (0 hr)** **Day 14—pre-patch application (0 hr), and 0.5, 1, 1.5, 2, 3, 6, 8, 12, 16,**

	and 24 hrs post patch application in each treatment period. Following the very last patch application (period 4), pharmacodynamic blood sampling was extended with additional samples taken at 26, 28, 32, 36, and 40 hrs For treatment with capsules Day 14: pre-dose (0 hr), and 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.5, 12.75, 13, 13.5, 14, 15, 16, 18, 20, 22 and 24 hrs post-dose. Following the very last dose (period 4), pharmacodynamic blood sampling was extended with additional samples taken 27, 30, and 36 hrs post morning dose on the last day of treatment Parameters: AUC24, Emax, Tmax
Other Assessment	Patch adhesion assessment: at **pre-dose (previous day's patch), 6 hrs,** 12 hrs, and 24 hrs post administration. Following scores were used to evaluate patch adhesion. **0 = The patch remained completely on – no adherence associated** problems 1 = The edges of the patch were lifting off 2 = The patch was approximately half off 3 = The patch was barely on and was mostly non-adhering 4 = The patch was completely detached

Pharmacokinetic Results:

The main pharmacokinetic exposure parameters of rivastigmine and NAP226-90 are shown in the following Tables:

Table: Comparative rivastigmine exposure parameters following rivastigmine multiple oral (b.i.d.) capsule or dermal (o.d.) patch applications

Rivastigmine	Capsule			Patch		
	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	Fluctuation index	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	Fluctuation index
	1.5 mg bid (3 mg per day, n = 26)			**5 cm² (9 mg loaded, n = 22)**		
Mean ± SD	3.34 ± 2.36	12.5 ± 8.91	6.24 ± 3.15	2.71 ± 1.23	46.3 ± 17.2	0.58 ± 0.40
CV%	70.5	71.2	50.5	45.2	43.2	69.2
Median	2.59	9.60	5.67	2.57	47.6	0.61
Min-max	1.11-10.8	3.63-40.5	2.37-17.2	1.19-5.39	20.0-81.4	0.00-1.17
Geo. mean	2.74	10.3	5.85	2.45	43.2	-
CV% Geo. mean	68.6	69.4	46.6	49.7	40.7	-
	3 mg bid (6 mg per day, n = 24)			**10 cm² (18 mg loaded, n = 22)**		
Mean ± SD	9.70 ± 5.13	57.7 ± 39.1	3.96 ± 1.24	7.68 ± 2.88	127 ± 41.4	0.77 ± 0.32
CV%	52.9	67.8	31.4	36.6	32.6	42.2
Median	8.71	51.3	3.76	7.79	129	0.76
Min-max	2.68-21.3	17.3-183	2.01-8.24	2.76-12.9	41.4-198	0.15-1.26
Geo. mean	8.48	47.7	3.79	7.32	120	0.69
CV% Geo. mean	58.6	68.8	29.7	43.1	38.1	57.4
	4.5 mg bid (9 mg per day, n = 19)			**15 cm² (27 mg loaded, n = 19)**		
Mean ± SD	16.8 ± 6.60	106 ± 76.7	4.10 ± 2.35	14.1 ± 6.30	233 ± 83.2	0.72 ± 0.36
CV%	39.3	72.3	57.3	44.6	35.7	50.5
Median	18.2	84.9	3.46	15.3	255	0.61
Min-max	5.44-27.0	41.2-382	1.56-10.1	4.32-25.7	93.3-345	0.03-1.30
Geo. mean	15.3	89.2	3.58	12.6	217	0.60
CV% Geo. mean	49.1	61.2	55.9	55.4	42.9	81.3
	6 mg bid (12 mg per day, n = 17)			**20 cm² (36 mg loaded, n = 13)**		
Mean ± SD	29.3 ± 13.2	191 ± 140	4.15 ± 2.46	19.5 ± 7.51	345 ± 127	0.57 ± 0.35
CV%	45.2	73.0	59.3	38.4	36.7	62.3
Median	25.8	173	3.55	20.7	370	0.63
Min-max	12.5-56.0	60.3-658	1.29-10.5	7.55-33.7	149-529	0.00-1.12
Geo. mean	26.8	160	3.59	18.1	320	-
CV% Geo. mean	44.6	65.3	59.5	44.8	45.2	-

-: not applicable

Figure: Individual rivastigmine Cmax and AUC24h vs dose strengths following multiple doses of Exelon(Registered) capsule b.i.d. or Exelon(Registered) transdermal patch daily to AD patients

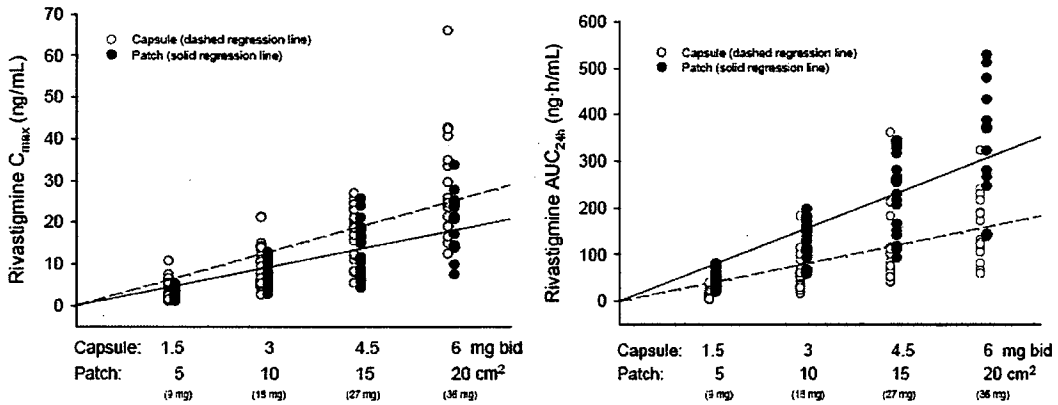
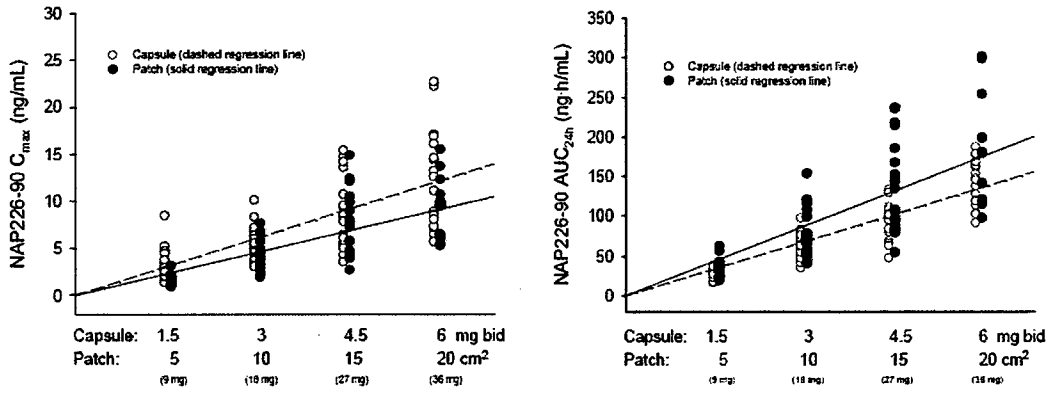


Table: Comparative NAP226-90 exposure parameters following multiple rivastigmine multiple oral (b.i.d.) capsule or dermal (o.d.) patch applications

NAP226-90	Capsule			Patch		
	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	Fluctuation index	C_{max} (ng/mL)	AUC_{24h} (ng·h/mL)	Fluctuation index
	1.5 mg bid (3 mg per day, n = 26)			**5 cm² (9 mg loaded, n = 22)**		
Mean ± SD	3.10 ± 1.45	27.2 ± 5.78	2.42 ± 1.64	1.65 ± 0.633	32.1 ± 11.5	0.34 ± 0.22
CV%	46.9	21.2	75.8	38.5	35.9	64.7
Median	2.83	28.6	1.99	1.62	31.0	0.33
Min-max	1.39-8.47	16.5-38.6	0.60-10.7	0.968-3.16	19.6-63.2	0.03-0.77
Geo. mean	2.65	26.6	2.11	1.54	30.4	0.25
CV% Geo. mean	41.2	20.0	49.6	37.2	33.9	120
	3 mg bid (6 mg per day, n = 24)			**10 cm² (18 mg loaded, n = 22)**		
Mean ± SD	5.57 ± 1.73	65.1 ± 15.0	1.62 ± 0.47	4.05 ± 1.57	75.5 ± 28.3	0.44 ± 0.29
CV%	31.1	23.1	28.9	38.7	37.5	64.7
Median	5.50	64.6	1.64	3.82	72.2	0.41
Min-max	3.08-10.1	35.2-98.2	0.66-3.24	1.93-7.63	40.8-154	0.00-1.03
Geo. mean	5.32	63.3	1.57	3.78	71.2	-
CV% Geo. mean	32.0	20.0	27.2	39.7	35.7	-
	4.5 mg bid (9 mg per day, n = 19)			**15 cm² (27 mg loaded, n = 19)**		
Mean ± SD	8.53 ± 3.69	95.0 ± 23.5	1.65 ± 0.74	7.47 ± 3.48	139 ± 57.4	0.47 ± 0.31
CV%	43.2	24.7	44.7	46.6	41.3	64.8
Median	8.14	97.2	1.55	7.30	135	0.48
Min-max	3.56-15.4	47.8-134	0.71-3.16	2.89-14.9	55.0-237	0.00-0.94
Geo. mean	7.81	92.0	1.51	6.71	128	-
CV% Geo. mean	45.6	30.0	44.9	51.3	44.4	-
	6 mg bid (12 mg per day, n = 17)			**20 cm² (36 mg loaded, n = 13)**		
Mean ± SD	12.5 ± 5.29	142 ± 29.7	1.65 ± 0.76	9.28 ± 3.24	165 ± 67.7	0.29 ± 0.24
CV%	42.2	21.0	45.7	35.0	36.6	80.3
Median	12.6	146	1.54	9.46	181	0.23
Min-max	5.72-22.7	91.9-188	0.52-3.50	5.31-15.5	98.3-302	0.01-0.65
Geo. mean	11.5	139	1.50	8.76	174	0.18
CV% Geo. mean	45.1	20.0	48.3	38.5	38.0	176

-: not available

Figure: Individual NAP226-90 Cmax and AUC24h vs rivastigmine dose strengths following multiple doses of Exelon(Registered) capsule b.i.d. or Exelon(Registered) transdermal patch daily to AD patients



The mean plasma concentration time profiles are shown in the following Figures:

Figure: Rivastigmine plasma concentrations (mean +/- SD) following multiple oral (bid) capsule (left panel) or dermal (o.d.) patch applications (right panel)

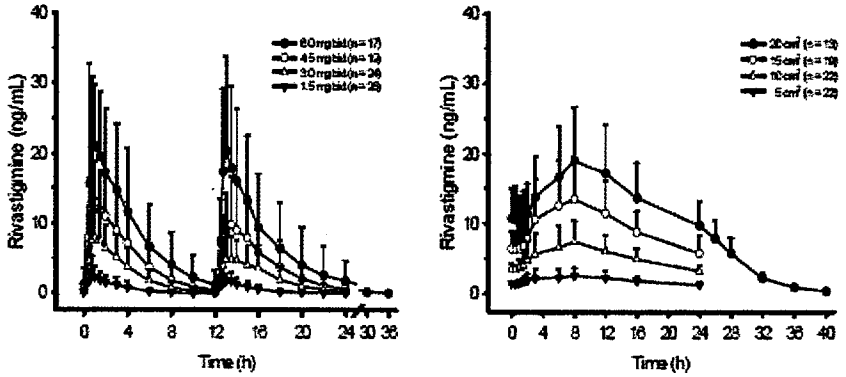
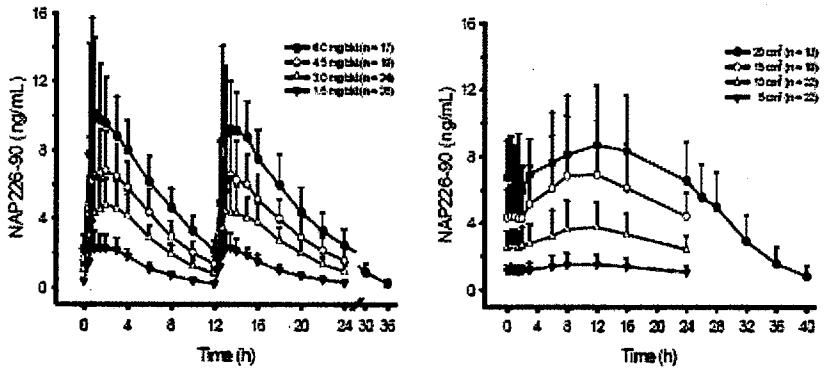


Figure: NAP226-90 plasma concentrations (mean +/- SD) following multiple rivastigmine oral (bid) capsule (left panel) or dermal (o.d.) patch applications (right panel)



Observations:

- *Dose over proportionality less pronounced for patch:*

  Exposure to rivastigmine (AUC) increased over-proportionally with rising doses after both oral and dermal applications. As assessed by compartmental analysis on escalating through the patch sizes of 5, 10, 15 and 20 cm^2, the increase in rivastigmine exposure relative to the lowest dose (5 cm^2) was 2.6, 4.9 and 7.8 fold for the 10, 15 and 20 cm^2 patch, respectively.

For comparison, this increase was 3.4, 6 and 11.2 fold on escalating oral b.i.d. doses. Thus, deviation of rivastigmine exposure from dose linearity (i.e. dose over-proportionality) was less pronounced with the patch formulation.

- *Fluctuation index lower for patch:*

  The fluctuation index (i.e. measure of peak/trough fluctuation) for rivastigmine was in the range of 0.57 to 0.77 for the patch and 3.96 to 6.24 for the oral form, demonstrating a much lower fluctuation (9 times lower) between peak and trough concentrations with the patch. Similar results were found for NAP226-90, though less pronounced.

- *Inter-patient variability lower for patch:*

  The inter-patient variability in the exposure parameters of rivastigmine (C_{max} and AUC_{τ}) as assessed by the coefficients of variation (CVs) was generally lower after the patch (CVs of 33- 45%) as compared to the oral form (CVs of 39-83%).

- *Less metabolism after patch application:*

  The metabolite NAP226-90 showed a fairly comparable pharmacokinetic pattern to the parent drug, and also exhibited over-proportional increase in exposure with rising doses of rivastigmine, although less pronounced than with the parent. The metabolite-to-parent AUC_{24h} ratio ranged from 1.10 (6 mg b.i.d.) to 3.15 (1.5 mg b.i.d.) after oral administration, and from 0.60 (20 cm_2) to 0.72 (5 cm_2) after the patch, indicating that much less metabolism occurred after dermal compared to the oral treatment. Lesser NAP226-90 was formed following patch administration, presumably because of the lack of presystemic (hepatic first pass) metabolism.

Residual drug contents:
On average, the amount of rivastigmine released from the patches over 24 hours was approximately 50% of drug load, and was 4.57 ± 0.87 mg (i.e. 50.7 ± 9.67% of dose load) for the 5 cm^2, 9.46 ± 1.55 mg (i.e. 52.5 ± 8.60%) for the 10 cm^2, 13.3 ± 2.57 mg (i.e. 49.4 ± 9.52%) for the 15 cm^2, and 17.4 ± 3.47 mg (48.3 ± 9.63%) for the 20 cm^2 patch sizes.

Comparison between oral and transdermal rivastigmine exposure

Exposure (i.e. AUC_{24h}) achieved following application of the 20 cm^2 patch was, on average, 1.8-fold higher than following the 6 mg b.i.d. (12 mg/day) oral dose, while the C_{max} was 1.5- fold lower. The ratios for comparisons at other patch and capsule doses are shown in the following Table:

Table: Rivastigmine mean C_{max} and AUC_{24h} ratios of patch over capsule (reference) treatments

		Capsule			
		1.5 mg bid (3 mg/day)	3.0 mg bid (6 mg/day)	4.5 mg bid (9 mg/day)	6.0 mg bid (12 mg/day)
	C_{max}[1] (ng/mL):	3.34 ng/mL	9.70 ng/mL	16.8 ng/mL	29.3 ng/mL
	AUC_{24h} (ng·h/mL):	12.5 ng·h/mL	57.7 ng·h/mL	106 ng·h/mL	191 ng·h/mL
Patch					
5 cm^2	C_{max} = 2.71 ng/mL	0.81	0.28 **	0.16 **	0.09 **
	AUC_{24h} = 46.3 ng·h/mL	3.70 **	0.80	0.44 **	0.24 **
10 cm^2	C_{max} = 7.88 ng/mL	2.36 **	0.81	0.47 **	0.27 **
	AUC_{24h} = 127 ng·h/mL	10.2 **	2.20 **	1.20	0.66
15 cm^2	C_{max} = 14.1 ng/mL	4.22 **	1.45 *	0.84	0.48 **
	AUC_{24h} = 233 ng·h/mL	18.6 **	4.04 **	2.20 **	1.22
20 cm^2	C_{max} = 19.5 ng/mL	5.84 **	2.01 **	1.16	0.67 *
	AUC_{24h} = 345 ng·h/mL	27.6 **	5.98 **	3.25 **	1.81 **

1 morning dose

* P≤0.05 (based on ratio of geometric means)

** P≤0.001 (based on ratio of geometric means)

Compartmental analysis (discussed in detail after this study report) indicated that the 20 cm^2 patch exhibited exposure (AUC) that would be provided by about 9-10 mg b.i.d. orally, while the 10 cm^2 patch exhibited exposure provided by an oral dose of about 6 mg b.i.d.

Time-invariance of PK

The comparison between Day 3 and Day 14 PK data in this study demonstrated that rivastigmine pharmacokinetics were time-invariant. Steady-state concentrations of rivastigmine were achieved rapidly in accordance with the short half-life of rivastigmine. For both the patch and the capsule, there was no statistically significant difference in the PK parameters C_{max} and AUC_{24h} of rivastigmine and NAP226-90 between Day 3 and Day 14 (pre-protocol Amendment #2) patients after repeated administrations.

Table Statistical assessment of amendment effect

Analyte	Parameters (unit)	Amendment	N	Arithmetic mean	Standard deviation	Percent difference	p-value
ENA713	Dose Normalized AUC(0-24) ((ng.h/mL)/mg)	Original&Amendment1	103	12.3	9.1	-34.66	0.425
		Amendment2	41	18.8	22.3		
	Dose Normalized Cmax ((ng/mL)/mg)	Original&Amendment1	103	2.0	2.1	-4.50	0.358
		Amendment2	41	2.1	2.0		
NAP226-90	Dose Normalized AUC(0-24) ((ng.h/mL)/mg)	Original&Amendment1	103	12.9	9.4	3.31	0.239
		Amendment2	41	12.4	7.8		
	Dose Normalized Cmax ((ng/mL)/mg)	Original&Amendment1	103	1.2	1.1	17.00	0.744
		Amendment2	41	1.0	0.8		

This statistical analysis was also done for each period and showed similar insignificant p-values.

Assessment of dose proportionality:

Rivastigmine exhibits nonlinear pharmacokinetics following both oral and intravenous administrations because of capacity-limited elimination. This study showed that the patch formulation also displays nonlinear rivastigmine pharmacokinetics which, however, was less pronounced than with the oral formulation.

Treatment	Analyte	Parameters (unit)	Estimated slope log(dose)	90% confidence limit for the slope	Estimated increase across the dose range	90% confidence limit for the increase	Dose prop.?*	Proportionality dose range**
Patch	ENA713	Dose Normalized AUC(0-24) ((ng.h/mL)/mg)	0.46	(0.37, 0.54)	1.88	(1.68, 2.12)	No	1.51
	NAP226-90	Dose Normalized AUC(0-24) ((ng.h/mL)/mg)	0.31	(0.23, 0.39)	1.54	(1.38, 1.71)	No	1.78
		Dose Normalized Cmax ((ng/mL)/mg)	0.32	(0.23, 0.42)	1.56	(1.37, 1.78)	No	1.71
Capsule	ENA713	Dose Normalized AUC(0-24) ((ng.h/mL)/mg)	0.88	(0.81, 0.95)	3.39	(3.07, 3.74)	No	1.26
	NAP226-90	Dose Normalized AUC(0-24) ((ng.h/mL)/mg)	0.21	(0.17, 0.24)	1.33	(1.27, 1.39)	No	2.53
		Dose Normalized Cmax ((ng/mL)/mg)	0.02	(-0.08, 0.13)			Yes	

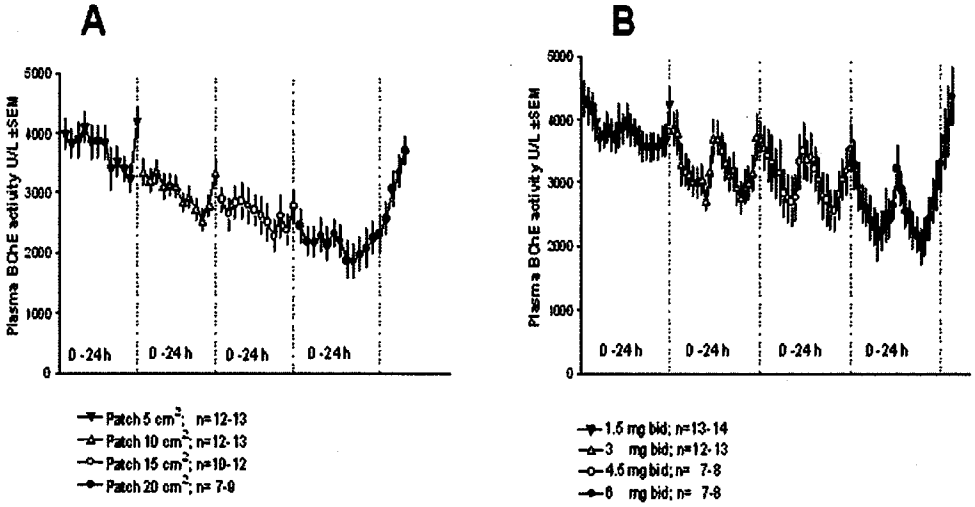
Note:
1. The power model, ln(parameter/dose) = a + b*ln(dose) + patient + error, was used to estimate the slope, corresponding 90% confidence interval, and the p-value testing dose proportionality (b=0).
* Could dose proportionality across the whole dose range be shown? The critical region for the 90% confidence interval for the slope in order to conclude dose proportionality across the dose range considered is -.16 - .16. Dose range = ratio highest to lowest = 4.
** Maximum dose range (rmax<r) within which the increase in the pharmacokinetic parameter can still be considered proportionality to the increase in dose.

For a dose-normalized PK parameter to be regarded as dose proportional the 90% confidence interval for the estimate of slope had to be included within the critical region (-0.16, 0.16). The only parameter to meet this criterion was C_{max} of NAP226-90 with capsule treatment where the 90% confidence interval was (-0.08, 0.13). All other parameters exhibited overproportionality.

Pharmacodynamics:

Both the transdermal and the oral administration of rivastigmine exerted a dose related, albeit underproportional, inhibition of the plasma BuChE, with much smaller fluctuations of inhibition over the 24-hour period with the transdermal route. See figure below:

Figure: Plasma BuChE activity following transdermal patch (A) or oral (b.i.d.) capsule (B) rivastigmine administration



With multiple dosing, following the application of a new rivastigmine patch, the plasma BuChE inhibition increased slowly, with maximum effect after about 16 h, 12 h, 8 h and 8 h after the application of the 5 cm², 10 cm², 15 cm² and 20 cm² patch respectively. As the rivastigmine dose increased, plasma BuChE inhibition increased as well, but in a less than proportional fashion. Within 16 hours after removal of the last patch in the study (at the highest dose of 20 cm², 40 h) the BuChE activity returned to about the same level as that observed at the time of removal of the 5 cm² patch (trough level of BuChE inhibition). See Table below:

Table: Summary for BuChE activity in plasma samples of AD patients following rivastigmine patch administration. Values express enzyme activity in U/L +/- SD (n = 7 – 13)

	Patch 5 cm²			Patch 10 cm²			Patch 15 cm²			Patch 20 cm²		
Sample Time (h)	BuChE activity U/L	±SD	N	BuChE activity U/L	±SD	N	BuChE activity U/L	±SD	N	BuChE activity U/L	±SD	N
0.0	3809	852	12	3202	666	13	2647	861	11	2192	676	8
0.5	3880	1044	12	3360	666	12	2838	873	11	2177	758	8
1.0	4095	905	12	3100	671	12	2862	903	10	2293	803	8
1.5	3830	1044	13	3130	661	13	2782	950	11	2135	813	8
2.0	3845	987	12	3103	615	13	2705	838	11	2315	626	7
3.0	3828	1048	12	2846	482	12	2625	979	11	2200	739	7
6.0	3379	1277	13	2928	600	12	2500	966	10	1876	835	7
8.0	3508	940	12	2736	619	12	2284	846	11	1854	766	7
12.0	3382	809	13	2540	611	12	2614	1138	11	1974	828	8
16.0	3223	864	13	2793	623	13	2385	844	11	2069	939	8
24.0	4183	926	13	3335	735	12	2778	863	10	2239	765	8
26.0										2304	846	8
28.0										2572	804	8
32.0										3053	850	8
36.0										3344	770	8
40.0										3706	689	8

The oral b.i.d. rivastigmine administration resulted in two peaks of plasma BuChE inhibition in each 24-hour period, similarly to what was observed in rivastigmine plasma concentrations. The first peak was observed about 2, 6, 4, and 3 hours after the morning capsule of 1.5, 3, 4.5 and 6 mg, respectively. The second peak of plasma BuChE inhibition occurred about 2, 3, 4 and 5 hours after the evening drug administration of 1.5, 3, 4.5 and 6 mg, respectively. As the capsule dose increased, so did plasma BuChE inhibition, but similarly to the transdermal treatment, this increase was less than proportional. When the oral treatment was stopped at the end of the study, the BuChE activity returned to values seen with the lowest dose 30 hours after the last morning dose of 6 mg b.i.d., i.e. 6 hours after the next dose would be due if the treatment was to continue.

Table: Summary for BuChE activity in plasma samples of AD patients following oral (b.i.d.) rivastigmine administration. Values express enzyme activity in U/L +/- SD (n = 7 – 13)

	Capsule 1.5 mg bid			Capsule 3 mg bid			Capsule 4.5 mg bid			Capsule 6 mg bid		
Sample Time (h)	BuChE activity U/L	±SE	N	BuChE activity U/L	±SE	N	BuChE activity U/L	±SE	N	BuChE activity U/L	±SE	N
0.00	4304	1085	14	3851	971	13	3535	971	8	3268	1129	8
0.50	4200	1120	14	3793	1225	12	3424	1252	9	2928	1059	8
0.75	4105	1098	13	3287	1117	11	3320	1304	9	2650	866	8
1.00	3949	1084	13	3196	890	13	3147	1125	9	2593	854	8
1.50	3671	707	13	3143	849	13	3151	1340	7	2433	1015	8
2.00	3738	714	13	3027	834	13	2839	1102	9	2303	870	8
3.00	3859	924	14	3007	837	13	2752	1086	9	2133	999	7
4.00	3735	979	14	3055	866	13	2701	1085	8	2238	905	8
6.00	3686	865	14	2724	513	11	2769	1070	9	2480	1113	7
8.00	3889	1154	11	3180	856	13	3336	1265	9	2430	847	7
10.0	3832	925	14	3705	1046	13	3500	1319	9	2651	661	8
12.0	3977	1017	14	3710	966	13	3353	918	9	3220	1066	8
12.5	3822	949	14	3515	975	13	3398	1158	9	2897	777	8
12.7	3778	842	14	3323	1006	13	3223	1004	9	2551	823	8
13.0	3654	914	14	3124	938	13	3046	1084	9	2417	865	8
13.5	3558	898	14	3201	935	12	2791	1042	9	2247	820	8
14.0	3547	765	14	2934	1023	13	2734	1197	9	2185	803	8
15.0	3554	835	13	2773	881	13	2576	936	9	1984	841	8
16.0	3565	771	13	2949	907	13	2565	948	9	2135	880	8
18.0	3552	769	14	3003	971	13	2803	1094	9	2426	953	8
20.0	3645	901	13	3158	987	13	3042	946	9	2713	996	8
22.0	3654	1015	14	3722	1284	13	3179	1093	9	2945	1099	8
24.0	4215	1078	14	3710	825	12	3538	1094	9	3306	1334	8
27.0										3682	1334	8
30.0										3950	1492	7
36.0										4354	1302	8

The mean PD parameters are given below for the two formulations:

Subject Group: Original and Amendment 1

Treatment	Period		Emax (U/L)	Tmax (h)	AUC24h (U.h/L)
Patch	1	n	11	11	11
		mean	4248.9	11.318	79791.409
		SD	939.64	12.1435	21094.4241
		minimum	2871	0.50	49583.50
		median	4430.0	1.000	75293.000
		maximum	5698	24.00	116173.00
	2	n	11	11	11
		mean	3369.0	13.636	63741.114
		SD	802.43	11.9271	14019.3035
		minimum	2201	0.50	46795.75
		median	3152.0	24.000	61929.750
		maximum	4651	24.00	92530.00
	3	n	9	9	9
		mean	2924.9	12.889	56256.556
		SD	868.97	11.0306	20482.4056
		minimum	1836	0.50	34055.50
		median	2906.0	12.000	50224.250
		maximum	4659	24.00	103182.50
	4	n	7	7	7
		mean	3620.1	39.429	47088.643
		SD	695.64	1.5119	18413.8977
		minimum	2689	36.00	24485.00
		median	3834.0	40.000	41000.000
		maximum	4461	40.00	71675.50

Subject Group: Original and Amendment 1

Treatment	Period		Emax (U/L)	Tmax (h)	AUC24h (U.h/L)
Capsule	1	n	13	13	13
		mean	4546.3	9.135	88465.154
		SD	1080.42	10.8141	21744.9547
		minimum	2279	0.50	50334.00
		median	4559.0	1.500	89493.625
		maximum	6711	24.00	128597.00
	2	n	12	12	12
		mean	4190.0	13.854	77915.573
		SD	1202.08	9.7050	18776.3315
		minimum	2332	0.50	47028.88
		median	4077.0	12.375	78514.063
		maximum	7176	24.00	113009.25
	3	n	8	8	8
		mean	3925.8	11.563	75515.172
		SD	1207.80	8.2481	24596.5670
		minimum	2082	0.50	35158.63
		median	3817.5	12.250	73173.063
		maximum	6288	24.00	120175.88
	4	n	7	7	7
		mean	4569.4	35.143	63695.304
		SD	1342.13	2.2678	16435.6105
		minimum	2438	30.00	42009.88
		median	4854.0	36.000	63272.625
		maximum	6663	36.00	93300.25

Subject Group: Amendment 2

Treatment	Period		Emax (U/L)	Tmax (h)	AUC24h (U.h/L)
Patch	1	n	6	6	6
		mean	4206.3	8.750	86535.458
		SD	1192.96	11.8522	25146.2323
		minimum	2895	0.50	55793.00
		median	4159.0	1.750	88654.000
		maximum	5714	24.00	114265.50
	2	n	6	6	6
		mean	3072.5	8.917	61106.333
		SD	782.54	11.6979	18095.2639
		minimum	2107	0.50	37651.50
		median	3229.5	2.000	63384.375
		maximum	3992	24.00	82521.25
	3	n	5	5	5
		mean	2656.2	8.900	50345.450
		SD	1353.87	9.5420	26841.3552
		minimum	1429	0.50	25273.50
		median	2366.0	6.000	41396.500
		maximum	4894	24.00	94484.75
	4	n	3	3	3
		mean	3320.3	40.000	36576.917
		SD	1060.82	0.0000	15853.4891
		minimum	2206	40.00	21120.00
		median	3437.0	40.000	35811.500
		maximum	4318	40.00	52799.25

Subject Group: Amendment 2

Treatment	Period		Emax (U/L)	Tmax (h)	AUC24h (U.h/L)
Capsule	1	n	7	7	7
		mean	3734.1	17.214	79162.411
		SD	650.53	9.2909	14236.9274
		minimum	2794	0.50	58986.38
		median	3726.0	24.000	77900.750
		maximum	4618	24.00	98832.13
	2	n	6	6	6
		mean	3119.8	15.958	60055.083
		SD	573.76	6.3095	10580.2041
		minimum	2509	10.00	47725.75
		median	3086.5	12.625	59100.188
		maximum	3998	24.00	78359.50
	3	n	6	6	6
		mean	2666.3	10.333	48743.896
		SD	494.32	8.8581	9923.6205
		minimum	1982	0.50	33867.50
		median	2594.0	12.250	48832.625
		maximum	3352	24.00	63210.00
	4	n	5	5	5
		mean	3019.8	34.800	36729.450
		SD	421.96	2.6833	9225.8422
		minimum	2532	30.00	23671.25
		median	3057.0	36.000	36868.875
		maximum	3651	36.00	47776.13

Patch Adhesion:

Adhesion of the patches was generally very good, with almost all patients having the patch completely attached (rating of 0) or just the edges lifting off (rating of 1) at 24 hours after application. Among pre- Amendment #2 patients, only 1 in Period 2 (10 cm^2 patch, and 1 in Period 3 (15 cm^2 patch) had complete detachment (rating of 4) at 24 hours. In addition, 1 patient in Period 2 had his patch mostly detached (rating of 3) at 24 hours. Among post- Amendment #2 patients, only 2 had their patch mostly detached: 1 in Period 2 at 0 hours and 1 in Period 4 at 24 hours.

Conclusions:

- Plasma exposure to rivastigmine increased with the dose in an over-proportional manner with both transdermal and oral administrations, but the degree of over-proportionality was smaller with the transdermal route of administration.
- Comparison of rivastigmine exposure at individual doses demonstrated that AUC_{24h} with the 20 cm^2 patch q.d. was 1.8-fold higher than with the 6 mg capsule b.i.d., while C_{max} was 1.5 times lower.
- The fluctuation index (i.e. measure of peak/trough fluctuation) was much lower after the patch (0.57 to 0.77) than for the capsule (3.96 to 6.24).
- Rivastigmine PK were time-invariant over the 14-day treatment duration with either route of administration (5 to 20 cm^2 patch q.d. and 1.5 to 6 mg capsule b.i.d.).
- Adhesive properties of the patch appeared to be good, although complete or nearly complete detachment between 12 and 24 hours after application was observed in 4 patients on one occasion each.
- Plasma BuChE activity was inhibited in a dose dependent, albeit underproportional, manner with both routes of administration. The time course of BuChE inhibition over the 24-hour dosing interval followed closely, although with some delay, the PK profile of rivastigmine. The degree of inhibition over 24 hours at steady-state appeared to be higher with the 20 cm^2 patch q.d. than with 6 mg capsule b.i.d.

Study 1201: A Phase II study of ENA713 transdermal in patients with mild-to-moderate Alzheimer's disease

This study was not sumitted as part of the clinical pharmacology study section, but since trough samples were taken in this study, the results of the PK analysis are summarized here with a brief overview of the study design.

Objectives: The primary objective was to evaluate the safety and tolerability of four (5 cm^2, 10 cm^2, 15 cm^2, 20 cm^2, titration group B) and five (5 cm^2, 7.5 cm^2, 10 cm^2, 15 cm^2, 20 cm^2, titration group A) ENA713 patch sizes/doses, using a 4-week titration interval regimen in patients with mild to moderate **dementia of the Alzheimer's type (MMSE 10-20)**.
The secondary objectives were to evaluate the skin irritation and adhesion of all five ENA713 patch sizes/doses; to evaluate the pharmacokinetics of ENA713 and its metabolite NAP226-90, and the pharmacodynamics of BuChE in this population; to compare the safety and tolerability of titration methods A and B and to evaluate the efficacy of ENA713 patches at Week 24 on both efficacy measurements, ADAS-J cog and MMSE.

Study design: A total of 64 patients were evaluated (32 patients in each titration group). A single study drug patch was administered once daily in the morning. The patch was applied to the upper scapular back area and changed every 24 hours at approximately the same time of day. Placement was alternated daily from right to left side of the back. The starting dose was ENA713 patch size 5 cm^2. The duration of administration for each patch size was 4 weeks. Blood samples were collected at baseline and about 24 hours after the application of the patches on the days before weeks 4, 8, 12, 16, 20, and 24 of treatment (or the discontinuation of treatment) to measure blood drug concentrations.

Trough plasma ENA713 and NAP226-90 concentration:
Plasma concentrations of ENA713 and NAP226-90 and dose- and body weight-corrected trough concentrations are shown in the following Tables. About 43-50% of the dose was absorbed across the different patch sizes.

Table: Descriptive statistics for trough ENA713 concentration

Dose (cm^2)	Conc. (ng/mL) Mean (SD)	Conc./Dose (ng/mL/cm^2) Mean (SD)	Conc./dose/weight ((ng/mL)/(cm^2/kg)) Mean (SD)
Group A			
5	2.83 (1.56)	0.57 (0.31)	27.4 (15.0)
7.5	5.94 (5.74)	0.79 (0.77)	35.8 (29.5)
10	8.22 (5.36)	0.82 (0.54)	37.3 (20.4)
15	14.33 (14.21)	0.96 (0.95)	42.6 (32.4)
20	20.09 (13.58)	1.01 (0.68)	43.2 (24.1)
Group B			
5	2.32 (1.47)	0.46 (0.29)	24.2 (16.3)
10	7.15 (3.56)	0.72 (0.36)	36.5 (18.0)
15	12.28 (6.95)	0.82 (0.46)	44.2 (27.4)
20	19.30 (10.77)	0.97 (0.54)	51.4 (34.4)

Table: Descriptive statistics for trough NAP226 concentration

Dose (cm^2)	Conc. (ng/mL) Mean (SD)	Conc./Dose (ng/mL/cm^2) Mean (SD)	Conc./dose/weight ((ng/mL)/(cm^2/kg)) Mean (SD)
Group A			
5	1.76 (0.62)	0.35 (0.12)	17.5 (7.4)
7.5	3.19 (1.08)	0.42 (0.14)	19.9 (6.0)
10	4.58 (2.20)	0.46 (0.22)	21.1 (9.8)
15	7.91 (2.31)	0.53 (0.15)	25.4 (7.2)
20	10.31 (5.40)	0.52 (0.27)	22.9 (10.0)
Group B			
5	1.49 (0.74)	0.30 (0.15)	15.6 (8.3)
10	4.32 (1.89)	0.43 (0.19)	21.6 (9.1)
15	6.43 (2.87)	0.43 (0.19)	24.1 (12.6)
20	9.10 (3.92)	0.46 (0.20)	24.0 (10.5)

In both groups, trough concentrations determined in plasma samples collected after 28 days application of ENA713 patch and trough concentrations of NAP226 tended to increase in proportion to increasing doses of ENA713.

The sponsor has compared these trough concentrations in the Japanese to the Caucasians from Study 2331.

Plasma levels in this study were approximately 1.6 to 2.3-fold (rivastigmine) and 1.4 to 1.8- fold (NAP226-90) higher than those achieved with the corresponding patch sizes in mostly Caucasian patient study [Study 2331]. The sponsor attributed this difference in exposure was attributed to the lower bodyweight of Japanese patients (mean of 50.6 kg) compared to non- Japanese patients (mean of 78.7 kg). According to the sponsor, the pattern of AEs was similar to that seen in the other study populations (i.e. non Japanese), although the incidence was substantially higher. This was attributed to a number of factors including soliciting of AEs and more frequent visits, but the substantially greater exposure achieved in this Japanese population may also have been a contributory factor.

Table:Rivastigmine trough plasma concentrations (mean plus/minus SD) following multiple 24-hr application of rivastigmine patch to AD patients (studies —— 13D1201 and —— 13D2331)

b(4)

Dose (cm^2)	Trough concentration (ng/mL)		
	Study —— /13D1201 Titration method A	Study —— 13D1201 Titration method B	Study —— /13D2331
5	2.83 ± 1.56 (30)	2.32 ± 1.47 (41)	1.42 ± 0.35 (23)
7.5	5.94 ± 5.74 (26)	-	-
10	8.22 ± 5.36 (26)	7.15 ± 3.56 (38)	3.54 ± 0.90 (22)
15	14.33 ± 14.21 (14)	12.28 ± 6.95 (22)	6.41 ± 2.42 (19)
20	20.09 ± 13.56 (7)	19.30 ± 10.77 (18)	10.8 ± 4.20 (13)

Reviewer's Comment:

It is not clear why the Japanese subjects in his study are showing higher trough concentrations as compared to the Caucasians in Study 2331. LC/MS/MS method was the analytical method in this study 1201. In another study (Study 2335) comparing the pharmacokinetics of rivastigmine and metabolite in Japanese versus Caucasians, no meaningful difference in the PK parameters was observed.

Study 0401: ***An open label Phase II study to evaluate the adhesiveness and skin irritation of different sizes of ENA713 transdermal patches in patients with mild-to-moderate Alzheimer's disease***

This study was also not submitted as part of the clinical pharmacology study section, but since blood samples were taken in this study as an secondary objective, the results of the PK analysis are summarized here with a brief overview of the study design.

Study Design: This was a multicenter, open-label, inpatient/outpatient titration study in patients with mild to moderately severe AD. Patients were titrated from a starting patch size of 10 cm^2 to successively larger patch sizes (15 cm^2, and 20 cm^2 overall) at 14-day intervals and received up to 42 days of transdermal treatment. A total of 64 patients completed the study.

Blood Samples: A total of 12 samples were collected from each patient according to the following schedule: baseline (collected within 0.5 hours prior to dosing); at 0.5, 2, 4, 6, 8, 12, 16 and 24 hours after the application of the 10 cm^2 patch (collected on Days 1 and 2); 24 hours after the application of the final 10 cm^2 patch (collected on Day 15); 24 hours after the final application of the 15 cm^2 patch (collected on Day 29); and 24 hours after the final application of the final overall 20 cm^2 patch application (collected on Day 43).

47 patients on day 1 (first 10 cm^2 patch), and 2 patients on day 15 (last day of 10 cm^2 patch), provided full pharmacokinetic profiles.

Pharmacokinetics: The summary of the pharmacokinetic variables for the 10 cm^2 patch is given in the following Table:

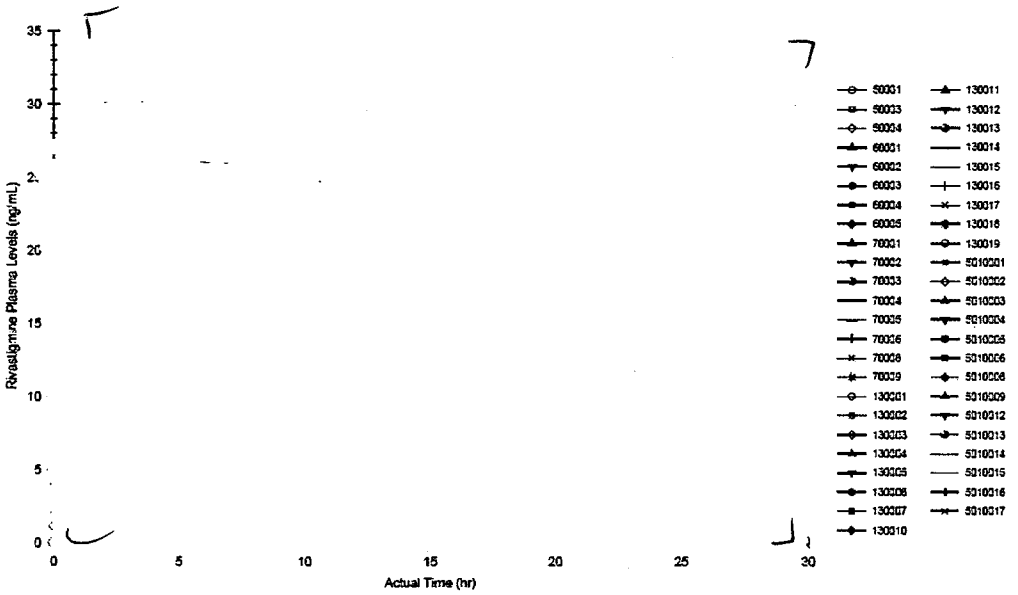
Table: Summary of pharmacokinetic variables for 10 cm_2 patch size

Statistics	t_{lag} (hr)	C_{max} (ng/mL)	t_{max} (hr)	AUC_{0-t} (ng.hr/mL)
		Day 1 – 10 cm^2 patch (N=45)		
Mean	1.79	7.0	14.0	112.2
Standard Deviation	1.72	6.55	5.99	111.4
Coefficient of Variation	95.8	93.2	42.7	99.3
Minimum	0.00	0.74	6.00	9.87
Maximum	6.17	30.68	24.50	525.6
Median	1.98	4.71	12.0	73.23
Geometric Mean	na	5.17	12.8	79.3
		Day 15 – 10 cm^2 patch (N=2)		
Mean	0.00	5.48	8.0	98.64
Standard Deviation	0.00	1.70	0.00	20.47
Coefficient of Variation	0.00	31.0	0.00	20.7

Reviewer's Comment:
This study shows a % CV of 93-99% for the PK parameters, which is much higher than that observed in other Clinical Pharmacology studies. There were two subjects with concentrations relatively high. The safety implications of these high concentrations in

these subjects will be evaluated by the Medical Officer. According to this reviewer, no serious adverse events were observed with the 10 cm2 patch in these patients.

The individual rivastigmine profile for all subjects with PK evaluated on Day 1 is given below:



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Considering that pK samples were taken on the 1st day of dosing (10 cm^2) patch, implications of these high concentrations are unlikely to be observed.

POPULATION PK-PD ANALYSIS OF STUDY 2331:

Modeling methods:

Pharmacokinetic evaluation:
The sponsor analyzed the pharmacokinetic data using non-linear mixed effects models. One compartment models were independently fitted for both Capsule and Patch data and both ENA713 (rivastimine) and NAP226-90 analytes, with absorption lag time, using NONMEM software. Random effects were associated to clearance and volume parameters. In each case, a base model and a final model with covariates were investigated. Covariates selection was approached by forward-backward selection methods. External validation of the model was carried out by comparison with data from other studies.

Exposure-response evaluations:

- To investigate the relationship between NAP226-90 pharmacokinetics and butyrylcholinesterase (BuChE) activity, an Emax model was used. NAP226-90 was preferred to the parent ENA713 because no delay between the kinetics of the metabolite and the suppression effects was observed.
- Adverse events (nausea, vomiting, and dizziness) were descriptively summarized by quintiles of pharmacokinetic parameters (average concentration, concentration fluctuation index, Cmax). Diarrhea was not considered due to the small number of events.

Modeling Results:

Pharmacokinetics:
The pharmacokinetics of rivastigmine and NAP226-90 were adequately described by a 1 compartmental model.

CAPSULES:

For oral administration, data from 26 patients were available, including 11 females and 15 males, with overall median weight of 72.3 kg.

The model derived pharmacokinetic parameter estimates for the rivatigmine is given in the following Table.

Table: Parameter estimates from the final one-compartment model (including body weight and gender as covariates) for Capsules / ENA713

Parameter	Estimate	std. error
θ_1 Nominal TVKA (h^{-1})	0.39	0.025
θ_2 Nominal TVCL (L/h)	280	42
θ_3 Nominal TVK - TVKA (h^{-1})	7.46	1.32
θ_4 Relative bioavailability fraction for Capsule=3mg	1.69	0.07
θ_5 Relative bioavailability fraction for Capsule=4.5mg	1.98	0.09
θ_6 Relative bioavailability fraction for Capsule=6mg	2.78	0.25
θ_7 V exponent for weight	0.44	0.75
θ_8 CL exponent for weight	0.035	0.27
θ_9 KA exponent for weight	0.56	0.71
θ_{10} V coefficient for gender	0.67	0.18
θ_{11} CL coefficient for gender	0.91	0.13
θ_{12} KA coefficient for gender	0.78	0.17
Ω_{11} Inter-subject variance for V/f	2.48	0.92
Ω_{22} Inter-subject variance for CL/f	0.28	0.09
σ_1 standard deviation for multiplicative error	0.29	0.06
σ_2 standard deviation for additive error	0.45	0.17
NONMEM objective function		
[1] The NONMEM program converged	3638.2	

* Flip-flop kinetics was observed

The apparent KA was very high (KA=7.85 h-1), corresponding to a fast absorption. The % CV=30% for intra-individual variability, CV=157% for inter-subject variability of V/f and CV=53% for inter-subject variability of CL/f.

The relative bioavailability fractions were estimated to be 1.69, 1.98, and 2.78 respectively for doses of 3mg, 4.5mg and 6mg, showing a marked dose non-linearity.

The model derived pharmacokinetic parameters for the NAP226-90 is given in the following Table.

Table Parameter estimates from the final one-compartment model (including body weight and gender as covariates) for Capsules / NAP226-90

Parameter	Estimate	std. error
θ_1 Nominal TVK (h^{-1})	0.14	0.03
θ_2 Nominal TVCL (L/h)	109	7.43
θ_3 Nominal TVKA - TVK (h^{-1})	2.88	2.97
θ_4 Absorption lag time (h)	0.18	0.32
θ_5 Relative bioavailability fraction for Capsule=3mg	1.13	0.04
θ_6 Relative bioavailability fraction for Capsule=4.5mg	1.24	0.06
θ_7 Relative bioavailability fraction for Capsule=6mg	1.31	0.07
θ_8 V exponent for weight	-0.76	0.75
θ_9 CL exponent for weight	0.64	0.37
θ_{10} KA exponent for weight	2.01	1.48
θ_{11} V coefficient for gender	0.85	0.16
θ_{12} CL coefficient for gender	1.07	0.13
θ_{13} KA coefficient for gender	1.17	0.72
Ω_{11} Inter-subject variance for V/f	0.15	0.065
Ω_{22} Inter-subject variance for CL/f	0.04	0.01
σ_1 standard deviation for multiplicative error	0.14	0.018
NONMEM objective function[1]		
[1] The NONMEM program converged	2185.93	

The inter-subject variability was about 39% for V/f and 20% for CL/f. Relative bioavailability fractions F were estimated to be 1.13, 1.24, and 1.31, respectively for doses of 3mg, 4.5mg and 6mg, showing a less pronounced dose non-linearity in exposure compared to the parent.

TRANSDERMAL PATCH:

The population pharmacokinetics of ENA for transdermal administration could be adequately described by a one-compartment model, with absorption lag time included. Here again, flip-flop kinetics were observed, since the elimination constant was estimated to be higher than the absorption rate.

The model derived pharmacokinetic parameters for the rivastigmine is given in the following Table:

Table: Parameter estimates from the final one-compartment model (including body weight, gender and actual released dose as covariates) for Patches / ENA713

Parameter	Estimate	std. error
θ_1 Nominal TVKA (h^{-1})	0.0667	0.0136
θ_2 Nominal TVCL (L/h)	148	13.8
θ_3 Nominal TVK - TVKA (h^{-1})	0.039	0.03
θ_4 Absorption lag time (h)	0.695	0.087
θ_5 Relative bioavailability fraction for Patch of size=10 cm^2	1.31	0.053
θ_6 Relative bioavailability fraction for Patch of size=15 cm^2	1.64	0.1
θ_7 Relative bioavailability fraction for Patch of size=20 cm^2	1.96	0.17
θ_8 V exponent for actual released dose	-1.51	0.85
θ_9 CL exponent for actual released dose	-0.914	0.25
θ_{10} KA exponent for actual released dose	-0.107	0.25
θ_{11} V exponent for weight	-0.805	2.87
θ_{12} CL exponent for weight	1.06	1.25
θ_{13} KA exponent for weight	2.99	1.7
θ_{14} V coefficient for gender	0.227	0.23
θ_{15} CL coefficient for gender	0.676	0.20
θ_{16} KA coefficient for gender	0.779	0.35
Ω_{11} Inter-subject variance for V/f	1.86	0.89
Ω_{22} Inter-subject variance for CL/f	0.064	0.028
σ_1 standard deviation for multiplicative error	0.0597	0.009
σ_2 standard deviation for additive error	0.015	0.025
NONMEM objective function [1]		
[1] The NONMEM program converged	1234.74	

The apparent absorption rate (KA=0.106 h-1) was much lower than for the oral formulation. CL/f was estimated to be 148 L/h for the smallest Patch and K=0.07 h^{-1}. Absorption lag time was estimated to be about 42 min, much longer than for oral administration.

In addition, the inter-subject as well as the intra-subject variability were again very high, especially regarding absorption parameters: CV=136% for inter-subject variability of V/f and CV=25% for inter-subject variability of CL/f.

The relative bioavailability fractions were estimated to be 1.31, 1.64, and 1.96 respectively for Patch sizes of 10 cm^2, 15 cm^2, and 20 cm^2, still showing a high dose non-linearity in exposure, but significantly less pronounced than for the Capsules.

The model derived pharmacokinetic parameters for the NAP226-90 is given in the following Table:

Table Parameter estimates from the final one-compartment model (including body weight, gender and actual released dose as covariates) for Patches / NAP226-90

Parameter	Estimate	std. error
θ_1 Nominal TVKA (h^{-1})	0.047	0.022
θ_2 Nominal TVCL/f (L/h)	174	42.6
θ_3 Nominal TVK - TVKA (h^{-1})	0.039	0.042
θ_4 Absorption lag time (h)	1.33	0.09
θ_5 Relative bioavailability fraction for Patch of size=10 cm^2	1.16	0.044
θ_6 Relative bioavailability fraction for Patch of size=15 cm^2	1.41	0.069
θ_7 Relative bioavailability fraction for Patch of size=20 cm^2	1.53	0.085
θ_8 V exponent for actual released dose	-0.50	0.67
θ_9 CL exponent for actual released dose	-0.55	0.23
θ_{10} KA exponent for actual released dose	0.51	0.45
θ_{11} V exponent for weight	-1.39	1.82
θ_{12} CL exponent for weight	0.64	0.93
θ_{13} KA exponent for weight	1.43	1.3
θ_{14} V coefficient for gender	0.58	0.34
θ_{15} CL coefficient for gender	1.22	0.29
θ_{16} KA coefficient for gender	1.29	0.39
Ω_{11} Inter-subject variance for V/f	1.38	0.86
Ω_{22} Inter-subject variance for CL/f	0.051	0.014
σ_1 standard deviation for multiplicative error	0.038	0.005
NONMEM objective function[1]		
[1] The NONMEM program converged	119.02	

The apparent absorption rate (KA'=0.106 h^{-1}) was much lower than for the oral formulation. CL/f was estimated to be 174 L/h for the smallest Patch and K= 0.047 h^{-1}. Absorption lag time was estimated to be about 1.5 h, so twice as long as for the parent with the Patch, and much longer than for NAP after oral administration. The % CV=117% for inter-subject variability of V/f and CV=23% for inter-subject variability of CL/f.

The relative bioavailability fractions were estimated to be 1.16, 1.41, and 1.53

respectively for Patch sizes of 10 cm^2, 15 cm^2, and 20 cm^2, still showing a dose non-linearity in exposure, but substantively less pronounced than for the Capsules.

Comparison of Capsule vs. Patch formulations:

Using the base models typical PK profiles for each Patch sizes were plotted for ENA and NAP in the following Figures. They show that steady state plasma concentrations are reached within 2 days.

Figure: Predicted typical subject ENA pharmacokinetic profiles for different Patch sizes following once-daily multiple dosing

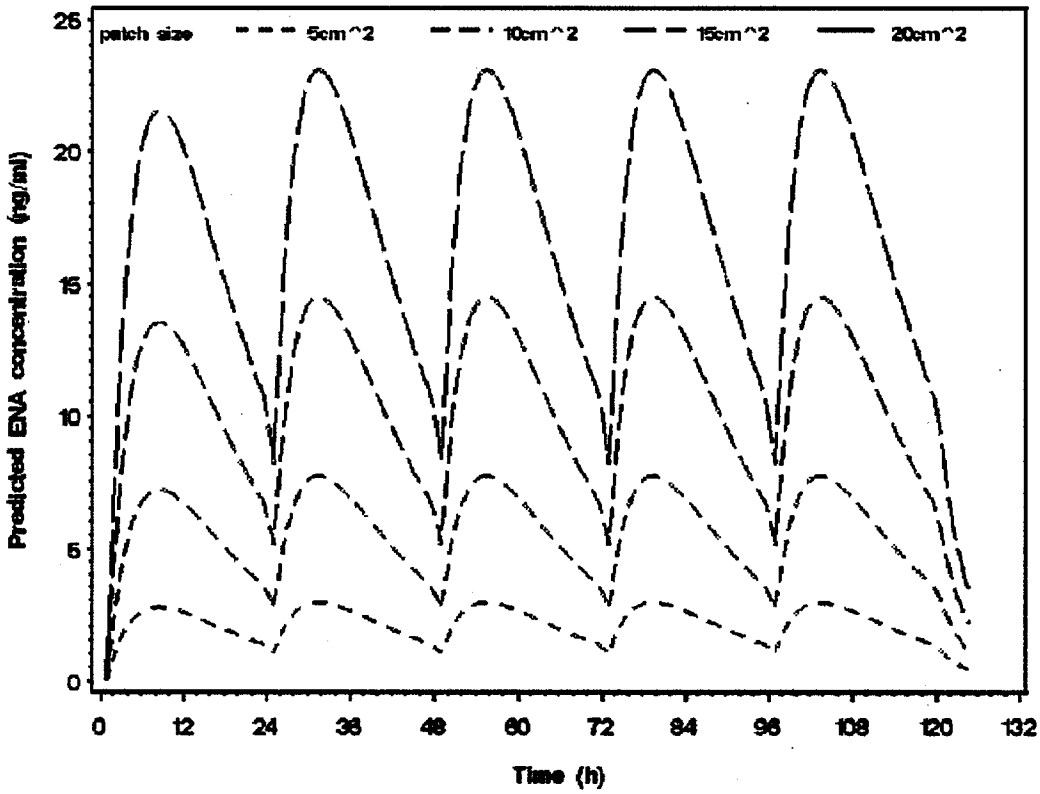
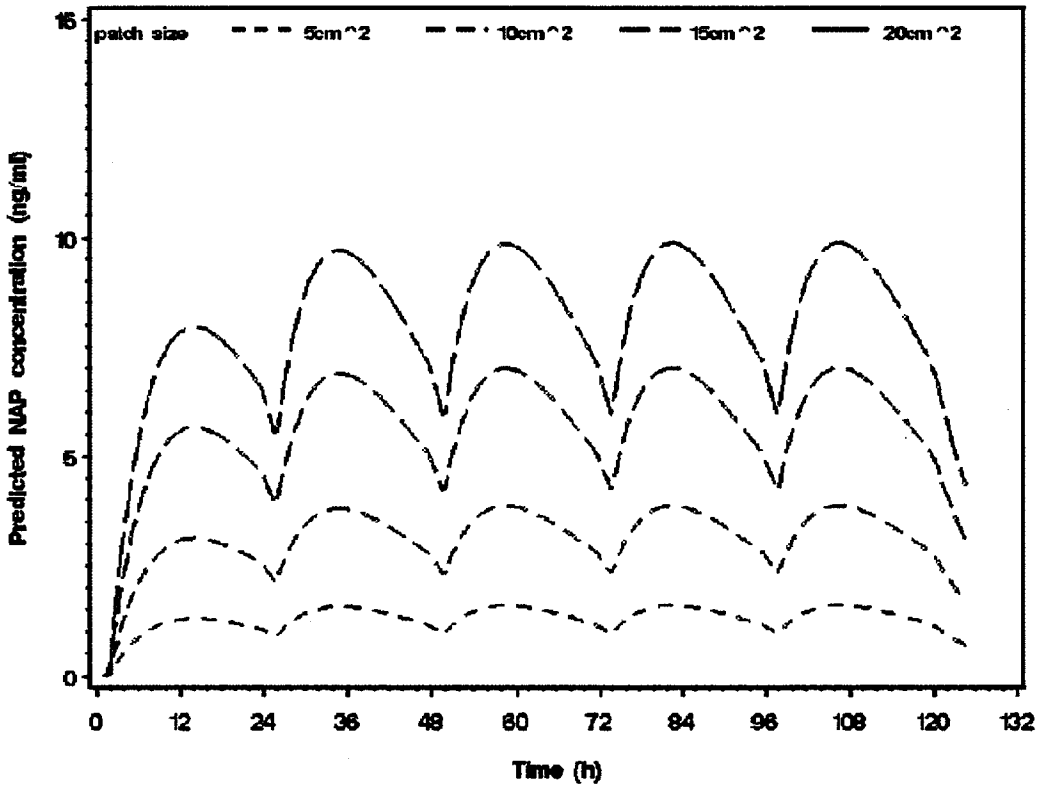


Figure: Predicted typical subject NAP pharmacokinetic profiles for different Patch sizes following once-daily multiple dosing



Simulations were performed to compare the plasma concentrations after oral and transdermal administrations, 1000 PK parameters were simulated from the final population model (for a typical male patient), and values of C_{min}, C_{ave} and C_{max} of ENA and NAP were derived. The corresponding summary statistics are reported for each dose and both Capsules and Patches in the following Tables:

Table: Minimum, average and maximum concentrations of ENA713 and NAP226-90 at steady state for Capsules (by dose) with inter-subject Variability

	compound	Population median concentration (25%-75% quantiles)			
		Dose=1.5 mg b.i.d.	Dose=3 mg b.i.d.	Dose=4.5 mg b.i.d.	Dose=6 mg b.i.d.
C_{min} (ng/mL)	ENA	0.02	0.07	0.12	0.22
		(0.01-0.05)	(0.03-0.17)	(0.05-0.3)	(0.1-0.56)
	NAP	0.47	1.06	1.75	2.46
		(0.31-0.65)	(0.70-1.47)	(1.16-2.43)	(1.63-3.42)
C_{ave} (ng/mL)	ENA	0.44	1.5	2.63	4.93
		(0.19-1.02)	(0.64 -3.46)	(1.13-6.07)	(2.12-11.37)
	NAP	1.17	2.65	4.37	6.15
		(0.94-1.43)	(2.13-3.24)	(3.51-5.33)	(4.94-7.51)
C_{max} (ng/mL)	ENA	2.01	6.78	11.92	22.31
		(0.89-4.58)	(3.02-15.48)	(5.31-27.21)	(9.93-50.94)
	NAP	2.38	5.38	8.86	12.47

Table: Minimum, average and maximum concentrations of ENA713 and NAP226-90 at steady state for Patches (by Patch size) with intersubject variability

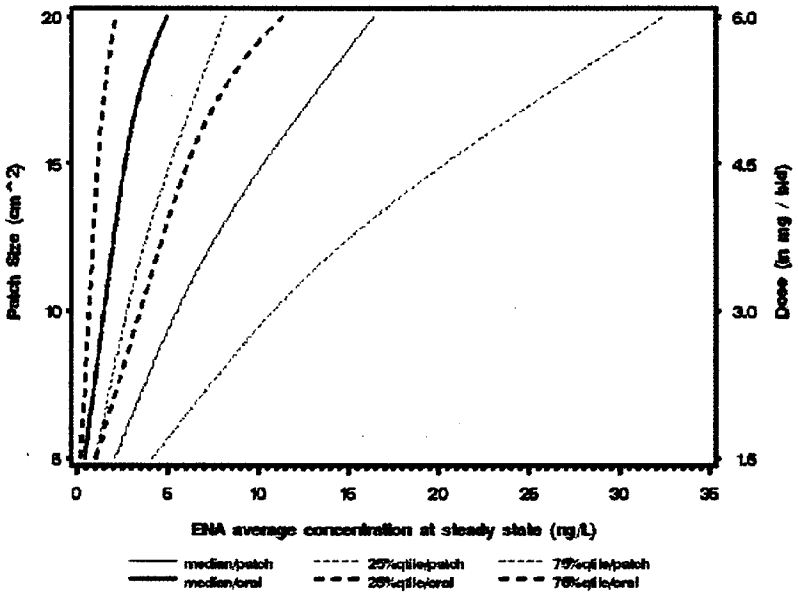
compound		Population median concentration (25%-75% quantiles)			
		Dose=5 cm2	Dose=10 cm2	Dose=15 cm2	Dose=20cm2
Cmin (ng/mL)	ENA713	1.47 (0.63-3.33)	3.85 (1.64-8.73)	7.24 (3.08-16.4)	11.53 (4.90-26.12)
	NAP226-90	1.15 (0.48-2.54)	2.66 (1.12-5.88)	4.84 (2.04-10.73)	7.01 (2.95-15.52)
Cave (ng/mL)	ENA713	2.1 (1.04 - 4.14)	5.49 (2.74-10.85)	10.32 (5.14-20.37)	16.44 (8.19-32.45)
	NAP226-90	1.46 (0.67-2.95)	3.38 (1.56-6.85)	6.17 (2.84-12.48)	8.92 (4.10-18.06)
Cmax (ng/mL)	ENA713	2.58 (1.33-4.89)	6.76 (3.49-12.82)	12.69 (6.56-24.07)	20.22 (10.46-38.36)
	NAP226-90	**1.66 (0.79-3.14)**	**3.85 (1.82 – 7.3)**	**7.02 (3.33-13.30)**	**10.16 (4.81-19.24)**

The values of Cmaxs obtained from this simulation are similar to that obtained from the actual study.

Equivalency of capsule and Patch in terms of Cave

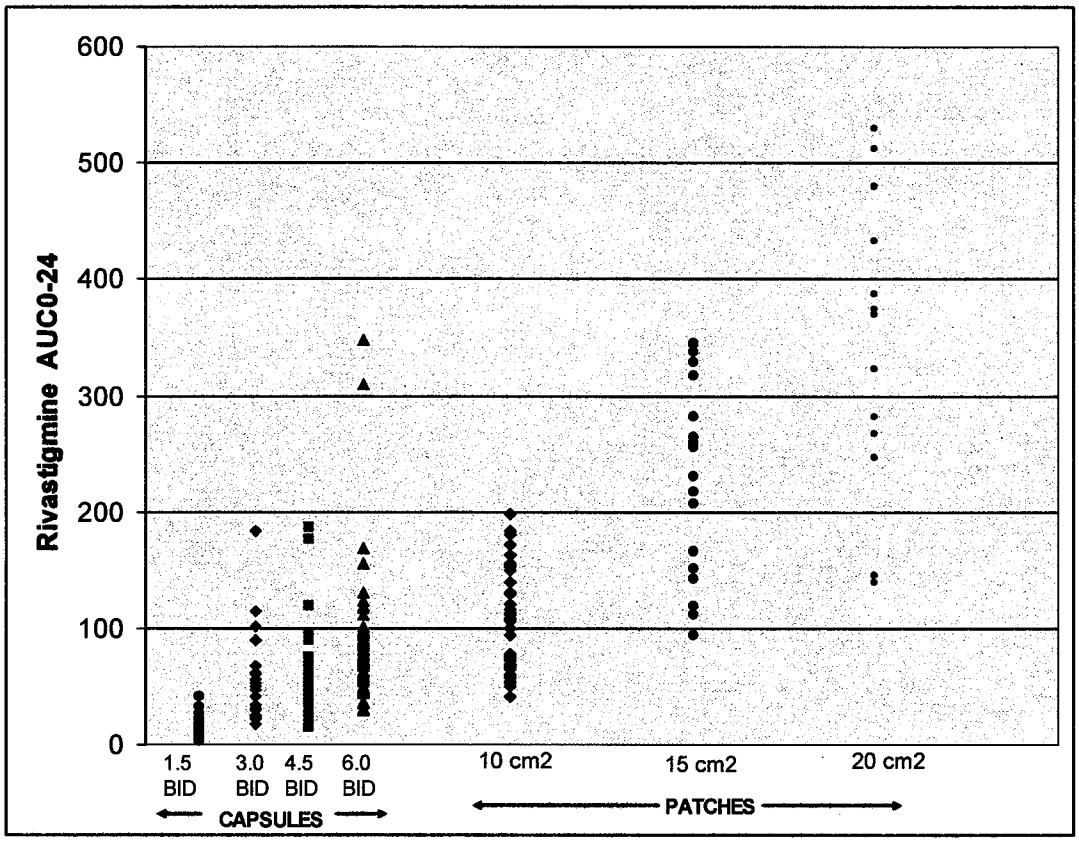
In order to assess equivalent doses between Patches and Capsules, doses and Patch sizes were displayed against C_{ave} in the following Figure. According to the sponsor a Patch of size 10 cm^2 was equivalent to a Capsule strength of about 6 mg b.i.d. (i.e. 12 mg per day) based on these simulations as shown in the following graph.

Figure Comparison of ENA713 average plasma concentration at steady state for different Capsule doses and Patch sizes



This was also confirmed by looking at the individual PK data from this study. The following figure shows that the 10 cm^2 patch gives exposures similar to the 6 mg BID capsule.

Figure Comparison of ENA713 AUC0-24 for 1.5, 3.0, 4.5 and 6 mg BID Capsule doses and 10, 15 and 20 cm2 Patch based on actual pharmacokinetic data from Study 2331



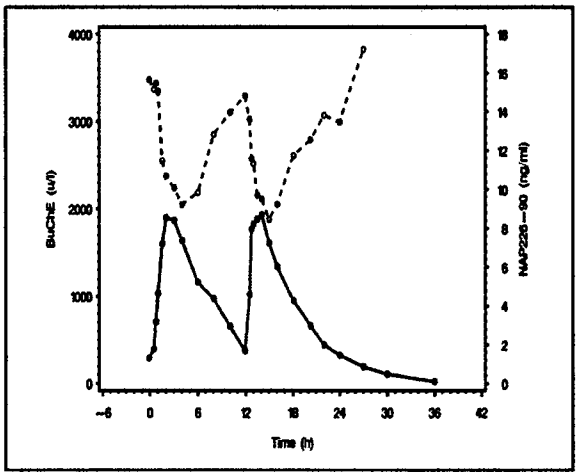
Based on this, the sponsor's proposal to switch patients on >6 mg/day oral rivastigmine to the 10 cm^2 patch and patients on 3 mg/day oral dose to 5 cm^2 patch is acceptable.

Pharmacodynamics:

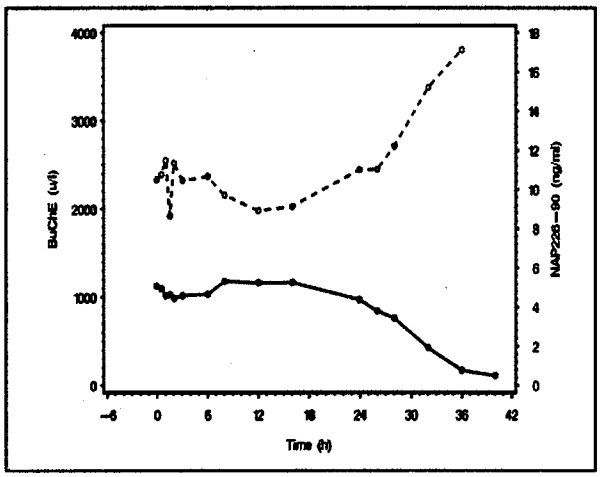
Pharmacokinetics and butyrylcholinesterase (BuChE) activity:

BuChE activity was available for 37 patients, with a median value of 50 measurements per patient (range: 23-95 measurements per patient). The time-course of NAP plasma concentrations and BuChE activity is illustrated in the following Figures for two subjects at the end of the last treatment period. These plots suggest a direct relationship between the pharmacokinetics of NAP and BuChE suppression.

For Capsules (6 mg BID):



For Patch (20 cm^2):



The estimates of the nonlinear mixed effect model relating BuChE activity to NAP plasma concentrations are summarized in the following Table. The estimated population median for IC50 was numerically lower for patients receiving the Patch (6.90 ng/mL) than for patients receiving the Capsule (11.03 ng/mL). However, this numerical difference (p-value=0.08) was small compared to the inter-subject variability of IC50 (CV of about 80%). There is also no pharmacological reason why the IC50 should depend on the route of administration. The model could fit the data well, with a small residual error.

Table Parameter estimates of the Emax model relating BuChE activity to NAP226-90 plasma concentrations

Parameter	Population median	Standard error (% CV)	Inter-individual variability (% CV)
IC50 (ng/mL) Capsule	11.03	17	79
IC50 (ng/mL) Patch	6.90	19	79
BuChE baseline (u/L)	4000	4	25

Finally, ENA Patch and Capsule were compared in terms of dose non-linearity with respect to ENA exposure. Using the median average concentration as a measure of exposure, the increase of exposure relative to the lowest dose for Capsules and lowest size for Patches was calculated. The investigated dose escalations are presented in the following Table:

Table: Comparison of nonlinear increase in ENA713 exposure with increasing dose of Capsules and Patches (relative increases)

Oral b.i.d. dose (mg)	Increase in exposure relative to lowest dose	Patch size (cm^2)	Increase in exposure relative to lowest Patch size/dose
1.5	1	5	1
3	3.4	10	2.6
4.5	6	15	4.9
6	11.2	20	7.8

On escalating through the Patch sizes of 5, 10, 15 and 20 cm^2, the increase in relative ENA exposure was 1, 2.6, 4.9 and 7.8 fold, respectively, relative to the lowest Patch size/dose. For comparison, this increase was 1, 3.4, 6 and 11.2 fold on escalating oral b.i.d. doses, showing that over-proportionality was more pronounced for the Capsules.

With respect to NAP metabolite, it appears that over-proportionality in NAP exposure is still apparent but to a lesser extent than for ENA, and comparable for the Capsules and Patches.

Table: Comparison of nonlinear increase in NAP226-90 exposure with increasing dose of Capsules and Patches (relative increases)

Oral b.i.d. dose (mg)	Increase in exposure relative to lowest dose	Patch size (cm^2)	Increase in exposure relative to lowest Patch size/dose
1.5	1	5	1
3	2.3	10	2.3
4.5	3.7	15	4.2
6	5.2	20	6.1

Pharmacokinetics and adverse events:

Due to the small number of patients and adverse events, no conclusive relationships between adverse events and pharmacokinetic parameters were found.

Conclusions from the modeling report:

- The 10 cm^2 patch is equivalent to the 6 mg BID capsule and labeling statement in this regard is acceptable.
- The modeling report reconfirms the conclusions observed from the traditional pharmacokinetic non compartmental analysis.

EXPLORATORY PK-PD ANALYSIS OF STUDY 2320:

Objectives:

The objectives of the PK and PK/PD analyses for patients treated with rivastigmine patch were:

- Describe the relationship of steady-state concentrations of ENA713 and NAP226-90 with dose, patient demographics and baseline laboratory values.
- Explore the relationship between key efficacy measures and steady-state concentrations of ENA713 and NAP226-90.
- Explore the relationship between key safety or tolerability measures and steady-state concentrations of ENA713 and NAP226-90.

Experimental methods:

This PK-PD analysis was done on the pivotal Phase III study 2320. In study 2320, approximately half of the 1195 randomized patients with probable Alzheimer's disease received patch treatment of rivastigmine for 24 weeks. The study consisted of two periods: a 16 week titration period, followed by an 8 week maintenance period. In the titration period, rivastigmine patch-treated patients were titrated to their target patch size (10 cm^2 or 20 cm^2) in four week intervals, starting with a patch size of 5 cm2. The 5, 10, 15, and 20 cm^2 patch sizes were loaded with 9, 18, 27, and 36 mg of ENA713, respectively. For 310 of the patch treated patients, a single plasma concentration measurement of ENA713 (rivastigmine) and/or its main metabolite NAP226-90 (also known as ZNS114-666) was available at steady-state (end of maintenance period).

The patient demographics/covariates from this analysis is given in the following Table:

Table: Patient demographics and baseline laboratory values

Covariates	Median (range)
Body weight (kg)	66.4 (35.0 - 103.9)
Age (yrs)	75.0 (51.0 - 89.0)
SGOT (U/L)	21.0 (11.0 - 70.0)
SGPT (U/L)	17.0 (5.0 - 86.0)
Bilirubin (umol/L)	7.0 (3.0 - 31.0)
Creatinine clearance (mL/min)	61.6 (26.3 - 190.3)
Sex	203 female , 107 male
Race	223 Caucasian, 33 Oriental, 2 Black, 52 Other

Data analysis and modeling methods:

Pharmacokinetics: The steady-state plasma concentrations were descriptively summarized by loaded dose. To explain the variability of drug exposure (steady-state concentrations of ENA713 and NAP226-90), the relationship with patient demographics

(body weight, age, sex, race) and baseline laboratory values (SGOT, SGPT, bilirubin, creatinine clearance) was explored by linear regression.

Pharmacokinetics and efficacy: The relationship between measures of efficacy (ADAS-Cog, ADCSCGIC, ADCS-ADL, NPI) and drug exposure was explored by linear or logistic regression.

Pharmacokinetics and safety: The relationship between selected adverse events in the maintenance period (nausea, vomiting, dizziness) and drug exposure was explored descriptively.

Results:

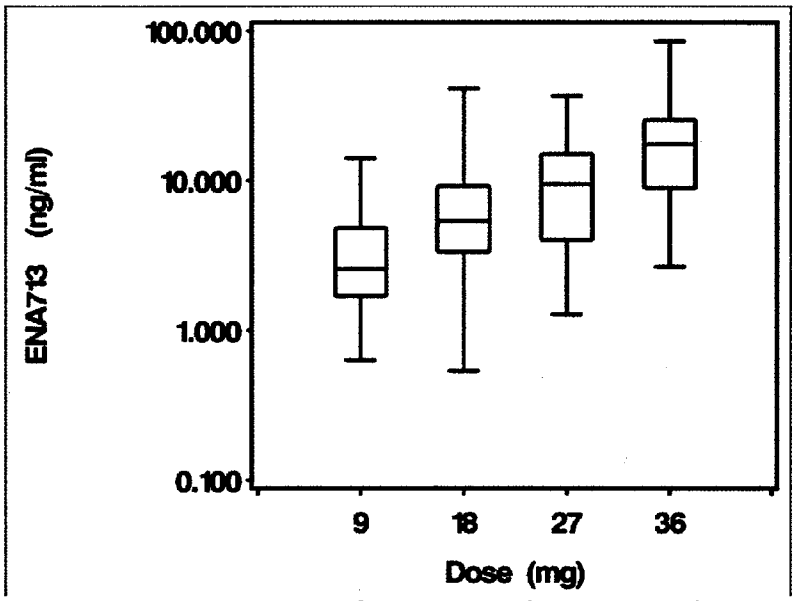
Pharmacokinetics:
In study 2320, 515 patients in the ITT population received patch treatment of rivastigmine, and 470 of these patients completed the study. ENA713 plasma concentrations were measured in 352 of these patients, and NAP226-90 plasma concentrations were measured in 353 of these patients.

The distribution of steady-state plasma concentrations is summarized in the following Table, and shown graphically in the following Figures (boxplots show minimum, lower quartile, median, upper quartile, maximum). These results suggest an overproportional increase of ENA713 steady-state concentrations with dose, while NAP226-90 steady-state concentrations appear to be dose-proportional. It should be noted that variability includes both between-patient variability and within-patient variation during the day.

Table: ENA713 and NAP226-90 steady-state concentrations by patch loaded dose

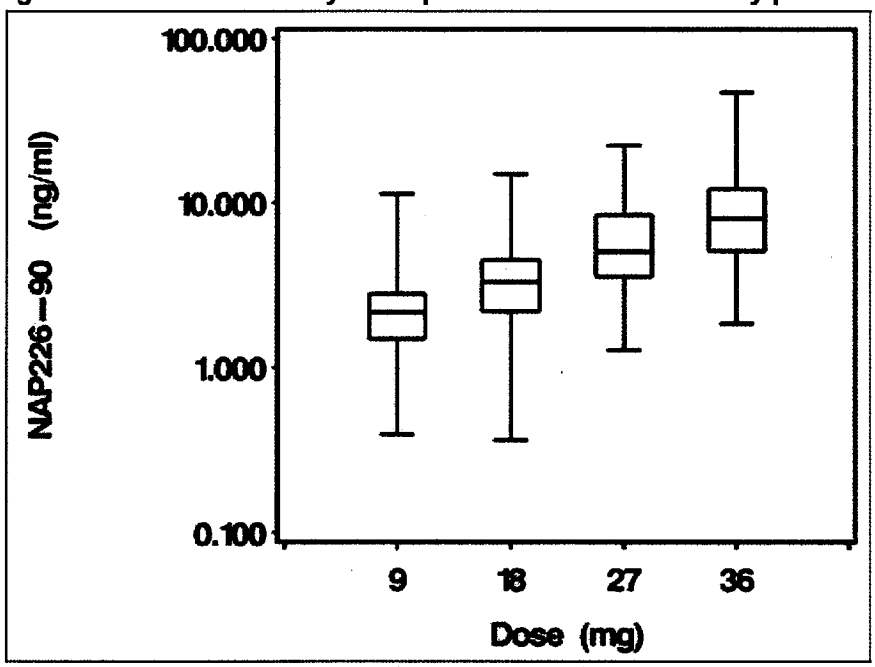
Loaded dose (mg)	ENA713			NAP226-90		
	Median (ng/mL)	Median/loaded dose (ng/mL/mg)	CV (%)	Median (ng/mL)	Median/loaded dose (ng/mL/mg)	CV (%)
9 (5 cm^2)	2.55 (n=20)	0.28	84	2.17 (n=18)	0.24	90
18 (10 cm^2)	5.37 (n=173)	0.30	89	3.29 (n=172)	0.18	64
27 (15 cm^2)	9.47 (n=18)	0.35	87	5.04 (n=18)	0.19	80
36 (20 cm^2)	17.45 (n=98)	0.48	77	8.03 (n=98)	0.22	66

Figure: ENA713 steady-state plasma concentrations by patch loaded dose



Loaded doses: 9 mg (5 cm^2) 18 mg (10 cm^2) 27 mg (15 cm^2) 36 mg (20 cm^2)

Figure: NAP226-90 steady-state plasma concentrations by patch loaded dose



Loaded doses: 9 mg (5 cm^2) 18 mg (10 cm^2) 27 mg (15 cm^2) 36 mg (20 cm^2)

To explain some of the variability seen in the steady-state concentrations of ENA713 and

NAP226-90, the relationship with patient demographics and baseline laboratory values was investigated.

A linear regression of logarithmized steady-state concentrations of ENA713 against dose (as categorical factor), race (categorical), sex (categorical) and logarithmized numerical covariates (body weight, age, SGOT, SGPT, bilirubin, creatinine clearance) was done.

Effect of Body weight:
This analysis showed a clear effect of dose (p=0.0001) and body weight (p=0.0003) on steady-state concentrations of ENA713.

The relative steady-state concentrations of ENA713 for patients with various body weights relative to the steady-state concentration of a patient with a body weight of 65 kg was estimated as:
$ENA713_{ss} / ENA713_{ss,65kg} = (\text{Body weight}/65\ kg)^{\beta}$, where $\beta = -1.33$ (standard error: 0.23)

A similar regression analysis was also done for NAP226-90. The linear regression showed again a clear effect of dose (p=0.0001) and body weight (p=0.0065) on steady-state concentrations of NAP226-90.

Table: Relative steady-state concentrations for patients with selected body weights as compared to a patient with a body weight of 65 kg

Body weight:	35 kg	50 kg	65 kg	80 kg	100 kg
ENA713	228%	142%	100%	76%	56%
NAP226-90	167%	124%	100%	84%	70%

Figure: Loaded dose normalized ENA713 steady-state plasma concentrations against body weight

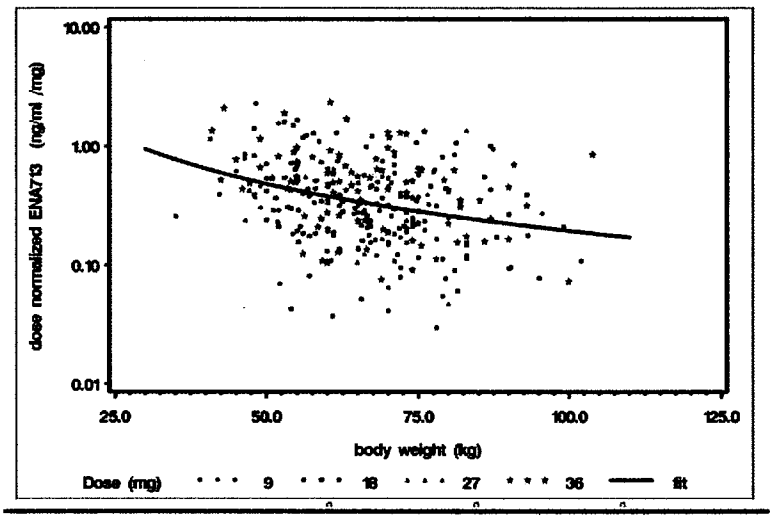
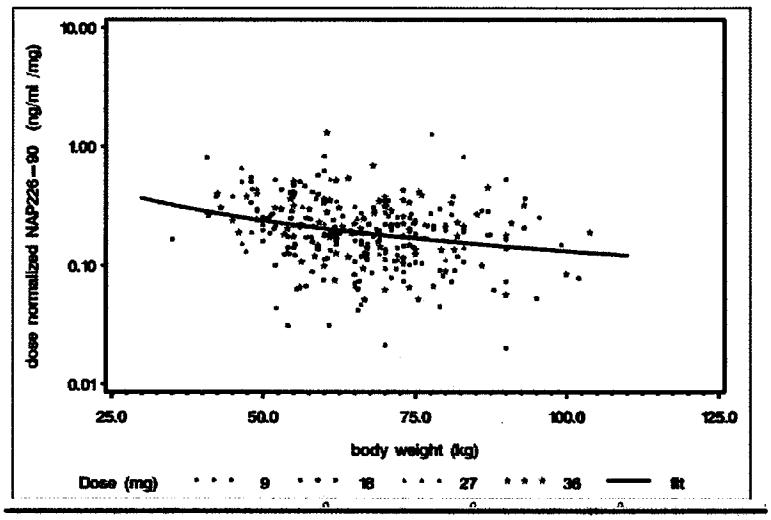


Figure: Loaded dose normalized NAP226-90 steady-state plasma concentrations against body weight



Effect of Race:

There appeared also to be a small effect of race (p=0.05); however this seemed to be due to the 2 black patients. When excluding the 2 black patients, no effect of race was seen (p=0.38). Due to the very small number of black patients, no reliable conclusions can be drawn based on this data on potential differences with respect to pharmacokinetics for black vs. non-black patients.

Other covariates:
The other covariates showed no clear effect on ENA713 steady-state concentrations (sex: p=0.78; age: p=0.09; SGOT: p=0.14; SGPT: p=0.44; bilirubin: p=0.39; creatinine clearance: p=0.72) and also on NAP (race: p=0.32; sex: p=0.91; age: p=0.72; SGOT: p=0.12; SGPT: p=0.19; bilirubin: p=0.99; creatinine clearance: p=0.54).

Exposure and Pharmacodynamics:

The relationship between measures of efficacy and drug exposure was explored for the patients who received rivastigmine patch. Drug exposure was defined as the steady-state measured plasma concentration of ENA713 or NAP226-90. The patients treated with Exelon patch Drug exposure was defined as the steady-state measured plasma concentration of rivastigmine (Exelon), which were considered to be steady-state if:
• the date and time of sampling and of last dose were available
• the elapsed time between PK sampling and last dose was between 0 and 36 hours
• on the 5 days preceding PK sampling, doses were identical and different from 0
This selection process resulted in 326 patch-treated patients with measurements of plasma concentrations of rivastigmine.

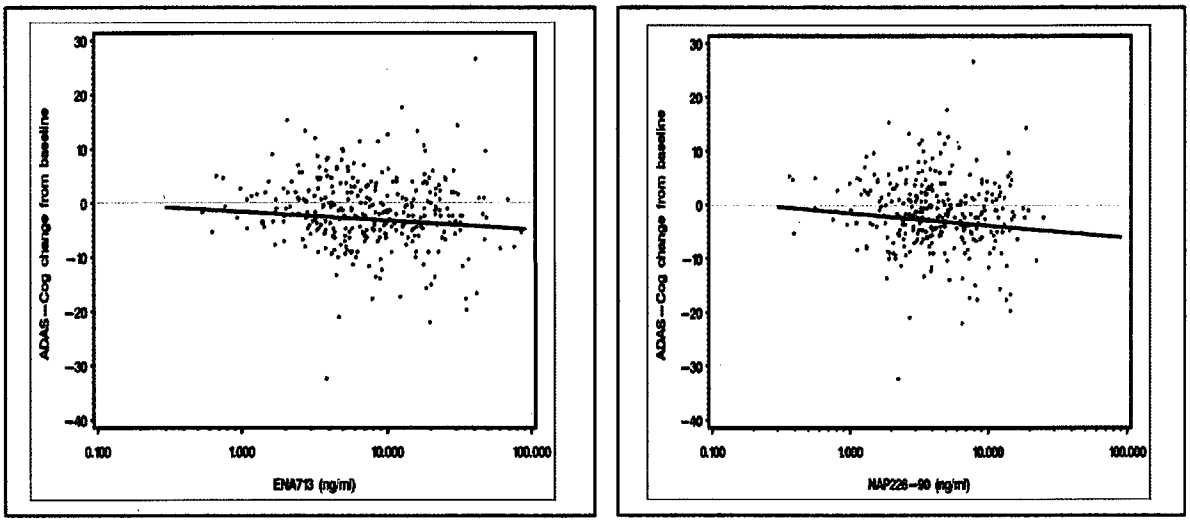
ADAS-Cog:
In the following Table, the mean ADAS-Cog change from baseline to week 24 is shown for different levels of drug exposure (quintiles). These summary measures suggest that the reduction (i.e. improvement) in ADAS-Cog scores from baseline to Week 24 was larger for higher levels of drug exposure. A linear regression of the ADAS-Cog change from baseline against logarithmized ENA713 exposure showed a trend for increased efficacy with increasing drug exposure (p=0.07). A similar relationship was seen when the logarithmized NAP226-90 exposure was used as a factor in the linear regression (p=0.04).

Table: ADAS-Cog change from baseline by exposure levels

Steady-state concentration (ng/mL)		ADAS-Cog change from baseline		
		N	Mean	Standard Error
ENA713	≤3.4	64	-0.07	0.63
	3.4-5.6	59	-1.75	0.98
	5.6-9.4	61	-2.36	0.78
	9.4-18.3	63	-1.42	0.76
	>18.3	61	-2.60	1.02
NAP226-90	≤2.3	64	-1.06	0.87
	2.3-3.4	59	-1.17	0.77
	3.4-4.9	63	-0.85	0.74
	4.9-8.3	58	-2.25	1.03
	>8.3	61	-2.68	0.85

Negative ADAS-Cog change from baseline indicates improvement

Figure: ADAS-Cog change from baseline against ENA713 and NAP exposure



Negative ADAS-Cog change from baseline indicates improvement

ADCS-CGIC:

In the following Table, the percentage of ADAS-CGIC responders is shown for different levels of drug exposure (quintiles). It appears that more patients tended to respond to higher levels of drug exposure. A logistic regression of response against logarithmized ENA713 exposure showed an increased response rate with increasing drug exposure (p=0.04). A corresponding trend was also seen when the logarithmized NAP226-90 exposure was used as a factor in the logistic regression (p=0.06).

Table: ADCS-CGIC response by exposure levels

Steady-state concentration (ng/mL)		ADAS-CGIC responders		
		N	Percentage	Standard Error
ENA713	≤3.4	64	20	5
	3.4-5.6	59	39	6
	5.6-9.4	61	39	6
	9.4-18.3	63	41	6
	>18.3	61	33	6
NAP226-90	≤2.3	64	27	6
	2.3-3.4	60	28	6
	3.4-4.9	62	47	6
	4.9-8.3	58	33	6
	>8.3	61	39	6

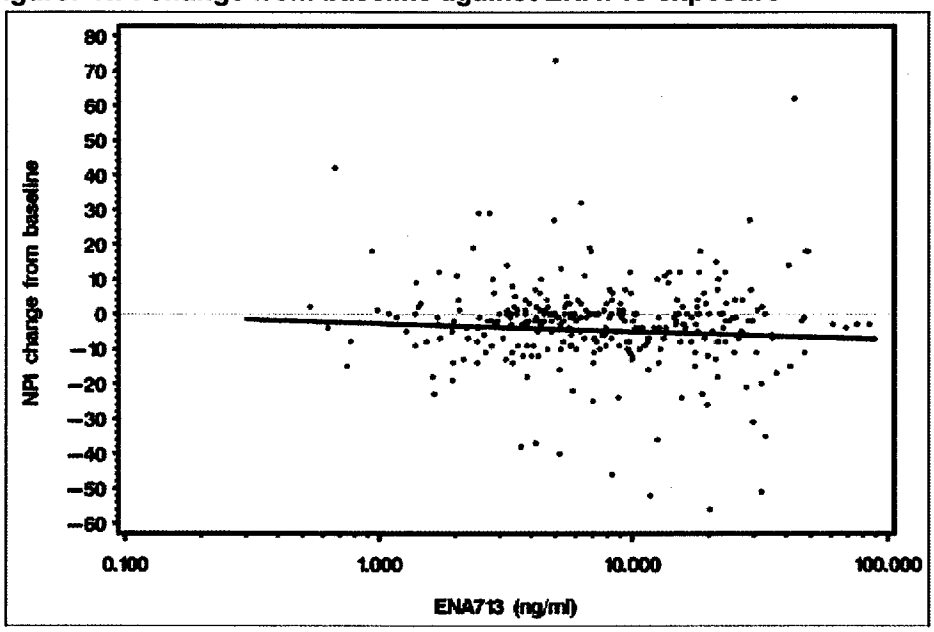
ADCS-ADL:

A linear regression of the ADCS-ADL change from baseline against logarithmized ENA713 exposure showed no exposure-response relationship within the observed exposure range (p=0.82). The corresponding analysis using the logarithmized NAP226-90 exposure as a factor in the linear regression gave similar results (p=0.86).

NPI:

There is a reduction in NPI score from baseline to Week 24 which is larger for higher levels of drug exposure. However, a linear regression of the NPI change from baseline against logarithmized ENA713 exposure showed no clear evidence of an exposure-response relationship within the observed exposure range (p=0.20), due to the high variability in NPI. The linear regression with factor logarithmized NAP226-90 exposure gave similar results (p=0.17).

Figure: NPI change from baseline against ENA713 exposure



Negative NPI change from baseline indicates improvement

Exposure and Safety:

The relationship between selected adverse events (nausea, vomiting, dizziness) and drug exposure was explored for the patients who received patch treatment of rivastigmine. Drug exposure was defined as the steady-state plasma concentration of ENA713 and NAP226-90, respectively. Only those patients who had evaluable steady-state concentrations were included in the analyses.

In the following Table, the number of patients with adverse events in the maintenance period is shown for different levels of drug exposure (quintiles). Only very few patients experienced nausea, vomiting or dizziness in the maintenance period, and no relationship with drug exposure was seen.

Table: Adverse events in the maintenance period by exposure levels

Steady-state concentration (ng/mL)		Number of patients with AE			
		N	Nausea	Vomiting	Dizziness
ENA713	≤3.4	63	1	4	0
	3.4-5.7	59	0	0	0
	5.7-9.6	60	4	1	1
	9.6-18.5	62	0	1	1
	>18.5	60	2	3	2
NAP226-90	≤2.3	62	0	1	1
	2.3-3.4	59	2	2	0
	3.4-4.9	61	3	2	0
	4.9-8.4	59	0	1	2
	>8.4	60	1	2	1

Overall Conclusions:

The PK and PK/PD analyses for patients treated with rivastigmine patch showed:

- An over-proportional increase of the drug exposure (steady-state concentrations of ENA713) with dose, and a clear relationship between drug exposure (steady-state concentrations of ENA713 and NAP226-90) and body weight.
- An increased efficacy (ADAS-Cog, ADCS-CGIC) with increasing drug-exposure (steady-state concentrations of ENA713 and NAP226-90).
- No relationship between drug exposure (steady-state concentrations of ENA713 and NAP226-90) and the few AE's (nausea, vomiting or dizziness) in the maintenance period.

The increasing efficacy with increasing drug exposure suggests that each patient should be titrated to his/her maximal well-tolerated dose. The clear effect of body weight on drug exposure suggests special attention to patients with very low body weight during up-titration.

BIOANALYTICAL METHODS

Rivastigmine and NAP226-90 in plasma:

1. METHOD 1: GC/MS [redacted] Report 303-263) b(4)

The older studies utilized this method. The studies in which this method was adopted were: Study 152, 153, 155 and 159

Linearity: 0.11-34 ng/ml for rivastigmine and 0.12-35 ng/ml for NAP226-90
LLOQ: 0.11 ng/ml for rivastigmine and 0.12 ng/ml for NAP226-90
Interday Precision: % CV within 3.4-14.5% for rivastigmine and 3-20.5% for NAP226-90
Interday Accuracy: within -8.4-3.7% for rivastigmine and -5.6-6.1% for NAP226-90
Stability : 2 freeze thaw cycles and up to 20 months at various stages of sample processing
Recovery : 84% for rivastigmine and 46% for NAP226-90

2. METHOD 2: Selective HPLC/MS/MS (Reports DMP(F) R01-1020, DMP(F) R01-1020-02 and DMP(F) R01-1020-03)

The more recent studies utilized this method. These studies include Study 2331, 2332 and 2320. This method was transferred to another location and validated there (Report PCS(EU R0400034 and PCS(EU R0400034-01). Samples for Study 2335, 2338, 1101 and 1201 was analyzed at this site. These were then cross-validated with the original HPLC method. The cross validation report was BAPK(EU) R0400478)

Linearity: [redacted] g/ml for rivastigmine and NAP226-90
LLOQ: 0.2 ng/ml for rivastigmine and NAP226-90
Interday Precision: % CV within [redacted] % for rivastigmine and [redacted] for NAP226-90 b(4)
Interday Accuracy: within [redacted] or rivastigmine and [redacted] for NAP226-90
Stability : Rivastigmine and NAP226-90 were found to be stable in plasma:
- in stock solutions for at least 1 month at about +5°C
- in human plasma after 24 h at room temperature
- in spiked plasma after 3 freeze-thaw cycles below -18°C
- in spiked human plasma for at least 19 months storage below -18°C
- in human plasma for at least 19 months storage below -18°C
- in plasma extract for 30 h at room temperature on the autosampler.

Recovery : [redacted] for rivastigmine and [redacted] for NAP226-90

The performance in terms of specificity, accuracy, precision and LLOQ were similar using APCI or turbo ion spray (TIS) detection (Report DMP(F) R01-1020-02)
• Accuracy and precision using a calibration curve prepared in plasma treated with a

solution of physostigmine in water were similar to QC prepared:
-in plasma after centrifugation of blood treated with a solution of physostigmine in ethanol
-in plasma after centrifugation of blood treated with a solution of physostigmine in ethanol evaporated to dryness.
• Dilution of human plasma samples with human blank plasma by factors 2, 2.5, 5 and 10 was validated (Report DMP(F) R01-1020-03)

3. **Cross-validation of Method 1 and Method 2 (Reports DMP(F) R01-1020-01, BAPK(F) R00-2106)**

Cross-validation data performed by the analysis of 6 spiked plasma samples (QCS) and 38 actual plasma samples showed good correlation between GC/MS and LC/MS/MS method.
Both methods yielded very similar pharmacokinetic profiles for ENA713 and NAP 226-90 in man following oral administration of Exelon. Thus, use of GC/MS and LC/MS/MS methods are interchangeable in pharmacokinetic evaluation of ENA713 and NAP 226-90.

The mean ratio [LC/MS/MS(test)/GC/MS(reference)] was 1.07 (CV: 3.7%) for ENA713 and 1.02 (CV: 4.9%) for NAP 226-90.

The mean difference (Test-reference/reference %) between the two methods for the actual samples are 7.4 ± 4.0% for ENA713 and 2.2 ± 4.8% for NAP 226-90. These differences are in the acceptance criteria (should not exceed 20%).

4. **Cross Validation report due to transfer to another site:**

The HPLC-MS/MS method in plasma described above was transferred to a CRO [redacted] and validated ([PCS(EU) R0400034]; [PCS(EU) R0400034-01]) to analyze plasma samples from clinical studies (2335, 2338, 1101 and1201). A cross-validation was performed between the two laboratories by the analysis of 24 spiked plasma samples [redacted] R0400478]). The concentrations from spiked samples obtained from the two laboratories [redacted] (reference) and [redacted] (test)] met the acceptance criteria [the normalized difference for 2/3 of all spiked samples was within ± 15% (± 20% at LLOQ), internal standard operating procedures] indicating that the two laboratories obtained similar plasma concentration results for rivastigmine and NAP226-90. b(4)

At the new site the inter-day accuracy and precision were as follows: For rivastigmine, at LLOQ, the C.V. was equal to 2.65% and the bias was equal to 15.00%. Above LLOQ, the C.V. ranged from 2.71% to 4.02% and the bias ranged from 11.40% to 14.50%.
For NAP226-90, at LLOQ, the C.V. was equal to 3.34% and the bias was equal to 0.50%. Above LLOQ, the C.V. ranged from 2.60% to 3.73% and the bias ranged from 0.00% to 5.20%.

Rivastigmine and NAP226-90 in urine

METHOD: HPLC/MS/MS (Report DMPK R0400035)

Linearity: 0.5-2500 ng/ml for rivastigmine and NAP226-90
LLOQ: 0.5 ng/ml for rivastigmine and NAP226-90
Interday Precision: % CV within 1-4.7 % for rivastigmine and 3.1-10.3 % for NAP226-90
Interday Accuracy: within -8.7 to -5.5 % for rivastigmine and -2.9 to -1.4% for NAP226-90
Stability : Rivastigmine and NAP226-90 were found to be stable in urine:
-in stock solutions for at least 1 month at about 5°C and for 6 h at room temperature
-in working stock solutions for 70 days at about 5°C
-in extracts at least 101 h at room temperature
-in QCS for at least 21 h at room temperature, after 3 freeze-thaw cycles at about -24°C. Rivastigmine was stable for at least 3 months at about -24°C but the stability of NAP226-90 was not fully demonstrated, and was not available.

Recovery : 80-87% for rivastigmine and 87-90% for NAP226-90

IN VITRO RELEASE

Dissolution Method:

The sponsor's proposed dissolution method is:

Apparatus: USP Apparatus 6 (cylinder)
Medium: 0.9% Sodium Chloride solution
Temperature: 32°C ± 0.5 °C
Speed: 50 rpm

Sponsor Proposed Specifications:

Time Points	Percent Released
2 hours	[redacted]
4 hours	
7 hours	

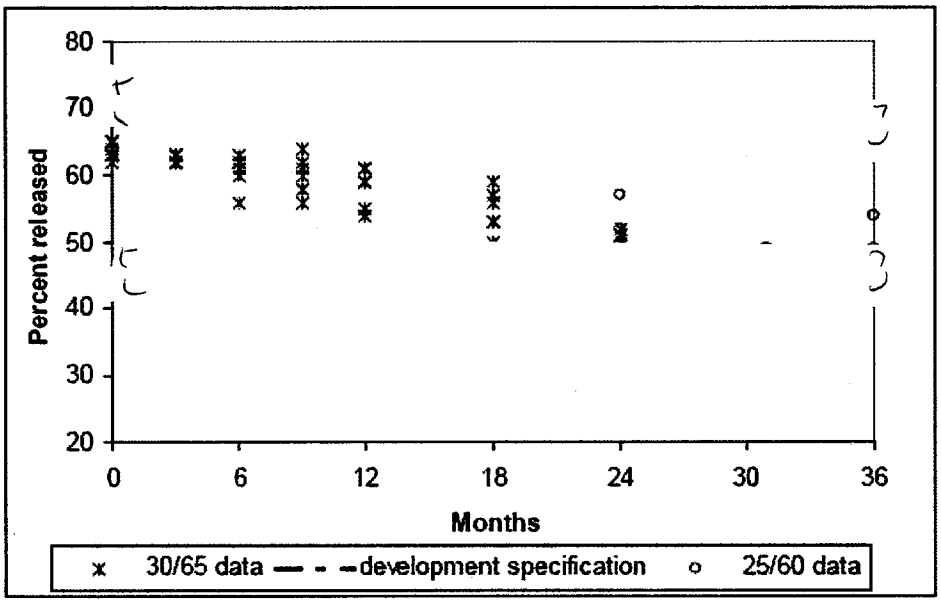
The sponsor has initially set development specifications (Table below) based on limited development stability data on two technical batches (9mg/5cm² and 36mg/20cm² patches with 7000 units each) stored under 25°C/60% RH (long-term conditions) and 40°C/75% RH (accelerated conditions). During the registration stability protocol testing, a consistent trend of decrease in release rate with increasing storage time was observed under both long-term (30°C/65%RH) and accelerated conditions (40°C/75%RH).

Time Points	Percent Released
2 hours	[redacted]
4 hours	
7 hours	

b(4)

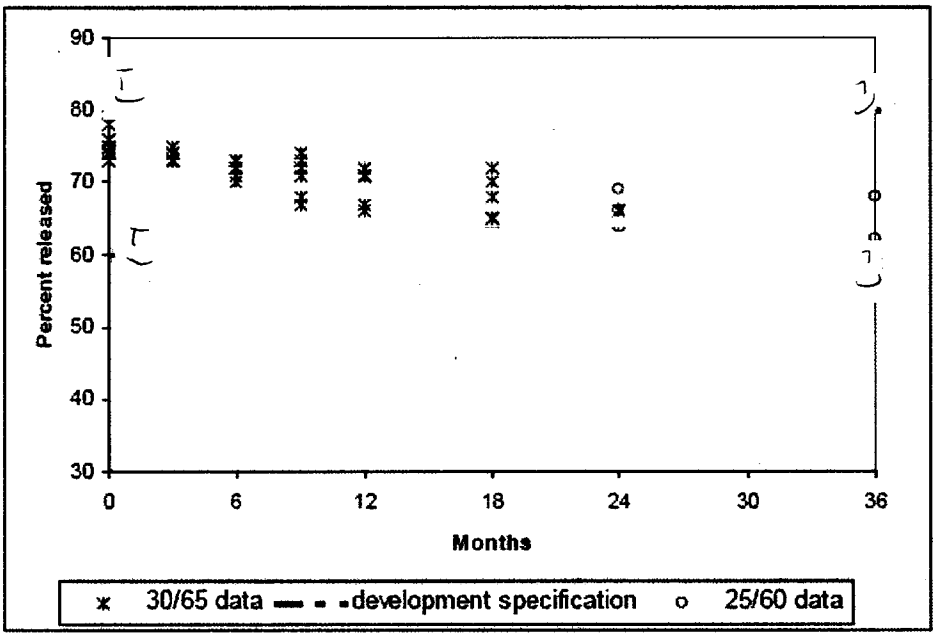
The in vitro release data for the 2, 4 and 7 hours is shown in the following Figures. Each point is a mean percent released for each batch:

Figure 1: Drug release data at 2 hours (all batches, 30 degree celsius/65 percent RH and 25 degree celsius/60 percent RH, all time points)



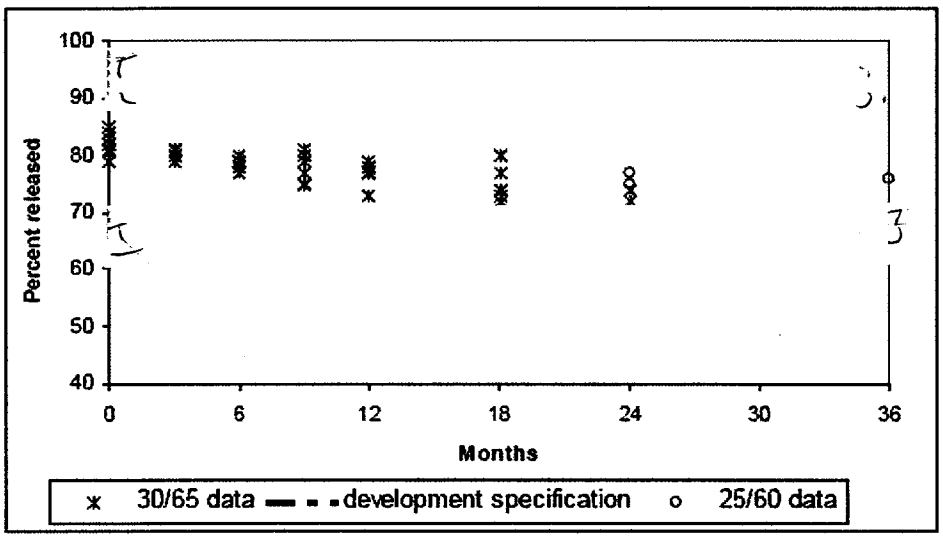
b(4)

Figure 2: Drug release data at 4 hours (all batches, 30 degree celsius/65 percent RH and 25 degree Celsius/60 percent RH, all time points)



b(4)

Figure 3: Drug release data at 7 hours (all batches, 30 degree Celsius/65 percent RH and 25 degree Celsius/60 percent RH, all time points)



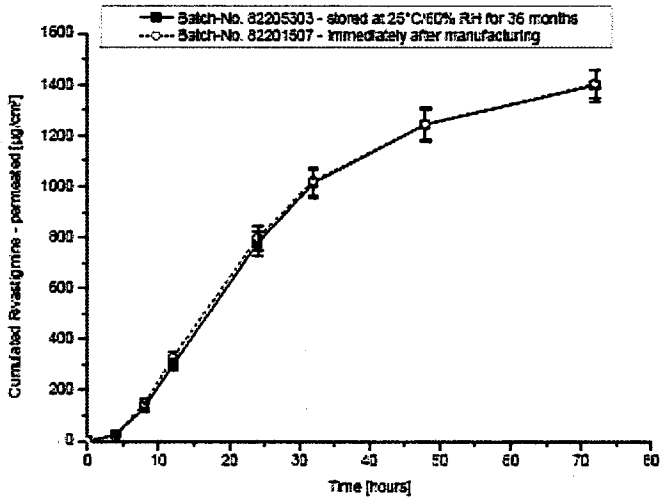
b(4)

These figures show a consistent trend of decrease in release rate with increasing storage time.

The sponsor supports the lack of correlation between the results of the in-vitro release test and the in-vivo performance by the following observations:

I. No difference was found in the in-vitro human skin permeation assay, which is considered by the sponsor to be a suitable representation of in-vivo conditions, between newly manufactured transdermal patches from batch 82201507 and those from validation batch 82205303 (PK studies D2320 and D2331), which had been stored for 36 months at 25°C/60%RH (Figure 1-1). Independent of the age of the patches, the skin permeation results obtained were identical. A two sided t-test was performed and the results are not significantly different on a 0.05 significance level.

Figure 1-1 Human skin permeation results of ENA713 transdermal patches of different ages



On the other hand, in the in-vitro release rate test, the validation batch 82205303 stored for 36 months at 25°C/60%RH showed a considerably slower release rate to that found for batch 82201507 (Figure 1-2), although immediately after manufacturing, these batches demonstrated nearly identical in-vitro dissolution behavior (Figure 1-3). Therefore, according to the sponsor the available data support the argument that after 36 months storage there is up to a 20% decrease in release rate in the in-vitro release test that is not evident in the in-vitro human skin membrane permeation test.

Figure 1-2 : In-vitro release results of the samples fresh after manufacture and after 36 month storage at 30 degree celsius/65 percent RH

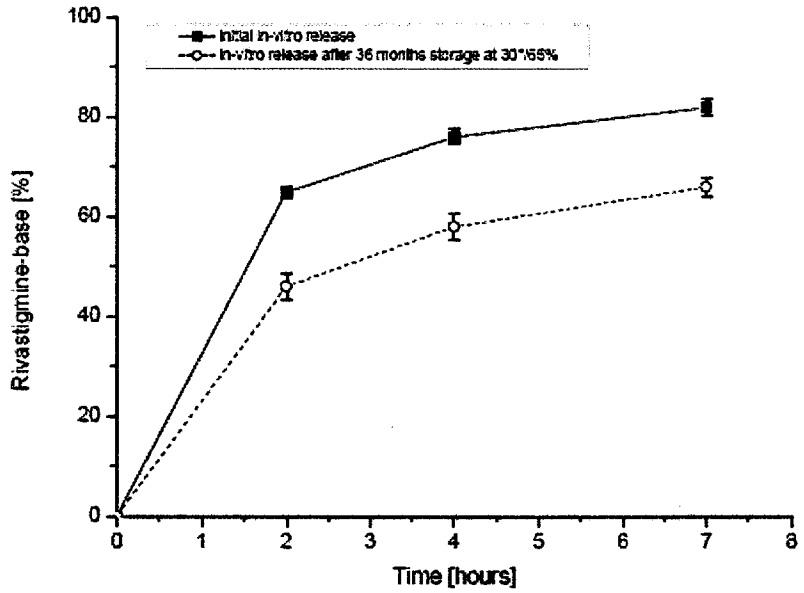
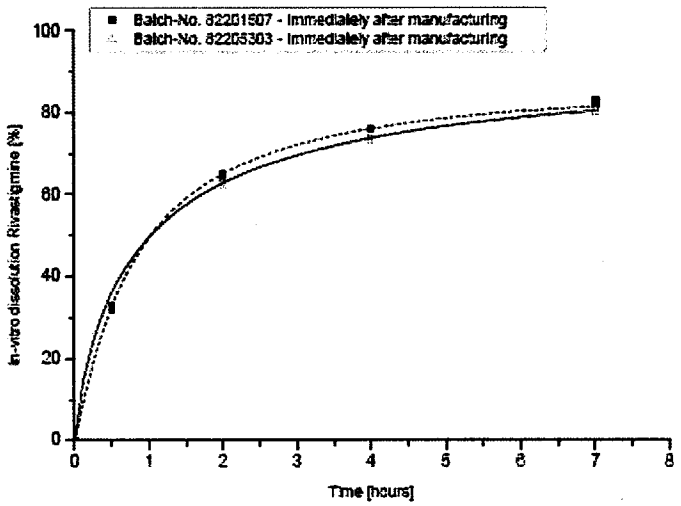


Figure 1-3 Comparison of initial in-vitro release rate results of ENA713 transdermal patch batch 82201507 and validation batch 82205303



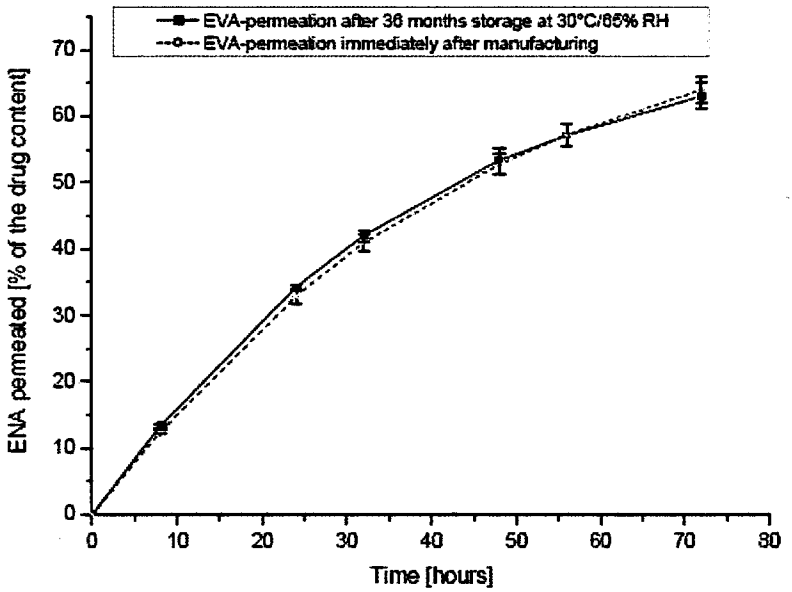
II. According to the sponsor, for ENA713 patch on average only about 45 to 50% of the drug in the patch will penetrate the skin during the 24 hour application regardless of the dosage strength. The *in vitro* release rate in 7 hours exceeds the *in vivo* delivery rate observed in 24 hours. From this argument, it can be concluded that the rates of drug dissolution in the in-vitro release test are not comparable to rates of in-vivo dermal absorption.

III. The sponsor also used an EVA (ethylene vinyl acetate) membrane permeation test. This test mimics the drug permeation through human skin and it eliminates the variation caused by the biological and preparation differences inherent with in vitro skin permeation methods, and is used generally as a developmental tool.

One set of patches was stored at 30°C/65%RH for 3 years prior to testing. Another set of patches was recently manufactured. Both sets came from [redacted] batches. Using the pharmacopoeial dissolution test as specified in the drug product testing monograph, the release rate after 36 months was significantly lower when compared to the initial release rate (see Figure1-2 on Page 181) b(4)

EVA membrane permeation results for zero time and 36 month samples, however, did not show significant change in release rate. In 24 hours about 35% of drug load permeated through the membrane for both zero time and 36 month samples (Figure below).

Figure: Results of EVA membrane permeation test



This result demonstrates that the decreasing release rate observed in the release rate test by HPLC does not affect the EVA permeation rate.

It is therefore concluded by the sponsor that the decreasing in vitro release rates after 36 month storage at 30°C/65%RH do not indicate impairment of the bioavailability of rivastigmine. The regulatory application of in vitro permeation alone is unclear. However, literature indicates correlation between in vitro permeation and in vivo bioavailability.

There is typically no in vitro (dissolution) and in vivo correlation for transdermal patches and the release rate test is therefore used as a QC-tool only.

Reviewer's Comment:

In addition to the above information, the reviewer requested the sponsor to provide a tabular listing of the clinical study numbers and titles, the FMI batches used, date of manufacture, and the time elapsed between manufacturing date and application in clinical/pharmacokinetic studies. Based on this information provided by the sponsor the following information was tabulated on the exposures in these studies in which the patches were used at different times since manufacture:

Table: AUC0-24± SD (% CV) from the various studies in which patches were used through 24 months

Patch Size	Duration of elapsed time since manufacture of patch and end of Study			
	7 months	14 months	21 months	24 months
10 cm^2	153±41 (26%)	122 ± 55 (45%)	91.2 ± 74.8 (81%)	127 ± 41.4 (32%)
		119 ± 58.3 (48%)		
5 cm^2	62.9 ± 18.7 (30%)	45.6 ± 18.3 (39%)		46.3 ± 17.2 (37%)

This table shows that the AUC0-24 for the 5 and 10 cm^2 patches is similar at 14 months and 24 months since manufacture (similar conclusions were found for Cmax). There is no indication or consistent pattern in this Table of decreased exposure with increased stoprage time (Note: Cross study comparisions). What is not known is the number of subjects that received the patches at these months. However, the inter subject variability as given by the % CV is also similar between studies (30-45%)

Based on this information it is possible to accept the proposed specification with a shelf life of 24 months. The final method and specifications are given below:

Final Recommended Method and Specifications:

Dissolution Method:
Apparatus: USP Apparatus 6 (cylinder)
Medium: 0.9% Sodium Chloride solution
Temperature: 32°C ± 0.5 °C
Speed: 50 rpm
Proposed Specifications:

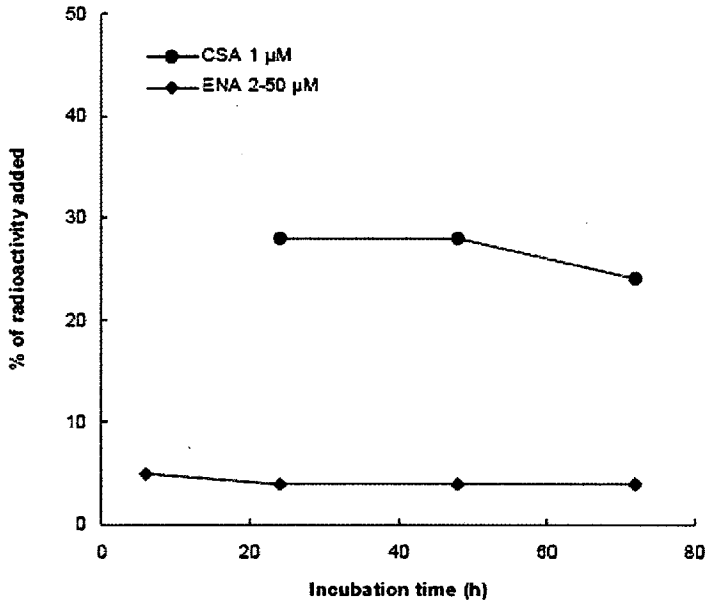
Time Points	Percent Released
2 hours	[redacted]
4 hours	
7 hours	

b(4)

METABOLISM IN HUMAN IN VITRO DERMAL MODEL (Study DMPK 1997/229)

Metabolism of SDZ ENA 713 was investigated in a human in vitro skin model (ATS skin ZK 1100). Skin equivalents were exposed to 2, 10 and 50 µM of [^{14}C]SDZ ENA 713 over a period of 72 h. [^{3}H]Cyclosporin A (CSA, 1 µM) was included in the study as a positive control because it had been previously shown to be metabolized by this human dermal skin model.

At all concentrations, ~5% of the radioactivity of SDZ ENA 713 was associated with the cells. HPLC analysis revealed that SDZ ENA 713 was poorly metabolized by dermal cells. After 72 h of culture less than 2% of the total radioactivity was recovered in three peaks. The sole metabolite formed by live cells was the N-oxide of SDZ ENA 713, peak 71. Its formation was almost linear with time and amounted to 29, 124 and 471 pmol/mg protein at 72 h of culture with 2, 10 and 50 nmoles added, respectively.



Dermal cell viability, as assessed by the MTT assay, was slightly but concentration dependently decreased with SDZ ENA 713 treatment from 96% at 2 µM to 89% at 50 µM of the vehicle control at 72 h. Concomitantly, a 17% increase in IL-6 release was observed with 50 µM of SDZ ENA 713.
[14C]SDZ ENA 713 was poorly metabolized by human dermal cells. In comparison, Cyclosporin A (1µM) displayed a higher cellular uptake (24%) and an up to 30-fold greater rate of metabolism. The results suggest that SDZ ENA 713 would not be subject to significant dermal metabolism.

4.2 APPENDIX II

OCP FILING REVIEW

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	**N22-083**	**Brand Name**	**Exelon TDS**
OCP Division (I, II, III)	**DCP-I**	**Generic Name**	**Rivastigmine**
Medical Division	**HFD-120**	**Drug Class**	**Anticholinesterase**
OCP Reviewer	**Veneeta Tandon**	**Indication(s)**	**Dementia of Alzheimers type (AD) and Parkinson's type (PDD)**
OCPB Team Leader	**Ramana Uppoor**	**Dosage Form**	**5, 10, [redacted] cm^2 patches** b(4)
		Dosing Regimen	**Start with patch 5, after 4 weeks can increase to patch 10. [redacted]** b(4)
Date of Submission	**9/8/06**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**5/8/07**	**Sponsor**	**Novartis**
PDUFA Due Date	**7/8/07**	**Priority Classification**	**Standard**
Division Due Date	**6/8/07**		

Clin. Pharm. and Biopharm. Information

Summary: The efficacy and safety of Exelon patches has been investigated in 549 patch-treated patients with AD in one pivotal study with a long term extension phase which is ongoing. Supportive data were provided from a further 3 uncontrolled studies in AD patients and 9 studies in healthy volunteers. The efficacy and safety of Exelon patches in patients with PDD have not been investigated in a clinical study. Approval for PDD is requested on the basis of:

- Patients with AD and patients with PDD both have cholinergic deficit in the brain.
- Efficacy and safety of Exelon capsules have been demonstrated previously in patients with PDD.
- Modeled pharmacokinetic data from a study conducted with Exelon Patch in Alzheimer's disease patients showed that the total daily exposure (AUC) of the Exelon Patch 10 is approximately equivalent to the exposure of a 6 mg b.i.d. capsule dose.
- 6 mg b.i.d. capsule dose was the highest dose used in patients with PDD. The mean daily maintenance capsule dose which showed superior efficacy compared to placebo in both ADAS-Cog and ADCS-CGIC was 8.7 mg rivastigmine.

The pharmacokinetics of rivastigmine and NAP226-90 after patch application were investigated in healthy (young and elderly) volunteers (n = 161) and in AD patients (n = 381) in 13 studies.
The patches are compositionally proportional. The FMI is used in pivotal clinical studies as well as several clinical pharmacology studies.

Rivastigmine (Exelon) patch was investigated in studies with the following objectives:

- BE relative to solution
- Permeability through human skin and adhesion
- Application site differences in bioavailability, also looked at adhesion at different sites
- Ethnic differences
- Dose proportionality and comparison to capsules at steady state
- Delivery rate

Population PK/PD was conducted in two separate analyses with the following main objectives:
Rich Sampling (Study 2331): Emax Model was used

- Estimate the population mean pharmacokinetic parameters
- Assess the impact of the Patch delivery rate on the kinetics of ENA713 and NAP226-90
- **Define the "equivalent" dose of the Patch compared** to the oral Capsule formulation in a typical patient
- Covariate Analysis
- relationship between plasma exposure and butyrylcholinesterase activity
- relationship between plasma exposure and adverse events

Sparse Sampling (Study 2330-Phase 3): Linear regression was used

- Describe the relationship of steady-state concentrations of rivastigmine (ENA713) and its main metabolite NAP226-90 with dose, patient demographics and baseline laboratory values.
- Explore the relationship between key efficacy and safety measures and steady-state concentrations of ENA713 and NAP226-90.

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	11	11	
I. Clinical Pharmacology				
Mass balance:	-	-		
Isozyme characterization:	-	-		
Blood/plasma ratio:	-	-		
Plasma protein binding:	-	-		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	6	6	Evaluating permeation, adhesion, skin irritation, photo allergy etc
multiple dose:	X	1	1	
Patients-				
single dose:	-	-	-	
multiple dose:	X	1	1	Multidose information is also obtained from the Phase III study and two Phase 2 studies
Dose proportionality -				
fasting / non-fasting single dose:	-	-		
fasting / non-fasting multiple dose:	X	1	1	This study also compares the patch to the capsule dosage form and is conducted in patients
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	-	-		
In-vitro:	-	-		
Subpopulation studies -				

ethnicity:	X	2	2	Caucasian and Japanese
gender:	-	-		Evaluated in population analysis
pediatrics:	-	-		
geriatrics:	-	-		Relative BA study was done in elderly (patch vs. capsules)
Renal impairment:	-	-		Evaluated in population analysis
Hepatic impairment:	-	-		Evaluated in population analysis
PD:		-		
Phase 2:	X	2	2	
Phase 3:	X	1	1	
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:	X	1	1	
Population Analyses -				
Data rich:	X	1	1	
Data sparse:	X	1	1	
II. Biopharmaceutics				
Absolute bioavailability:	-	-		
Relative bioavailability -				
solution as reference:	X	1	1	
alternate formulation as reference:	**X**	1	1	Comparison to capsule in the dose proportionality study Also evaluates application site differences
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:	-	-		
Food-drug interaction studies:	-	-		
Dissolution:	X	1	**1**	
(IVIVC):	-	-		
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies	-	-		
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**13**	**9 PK+ 1 PK/PD+ 1 POP PK+ 4 ASSAY+ 1 dissolution**	

Filability and QBR comments				
I.	**"X" if yes**	Comments		
II. Application filable?		Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
III. Comments sent to firm? **IV.**	**X**	1. The NONMEM control streams and output files should be submitted as text files for Modeling report for Study 2331.		
QBR questions (key issues to be considered)	• How does the bioavailability from the patch compare to the approved capsule and oral solution dosage form? • Are the different patch sizes dose proportional? • Are there any application site differences for the patch? • Is the permeation, adhesion, contact irritation etc characterized for the patches? • What are the differences in metabolism from dermal and oral routes? • How can one switch from the oral to dermal route of administration?			
Other comments or information not included above				
Primary reviewer Signature and Date	Veneeta Tandon			
Secondary reviewer Signature and Date	Ramana Uppoor			

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Veneeta Tandon
6/14/2007 02:05:49 PM
BIOPHARMACEUTICS

Atul Bhattaram
6/14/2007 02:31:00 PM
BIOPHARMACEUTICS

Yaning Wang
6/14/2007 11:06:15 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
6/15/2007 06:58:57 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
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OCP Reviewer	**Veneeta Tandon**	**Indication(s)**	**Dementia of Alzheimers type (AD) and Parkinson's type (PDD)**
OCPB Team Leader	**Ramana Uppoor**	**Dosage Form**	**5, 10 [redacted] cm^2 patches** b(4)
		Dosing Regimen	**Start with patch 5, after 4 weeks can increase to patch 10 [redacted]** b(4)
Date of Submission	**9/8/06**	**Route of Administration**	**Topical**
Estimated Due Date of OCP Review	**5/8/07**	**Sponsor**	**Novartis**
PDUFA Due Date	**7/8/07**	**Priority Classification**	**Standard**
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- Delivery rate

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- relationship between plasma exposure and adverse events

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	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	11		
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Mass balance:	-	-		
Isozyme characterization:	-	-		
Blood/plasma ratio:	-	-		
Plasma protein binding:	-	-		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	6	-	Evaluating permeation, adhesion, skin irritation, photo allergy etc
multiple dose:	X	1	-	
Patients-				
single dose:	-	-	-	
multiple dose:	X	1	-	Multidose information is also obtained from the Phase III study and two Phase 2 studies
Dose proportionality -				
fasting / non-fasting single dose:	-	-		
fasting / non-fasting multiple dose:	X	1		This study also compares the patch to the capsule dosage form and is conducted in patients
Drug-drug interaction studies -				

In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	-	-		
In-vitro:	-	-		
Subpopulation studies -				
ethnicity:	X	2		Caucasian and Japanese
gender:	-	-		Evaluated in population analysis
pediatrics:	-	-		
geriatrics:	-	-		Relative BA study was done in elderly (patch vs. capsules)
Renal impairment:	-	-		Evaluated in population analysis
Hepatic impairment:	-	-		Evaluated in population analysis
PD:		-		
Phase 2:	X	2		
Phase 3:	X	1		
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:	X	1		
Population Analyses -				
Data rich:	X	1		
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:	-	-		
Relative bioavailability -				
solution as reference:	X	1		
alternate formulation as reference:	**X**	1		Comparison to capsule in the dose proportionality study Also evaluates application site differences
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:	-	-		
Food-drug interaction studies:	-	-		
Dissolution:	X	1		
(IVIVC):	-	-		
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies	-	-		
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**13**		

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?	**X**	1. The NONMEM control streams and output files should be submitted as text files for Modeling report for Study 2331.		
QBR questions (key issues to be considered)	• How does the bioavailability from the patch compare to the approved capsule and oral solution dosage form? • Are the different patch sizes dose proportional? • Are there any application site differences for the patch? • Is the permeation, adhesion, contact irritation etc characterized for the patches? • What are the differences in metabolism from dermal and oral routes? • How can one switch from the oral to dermal route of administration?			
Other comments or information not included above				
Primary reviewer Signature and Date	Veneeta Tandon			
Secondary reviewer Signature and Date	Ramana Uppoor			

Table 3-1 Summary of key pharmacokinetic studies

Study No.	Study Objective, Population	No. of Subjects	Treatment Duration	Medication dose/day	Parameters (primary)
Healthy volunteers					
2332	Relative bioavailability study, single dose, patch vs. Exelon® oral solution, males and females	48*: 21M/27F	Single dose	10 cm^2 (18 mg) patch vs. 3 mg Exelon® oral solution	C_{max}, t_{max}, AUC_{24h}, AUC_∞
2335	Ethnic sensitivity study (Japanese vs. Caucasians), single dose, males	20 (Cauc.): 20M/0F 19 (Jap.): 19M/0F	Single dose	5 cm^2 (9 mg), 7.5 cm^2 (13.5 mg), 10 cm^2 (18 mg), 15 (27 mg) cm^2	C_{max}, t_{max}, AUC_{0-t}, AUC_∞, Ae
2338	Relative bioavailability: Effect of application site, single dose, males and females	40: 17M/23F	Single dose	10 cm^2 (18 mg) patch	C_{max}, t_{max}, AUC_{0-t}, AUC_∞
1101	Multiple dose study in Japanese subjects, males	24: 24M/0F	Multiple doses	5 cm^2 (9 mg), 7.5 cm^2 (13.5 mg), 10 cm^2 (18 mg)	C_{max}, t_{max}, AUC_{24h}, Ae

Study No.	Study Objective, Population	No. of Subjects	Treatment Duration	Medication dose/day	Parameters (primary)
AD Patients					
2331	Dose proportionality study, multiple doses, rivastigmine patch vs. Exelon® oral capsules, males and females	51: 37M/14F	Multiple doses	5 cm^2 (9 mg), 10 cm^2 (18 mg), 15 cm^2 (27 mg), 20 cm^2 (36 mg) 1.5, 3, 4.5, 6 mg b.i.d.	C_{max}, t_{max}, AUC_{24h}, AUC_τ
1201	Phase IIa Study of rivastigmine patch in Japanese patients with mild to moderate dementia of Alzheimer's type (MMSE10-20), males and females	64: 17M/47F	Multiple doses	5 cm^2 (9 mg), 7.5 (13.5 mg), 10 cm^2 (18 mg), 15 cm^2 (27 mg), 20 cm^2 (36 mg)	Steady-state concentrations
2320	24-week, multicenter, randomized, double-blind, placebo- and active (Exelon® capsule)-controlled, parallel-group study, males and females	1195**: 398M/792F	Multiple doses	5 cm^2 (9 mg), 10 cm^2 (18 mg), 15 cm^2 (27 mg), 20 cm^2 (36 mg) 1.5, 3, 4.5, 6 mg b.i.d.	Steady-state concentrations

Reference: [Synopses of Individual Studies] [Tabulations of all Clinical Studies]

Description
Study W155: A randomized, open-label, five-period, cross-over study evaluating the adhesive properties, pharmacokinetics, local skin irritation, safety and tolerability of five different formulations of SDZ ENA 713 Transdermal Delivery System (TDS) in non-patient, male volunteers
Study W159: A study to evaluate adhesiveness of five formulations of SDZ ENA 713 transdermal delivery system (TDS) and two application sites employing an Estraderm placebo reference in healthy male volunteers.
Study W160: An open-label study evaluating the potential of SDZ ENA 713 Transdermal Delivery System to induce contact irritation and/or allergic sensitization after repeated applications to non patient volunteers
Study 2333: A study of the phototoxic potential of 7.5 cm2 ENA713 transdermal patch when administered to the skin of healthy subjects.
Study 2334: A study on the photoallergy potential of the ENA713 transdermal patch when administered to the skin of healthy subjects.
Study 1101: Phase I multiple application study of Exelon patch in Japanese young healthy male volunteers

Population Pharmacokinetic Study Reports
Study 2320: Modeling report. A 24-week, Multicenter, Randomized, Double-blind, Placebo- and Active-controlled, Parallel-group Evaluationof the Efficacy, Safety, and Tolerability of the Once-daily Exelon Patch Formulation in Patients with Probable Alzheimer's Disease (MMSE 10-20): Pharmacokinetic and Pharmacokinetic/Pharmacodynamic Analysis
Study 2331: Modeling report. Population pharmacokinetics of ENA713 and NAP226-90 in patients with mild-to-moderate Alzheimer's Disease treated with transdermal Patches or Capsules

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/s/

Veneeta Tandon
12/12/2006 12:25:23 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
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