CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-083

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Rivastigmine
PRODUCT (Brand Name):	EXELON PATCH
NDA:	22-083
DOSAGE FORM:	Transdermal Patch
DOSAGE STRENGTHS:	5, 10, b(4)
INDICATION:	**Treatment of dementia of Alzheimer's type (AD) and Parkinson's type (PDD)**
NDA TYPE:	1S
SUBMISSION DATES:	9/8/06, 1/22/07
SPONSOR:	Novartis
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1.0 EXECUTIVE SUMMARY

Exelon® (rivastigmine) is a slowly reversible inhibitor of both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE).

Exelon® Patch is a new, once-daily, transdermal patch formulation of rivastigmine free base. The proposed indications of this Exelon transdermal patch are:
1. **The symptomatic treatment of mild to moderately severe Alzheimer's disease (AD)**
2. The symptomatic treatment of mild to moderately severe dementia associated with **Parkinson's disease (PD)**

Currently two rivastigmine formulations are approved and marketed worldwide, Exelon® capsule and the bioequivalent oral solution. Exelon® Patch is a line extension proposed for the same indications as that approved for the oral products. Exelon® Patch is proposed to be marketed in strengths/sizes: 5 cm^2, 10 cm^2, [redacted], with a rivastigmine dose of 9 mg, 18 mg [redacted], respectively. About 50% of the drug load is released in each case. b(4)

Exelon transdermal patches, with once-a-day dosing and without the need for oral administration with food, are intended to offer the advantage of improved caregiver and patient convenience which may lead to improved patient compliance. In addition this formulation would be useful for patients with swallowing difficulties who are unable to take oral medication.

1.1 RECOMMENDATION

The Office of Clinical Pharmacology/Division of Clinical Pharmacology I (OCP/DCP-1) has reviewed NDA #22-083.

OCP finds this application acceptable provided that labeling recommendations by the Agency on page 50 of the review are accepted by the sponsor.

The following comment should be sent to the sponsor:

The sponsor proposed dissolution method and specifications are acceptable for quality control. When major changes are made in the future, in vivo biostudies will be required.

1.2 OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

In all the clinical studies a total of 440 healthy volunteers (of whom 44 were Japanese) and 1374 Alzheimer's Disease patients were administered Exelon® Patch of various strengths. Most studies were done with the Final Marketing Image (FMI), except two clinical pharmacology studies. Throughout this review the Exelon® Patches are also referred to as ENA713 or rivastigmine patches.
The findings from overall clinical pharmacology and biopharmaceutics section are as follows:

Exposure-Response for Effectiveness:
According to the sponsor the primary efficacy results showed that both the 10 cm^2 and the 20 cm^2 were superior to placebo at week 24 for ADAS-Cog (based on simultaneous testing of ADAS-cog and ADCS-CGIC in the ITT (LOCF) population). The ADAS-Cog were numerically higher for the Exelon 20 cm^2 group than for the Exelon 10 cm^2 and Exelon capsule groups suggesting a dose response between the two Exelon patch size groups. Age, gender, race and body weight did not influence the effectiveness.
The relationship between measures of efficacy and exposure (steady-state plasma concentrations of rivastigmine) showed the following results:

- ADAS-Cog: The reduction (i.e. improvement) in ADAS-Cog score from baseline to Week 24 tended to be larger for increased exposure to rivastigmine (linear regression: $p = 0.07$).
- ADCS-CGIC: An increased ADCS-CGIC response rate (defined as marked, moderate, or minimal improvement at week 24 compared to baseline) was shown with increased exposure to rivastigmine (logistic regression: $p = 0.04$).
- ADCS-ADL and NPI: No relationship was found with these clinical endpoints.

Exposure-Response for Safety:
The common adverse events were nausea, vomiting and dizziness.
The incidence of adverse events in the Exelon 20 cm^2 group was similar to that in the Exelon Capsule group. The overall incidences of adverse events were lower in the Exelon 10 cm^2 group. No clear relationship was observed between drug exposure (steady state concentrations) and adverse events.

General Pharmacokinetics (ADME characteristics):
Absorption: Absorption of rivastigmine from the patch was slow with a lag time of approximately 0.5 - 1 h after the first application. Concentrations subsequently increased slowly, typically reaching a plateau close to maximum at approximately 8 h, although Tmax typically occurred between 8-26 hours, with mean usually around 14-16 hours across studies.

Distribution: Rivastigmine is weakly (approximately 40%) bound to plasma proteins.

Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily via esterase-mediated hydrolysis of the carbamate moiety to the phenolic metabolite NAP226-90 and its sulfate conjugate following oral administration to animals and man. NAP226-90 is considered to be pharmacologically inactive. Rivastigmine has a low affinity for cytochrome P450 enzymes. Lower metabolite-to-parent AUC_{24h} ratio (3 to 5-fold) was observed after dermal compared to oral administration, indicating that much less metabolism occurred after dermal compared to the oral treatment. There were no indications of dermal metabolism either.

Elimination: Major pathway of elimination is via the kidneys. Rivastigmine was mainly excreted in urine as the sulfate conjugate of NAP226-90 (renal clearance was 13 – 25 L/h, CV = 19-37%). Approximately 3% of the rivastigmine dose was excreted unchanged in urine following patch, administration.
The plasma elimination half-life ($t_{½}$) of rivastigmine after multiple 24-hour 20 cm^2 patch applications in AD patients was 3.4 ± 0.7 h (CV = 22%).

Single dose and multiple dose pharmacokinetics:
The pharmacokinetics of rivastigmine was time in variant. Steady-state plasma concentrations of rivastigmine were achieved at the second day of dosing dose level in accordance with the short half-life of rivastigmine. The accumulation factor was 1.02 for the Exelon 10 cm^2 patch.

Dose proportionality: Rivastigmine exhibits nonlinear pharmacokinetics following both oral and intravenous administrations because of capacity-limited elimination. The patch formulation also displays nonlinear rivastigmine pharmacokinetics which, however, was less pronounced than with the oral formulation.

Pharmacokinetics in patients: The pharmacokinetics of rivastigmine and NAP226-90 are similar in the AD patients and healthy volunteers when given the same patch size applied to the same body site.

Special Populations:

Renal Impairment: No new studies have been conducted with Exelon patches in subjects with renal impairment. Based on population analysis creatinine clearance did not show any clear effect on rivastigmine steady state concentrations
Hepatic Impairment: No new studies have been conducted with Exelon patches in subjects with hepatic impairment. Based on population analysis SGOT and SGPT did not show any clear effect on rivastigmine steady state concentrations (p=0.12 and 0.19 respectively).
Age:

Elderly: Population analysis of the pivotal clinical trial, showed that the steady state concentrations of rivastigmine was not influenced by age (p=0.72)
Pediatrics: Exelon patch was not investigated in children or adolescents.
Gender: Based on a population analysis, gender (107 males and 203 females) did not affect the steady state concentrations of rivastigmine (p=0.78)
Race: No meaningful race effect was observed.

Drug-drug Interactions:
No new drug interaction studies were conducted with Exelon Patch.

Biopharmaceutics:

Relative bioavailability to oral solution: Under both normalized and unmormalized condition the Exelon FMI 10 cm^2 patch had higher exposure than the 3 mg solution. The normalized C_{max} (for amount of drug delivered from the patch per kg body weight) achieved by Exelon FMI 10 cm^2 patch was about 30% of the C_{max} achieved by the 3 mg ENA713 oral solution. The normalized AUC_{last} and AUC_{∞} achieved by 10 cm^2 patch were 261 and 250% (based on geometric mean) or 327 and 307% (based on arithmetic mean), respectively, of the 3 mg ENA713 oral solution.

Relative bioavailability to oral Capsule:
The relative bioavailaibility to the oral capsule was not conducted in a crossover study, but was obtained from a parallel design.
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. Modeling and simulation have shown that the exposure after 10 cm^2 patch is approximately equivalent to the exposure after 6 mg b.i.d capsules.

Relative bioavailability at different application sites:
Taking the upper back application site as the reference site (since upper back was used as the application site in most clinical pharmacology studies conducted), the chest, abdomen, outer thigh, and upper arm application sites achieved 100%, 80%, 71%, and 92%, respectively, of exposure (AUC_{∞}) achieved by the upper back application site.
Bioequivalence: The Final Marketing Image was used in the pivotal clinical trial (Study 2320) and many of clinical pharmacology studies. All strengths of the patches have been used in these studies, hence a bioequivalence study is not needed in this case.

Food Effect: Because of the dermal route of administration, no food effect study was conducted with the rivastigmine patch.

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)

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2.0 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

2.1.1 Drug/Drug Product Information:

Dosage Form/Strengths: Transdermal patch formulation of rivastigmine free base.

Patches	rivastigmine base dose load	rivastigmine base *in vivo* release rates per 24 h
Exelon Patch 5	9 mg	4.6 mg
Exelon Patch 10	18 mg	9.5 mg
[redacted]		

b(4)

Indication: -Treatment of mild to moderate dementia of the Alzheimer's type
- Treatment of mild to moderate Parkinson's disease dementia

Dosage and administration (Sponsor's Proposed): Once a day.

Pharmacologic Class: Anticholinesterase

Chemical Name: ((S)-N-ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenylcarbamate. ENA713 is the Novartis internal code for rivastigmine

Other Names: ENA713

Physical Characteristics: A viscous, clear and colorless to yellow to very slightly brown liquid, sparingly soluble in water and very soluble in ethanol, acetonotrile, n-octanol and ethyl acetate.

Mechanism of action: Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by

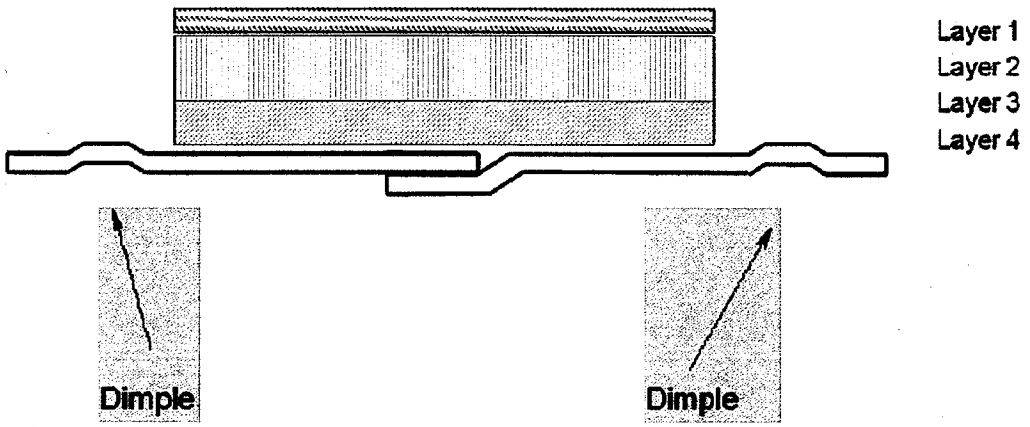
functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson's disease. Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes.

Formulation: Exelon® Patch will be available in packages of 30 patches in different sizes: 5 cm^2, 10 cm^2 b(4)

Exelon® Patches are circular patches delivering rivastigmine for transdermal administration. They are intended to be worn for one day and then replaced by a new patch. The different strengths that are manufactured from the same four layer laminate consist of beige colored backing film, drug product (acrylic) matrix, adhesive (silicone) matrix, and protective release liner. The drug substance is

A diagrammatic representation is shown in Figure 1. The description of the patches is presented in Table 1.

Figure 1: Diagrammatic representation of ENA713 9mg/5cm^2, 18mg/10cm^2, transdermal patch b(4)



Layer 1 = Backing film
Layer 2 = Drug product (acrylic) matrix
Layer 3 = Adhesive (silicone) matrix
Layer 4 = (Protective) release liner b(4)

Table1: Composition of ENA713 9mg/5cm^2, 18mg/10cm^2, [redacted] transdermal patch b(4)

Ingredient	Amount [per 10cm2]	Function	Reference to standards
Acrylic matrix solution (Drug product matrix):			
[redacted]			Internal monograph Ph. Eur., USP Internal monograph Internal monograph Ph. Eur., USP
Silicone adhesive solution (Adhesive matrix):			b(4)
[redacted]			Internal monograph USP Ph. Eur., USP Ph. Eur., USP
Polymeric films			
[redacted]			Internal monograph Internal monograph Internal monograph Internal monograph
[redacted]			b(4)

Patches only differ in the amount of drug loaded in each, which is strictly proportional to the patch surface.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the clinical studies used to support dosing or claims and what are their design features?

Dementia of the Alzheimer's type (mild to moderately severe)

The efficacy and safety of Exelon patches has been investigated in 549 patch-treated patients with AD in one pivotal study and open label extension of this study.

The initial dose selection was based on a phase II study (Study 0401), which was an open-label study to evaluate the adhesiveness, skin irritation, safety and tolerability of different sizes of the final formulation of Exelon patch in patients with mild to moderately severe AD. Patients commenced treatment at an Exelon patch size of 10 cm^2 per day. On the basis of acceptable tolerability, the Exelon patch size was subsequently increased in 5 cm^2 increments at 2 week intervals to a maximum patch size of 20 cm^2 per day. Efficacy was not evaluated in this study. Only one of the 64 patients was down-titrated to a 5 cm^2 patch size as a result of tolerability problems with the initial 10 cm^2 patch. The study also demonstrated that approximately 70% of the patients were able to achieve an
Exelon patch size of 20 cm^2. To further reduce the incidence of tolerability problems in the pivotal efficacy study[Study 2320] an initial patch size of 5 cm^2 per day with any subsequent up-titration at 4 week intervals in increments of 5 cm^2 was chosen by the sponsor.

The following is a tabulation of the controlled and uncontrolled efficacy studies to support the indication of treatment of dementia of the AD type.

Controlled studies:

Study No.	Study objective, population	Planned patients	Treatment duration	Dosage	Efficacy endpoint
2320*	Efficacy, safety, and tolerability of Exelon Patch in patients with probable AD (MMSE 10-20)	1040**	24 weeks	• Exelon® patch size titrated from 5 to 10 cm2 • Exelon® patch size titrated from 5 to 10, 15, and 20 cm2 • Exelon® capsule titrated from 3 to 6, 9 and 12 mg/day • Matching placebo	Primary: ADAS-Cog, ADCS-CGIC Secondary: ADCS-ADL, NPI (including NPI-D), MMSE, Ten Point Clock Test, Trail Making Test (Part A)

* study 2320 was both placebo-controlled and active-controlled

**1195 patients were enrolled to provide 1040 evaluable patients, N=303 patch 20 cm^2, N=291 pact 10 cm^2, N-=294 capsules, N=302 placebo

Uncontrolled studies

Study No.	Study objective, population	Patients enrolled	Treatment duration	Dosage	Efficacy endpoint
1201	Efficacy, safety, and tolerability of Exelon Patch in Japanese patients with mild to moderate AD	64	24 week	• Exelon® patch size titrated from 5 to 10, 15, and 20 cm2 • Exelon® patch size titrated from 5 to 7.5 to 10, 15, and 20 cm2	Primary: None Secondary: change from baseline at Week 24 for ADAS-J Cog and MMSE
2320E1	Long-term efficacy, safety, and tolerability of Exelon patch in patients with probable AD (MMSE 10-20)	632	28 week	• Exelon® patch size titrated from 10 to 15 to 20 cm2	ADAS-Cog, ADCS-CGIC, ADCS-ADL, NPI (including NPI-D), MMSE, Ten Point Clock Test, Trail Making Test (Part A)

Dementia associated with Parkinson's Disease (mild to moderately severe)
The efficacy and safety of Exelon patches in patients with PDD have not been investigated in a clinical study. The sponsor's proposal for this indication is based in the following:

- 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.

2.2.2 What are the clinical end points and how are they measured in clinical pharmacology and clinical studies?

The clinical endpoint used for the evaluation of effectiveness is described below:

Primary endpoints:

Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog): The ADAS is a performance-based test that measures specific cognitive and behavioral dysfunctions in patients with AD. The cognitive subscale of the ADAS (ADAS-Cog) comprises 11 items that are summed to a total score ranging from 0 to 70, with lower scores indicating less severe impairment (improvement).

Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC): The ADCS-CGIC scale provides a single global rating of change from baseline. An independent rater conducts separate semi-structured interviews with the patient and caregiver and, based on this information, determines the global rating of change from baseline using the 7-point ADCS-CGIC scale (range 1 - 7, where 1 - 3 indicates improvement, 4 unchanged and 5 - 7 worsening).

Secondary endpoints:

Alzheimer's Disease Cooperative Study-Activities of Daily Living-(ADCS-ADL): The ADCS-ADL is a caregiver-based ADL scale composed of 23 items developed for use in dementia clinical studies. It is designed to assess the patient's performance of both basic and instrumental activities of daily living such as those necessary for personal care, communicating and interacting with other people, maintaining a household, conducting

hobbies and interests, as well as making judgments and decisions.

Neuropsychiatric Inventory (NPI and NPI-D): The NPI assesses a wide range of behavioral problems encountered in dementia patients. Ten behavioral problems and two neurovegetative domains are evaluated through an interview with the caregiver by a mental health professional. The scale includes both frequency and severity ratings from each domain as well as a composite domain score (frequency x severity). The sum of the composite scores for the 12 domains yields the NPI total score. The NPI-D provides a measure of the distress experienced by caregivers in relation to the individual symptom domains assessed by the NPI. The NPI-D rating ranges from 0 (not at all distressing) to 5 (very severe or extremely distressing) for each domain.

Mini-Mental State Examination (MMSE): The MMSE is a brief, practical screening test for cognitive dysfunction. The test consists of five sections (orientation, registration, attention-calculation, recall, and language) and results in a total possible score of 30, with higher scores indicating better function.

Ten Point Clock Test: This test measures executive functioning and visuospatial skills. A maximum of ten points is awarded for drawing the numbers and hands of a clock correctly on a circle.

Trail Making Test (Part A): The TMT part A has been shown to be a sensitive indicator of the presence of brain injury. The basic task of trail-making is to connect a series of numbers, in a specified order as quickly as possible. The score derived for the test is the number of seconds required to complete the task. The test is used to assess attention, visual search and motor speed. A higher score indicates more impaired attention.

2.2.3 What are the characteristics of exposure/effectiveness relationships?

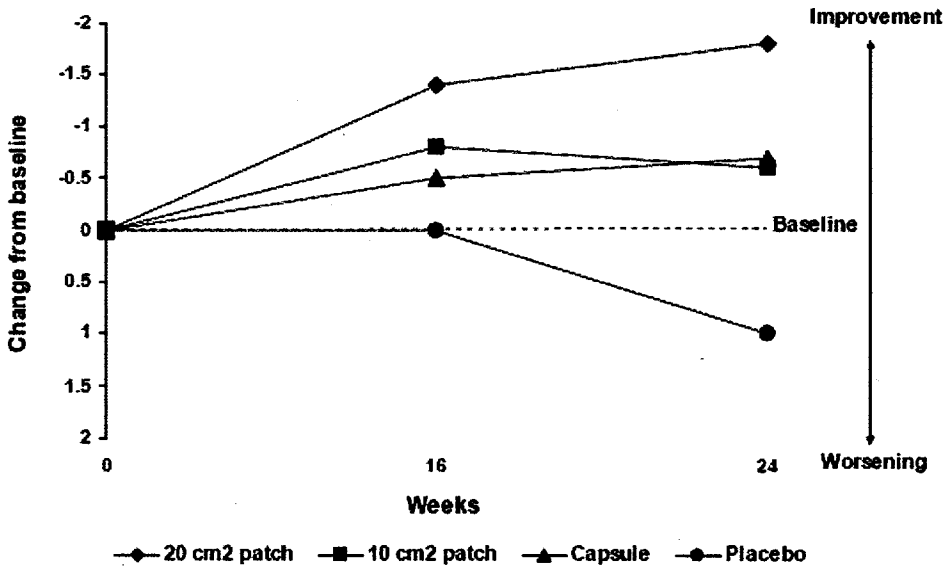
According to the sponsor the primary efficacy results showed that both the 10 cm^2 and the 20 cm^2 were superior to placebo at week 24 for ADAS-Cog (based on simultaneous testing of ADAS-cog and ADCS-CGIC in the ITT (LOCF) population (see p-values in the Table below). The p-value for ADCS-CGIC marginally exceeded the predefined significance level of 0.05, by 0.004.

		Variable	
	Objective	ADAS-Cog	ADCS-CGIC
1	Superiority of Exelon 20 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	$p < 0.001$	$p = 0.054$
2	Superiority of Exelon 10 cm^2 target patch size over placebo at Week 24, based on ADAS-Cog and ADCS-CGIC (simultaneous testing)	$p = 0.005$	$p = 0.010$

The ADAS-Cog were numerically higher for the Exelon 20 cm^2 group than for the Exelon 10 cm^2 and Exelon capsule groups suggesting a dose response between the two Exelon patch size groups.

In addition, the improvement in the target Exelon 20 cm^2 patch group at week 16 achieved statistical significance relative to placebo(p=0.007), but not for 10 cm^2 patch (p=0.09), i.e earlier time to response for the 20 cm^2 patch. The ADAS-Cog change from baseline for all the treatments at week 16 and 24 is shown in the following Figure:

Figure: ADAS-Cog change from baseline by treatment group



The efficacy of the 10 cm^2 patch was comparable to the currently marketed 6 mg b.i.d (12 mg/day) capsules). This similarity was observed in ADAS-cog, ADCS-CGIC and ADCS-ADL scales.
In addition, the responder rates for the 20 cm^2 patch at week 24 were consistently greater than the 10 cm^2 patch group (Table below).

Table: Overall responder analysis - ITT (LOCF) population

Visit		Exelon 20 cm^2	Exelon 10 cm^2	Exelon capsule	Placebo
Week 16	N	250	241	244	271
	n (%)	50 (20.0)	35 (14.5)	39 (16.0)	39 (14.4)
	p-value	0.129	0.952	0.598	
Week 24	N	257	242	248	276
	n (%)	52 (20.2)	42 (17.4)	47 (19.0)	29 (10.5)
	p-value	0.003*	0.037*	0.004*	

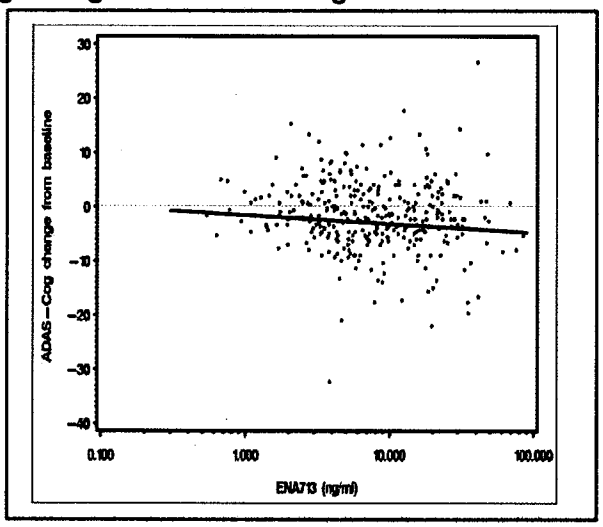
Overall responders are defined as patients with ADAS-Cog improvement of at least 4 points and ADCS-CGIC categories 1-4 (any improvement or no change) and ADCS-ADL change ≥ 0 points (no change or improvement)
p-values are derived from CMH test blocking for country and are based on pairwise comparisons of the Exelon and placebo treatment groups
* $p < 0.05$

Age, gender, race and body weight did not influence the effectiveness.

The relationship between efficacy and drug exposure was explored for 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. A single plasma concentration measurement of rivastigmine and its metabolite was available at steady state.
The relationship between measures of efficacy and exposure (steady-state plasma concentration of rivastigmine) showed the following results:

- ADAS-Cog: The reduction (i.e. improvement) in ADAS-Cog score from baseline to Week 24 tended to be larger for increased exposure to rivastigmine (linear regression: p = 0.07). A doubling of rivastigmine exposure was estimated to correspond to an incremental decrease of ADAS-Cog from baseline to Week 24 by 0.5 points.

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

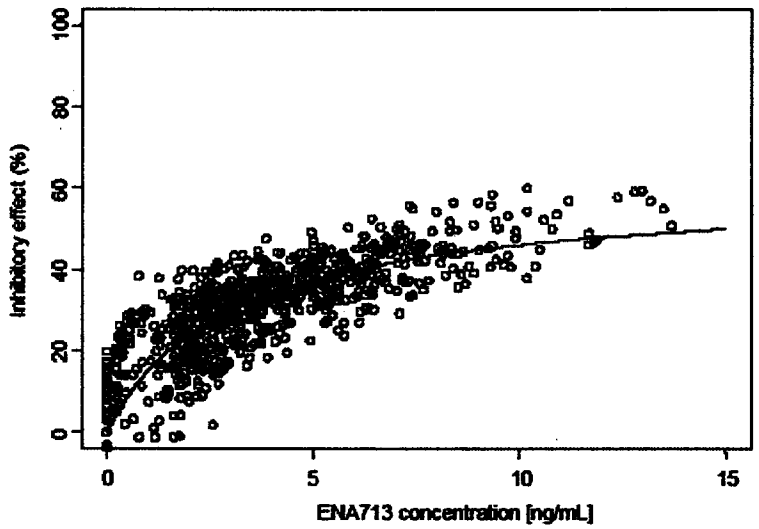


Negative ADAS-Cog change from baseline indicates improvement

- ADCS-CGIC: An increased ADCS-CGIC response rate (defined as marked, moderate, or minimal improvement at week 24 compared to baseline) was shown with increased exposure to rivastigmine (logistic regression: p = 0.04). A doubling of rivastigmine exposure was estimated to increase the odds for response by 20%.
- ADCS-ADL: No relationship was found between ADCS-ADL change from baseline to Week 24 and rivastigmine exposure (linear regression: p = 0.82).
- NPI: No clear relationship was found between NPI change from baseline to week 24 and rivastigmine exposure (linear regression: p = 0.20).

The sponsor also evaluated the relationship between the plasma concentrations of rivastigmine and inhibitory effects on Butylcholinesterase (BuChE) activity and showed that the inhibitory effect increased with increase of rivastigmine 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 (see Figure below)

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



2.2.4 What are the characteristics of exposure-safety relationships?

The common side effects were nausea, vomiting and dizziness.
According to the sponsor:

- Nausea and vomiting ocuured at similar rates in the Exelon 20 cm^2 patch and the 6 mg b.i.d capsules. In the Exelon 10cm^2 patch the incidence of nausea and vomiting was approximately one third of that of Exelon 20 cm^2 patch.
- Dizziness was more common in the Exelon 20 cm^2 patch and the 6 mg b.i.d capsules. In the Exelon 10cm^2 patch, dizziness was comparable to placebo
- There were no major age- or sex-related effects on the incidence of AEs following Exelon patch treatment.
- Exelon patch-treated patients with low weight at baseline (≤ 50 kg) experienced more AEs and discontinuations due to AEs than patients who were > 50 kg at baseline. This was particularly notable for patients in the target Exelon patch 20 cm^2 group.

The relationship between these common 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 (steady-state concentrations) 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

2.5.4 Are the proposed dosage regimens adequately supported by the clinical trial and consistent with the dose-response relationship and how does this compare to the oral Exelon regimen?

Dementia of the Alzheimer's type (mild to moderately severe)

Yes, the proposed dose and dosage regimen for dementia of Alzheimer's type seem adequate from a clinical pharmacology perspective and the pivotal clinical trial was done using the proposed regimen. However, the risk-benefit at the higher dose will be evaluated by the reviewing Medical Officer. [redacted]

b(4)

The following dosing regimen is proposed for the Exelon Patch:

Initial Dose	one Exelon Patch 5 once daily
Maintenance Dose	one Exelon Patch 10 once daily

b(4)

A dose-response was seen between the 10 and 20 cm^2 patches, as described in the previous sections.

The dosing regimen for oral administration of rivastigmine is as given below:

- For dementia of Alzheimer's type: 6-12 mg/day given as BID (3 to 6 mg BID): with increments every 2 weeks

It should be noted that the exposures with the 15 and 20 cm^2 patches are higher than that seen with the highest recommended dose for the capsules (6 mg BID)

Dementia of the Parkinson's Disease (mild to moderately severe)

Similar dosing regimen as dementia for Alzheimer's type is proposed for the dementia assoaciated with Parkinson's Disease, however no clinical studies were conducted in this disease state.

The dosing regimen for oral administration of rivastigmine is as given below:

- For dementia associated with Parkinson's disease: 3-12 mg/day given as BID (1.5 to 6 mg BID) with increments every 4 weeks

The sponsor's proposal for this indication is based in the following:

- 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.

Although, it should be noted that the sponsor is proposing doses higher than the Exelon Patch 10 cm^2 patches; i.e patches 15 and 20 cm^2 patches as well for both AD and PDD. These are doses higher than that evaluated for the capsule dosage form. It should also be noted that strict pharmacokinetic equivalence between the Exelon patch 10 and 6 mg b.i.d

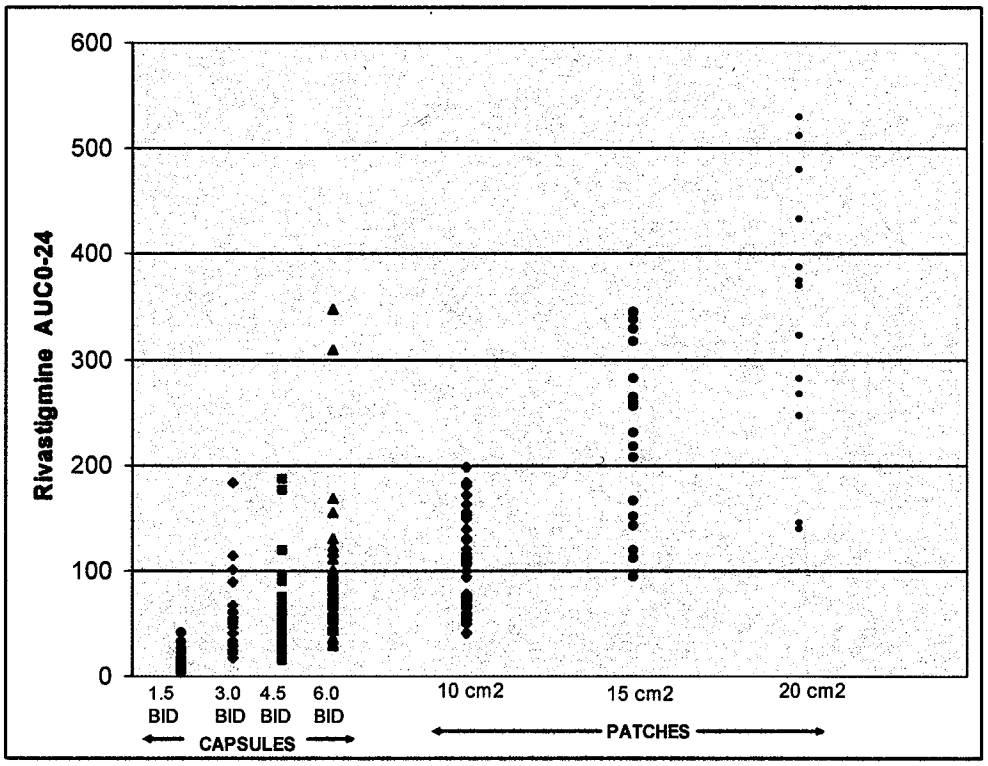
capsule has not been shown. However, exposures do seem to be in the range of the 6 mg b.i.d capsules.

Modeling and simulation showed that exposure from a Patch of size 10 cm^2 was approximately equivalent to the exposure from a Capsule strength of 6 mg b.i.d. (i.e. 12 mg per day). Therefore the 20 cm^2 patch will give exposure higher (equivalent to 18-20 mg per day according to the simulation, however, this should be viewed with caution as an extention of the capsule data than actually observed was needed to obtained the equivalence at a higher patch strength) than that currently found with the approved dosing regimen for the capsules.
The benefit-risk ratio in this patient population and the acceptability of similar patho physiology in the AD and PDD patient population will be assessed by the Medical Officer.

From a Pharmacokinetic perspective:

From a pharmacokinetic perspective, the following figure shows that the 10 cm^2 patch gives exposures (AUC0-24) similar to the 6 mg BID capsule. The exposure from the 4.5 mg BID capsule tended to be lower in most subjects. Based on the mean data, it appeared that the 4.5 mg BID dose had a mean that was closer to the 10 cm^2 patch, but taking into account the inter individual variability, the 6 mg BID exposure is similar to the 10 cm^2 patch.

Figure: Comparison of ENA713 AUC0-24 for 1.5, 3, 4.5 and 6 mg BID Capsule doses and 10, 15 and 20 cm^2 Patch based on actual pharmacokinetic data from Study 2331



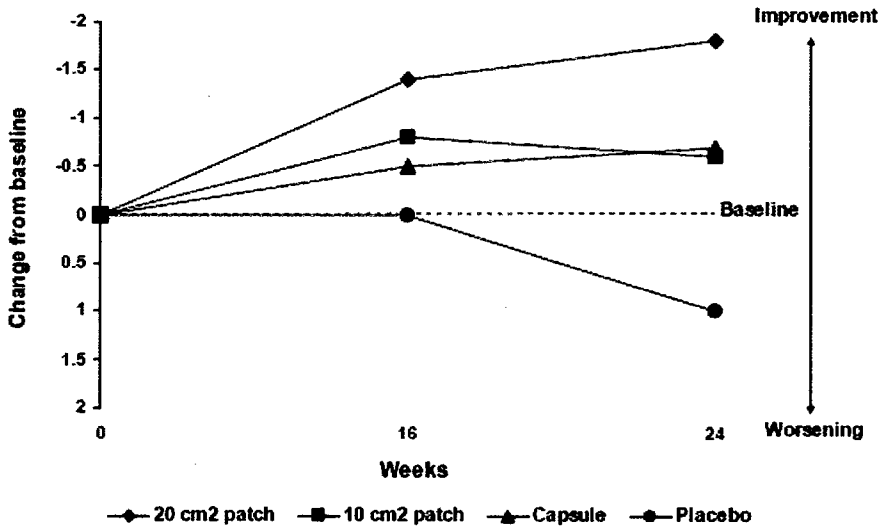
The sponsor has also conducted modeling and simulation that suggests that the 10 cm^2 patch has exposure similar to the 6 mg BID capsules. Therefore sponsor's simulations from the model derived parameters are supported by the actual observed PK data.

The sponsor's dosing recommendation on switchability of < 6 mg/day oral rivastigmine dose to a 5 cm^2 patch and for patients on 6-12 mg/day oral dose to switch to a 10 cm^2 patch is also acceptable. Clearly exposures from the 15 and 20 cm^2 patches are higher than the currenty approved doses of oral rivastigmine.

From an effectiveness perspective:

From an effectiveness perspective also, the 10 cm^2 patch had similar effectiness in Alzheimer's disease patients to the capsule arm in which most subjects were titrated up to the 12 mg/day dose (6 mg BID), as seen in the following Figure for ADAS-Cog scores. Similar comparisons were also seen from the ADCS-CGIC and ADCS-ADL scores:

Figure: ADAS-Cog change from baseline by treatment group



How the Dementia in Alzheimer's Disease model compares to the dementia in Parkinson's disease will be evaluated by the Medical officer. The benefit-risk ratio of the higher doses in this patient population will also be evaluated by the Medical Officer.

2.5.5 Does rivastigmine prolong QT or QTc interval?

Accroding to the sponsor, ECG findings did not indicate clinically meaningful abnormalities associated with Exelon treatment. ECG findings indicated that Exelon treatment was associated with an expected slight reduction in heart rate and increased RR interval. The decreases in heart rate, and increases in RR and PR intervals were slightly more pronounced in the target 20 cm^2 patch size group relative to the other active

treatment groups. However, these more pronounced effects in the higher dose patch group did not translate into greater increases in clinically notable abnormalities than were evident in other active treatment groups (with the exception of T-wave abnormalities).

2.5.6 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the parent rivastigmine and the metabolite NAP226-90 are adequately assessed in the plasma and the urine. In the early Clinical Pharmacology studies (W155, W159, C153 and C152) plasma concentrations of rivastigmine and its metabolite NAP226-90 were determined using a specific GC/MS method with [redacted]. b(4)

In the latter clinical studies (D2331, D2332 and D2320), plasma concentrations of rivastigmine and its metabolite NAP226-90 were determined using a validated selective HPLC-MS/MS. Both these methods were cross validated. The HPLC-MS/MS method was transferred to another site and cross-validation was also done between the two sites. For details please refer to the analytical validation section of this review in Appendix 1.

The assay validation parameters rivastigmine and metabolite NAP226-90 in plasma for the HPLC-MS/MS method is given below:

Linearity: 0.20-30 ng/ml for rivastigmine and NAP226-90
LLOQ: 0.2 ng/ml for rivastigmine and NAP226-90
Interday Precision: % CV within 2.8-8.7 % for rivastigmine and 3.1-11.8 % for NAP226-90
Interday Accuracy: within -9.4 to -4.9 % for rivastigmine and -5.9-0% 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: 113-118% for rivastigmine and 84-93% for NAP226-90

2.2.8 What are the general ADME characterstics of Exelon Patch?

The key ADME characteristics of Exelon Patch are summarized below:

Absorption:

- Absorption of rivastigmine from the patch was slow with a lag time of approximately 0.5 - 1 h after the first application. Its metabolite NAP226-90 appeared with a lag time of 1.2-2.6 hours. Based on population PK analysis the lag time after the patch was 42 minutes and for NAP226-90, the lag time was 1.5 hours.
- Concentrations subsequently increased slowly, typically reaching a plateau close to maximum at approximately 8 h, although Tmax typically occurred between 8-22 hours, with mean usually around 14-16 hours across studies.
- After the peak concentration, the plasma concentration of rivastigmine decreased gradually over the remaning 24 hours.
- The absolute bioavailability of rivastigmine after application of the rivastigmine patch was not studied.

Distribution:

- Rivastigmine is weakly (approximately 40%) bound to plasma proteins.
- It readily crosses the blood-brain barrier.
- The apparent volume of distribution is 1.8-2.7L/kg.

Metabolism:

- Rivastigmine is extensively metabolized, primarily via esterase-mediated hydrolysis of the carbamate moiety to the phenolic metabolite NAP226-90 and its sulfate conjugate following oral administration to animals and man.
- NAP226-90 is considered to be pharmacologically inactive.
- Rivastigmine has a low affinity for cytochrome P450 enzymes.
- No unique metabolic routes were detected in human skin in vitro. There is virtually no esterase activity in the skin; only low activity of P450-type enzymes is present. The results indicate that rivastigmine is not subject to significant dermal metabolism and that the transdermal route reduces, if not totally avoids, first pass metabolism.
- Lower metabolite-to-parent AUC_{24h} ratio (3 to 5-fold) was observed after dermal compared to oral administration.(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)

Elimination:

- Major pathway of elimination is via the kidneys. Rivastigmine was mainly excreted in urine as the sulfate conjugate of NAP226-90 (renal clearance was 13 –

25 L/h, CV = 19-37%). Approximately 3% of the rivastigmine dose was excreted unchanged in urine following patch, administration.

- The plasma elimination half-life ($t_{½}$) of rivastigmine after multiple 24-hour 20 cm_2 patch applications in AD patients was 3.4 ± 0.7 h (CV = 22%). Elimination was absorption rate limited, resulting in a longer $t_{½}$ compared with oral or i.v. administration (1.4 - 1.7 h). Estimation of $t_{½}$ was also likely to be confounded with some diffusion of rivastigmine from the skin into plasma after removal of the patch.
- Renal clearance of rivastigmine (based on oral data) was approximately 2.0 - 4.2 L/h (CV = 24 - 44%).

2.2.9 What are the basic pharmacokinetic parameters of rivastigmine after single and multiple doses?

Single Dose Pharmacokinetics:

The single dose pharmacokinetic parameters of rivastigmine and its metabolite after a single 24 hour application of the 5, 7.5, 10 and 15 cm^2 patches Final Marketing Image (FMI) is given in the following Table:

Table: Summary of single dose pharmacokinetic parameters (± SD(CV)) of rivastigmine after a single 24 hour application of patch in healthy subjects (study 2335, n = 20)

	Caucasian			
Parameter (unit)	5 cm^2 (n= 20)	7.5 cm^2 (n=12)	10 cm^2 (n=20)	15 cm^2 (n=3)
C_{max} (ng/mL)	2.76 ± 1.23 (44.6)	3.99 ± 1.47 (36.8)	7.29 ± 3.79 (52.0)	12.9 ± 4.27 (33.1)
$C_{max,norm}$ [(ng/mL)/(mg/kg)]	37.5 ± 12.0 (32.0)	39.9 ± 9.33 (23.4)	48.4 ± 20.5 (42.4)	57.6 ± 14.4 (25.0)
t_{max} (h)	12.0 [3.00-24.08]	14.0 [6.00-24.08]	12.0 [6.00-24.08]	10.03 [8.00-16.0]
AUC_{0-24h} (ng·h/mL)	45.6 ± 18.3 (40.1)	66.1 ± 26.3 (39.8)	119 ± 58.3 (49.0)	204 ± 71.9 (35.2)
$AUC_{0-24h,norm}$ [(ng·h/mL)/(mg/kg)]	624 ± 187 (30.0)	655 ± 181 (27.6)	794 ± 322 (40.6)	916 ± 270 (29.5)
AUC_{last} (ng·h/mL)	50.3 ± 19.2 (38.2)	76.7 ± 28.1 (36.6)	136 ± 63.9 (47.0)	237 ± 81.2 (34.3)
AUC_{∞} (ng·h/mL)	52.4 ± 18.9 (36.1)	77.5 ± 27.9 (36.0)	137 ± 63.8 (45.6)	239 ± 81.1 (33.9)
$AUC_{\infty,norm}$ [(ng·h/mL)/(mg/kg)]	723 ± 191 (26.4)	773 ± 192 (24.8)	918 ± 354 (38.5)	1080 ± 314 (29.1)
$t_{½}$ (h)	2.69 ± 0.73 (25.3)	2.10 ± 0.18 (8.6)	2.25 ± 0.28 (12.4)	2.50 ± 0.37 (12.8)
Vz/F (L)	453 ± 213 (47.0)	303 ± 112 (37.0)	284 ± 110 (38.7)	296 ± 98.4 (33.2)
Vz/F_{norm} (L/kg)	6.33 ± 2.89 (45.7)	4.23 ± 1.38 (32.6)	3.97 ± 1.39 (35.0)	4.15 ± 1.24 (29.9)
CL/F (L/h)	105 ± 29.9 (28.5)	97.9 ± 29.3 (29.9)	85.3 ± 25.9 (30.4)	69.9 ± 17.1 (24.5)
CL/F_{norm} (L/h/kg)	1.47 ± 0.38 (25.9)	1.37 ± 0.35 (25.5)	1.20 ± 0.33 (27.5)	0.98 ± 0.21 (21.4)

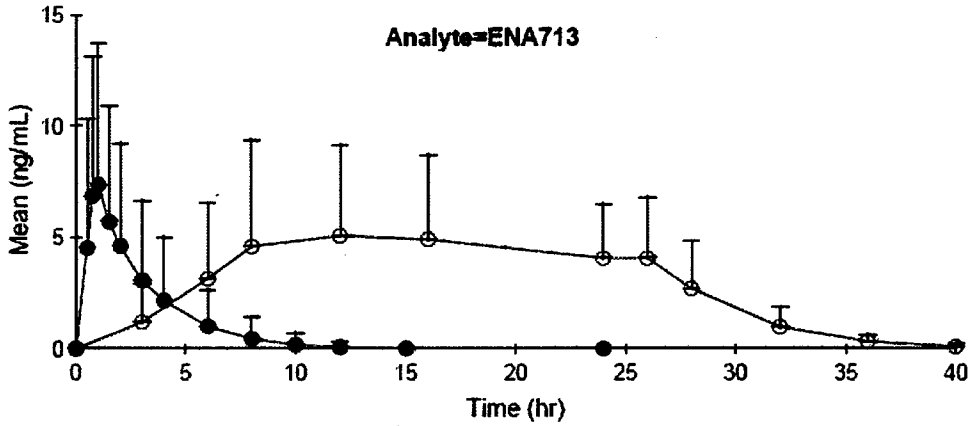
Table: Summary of single dose pharmacokinetic parameters (± SD(CV)) of NAP226-90 after a single 24 hour application in healthy subjects (study 2335, n = 20)

Parameter (unit)	Caucasian 5 cm^2 (n= 20)	7.5 cm^2 (n=12)	10 cm^2 (n=20)	15 cm^2 (n=8)
C_{max} (ng/mL)	1.64 ± 0.69 (42%)	2.45 ± 1.08 (44%)	3.70 ± 1.51 (41%)	6.65 ± 2.30 (35%)
$C_{max,norm}$ [(ng/mL)/(mg/kg)]	22.3 ± 5.89 (26%)	24.2 ± 66.87 (28%)	24.7 ± 6.65 (27%)	29.4 ± 6.57 (22%)
t_{max} (h)	12.00 [8.00-16.00]	12.00 [6.00-26.00]	12.00 [8.00-25.00]	12.04 [12.00-16.00]
AUC_{0-24h} (ng·h/mL)	25.9 ± 11.0 (41%)	40.2 ± 17.1 (43%)	62.0 ± 24.3 (39%)	103 ± 35.1 (33%)
$AUC_{0-24h,norm}$ [(ng·h/mL)/(mg/kg)]	366 ± 93.5 (26%)	399 ± 109 (27%)	415 ± 106 (26%)	477 ± 94.8 (20%)
AUC_{last} (ng·h/mL)	32.5 ± 11.6 (36%)	52.6 ± 18.9 (36%)	79.8 ± 26.3 (33%)	142 ± 39.7 (28%)
AUC_{∞} (ng·h/mL)	35.7 ± 11.3 (32%)	54.6 ± 18.6 (34%)	81.6 ± 26.3 (32%)	144 ± 39.4 (27%)
$AUC_{\infty,norm}$ [(ng·h/mL)/(mg/kg)]	491 ± 87.5 (18%)	550 ± 125 (23%)	552 ± 116 (21%)	645 ± 98.0 (15%)
$t_{½}$ (h)	5.06 ± 1.04 (21%)	5.27 ± 1.83 (35%)	4.13 ± 0.57 (14%)	4.31 ± 0.62 (14%)
$AUC_{metabolite}/AUC_{parent}$	0.70 ± 0.14 (20%)	0.74 ± 0.18 (24%)	0.65 ± 0.17 (26%)	0.63 ± 0.16 (25%)

Single dose pharmacokinetics with the Exelon 20 cm^2 patch is not available.

The plasma concentration time profile after a single 10 cm^2 patch is shown in the following figure:

Figure: Rivastigmine plasma concentrations (mean +/- SD) following single dermal (o.d.) patch application (open circles)



○—10 cm^2 (FMI) transdermal patch ●—single 3 mg Exelon oral solution

Multiple Dose Pharmacokinetics:

Two Clinical Pharmacology studies were conducted using repeated dose administrations. One study [Study 2331] was conducted in AD patients with 14 day application of rivastigmine patches 5 to 20 cm^2.

The other study [Study 1101] was conducted in Japanese healthy male volunteers given repeated daily applications for 5 days of rivastigmine patch of 5, 7.5 and 10 cm^2.

Both studies used a continous application of the patches with no washout between treatments. Study 1101 also had the pharmacokinetic profile taken at the beginning of each period.

Rivastigmine and NAP226-90 exposure at steady state after a 14 day application of the Final Marketing Image (FMI) patch is given in the following Tables. In this study PK profile at the beginning of each treatment was not taken.

The PK parameters after multiple dosing is given in the following Table:

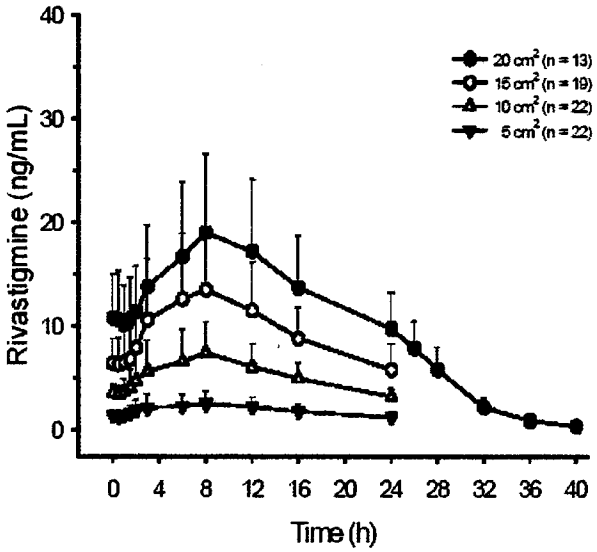
Table: Rivastigmine exposure parameters following rivastigmine multiple o.d. patch applications in AD patients (study 2331)

Rivastigmine	C_{max} (ng/mL)	t_{max} (h)	$C_{av,g}$ (ng/mL)	AUC_{24h} (ng·h/mL)	$t_{½}$ (h)	FI *
5 cm^2 (9 mg loaded dose, n = 22)						
Mean ± SD	2.71 ± 1.23	-	1.93 ± 0.718	46.3 ± 17.2	-	0.58 ± 0.40
CV%	45.2	-	37.2	43.2	-	69.2
Median	2.57	8.0	1.98	47.6	-	0.61
Range	1.19-5.39	0.0-12.08	0.718-1.98	20.0-81.4	-	0.00-1.17
Geo. mean	2.45	-	1.80	43.2	-	-
CV% Geo. mean	49.7	-	40.7	40.7	-	-
10 cm^2 (18 mg loaded dose, n = 22)						
Mean ± SD	7.88 ± 2.88	-	5.29 ± 1.73	127 ± 41.4	-	0.77 ± 0.32
CV%	36.6	-	32.6	32.6	-	42.2
Median	7.79	8.0	5.40	129	-	0.76
Range	2.76-12.9	3.0-16.0	2.43-8.25	41.4-198	-	0.15-1.26
Geo. mean	7.32	-	4.99	120	-	0.69
CV% Geo. mean	43.1	-	38.1	38.1	-	57.4
15 cm^2 (27 mg loaded dose, n = 19)						
Mean ± SD	14.1 ± 6.30	-	9.71 ± 3.47	233 ± 83.2	-	0.72 ± 0.36
CV%	44.6	-	35.7	35.7	-	50.5
Median	15.3	8.0	10.6	255	-	0.61
Range	4.32-25.7	3.0-16.0	3.89-14.4	93.3-345	-	0.08-1.30
Geo. mean	12.6	-	9.03	217	-	0.60
CV% Geo. mean	55.4	-	42.9	42.9	-	81.3
20 cm^2 (36 mg loaded dose, n = 13)						
Mean ± SD	19.5 ± 7.51	-	14.4 ± 5.28	345 ± 127	3.37 ± 0.73	0.57 ± 0.35
CV%	38.4	-	36.7	36.7	21.7	62.3
Median	20.7	8.0	15.4	370	3.08	0.63
Range	7.55-33.7	0.0-12.0	5.83-22.0	140-529	2.61-5.02	0.00-1.12
Geo. mean	18.1	-	13.3	320	3.30	-
CV% Geo. mean	44.8	-	45.3	45.2	20.2	-

- = not available or not applicable; * FI = fluctuation index

The amplitude between trough and peak plasma concentrations of rivatigmine (as measured by fluctuation index) was 60-80% after the patch.

Figure: Rivastigmine plasma concentrations (mean +/- SD) following multiple dermal (o.d.) patch applications for 14 days



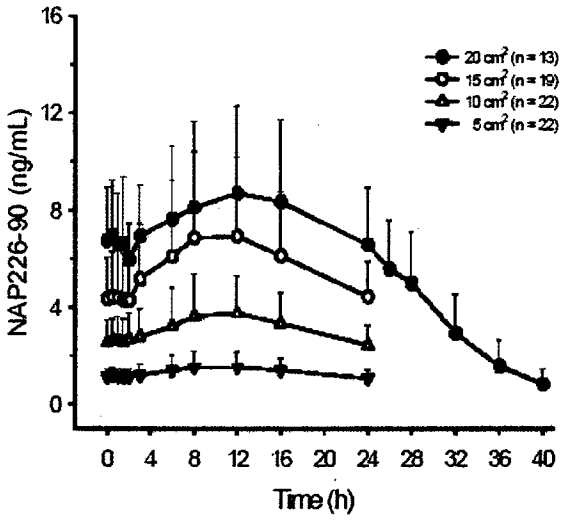
The PK parameters of the metabolite is given in the following Table:

Table: NAP226-90 exposure parameters following rivastigmine multiple o.d. patch applications in AD patients (study 2331)

NAP226-90	C_{max} (ng/mL)	C_{ss} (ng/mL)	t_{max} (h)	AUC_t (ng·h/mL)	$t_{1/2}$ (h)	FI*	Metabolite-to-parent ratio**
5 cm² (9 mg loaded dose, n = 22)							
Mean ± SD	1.65 ± 0.633	1.34 ± 0.481	-	32.1 ± 11.5	-	0.34 ± 0.22	0.72 ± 0.17
CV%	38.5	35.9	-	35.9	-	64.7	23.0
Median	1.62	1.29	8.0	31.0	-	0.33	0.72
Range	0.959-3.16	0.815-2.63	0.5-16.0	19.6-53.2	-	0.03-0.77	0.45-1.18
Geo. mean	1.54	1.27	-	30.4	-	0.25	0.70
CV% Geo. mean	37.2	33.9	-	33.9	-	120	23.1
10 cm² (18 mg loaded dose, n = 22)							
Mean ± SD	4.05 ± 1.57	3.15 ± 1.18	-	75.5 ± 28.3	-	0.44 ± 0.29	0.62 ± 0.18
CV%	38.7	37.5	-	37.5	-	64.7	29.3
Median	3.92	3.01	12.0	72.2	-	0.41	0.61
Range	1.93-7.63	1.70-6.40	0.5-16.0	40.6-154	-	0.00-1.03	0.34-1.11
Geo. mean	3.78	2.97	-	71.2	-	-	0.60
CV% Geo. mean	39.7	35.7	-	35.7	-	-	30.0
15 cm² (27 mg loaded dose, n = 19)							
Mean ± SD	7.47 ± 3.48	5.78 ± 2.39	-	139 ± 57.4	-	0.47 ± 0.31	0.53 ± 0.27
CV%	46.6	41.3	-	41.3	-	64.8	42.0
Median	7.30	5.64	12.0	135	-	0.48	0.53
Range	2.59-14.9	2.29-9.88	0.00-23.92	55.0-237	-	0.00-0.94	0.23-1.51
Geo. mean	6.71	5.32	-	128	-	-	0.50
CV% Geo. mean	51.3	44.4	-	44.4	-	-	39.4
20 cm² (36 mg loaded dose, n = 13)							
Mean ± SD	9.28 ± 3.24	7.71 ± 2.82	-	186 ± 67.7	5.33 ± 2.23	0.29 ± 0.24	0.53 ± 0.30
CV%	35.0	36.6	-	36.6	41.8	80.3	49.7
Median	9.46	7.53	12.0	181	4.95	0.22	0.49
Range	5.31-15.5	4.10-12.6	0.5-16.25	98.3-332	2.55-12.3	0.01-0.65	0.32-1.37
Geo. mean	8.76	7.25	-	174	5.04	0.18	0.55
CV% Geo. mean	36.5	38.0	-	38.0	33.1	176	48.1

-: not available or not applicable; * FI = fluctuation index; ** AUC_t metabolite/AUC_t parent

Figure: NAP226-90 plasma concentrations (mean +/- SD) following multiple dermal (o.d.) patch applications for 14 days



Plasma rivastigmine and NAP226-90 indicated no apparent accumulation after 5-day multiple applications in patch sizes, 5 cm^2, 7.5 cm^2 and 10 cm^2 based on data from Study 1101.

The results of this study is given in the next question that describes the time in variance of the patch formulation, although this study was not done with the FMI.

2.2.10 Do the pharmacokinetic parameters change with time following chronic dosing (time invariance)?

The pharmacokinetics of rivatigine was time in variant. Steady-state plasma concentrations of rivastigmine were achieved at the second day after each dose level in accordance with the short half-life of rivastigmine, and no statistically significant difference between PK parameters was found after 5 days of repeated administration Study 1101.

The multiple dose pharmacokinetic parameters for rivastigmine and NAP226-90 is given in the following Table:

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

<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

No statistically significant difference between PK parameters was found after 3 or 14 days of repeated administration based on data evaluated for Study 2331, in which the 15 and 20 cm^2 patch treatment arms were stopped at Day 3 in some subjects.

The steady state average concentrations from Study 2331 after 14 day dosing was also compared to the Cavg ss from the pivotal clinical Study 2320 after 1 year of dosing and no differences in the steady state average plasma concentration was observed.

Table Comparison of NAP226-90 steady state average plasma concentrations for study ——713D2320 and ——713D2331

b(4)

Dose (mg)	Patch size (cm^2)	Study ——713D2331 estimates (95% confidence interval) in ng/mL	Study ——13D2320 estimates (95% confidence interval) in ng/mL for a patient with a body weight of 65 kg
9	5	1.4 (0.9 – 2.0)	2.0 (1.5 - 2.7)
18	10	3.4 (2.1 - 4.7)	3.1 (2.9 - 3.5)
			[illegible]
27	15	6.2 (3.8 - 8.5)	5.4 (4.0 - 7.2)
36	20	8.7 (5.3 -12.0)	7.6 (6.7 - 8.7)

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.

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

2.2.11 What is the variability in the PK data?

The inter- and intra-individual variability in C_{max} and AUC values of rivastigmine and its major metabolite NAP226-90 after administration of rivastigmine patch are summarized in the following Table for three Clinical Pharmacology studies conducted in healthy volunteers and using the FMI patch.

PK parameter	Study No.	Patch size (loaded dose)	Rivastigmine (%CV)[1]		NAP226-90 (%CV)[1]	
			Intra-	Inter-	Intra-	Inter-
C_{max}	ENA713DW159	10 cm^2 (18 mg)	19%	60%	-	-
	[redacted]713D2332	10 cm^2 (18 mg)	42%	59%	37%	37%
	[redacted]713D2338	10 cm^2 (18 mg)	34%	44%	-	-
AUC_{0-t}	ENA713DW159	10 cm^2 (18 mg)	18%	62%	-	-
	[redacted]713D2332	10 cm^2 (18 mg)	56%	80%	31%	34%
	[redacted]713D2338	10 cm^2 (18 mg)	42%	52%	-	-
AUC_∞	ENA713DW159	10 cm^2 (18 mg)	-	-	-	-
	[redacted]713D2332	10 cm^2 (18 mg)	53%	77%	30%	33%
	[redacted]713D2338	10 cm^2 (18 mg)	35%	45%	-	-

-: not available ; [1] CVs obtained from the multiplicative model.

b(4)

The variability in rivastigmine PK was lower after the patch than after the oral capsule or the oral solution formulation.

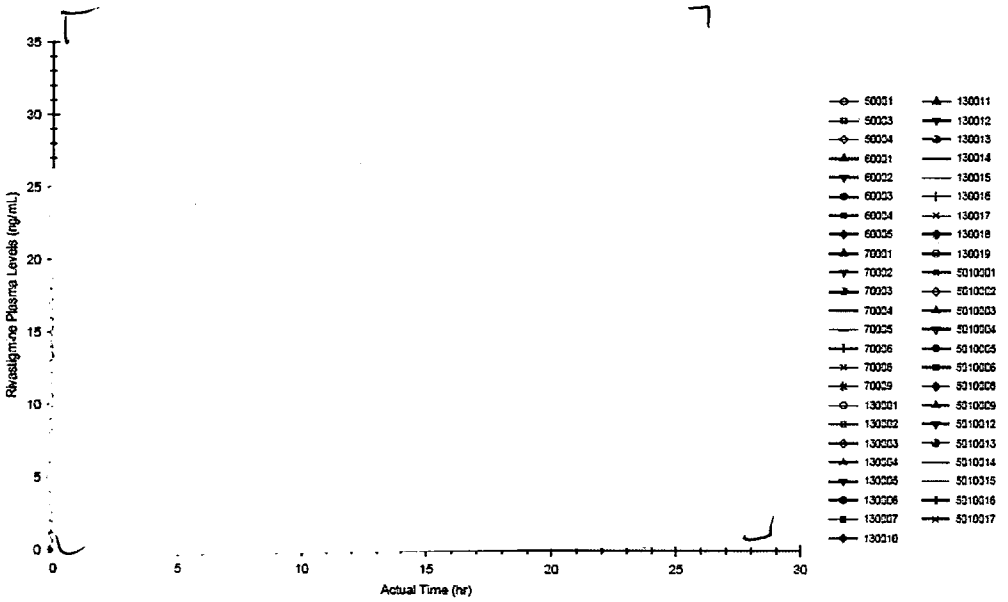
The inter-patient variability after the oral capsule formulation (Study 2331) was in the range 39-71% for C_{max} and 68-73% for AUC_{0-24h}, while it was in the range 37-45% and 33-43%, respectively, after the patches.

Similarly, the variability after the oral solution dose (Study 2332) was 74% for C_{max} and 103% for AUC_{0-24h} (both parameters normalized by dose/kg BW), while it was 43% and 49%, respectively, after the patch.

In all PK studies, except one (Study 0401) the plasma concentration profiles were well within this variability and no outliers were observed. Study 0401 was a Phase 2 study. Pharmcokinetic samples were taken from 47 patients on Day 1 after the application of a 10 cm^2 patch.

The % CV seen in this study was 93-99%, which is much higher than that observed in other studies. There were two subjects in this study that had concentrations that were relatively higher than the rest of the subjects (as seen in the Figure below). The safety implications of these high concentration in the two subjects is being evaluated by the Medical Officer. According to the sponsor there were no serious adverse events observed in these subjects.

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



b(4)

Such outliers were not observed in any other studies.

2.2.12 How do the pharmacokinetics of the drug in healthy volunteers compare to that in dementia patients?

The pharmacokinetics of rivastigmine and NAP226-90 are similar in the AD patients and healthy volunteers when given the same patch size applied to the same body site (upper back).

Rivastigmine exposure parameters C_{max} and AUC_{24h} measured in patients treated with the 10 cm^2 patch were 7.88 ± 2.88 ng/mL and 127 ± 41.4 ng·h/mL, respectively.
In healthy volunteers, these were 7.29 ± 3.79 ng/mL and 119 ± 58.3 ng·h/mL, respectively, in [study 2335] (n = 20), and 6.80 ± 3.20 ng/mL and 122 ± 54.9 ng·h/mL, respectively, in [study 2338] (n = 40). Comparing rivastigmine PK in single-dose studies [2335 and 2338] with the current multiple-dose study is adequate because there is no, or very little, accumulation of rivastigmine in plasma after multiple doses based on results of Study 1101 discussed earlier.

2.2.13 Based on the pharmacokinetic parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

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

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.

Based on a Power model for the assessment of dose proportionality, 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.

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.

2.2.14 What are the adhesive properties of the Exelon Patch?

Following scores was used to capture comments relating to patch adhesion:
0 = 90 % adhered (essentially no lift off of the skin)
1 = 75% to < 90% adhered (some edges only lifting off of the skin)
2 = 50% to < 75% adhered (less than half of the patch lifting off the skin)
3 = < 50% adhered but not detached (more than half the system lifting off of the skin without falling off)
4 = the patch was completely detached

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. Two patients had complete detachment (rating of 4) at 24 hours. In addition, 1 patient had his patch mostly detached (rating of 3) at 24 hours.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics? Based on what is known about exposure response relationships and their variability, is dosage adjustment needed for any of the subgroups?

The intrinsic factors have been discussed below:

2.3.1.1 Effect of Renal Impairment:

No new studies have been conducted with Exelon patches in subjects with renal impairment.
Based on population analysis creatinine clearance did not show any clear effect on rivastigmine steady state concentrations.

Dosage adjustment:
No dosage adjustment is necessary with oral Exelon as well as the patch.

2.3.1. 2 Effect of Hepatic Impairment:

No new studies have been conducted with Exelon patches in subjects with hepatic impairment.
Based on population analysis SGOT and SGPT did not show any clear effect on rivastigmine steady state concentrations (p=0.12 and 0.19 respectively).

Dosage adjustment:
No dosage adjustment is necessary for oral Exelon as well as the patch.

2.3.1. 3 Effect of age:

Elderly:

Population analysis of the pivotal clinical trial (Study 2320), showed that the steady state concentrations of rivastigmine was not influenced by age (p=0.72)

Dosage adjustment:
No dosage adjustment is necessary.

Pediatrics:

Exelon patch was not investigated in children or adolescents.

2.3.1.4 Effect of Gender:

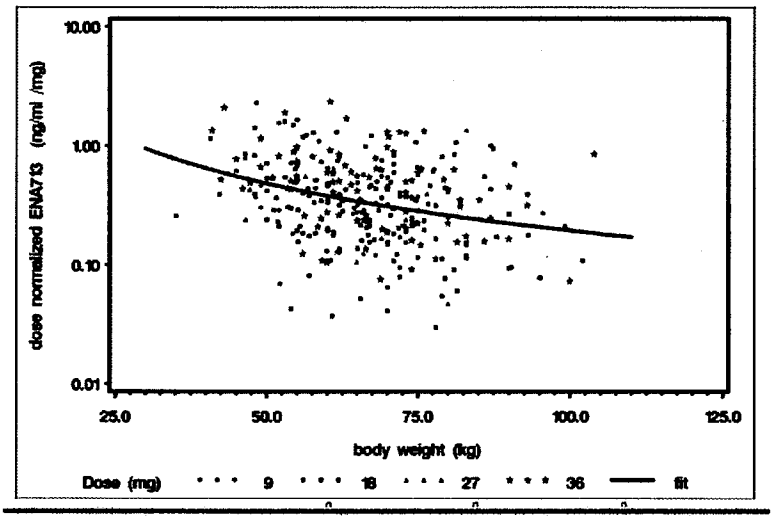
Based on a population analysis gender (107 males and 203 females) did not affect the steady state concentrations of rivastigmine (p=0.78)

Dosage adjustment:
No dosage adjustment is necessary.

2.3.1.5 Effect of Body Weight:

A clear relationship (p=0.0003, see following Figure) between rivastigmine exposure at steady state and bodyweight was observed in the large pivotal clinical trial in AD patients. Compared to a patient with a bodyweight of 65 kg, the rivastigmine steady-state concentrations in a patient with a bodyweight of 35 kg would be approximately doubled, while for a patient with a bodyweight of 100 kg the concentrations would be approximately halved. The steady-state concentrations of NAP226-90 were also clearly related to the patients bodyweight (p= 0.007). The effect of bodyweight on drug exposure suggests special attention to patients with very low bodyweight during up-titration.

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



Dosage adjustment:
No dosage adjustment is necessary, although caution should be exercised in titrating low body weight subjects to doses above 10 cm^2 patch.

2.3.1.6 Effect of Race:

Based on a pharmacokinetic study (#2335)

- No meaningful pharmacokinetic differences were apparent between Japanese and Caucasian subjects.
- The statistical evaluation showed that systemic exposure to rivastigmine was slightly higher in Japanese than in Caucasians. In contrast, for the rivastigmine's metabolite NAP226-90, Japanese had a slightly lower systemic exposure than Caucasians. After adjusting the statistical model for body weight, Japanese subjects had a lower exposure than Caucasians for both analytes.
- Japanese subjects showed higher inhibitory effect on BuChE. Although, the differences were not statistically significant. A possible reason for this finding could be the lower mean body weight for the Japanese compared to Caucasians.

Based on population analysis:
There appeared also to be a small effect of race (p=0.05) from the population anlaysis of the pivotal clinical study; however this seemed to be due to the 2 black patients, whose rivastigmine exposure was lower than the rest of the group. 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 population analysis on potential differences with respect to pharmacokinetics for black vs. non-black patients.

Dosage adjustment:
No dosage adjustment is necessary.

2.4 EXTRINSIC FACTORS

No new drug interaction studies are conducted with Exelon Patch.

2.4.1 Is rivastigmine a substrate, inhibitor or inducer of CYP enzymes?

Substrate: Rivastigmine is metabolized mainly through hydrolysis by esterases. Rivastigmine has a low affinity for cytochrome P450 enzymes.

Inhibitor: Rivatigmine is not an inhibitor of major CYP enzymes: 1A2, 2C8, 2C9/10, 2C19, 2D6, 2E1, 3A4/5

Inducer: Auto induction of esterases was not observed. Rivastigmine's ability to induce CYPs is not known.

2.4.2 Is rivastigmine a substrate and/or inhibitor of p-glycoprotein transport processes or any other transporter system?

This information is not known.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 What is the relative bioavailability of the Exelon Patch to the currently marketed products of rivastigmine; i.e capsule and solution dosage form?

Relative bioavailability to oral solution:
The relative bioavilability of a 24 hour application of Exelon Patch (FMI) 10 cm^2 (18 mg loaded dose) applied to the upper back was compared to the 3 mg oral solution in heathy elderly subjects (N=30) in a cross over study.

- Without normalization for dose, the 10 cm^2 patch produced a plasma exposure (AUC_∞) to rivastigmine 5.2 times higher than the single 3 mg oral solution dose, while the C_{max} of the patch was only 76.5% of that achieved with oral solution. Assuming that exposure after an evening oral dose is the same as after the morning dose, the exposure with once-daily dose of 10 cm^2 patch is expected to be 2.6 times higher than with a 3 mg bid (6 mg/day) dosing of oral solution.
- The normalized C_{max} (for amount of drug delivered from the patch per kg body weight) achieved by Exelon FMI patch was about 30% of the C_{max} achieved by the 3 mg ENA713 oral solution. The normalized AUC_{last} and AUC_∞ achieved by 10 cm^2 patch were 261 and 250% (based on geometric mean) or 327 and 307% (based on arithmetic mean), respectively, of the 3 mg ENA713 oral solution.
- The mean terminal elimination half-life of rivastigmine was 1.45 ± 0.43 h after administration of the oral solution and 3.02 ± 0.83 h after patch application.

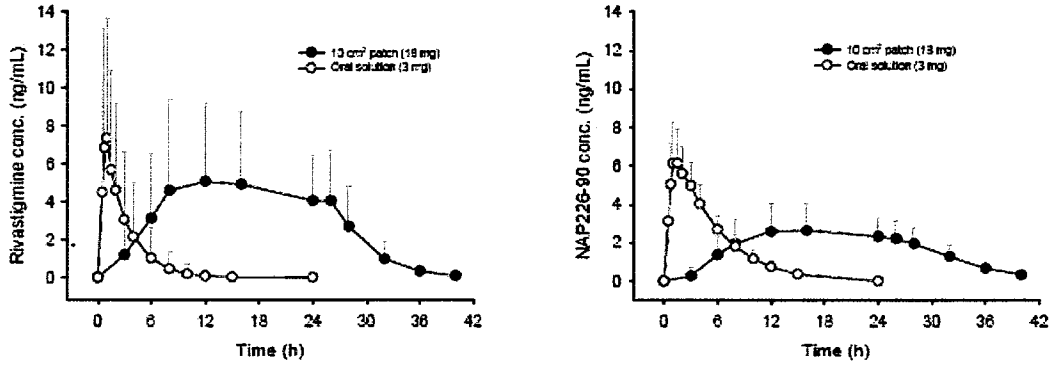
The relative ratios between the Exelon patch and the oral solution are summarized in the following Table:

Table: $C_{max,\ norm}$, $AUC_{0\text{-}24h,\ norm}$ $AUC_{last,\ norm}$ and $AUC_{\infty,\ norm}$ ratio for rivastigmine and NAP 226-90, (N=30)

Parameter	Test/Reference (Patch/Solution)	
	Rivastigmine	NAP 226-90
$C_{max,\ norm}$ ratio	0.353 ± 0.173 (49) [0.313]	0.165 ± 0.0599 (36) [0.155]
$AUC_{0\text{-}24h,\ norm}$ ratio	2.46 ± 1.87 (76) [1.93]	0.433 ± 0.144 (33) [0.410]
$AUC_{last,\ norm}$ ratio	3.27 ± 2.45 (75) [2.61]	0.661 ± 0.174 (26) [0.638]
$AUC_{\infty,\ norm}$ ratio	3.07 ± 2.13 (69) [2.50]	0.660 ± 0.166 (25) [0.639]

Values are mean ± SD (%CV) [geometric mean]

The comparative plasma concentration time profile for the Exelon Patch and solution is shown in the following Figure:



Relative bioavailability to oral Capsule:

A true relative bioavailability with the capsule formulation was not conducted. Instead in a parallel design the Exelon patch (5, 10, 15 and 20 cm^2) was compared to the oral capsule (1.5, 3, 4.5 and 6 mg BID) after 14 days of multiple dosing at each treatment level.

- 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 all patches 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)

The exposure parameters of the Exelon patch and capsule formulation is shown in the following Table:

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 cm^2 (9 mg loaded, n = 22)**		
Mean ± SD	3.34 ± 2.38	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	5.87	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 cm^2 (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	38.6	32.6	42.2
Median	8.71	51.8	3.76	7.79	129	0.76
Min-max	2.88-21.3	17.3-183	2.01-8.24	2.78-12.9	41.4-198	0.15-1.26
Geo. mean	8.48	47.7	3.79	7.32	120	0.69
CV% Geo. mean	58.8	68.8	29.7	43.1	38.1	57.4
	4.5 mg bid (9 mg per day, n = 19)			**15 cm^2 (27 mg loaded, n = 19)**		
Mean ± SD	16.8 ± 6.60	106 ± 76.7	4.10 ± 2.35	14.1 ± 6.30	233 ± 63.2	0.72 ± 0.36
CV%	39.3	72.3	57.3	44.6	35.7	50.5
Median	18.2	84.9	3.45	15.3	255	0.61
Min-max	5.44-27.0	41.2-362	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 cm^2 (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	3.56	20.7	370	0.63
Min-max	12.5-66.0	60.3-658	1.29-10.5	7.55-33.7	140-529	0.00-1.12
Geo. mean	28.9	160	3.59	18.1	320	-
CV% Geo. mean	44.6	65.3	59.5	44.8	45.2	-

-: not applicable

- *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. Fewer NAP226-90 was formed following patch administration, presumably because of the lack of presystemic (hepatic first pass) metabolism.

2.5.2. What is the relative bioavailability of rivastigmine from the Exelon Patch, when it is applied to different application sites?

Taking the upper back application site as the reference site (since upper back was used as the application site in most clinical pharmacology studies conducted), the chest, abdomen, outer thigh, and upper arm application sites achieved 100%, 80%, 71%, and 92%, respectively, of exposure (AUC_{∞}) achieved by the upper back application site.

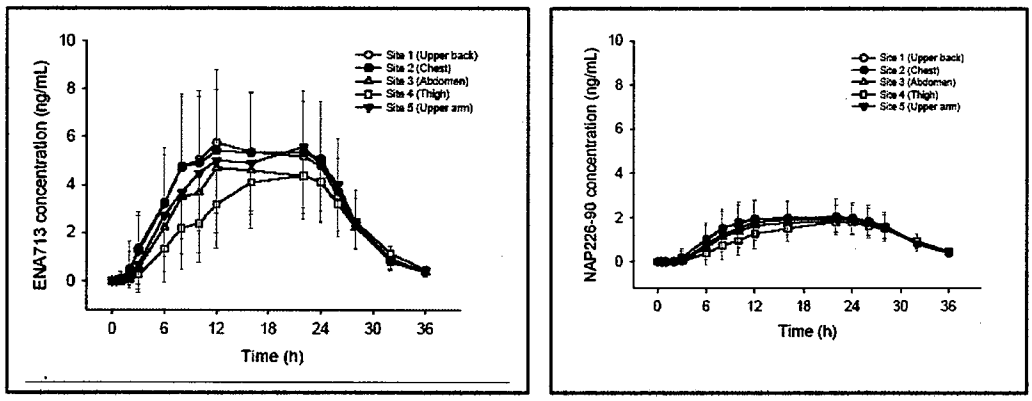
The relative bioavailability at different application sites was evaluated in a single dose crossover study, in which there was a 72 hour washout between two treatments (application site). The pharmacokinetic parameters at the various application sites are given in the Table below followed by the plasma concentration time profile:

Table: Summary of PK parameters (mean +/- SD)

Analyte	Site no.	C_{max} (ng/mL)	t_{max}* (h)	AUC_{last} (h•ng/mL)	AUC_{∞} (h•ng/mL)	$t_{½}$ (h)
rivastigmine	1 (Upper back)	6.80 ± 3.20	16.0 (8.0, 24.0)	122 ± 54.9	128 ± 51.7	3.21 ± 0.75
rivastigmine	2 (Chest)	6.34 ± 2.58	16.0 (8.0, 24.0)	123 ± 59.7	128 ± 57.7	3.35 ± 0.82
rivastigmine	3 (Abdomen)	5.44 ± 2.42	16.0 (6.0, 26.0)	101 ± 43.6	103 ± 44.0	3.37 ± 0.76
rivastigmine	4 (Thigh)	4.89 ± 1.91	22.0 (8.0, 26.0)	87.7 ± 37.6	91.0 ± 36.8	3.94 ± 2.30
rivastigmine	5 (Upper arm)	6.58 ± 2.69	16.0 (6.0, 26.0)	116 ± 41.8	118 ± 41.7	3.31 ± 0.82
NAP226-90	1 (Upper back)	2.27 ± 0.84	16.0 (8.0, 28.0)	48.7 ± 18.4	54.3 ± 15.1	5.08 ± 3.40
NAP226-90	2 (Chest)	2.26 ± 0.75	22.0 (10.0, 26.0)	49.3 ± 20.1	55.2 ± 19.0	5.08 ± 2.97
NAP226-90	3 (Abdomen)	1.99 ± 0.55	22.0 (8.0, 28.0)	43.4 ± 13.1	46.6 ± 13.5	4.78 ± 1.11
NAP226-90	4 (Thigh)	1.89 ± 0.56	22.0 (10.0, 26.0)	38.5 ± 13.9	43.8 ± 13.2	5.47 ± 1.99
NAP226-90	5 (Upper arm)	2.14 ± 0.61	22.0 (12.0, 28.0)	46.5 ± 14.6	50.3 ± 14.7	4.54 ± 1.06

* median (range)

Figure: Mean (+/- SD) plasma concentration-time plots of rivastigmine and NAP226-90 following single transdermal administration (10 cm^2, 18 mg rivastigmine) on different application sites



As seen, in the Table and figures above the abdomen and outer thigh sites showed reduced bioavailability as compared to the upper arm, chest and upper arm. The chest and upper arm were bioequivalent to the upper back. The descriptive results of relative bioavailability of rivastigmine from the patch was confirmed by statistical analysis and is summarized in the following Table.

Table: Summary of statistical analysis on relative bioavailability achieved by test application sites with the upper back application site as reference

PK Parameters	Patch site	N	Geometric Mean	Ratio of geometric mean	90% CI for ratio
AUC_{last} (ng·h/mL)	1 (Upper back)	35	113.53	--	--
	2 (Chest)	39	109.36	0.963	(0.825, 1.125)
	3 (Abdomen)	40	92.54	0.815	(0.698, 0.952)
	4 (Thigh)	39	77.80	0.685	(0.584, 0.804)
	5 (Upper arm)	39	109.87	0.958	(0.829, 1.130)
AUC_{∞} (ng·h/mL)	1 (Upper back)	35	117.55	--	--
	2 (Chest)	38	118.42	1.007	(0.883, 1.150)
	3 (Abdomen)	40	94.96	0.808	(0.708, 0.921)
	4 (Thigh)	39	82.69	0.703	(0.614, 0.806)
	5 (Upper arm)	39	113.60	0.966	(0.847, 1.102)
C_{max} (ng/mL)	1 (Upper back)	35	6.34	--	--
	2 (Chest)	39	5.97	0.942	(0.827, 1.073)
	3 (Abdomen)	40	5.01	0.79	(0.694, 0.900)
	4 (Thigh)	39	4.47	0.705	(0.616, 0.806)
	5 (Upper arm)	39	6.17	0.973	(0.854, 1.108)

The 90% CI of the ratio of geometric means for the bioavailability PK parameters (AUCs & Cmax) for the chest and upper arm applications are within the range required for showing bioequivalence (80-125%) with the upper back application site.

2.5.3 Is the proposed to-be-marketed formulation of rivastigmine patch bioequivalent to the formulation used in the clinical trials and pharmacokinetic studies?

The Final Marketing Image was used in the pivotal clinical trial (Study 2320) and many of clinical pharmacology studies. All strengths of the patches have been used in these studies, hence a bioequivalence study is not needed in this case.

2.5.4 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendations need to be made regarding the administration of Exelon Patch in relation to meals or meal types?

Because of the dermal route of administration, no food effect study was conducted with the rivastigmine patch.

The effect of food was similar with capsule and solution formulations, i.e. a slower rate of absorption (prolonged t_{max} by 90 min, and 30% reduced C_{max}) and a modestly increased exposure (AUC_∞) when compared with administration of rivastigmine under fasted state.

2.5.5 Was an IVIVC established for this product?

An IVIVC was not conducted with this product.

2.5.6 How do the dissolution/release rate conditions and specifications assure in vivo performance and quality of the product?

Proposed Dissolution Method

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

Proposed Specifications:

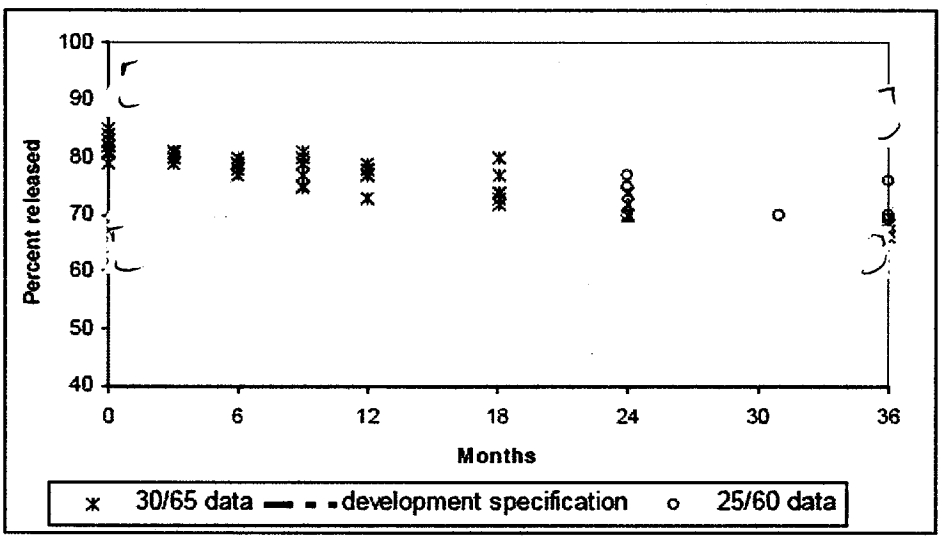
Time Points	Percent Released
2 hours	[redacted]
4 hours	
7 hours	

b(4)

These specifications although very wide were found acceptable for the following reasons:

- There is a trend towards decrease in in vitro release rate with increasing storage time. This was observed under both long-term (30°C/65%RH) and accelerated conditions (40°C/75%RH) (see the following Figure)

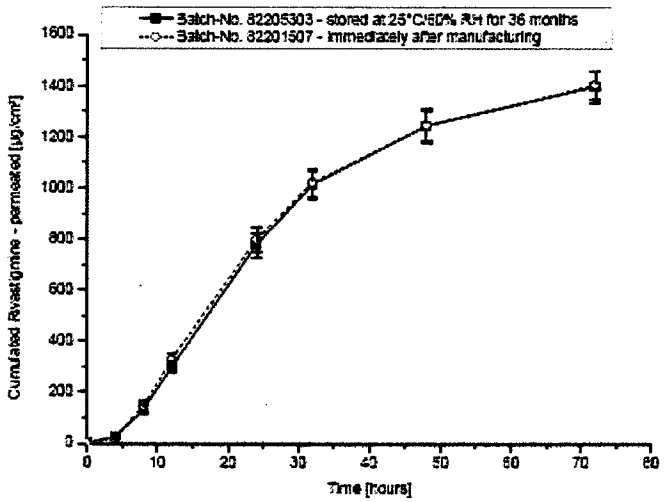
Figure: Drug release data at 7 hours (all batches, 30 degree Celsius/65 percent RH and 25 degree Celsius/60 percent RH, all time points)



b(4)

- However, no difference was found in the in-vitro human skin permeation assay, between newly manufactured transdermal patches and those which had been stored for 36 months at 25°C/60%RH (see figure below)

Figure: Human skin permeation results of ENA713 transdermal patches of different ages



- For Exelon 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. Therefore, in vitro dissolution in this case is a quality control test.

- More importantly the clinical/pharmacokinetic studies used patches that were manufactured 7-24 months before application. The exposures obtained from these patches at various times in the shelf life of product (i.e. 24 months) were similar and within the inter-individual variability seen in the studies (see Table below)

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 shows that although the in vitro release rate decreases upon storage, the in vivo exposures are not affected and that the in vitro dissolution test will mainly be used as a quality control tool

2.6 ANALYTICAL

2.6.1 What bioanalytical method is used to assess concentrations of active moieties and is the validation complete and acceptable?

The assay validation fro rivastigmine and metabolite NAP 266-90 in plasma and urine was adequate and acceptable. Cross validation between the methods was also conducted and was found acceptable. The analytical methods used to estimate rivastigmine and metabolite NAP226-90 in plasma were GC/MS and LC/MS/MS and that in urine was LC/MS/MS. These methods are summarized below.

Rivastigmine and NAP226-90 in plasma:

1. METHOD 1: GC/MS with electron impact ionization

The older studies utilized this method. The validation parameters are given below:

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

The more recent studies utilized this method.

Linearity: [redacted] ng/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
Interday Accuracy: within [redacted] % for 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.

b(4)

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

<u>Rivastigmine and NAP226-90 in urine</u>

METHOD: HPLC/MS/MS

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

3.0 DETAILED LABELING RECOMMENDATION

29 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.0 APPENDIX

4.1 APPENDIX I

4.1.1 INDIVIDUAL STUDY REVIEW

COMPARATIVE BA AND BE STUDIES

PATCH VS. ORAL SOLUTION:

Study 2332: ***A randomized open label, two-period, crossover study to compare the bioavailability of a single dose of 10 cm^2 (FMI) ENA713 transdermal patch with 3 mg dose of oral solution in healthy elderly subjects.***

Objectives:

- To assess and compare the bioavailability of 10 cm^2 (FMI) transdermal patch with 3 mg oral solution in healthy subjects.
- To evaluate the safety and tolerability of single dose administration of 10 cm^2 (FMI) transdermal patch and 3 mg oral solution in healthy subjects.

The study design is as follows:

Study Design	Single dose, open label, randomized, 2 period crossover study
Study Population	N=48 Healthy elderly subjects Age: 59-85 years (mean age 67.8 years) Gender: 21 males and 27 females Weight: 53-91 kg (mean 74 kg) Race: 39 Caucasian, 2 Black and 7 others
Treatment Group	A: 10 cm^2 (18 mg loaded dose) Patch B: 3 mg Oral Solution **This study used the final marketing image
Dosage and Administration	Patches (single dose) were applied on upper back (above the scapula). Whenever the patch looked like it was about to fall off (e.g. one third or less still adhering to the skin), it was to be pressed back to the skin in the same manner as during application. If the patch were to actually fall off, it was to be reapplied once to the same site, unless there were obvious localized reasons for poor adhesion, in which case a different site would be used. Diet: On dosing days, subjects were administered the assigned dose following an overnight fast and subjects continued to fast up to 2 hr following the administration. Standard breakfast, lunch and dinner meals were consumed at 2, 5, and 9.5 hr post-dose, respectively. Washout: 72-hour washout between two treatments
Sampling: Blood	For rivastigmine and its metabolite, NAP 226-90:

	After patch arm: At predose, 3, 6, 8, 12, 16, 24, 26, 28, 32, 36, 40 hrs post-application. After oral solution: 0 (pre-dose), 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 15, and 24 hrs postdose.
Urine	none
Feces	none
Analysis	LC/MS/MS method Lower Limits of Quantitation Plasma / Urine Rivastigmine 0.2 ng/mL none NAP 226-90 0.2 ng/ml none Plasma: Linear Range: 0.2-30 ng/ml in plasma for both moeities Quality control concentrations: 0.4, 7.50 and 25 ng/ml Inter-day precision: < 7.1% CV Inter-day accuracy: 99-102% of the nominal concentration
PK Assessment	AUC0-24, AUC0-∞,Cmax, Tmax, t1/2,
Safety Assessment	Laboratory tests, adverse events
PD Assessment	None

Pharmacokinetic Results:

48 subjects were enrolled and completed the study. 18 subjects from Group 1 erroneously received half of the 3 mg ENA713 oral solution (1.5 mg) required by the protocol. As a result, their plasma samples were assayed but were not included for the evaluation of pharmacokinetic parameters. The 30 subjects from Group 2 and Group 3 who all received the correct 3 mg ENA713 oral solution and completed the study according to the study protocol were included for pharmacokinetic evaluation.

Exposure parameters after patch administration were corrected for the drug amount delivered from the patch system. Generally all exposure parameters were normalized to the dose administered per kg body weight.

The drug amount delivered from the patch system throughout 24 hours was on average 8.15 ± 1.76 mg, which was 45.3 ± 9.8% of the drug load (18 mg).

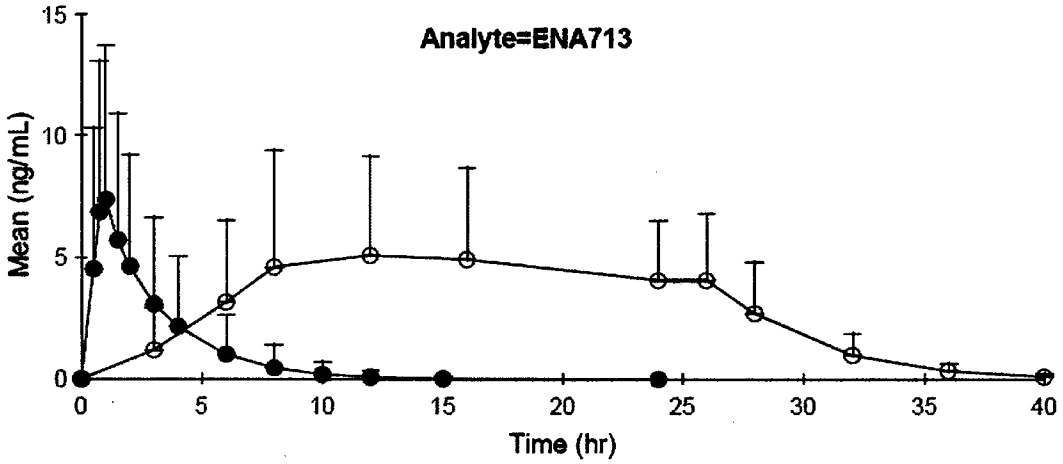
Rivastigmine:
The following Table summarizes the PK parameters of rivastigmine in healthy elderly subjects.

Table: Mean (± SD) pharmacokinetic parameters of rivastigmine in healthy elderly subjects, non-normalized and normalized for dose per kg body weight

Parameter	Arithmetic mean ± SD (CV%) [Geometric mean]	
	3 mg oral solution (N= 30)	10 cm^2 patch (18 mg) (N= 30)
t_{max} (h)*	1.00 (0.750 -1.50)	14.1 (8.0 - 26.0)
C_{max} (ng/mL)	7.63 ± 6.60 (87) [6.00]	5.84 ± 4.43 (76) [4.99]
$C_{max,\ norm}$ [(ng/mL)/(mg/kg)]	176 ± 130 (74) [145]	48.6 ± 20.8 (43) ** [45.6]
$AUC_{0\text{-}24h}$ (h·ng/mL)	22.3 ± 26.4 (119) [14.7]	91.2 ± 74.8 (82) [75.1]
$AUC_{0\text{-}24h,\ norm}$ [(h·ng/mL)/(mg/kg)]	507 ± 523 (103) [355]	748 ± 367 (49) ** [686]
AUC_{last} (h·ng /mL)	21.8 ± 26.1 (120) [14.2]	116 ± 92.5 (79) [97.8]
$AUC_{last,\ norm}$ [(h·ng/mL)/(mg/kg)]	497 ± 518 (104) [343]	963 ± 447 (47) ** [894]
$t_{½}$ (h)	1.45 ± 0.427 (30) [1.39]	3.02 ± 0.832 (28) [2.94]
AUC_{∞} (h·ng/mL)	22.6 ± 26.4 (117) [15.0]	118 ± 92.4 (78) [99.5]
$AUC_{\infty,\ norm}$ [(h·ng/mL)/(mg/kg)]	516 ± 524 (102) [364]	976 ± 445 (46) ** [909]

* median (range) for t_{max}, ** parameters were normalized to the drug amount delivered from the patch system per kg BW

The following figure shows the mean concentration time profile following both the formulations:



○—10 cm^2 (FMI) transdermal patch ●—single 3 mg Exelon oral solution

Both the non-normalized and the normalized AUClast's and AUC∞'s indicated a higher exposure to rivastigmine delivered by the patch formulation than the oral solution formulation. Absolute rivastigmine exposure (i.e. total AUC) was, overall, approximately 5.2-fold higher after the 10 cm^2 transdermal patch than after the 3 mg oral solution dose.

The mean terminal elimination half-life of rivastigmine was 1.45 ± 0.43 h after administration of the oral solution and 3.02 ± 0.83 h after patch application.

The inter-subject variability for the exposure parameters of rivastigmine was generally high, as characterized by coefficients of variation of parameters normalized by mg dose per kg body weight. The oral solution treatment arm had inter-subject variability of 74%-104%, and the patch treatment arm had inter-subject variability of 43-49%.

Based on the geometric means of ratios for the corresponding normalized values of AUClast and AUC∞, the bioavailability of rivastigmine from 10 cm^2 patch application [18 mg loaded dose, with mean delivered dose of 8.15 ± 1.76 mg (n=30)] was 261 and 250%, respectively, relative to the 3 mg oral solution. The intersubject variability of the AUC ratios for rivastigmine was high (CV of 69 and 75%).

Metabolite NAP226-90:

The following Table summarizes the PK parameters of NAP 226-90 in healthy elderly subjects.

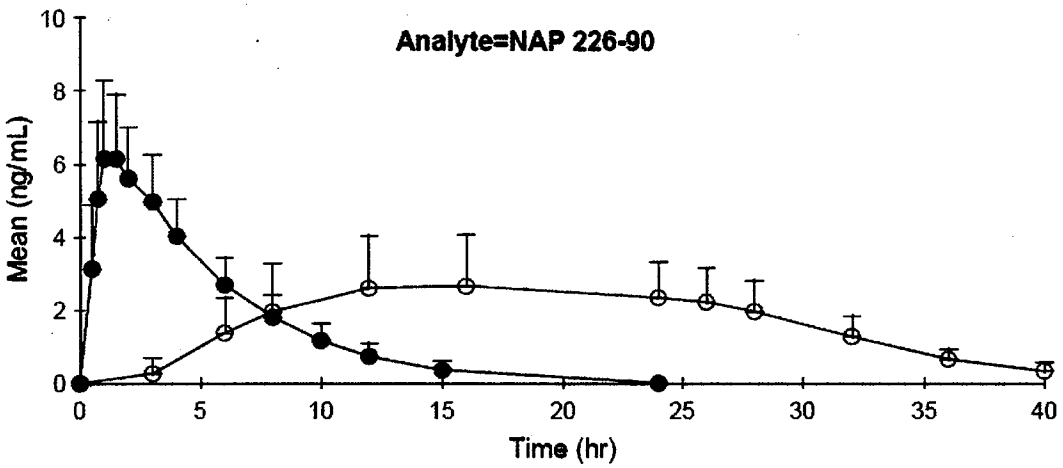
Table: Mean (± SD) pharmacokinetic parameters of NAP 226-90 in healthy elderly subjects, non-normalized and normalized for dose per kg body weight

Parameter	Arithmetic mean ± SD (CV%) [Geometric mean]	
	3 mg oral solution (N= 30)	10 cm² patch (18 mg) (N= 30)
t_{max} (h)*	1.50 (0.750 - 3.00)	16.0 (8.02 - 28.0)
C_{max} (ng/mL)	6.59 ± 1.96 (30) [6.31]	2.87 ± 1.42 (49) [2.60]
$C_{max,\ norm}$ [(ng/mL)/(mg/kg)]	157 ± 39.0 (25) [153]	24.6 ± 6.66 (27) ** [23.7]
$AUC_{0\text{-}24h}$ (h·ng/mL)	38.4 ± 10.0 (26) [37.2]	45.8 ± 24.6 (54) [40.5]
$AUC_{0\text{-}24h,\ norm}$ [(h·ng/mL)/(mg/kg)]	914 ± 162 (18) [901]	387 ± 119 (31) ** [370]
AUC_{last} (h·ng/mL)	37.1 ± 9.83 (27) [35.9]	66.8 ± 32.3 (48) [60.7]
$AUC_{last,\ norm}$ [(h·ng/mL)/(mg/kg)]	882 ± 156 (18) [870]	571 ± 142 (25) ** [555]
$t_{½}$ (h)	3.02 ± 0.515 (17) [2.98]	4.80 ± 0.907 (19) [4.72]
AUC_{∞} (h·ng/mL)	38.9 ± 10.0 (26) [37.6]	69.8 ± 32.9 (47) [63.8]
$AUC_{\infty,\ norm}$ [(h·ng /mL)/(mg/kg)]	924 ± 160 (17) [911]	599 ± 143 (24) ** [583]
AUC_{∞} ratio metabolite/parent	3.49 ± 3.44 (99) [2.51]	0.67 ± 0.19 (28) [0.64]

* median (range) for t_{max}, ** parameters were normalized to the drug amount delivered from the patch system per kg BW

The AUC∞ ratio of metabolite to parent compound for the oral solution (3.49) appeared to be higher than that for the patch formulation (0.67). The inter-subject variability for the exposure parameters of NAP 226-90 was notably lower than for the parent compound. In contrast to the parent compound, for the metabolite the variability tended to be lower after oral administration as compared to the patch formulation.

The mean concentration-time profile of NAP 226-90 is shown in the following figure:



○—10 cm^2 (FMI) transdermal patch ●—single 3 mg Exelon oral solution

Without normalization for dose, the 10 cm^2 patch produced a mean plasma exposure (AUC_∞) to rivastigmine 5.2 times higher than a single 3 mg oral solution dose. Thus, assuming that exposure after an evening oral dose would be the same as after the morning dose, the exposure with once-daily dose of 10 cm^2 patch is expected to be 2.6 times higher than with 3 mg bid dosing of the oral solution.

The geometric mean AUC ratios for NAP 226-90 amounted to 64%, relative to the oral solution. The intersubject variability of this ratio was lower (CV of 25 and 26%) as compared to the corresponding value for the parent compound.

The following Table summarizes the relative ratio between ENA713 patch formulation and the ENA713 oral solution.

Table: $C_{max,\ norm}$, $AUC_{0\text{-}24h,\ norm}$ $AUC_{last,\ norm}$ and $AUC_{\infty,\ norm}$ ratio for rivastigmine and NAP 226-90, (N=30)

Parameter	Test/Reference (Patch/Solution)	
	Rivastigmine	NAP 226-90
$C_{max,\ norm}$ ratio	0.353 ± 0.173 (49) [0.313]	0.165 ± 0.0599 (36) [0.155]
$AUC_{0\text{-}24h,\ norm}$ ratio	2.46 ± 1.87 (76) [1.93]	0.433 ± 0.144 (33) [0.410]
$AUC_{last,\ norm}$ ratio	3.27 ± 2.45 (75) [2.61]	0.661 ± 0.174 (26) [0.638]
$AUC_{\infty,\ norm}$ ratio	3.07 ± 2.13 (69) [2.50]	0.660 ± 0.166 (25) [0.639]

Values are mean ± SD (%CV) [geometric mean]

The following figures show the individual subject normalized Cmax and AUC∞ for the patch and the solution formulations for rivastigmine and NAP226-90:

Figure: C_{max}, AUC_∞ of rivastigmine normalized by mg dose per kg body weight following a single 24-hour application of a 10 cm² (FMI) Exelon® transdermal patch (loaded with 18 mg) and a single oral solution of 3 mg Exelon®

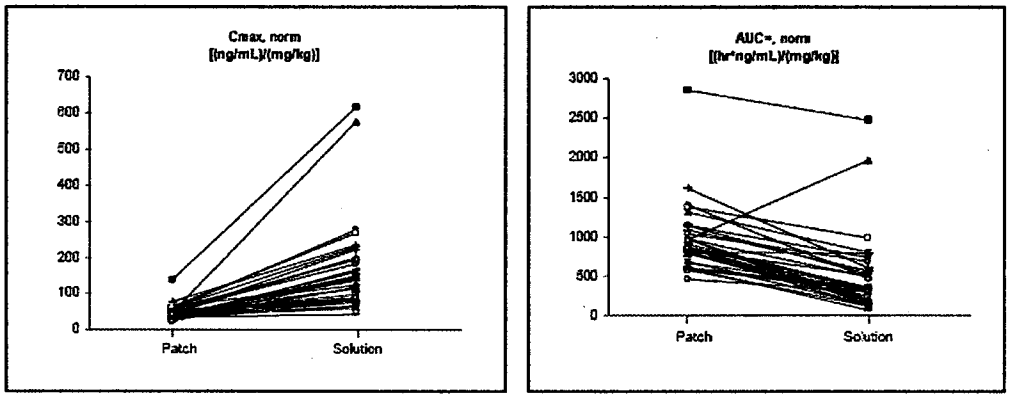
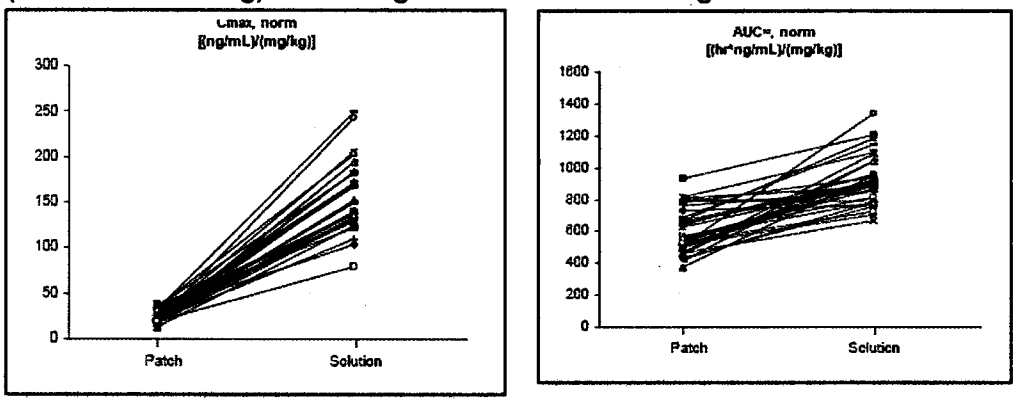


Figure: C_{max}, AUC_∞ of NAP226-90 normalized by mg dose per kg body weight following a single 24-hour application of a 10 cm² (FMI) Exelon® transdermal patch (loaded with 18 mg) and a single oral solution of 3 mg Exelon®



Residual Drug Analysis:

Drug residual analysis was performed on all used patches worn by the 30 subjects included for PK analysis.

All subjects participating in the study received one 10 cm^2 ENA713 FMI transdermal patch during the treatment period. Each 10 cm^2 patch was loaded with 18 mg of rivastigmine. From the drug residual analysis of the 30 subjects, the transdermal system delivered an average of 8.15 ± 1.76 mg (range 4.20 to 11.1 mg), which is 45.3 ± 9.79% (range 23.3-61.7) of the loaded drug (18mg).

In the 17 female subjects out of the total 30 subjects, the 10 cm^2 patch delivered an average of 7.90 ± 1.83 mg of rivastigmine, which is 43.9 ± 10.2% (range 23.3-59.4 %) of loaded drug .

In the 13 male subjects, the 10 cm^2 patch delivered an average of 8.49 ± 1.68 mg of rivastigmine, which is 47.2 ± 9.34% (range 33.3-61.7) % of loaded drug.

Although numerically the patch delivered a higher amount of rivastigmine in male than female subjects, the difference was not statistically significant ($p=0.85$, $\alpha=0.05$).

Overall Conclusions:

- The 10 cm^2 ENA713 FMI transdermal system in the current study demonstrated the ability to consistently deliver on average 8.15 ± 1.76 mg of rivastigmine, which is 45% of loaded dose (18 mg) when applied to the upper back of the healthy elderly subjects enrolled in this study.

- Without normalization for dose, the 10 cm^2 patch produced a plasma exposure (AUC_∞) to rivastigmine 5.2 times higher than the single 3 mg oral solution dose, while the C_{max} of the patch was only 76.5% of that achieved with oral solution. Assuming that exposure after an evening oral dose is the same as after the morning dose, the exposure with once-daily dose of 10 cm^2patch is expected to be 2.6 times higher than with a 3 mg bid (6 mg/day) dosing of oral solution.

- The normalized C_{max} (for amount of drug delivered from the patch per kg body weight) achieved by ENA713 FMI patch was about 30% of the C_{max} achieved by the 3 mg ENA713 oral solution. The normalized AUC_{last} and AUC_∞ achieved by 10 cm^2 patch were 261 and 250% (based on geometric mean) or 327 and 307% (based on arithmetic mean), respectively, of the 3 mg ENA713 oral solution.

- Nervous system and gastrointestinal system were the two body systems associated with the majority of the incidence of adverse events. The total number of subjects experiencing nervous system related adverse events was similar between the 10 cm^2 patch and the 3 mg ENA713 oral solution treatment. The total number of subjects experiencing gastrointestinal system disorder, however, was lower during the 10 cm^2 patch treatment than during 3mg ENA713 oral solution treatment.

SPECIAL POPULATION

RACE EFFECT:

Study 2335: ***An open label, three-period ascending dose study to evaluate the ethnic difference in the pharmacokinetics of ENA713 transdermal patches (FMI 5 cm^2, 10 cm^2, 15 cm^2) between Caucasian and Japanese healthy male subjects***

Objectives:

- To estimate potential differences in the pharmacokinetics of ENA713 and its metabolite NAP 226-90, including dose-proportionality, between Caucasian and Japanese healthy male subjects
- To evaluate the safety and tolerability of single dose administration of 5cm^2, 10 cm^2, 15 cm^2 (FMI) transdermal patch
- To compare the pharmacodynamics of BuChE in plasma in Caucasian and Japanese healthy male subjects and evaluate the PK/PD relationship
- To investigate the potential of ENA713 transdermal to induce contact irritation after single application to Caucasian and Japanese healthy male subjects

The study design is as follows:

<table>
<tr><td>Study Design</td><td>Open label, randomized, 3 period 3 treatment single ascending dose</td></tr>
<tr><td>Study Population</td><td>N= 40 (20 Healthy Caucasians and 20 healthy Japaense subjects)
<table>
<tr><th>Demographic variable</th><th>All subjects</th><th>Japanese</th><th>Caucasian</th></tr>
<tr><td>Number of subjects treated</td><td>39</td><td>19</td><td>20</td></tr>
<tr><td>Age (years), mean (SD)</td><td>25.9 (3.71)</td><td>26.9 (3.21)</td><td>24.9 (3.97)</td></tr>
<tr><td>Sex (male, n (%))</td><td>39 (100%)</td><td>19 (100%)</td><td>20 (100%)</td></tr>
<tr><td>Height (cm), mean (SD)</td><td>174.2 (7.46)</td><td>169.6 (5.68)</td><td>178.6 (6.29)</td></tr>
<tr><td>Weight (kg), mean (SD)</td><td>67.2 (7.07)</td><td>63.2 (6.18)</td><td>71.1 (5.60)</td></tr>
<tr><td>BMI (kg\m^2), mean (SD)</td><td>22.148 (1.7276)</td><td>21.991 (2.1252)</td><td>22.297 (1.2816)</td></tr>
</table></td></tr>
<tr><td>Treatment Group</td><td>• Treatment period 1: ENA713 5 cm^2 (9 mg loaded dose of rivastigmine) FMI transdermal patch
• Treatment period 2: ENA713 10 cm^2 (18 mg) FMI transdermal patch
• Treatment period 3: ENA713 15 cm^2 (27 mg) FMI transdermal patch or ENA713 7.5 cm2 (13.5 mg) FMI transdermal patch, in the case of tolerability problems in period 2.</td></tr>
<tr><td>Dosage and Administration</td><td>On day 1 of each treatment period the patch was applied in the morning after an overnight fast of at least 10 hours. Each of the three (3) treatment periods consisted of a 24-hour topical single application of ENA713 patch on the upper scapular region of the back

5 cm^2 (9 mg) FMI; KN # 3754249.00.004; Batch # 8/22061/02
10 cm2 (18 mg) FMI; KN # 3742509.00.023; Batch # 8/22063/02</td></tr>
</table>

	15 cm2 (27 mg) FMI; KN # 3746245.00.008; Batch # 8/22064/02 7.5 cm2 (13.5 mg) FMI; KN # 3754256.00.004; Batch #8/22062/02 Diet: all subjects had to undergo a 10 hour overnight fast prior to patch application and continue to fast for additional 2 hours post-patch application. Standard breakfast, lunch and dinner was served at 2, 5 and 10 hours post-patch application, respectively Washout: 72-hour washout between two treatments
Sampling: Blood	For rivastigmine and its metabolite, NAP 226-90: After patch arm: At predose, 3, 6, 8, 12, 16, 24, 26, 28, 32, 36, 40, 48 hrs post-application.
Urine	(0 hr), and during time intervals 0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 hrs post-patch application.
Feces	none
Analysis	LC/MS/MS method Lower Limits of Quantitation Plasma / Urine Rivastigmine 0.2 ng/mL 5 ng/mL NAP 226-90 0.2 ng/ml 5 ng/mL Plasma: Linear Range: 0.2-30 ng/ml in plasma for both moeities Quality control concentrations: 0.4, 7.50 and 25 ng/ml Inter-day precision: < 5.01% CV Inter-day accuracy: 99-102% of the nominal concentration Urine: Linear Range: 5-2500 ng/ml in plasma for both moieties Quality control concentrations: 15, 1000 and 2000 ng/ml Inter-day precision: < 4.25% CV Inter-day accuracy: 92-94.5% of the nominal concentration
PK Assessment	AUC0-24, AUC0-24norm, AUC0-∞, AUC0-∞ norm, Cmax, Cmaxnorm, Tmax, t1/2, Ae, Cl, Vd.
Safety Assessment	Laboratory tests, adverse events
PGx Assessment	Human genetic variation on drug response: genetic markers will be identified at the population level and not at the individual level Note: Pharmacogenetic results have not yet been analyzed.
PD Assessment	Skin irritation assessment: Approximately 0.5 hour after patch removal the test site was photographed and local skin irritation evaluation was assessed. After the 24.5 hours skin irritation evaluation was performed BuChE determination in plasma: pre-patch application (0 hr), and 3, 6,

	8, 12, 16, 24, 26, 28, 32, 36, 40 and 48 hrs postpatch application.

Pharmacokinetic Results:

The following Tables and Figures show the mean pharmacokinetic parameters and the profiles in the Caucasian and Japanese population for rivastigmine and its metabolite:

Table: Mean pharmacokinetic parameters of rivastigmine [plus/minus SD (CV percent), median and range for t_{max}] in Caucasian and Japanese healthy subjects given a single 24-hr application of a 5, 7.5, 10, and 15 cm^2 Exelon Transdermal

	Caucasian				Japanese			
Parameter (unit)	5 cm^2 (n= 20)	7.5 cm^2 (n=12)	10 cm^2 (n=20)	15 cm^2 (n=8)	5 cm^2 (n=19)	7.5 cm^2 (n=10)	10 cm^2 (n=19)	15 cm^2 (n=9)
C_{max} (ng/mL)	2.76 ± 1.23 (44.6)	3.99 ± 1.47 (36.8)	7.29 ± 3.79 (52.0)	12.9 ± 4.27 (33.1)	2.73 ± 0.89 (32.6)	4.58 ± 1.61 (35.2)	6.73 ± 2.40 (35.7)	12.5 ± 4.41 (35.3)
$C_{max,norm}$ [(ng/mL)/(mg/kg)]	37.5 ± 12.0 (32.0)	39.9 ± 9.33 (23.4)	48.4 ± 20.5 (42.4)	57.6 ± 14.4 (25.0)	35.8 ± 8.16 (22.8)	41.6 ± 11.4 (27.4)	44.5 ± 12.7 (28.5)	54.4 ± 13.8 (25.4)
t_{max} (h)	12.0 [3.00-24.08]	14.0 [6.00-24.08]	12.0 [6.00-24.08]	10.03 [8.00-16.0]	16.0 [6.00-16.02]	16.0 [8.00-16.03]	16.0 [8.00-16.07]	16.0 [8.02-16.03]
AUC_{0-24h} (ng·h/mL)	45.6 ± 18.3 (40.1)	66.1 ± 26.3 (39.8)	119 ± 58.3 (49.0)	204 ± 71.9 (35.2)	47.8 ± 16.7 (34.9)	75.3 ± 26.5 (35.2)	116 ± 42.7 (36.8)	216 ± 79.2 (36.7)
$AUC_{0-24h,norm}$ [(ng·h/mL)/(mg/kg)]	624 ± 187 (30.0)	655 ± 181 (27.6)	794 ± 322 (40.6)	916 ± 270 (29.5)	626 ± 157 (25.1)	685 ± 188 (27.4)	767 ± 218 (28.4)	944 ± 256 (27.1)
AUC_{tot} (ng·h/mL)	50.3 ± 19.2 (38.2)	76.7 ± 28.1 (36.6)	136 ± 63.9 (47.0)	237 ± 81.2 (34.3)	53.7 ± 18.7 (34.8)	86.6 ± 29.7 (34.3)	135 ± 49.1 (36.4)	255 ± 93.7 (36.7)
AUC_{∞} (ng·h/mL)	52.4 ± 18.9 (36.1)	77.5 ± 27.9 (36.0)	137 ± 63.8 (46.6)	239 ± 81.1 (33.9)	55.7 ± 18.1 (32.5)	88.1 ± 29.8 (33.8)	136 ± 49.1 (36.1)	256 ± 93.9 (36.7)
$AUC_{\infty,norm}$ [(ng·h/mL)/(mg/kg)]	723 ± 191 (26.4)	773 ± 192 (24.8)	918 ± 354 (38.6)	1680 ± 314 (29.1)	732 ± 171 (23.4)	902 ± 212 (26.4)	900 ± 253 (28.1)	1120 ± 312 (27.9)
$t_{½}$ (h)	2.89 ± 0.73 (25.3)	2.10 ± 0.18 (8.6)	2.25 ± 0.28 (12.4)	2.90 ± 0.37 (12.8)	2.68 ± 0.54 (20.1)	2.21 ± 0.29 (13.1)	2.12 ± 0.21 (9.9)	2.78 ± 0.31 (11.2)
Vz/F (L)	453 ± 213 (47.0)	303 ± 112 (37.0)	284 ± 110 (38.7)	296 ± 98.4 (33.2)	356 ± 119 (33.4)	269 ± 108 (40.1)	226 ± 51.6 (22.8)	279 ± 93.9 (33.7)
Vz/F_{norm} (L/kg)	6.33 ± 2.89 (45.7)	4.23 ± 1.38 (32.6)	3.97 ± 1.39 (35.0)	4.15 ± 1.24 (29.9)	5.60 ± 1.72 (30.7)	4.35 ± 1.87 (43.0)	3.58 ± 0.79 (22.1)	4.35 ± 1.46 (33.6)
CL/F (L/h)	105 ± 29.9 (28.5)	97.9 ± 29.3 (29.9)	85.3 ± 25.9 (30.4)	69.9 ± 17.1 (24.5)	90.5 ± 21.5 (23.8)	82.9 ± 24.5 (29.6)	74.5 ± 18.4 (24.7)	61.2 ± 16.7 (27.3)
CL/F_{norm} (L/h/kg)	1.47 ± 0.38 (25.9)	1.37 ± 0.35 (25.5)	1.20 ± 0.33 (27.5)	0.98 ± 0.21 (21.4)	1.43 ± 0.31 (21.7)	1.33 ± 0.38 (28.6)	1.18 ± 0.27 (22.9)	0.95 ± 0.24 (25.3)

Variability associated with estimated pharmacokinetic parameters was characterized by coefficients of intersubject variation often lower than 30%.

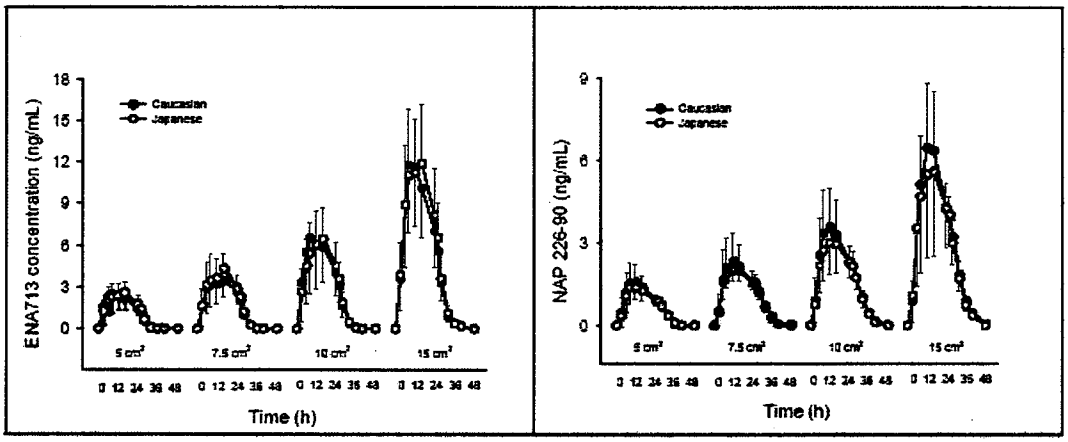
Urinary excretion of rivastigmine amounted to 2.5-3.3% of the dose in Caucasian and 3.5- 4.1% of the dose in Japanese. Renal clearance was from 2.14 to 2.78 L/h in Caucasians and from 1.95 to 3.25 L/h in Japanese with a trend to decrease with

increasing patch size. The excretion of metabolite NAP226-90 represented 17.7-20.0% of the dose in Caucasians and 16.9-18.5% of the dose in Japanese.

Table: Mean pharmacokinetic parameters of NAP226-90 [plus/minus SD (CV percent), median and range for t_{max}] in Caucasian and Japanese healthy subjects given a single 24-hr application of a 5, 7.5, 10, and 15 cm² Exelon Transdermal

	Caucasian				Japanese			
Parameter (unit)	5 cm² (n= 20)	7.5 cm² (n=12)	10 cm² (n=20)	15 cm² (n=6)	5 cm² (n=19)	7.5 cm² (n=10)	10 cm² (n=19)	15 cm² (n=9)
C_{max} (ng/mL)	1.64 ± 0.69 (42%)	2.45 ± 1.08 (44%)	3.70 ± 1.51 (41%)	6.65 ± 2.30 (35%)	1.49 ± 0.55 (37%)	2.09 ± 0.42 (20%)	3.20 ± 1.15 (36%)	5.76 ± 2.99 (52%)
$C_{max,norm}$ [(ng/mL)/(mg/kg)]	22.3 ± 5.89 (26%)	24.2 ± 66.67 (28%)	24.7 ± 6.65 (27%)	29.4 ± 6.57 (22%)	19.3 ± 4.23 (22%)	19.2 ± 2.67 (14%)	21.1 ± 5.09 (24%)	24.8 ± 8.27 (33%)
t_{max} (h)	12.00 [8.00-16.00]	12.00 [5.00-26.00]	12.00 [8.00-26.00]	12.04 [12.00-16.00]	12.00 [6.00-16.00]	16.00 [5.00-16.03]	12.02 [8.00-26.00]	16.00 [12.00-26.00]
AUC_{0-24h} (ng·h/mL)	26.9 ± 11.0 (41%)	40.2 ± 17.1 (43%)	62.0 ± 24.3 (39%)	106 ± 35.1 (33%)	24.6 ± 8.16 (33%)	37.2 ± 8.31 (22%)	54.7 ± 18.8 (34%)	99.7 ± 51.7 (52%)
$AUC_{0-24h,norm}$ [(ng·h/mL)/(mg/kg)]	366 ± 93.5 (26%)	399 ± 109 (27%)	415 ± 105 (26%)	477 ± 94.8 (20%)	321 ± 64.9 (20%)	341 ± 55.2 (16%)	360 ± 80.7 (22%)	423 ± 144 (34%)
AUC_{last} (ng·h/mL)	32.5 ± 11.6 (36%)	52.5 ± 18.9 (36%)	79.8 ± 26.3 (33%)	142 ± 39.7 (28%)	30.6 ± 9.17 (30%)	48.6 ± 9.41 (19%)	71.9 ± 21.7 (30%)	131 ± 57.2 (44%)
AUC_{∞} (ng·h/mL)	35.7 ± 11.3 (32%)	54.5 ± 18.6 (34%)	81.6 ± 26.3 (32%)	144 ± 39.4 (27%)	32.8 ± 9.38 (29%)	50.3 ± 9.61 (19%)	73.5 ± 21.6 (29%)	133 ± 57.0 (43%)
$AUC_{\infty,norm}$ [(ng·h/mL)/(mg/kg)]	491 ± 87.5 (18%)	550 ± 125 (23%)	552 ± 116 (21%)	645 ± 98.0 (15%)	432 ± 79.5 (18%)	461 ± 61.2 (13%)	486 ± 93.3 (19%)	575 ± 159 (28%)
$t_{½}$ (h)	5.06 ± 1.04 (21%)	5.27 ± 1.83 (35%)	4.13 ± 0.57 (14%)	4.31 ± 0.62 (14%)	4.70 ± 0.94 (20%)	3.93 ± 0.43 (11%)	3.90 ± 0.49 (13%)	3.76 ± 0.50 (13%)
AUC_{metab}/AUC_{parent}	0.70 ± 0.14 (20%)	0.74 ± 0.18 (24%)	0.65 ± 0.17 (26%)	0.63 ± 0.16 (25%)	0.61 ± 0.13 (21%)	0.60 ± 0.09 (15%)	0.56 ± 0.12 (21%)	0.54 ± 0.19 (35%)

Figure: Mean plus/minus SD plasma concentrations of rivastigmine and NAP226-90 in Caucasian and Japanese healthy subjects



Rivastigmine C_{max} and AUC_{∞} values appeared to increase slightly more than the increase in Exelon® Transdermal size (i.e. loaded dose), as illustrated in the bottom figure:

Figure: Dose-exposure relationship for rivastigmine C_{max} and AUC_{∞}.

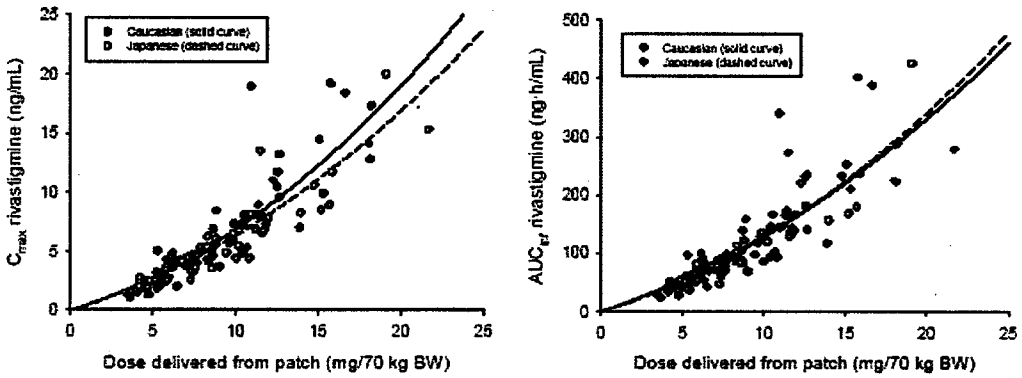
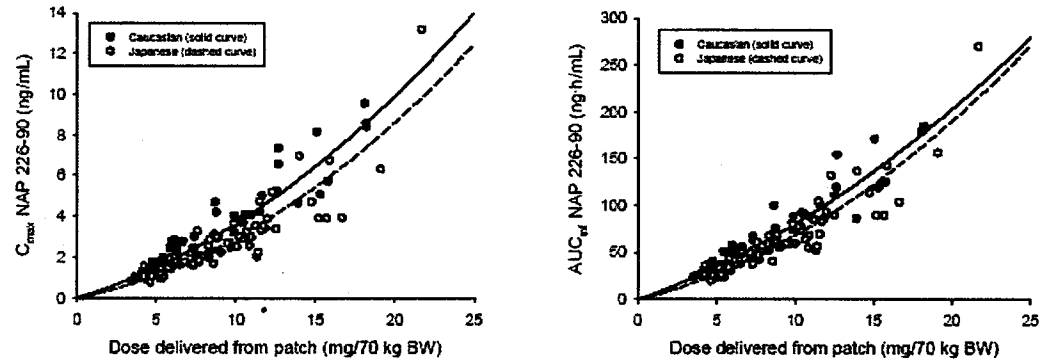


Figure: Dose-exposure relationship for NAP-226-90 **C_{max} and AUC_{∞}.**



Similar pattern was also seen for the metabolite NAP-226-90.

Within the dose range considered (ratio highest to lowest dose = 3), none of the pharmacokinetic parameters could be considered proportional to dose for both races and both analytes. The estimate of the slope β was always above 1 as well as the lower 90% confidence intervals of the slopes. Exposure therefore increased in an over proportional manner with increasing doses of transdermal rivastigmine.

The estimated geometric mean exposure to NAP226-90 was lower for Japanese than for Caucasian, while the estimated geometric mean exposure to rivastigmine was higher. Adjusting the model by the covariate body weight resulted in lower estimated geometric means for Japanese for both analytes as seen in the Tables below:

Table: Estimate of the geometric mean ratios in PK parameters between Japanese and Caucasian at each dose level (model adjusted for body weight)

Analyte	PK parameter	Dose (mg)	Ratio of geometric mean estimates (J/C)	Lower 90% confidence limit	Upper 90% confidence limit	In bioequivalence range
Rivastigmine	$AUC_{0-\infty}$	27	0.85	.66817	1.0727	No
		9	0.92	.74083	1.1539	No
		13.5	0.94	.75929	1.1705	No
		18	0.96	.76904	1.1880	No
		27	0.97	.77799	1.2210	No
	AUC_{0-24h}	9	0.92	.72616	1.1776	No
		13.5	0.94	.74514	1.1940	No
		18	0.96	.75478	1.2123	No
		27	0.98	.76287	1.2480	No
	AUC_{0-last}	9	0.92	.73541	1.1587	No
		13.5	0.94	.75322	1.1739	No
		18	0.95	.76229	1.1906	No
		27	0.97	.76996	1.2230	No
	C_{max}	9	0.91	.71169	1.1585	No
		13.5	0.91	.72058	1.1583	No
		18	0.92	.72281	1.1648	No
		27	0.92	.72023	1.1833	No

Analyte	PK parameter	Dose (mg)	Ratio of geometric mean estimates (J/C)	Lower 90% confidence limit	Upper 90% confidence limit	In bioequivalence range
NAP 226-90	$AUC_{0-\infty}$	9	0.87	.71885	1.0432	No
		13.5	0.87	.72731	1.0440	No
		18	0.88	.72980	1.0497	No
		27	0.88	.72840	1.0649	No
	AUC_{0-24h}	9	0.86	.68370	1.0722	No
		13.5	0.86	.69259	1.0727	No
		18	0.87	.69501	1.0791	No
		27	0.87	.69299	1.0968	No
	AUC_{0-last}	9	0.87	.71800	1.0590	No
		13.5	0.87	.72227	1.0536	No
		18	0.87	.72172	1.0551	No
		27	0.87	.71596	1.0645	No
	C_{max}	9	0.84	.66691	1.0603	No
		13.5	0.84	.67299	1.0560	No
		18	0.84	.67330	1.0592	No

Drug Residuals:

Approximately 50% of the drug load was released from the transdermal systems. On average, the percent of drug delivered from the system was 56.3% (5 cm^2); 51.9% (7.5 cm^2), 57.6% (10 cm^2), and 57.5% (15 cm^2) for Caucasians, and was 52.6% (5 cm^2), 49.9% (7.5 cm^2), 52.2% (10 cm^2), and 53.3% (15 cm^2) for Japanese.

BChE activity in plasma:

The transdermal administration of rivastigmine exerted a dose related inhibition of the plasma BChE in both populations, Japanese and Caucasians. At the lowest dose (patch 5 cm^2, loaded with 9 mg rivastigmine) the inhibitory influence of rivastigmine on plasma BChE started 3 h after patch application and smoothly increased over the following 13 hours to reach its maximum at about 16 hours (25% inhibition). The effect was maintained between 16 and 24 hours. The BChE activity returned to the predose values 24 hours after patch removal (i.e. 48 hours after patch application). The inhibition curves for both ethnic groups were very similar.

Similar inhibitory profiles were obtained at the higher doses, the maximal BChE inhibition was reached around 16 hours with 5, 7.5, 10 and 15 cm^2 patches (maximal inhibition was 24, 35, 44 and 55% in Japanese, and 22, 32, 40, and 50% in Caucasians, respectively).

Again, the differences between the curves of the two ethnic groups were not statistically significant, although the plasma inhibition curves obtained at all doses from Japanese subjects indicated a slightly higher inhibition in this group. A possible reason for this finding could be the lower mean body weight for the Japanese compared to Caucasians.

Figure: AUC of BChE inhibition by transdermal rivastigmine in Japanese and Caucasian subjects.

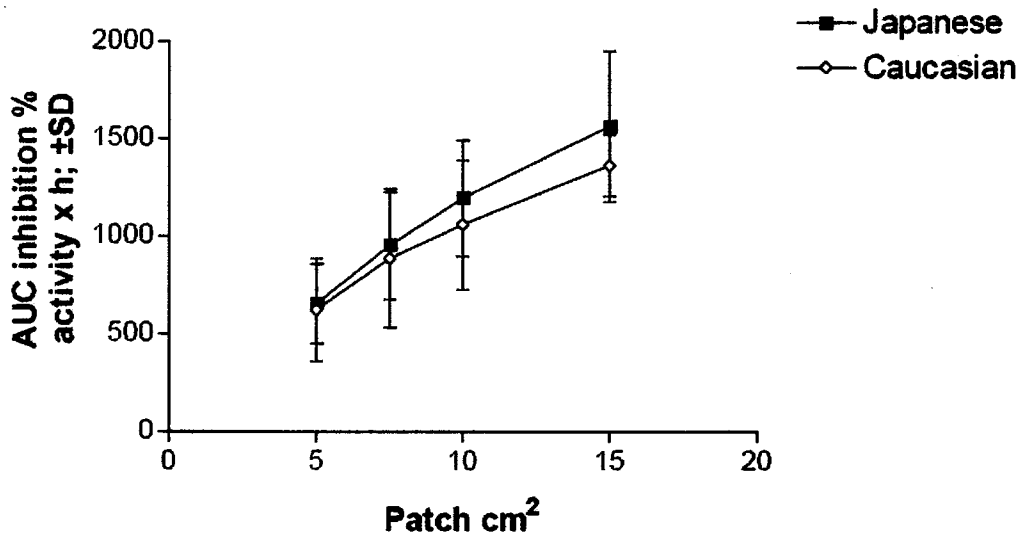


Table: Maximal inhibition of plasma BChE (percent) at time T max (h) after transdermal application of rivastigmine in Japanese and Caucasian subjects.

	Patch 5cm²; 9mg		Patch 7.5cm²; 13.5mg		Patch 10cm²; 18mg		Patch 15cm²; 28mg	
	Japan	Cauca	Japan	Cauca	Japan	Cauca	Japan	Cauca
E max (%Inhib)	24.1	22.1	34.5	32.4	43.5	40.3	55	49.5
T_{max} (Inhib (h))	16.4	15.9	16.2	15.9	16.2	15.9	16.2	15.9

Within the dose range considered (ratio highest to lowest dose = 3), the $AUC_{0\text{-last}}$ for the PD parameter BuChE could not be considered proportional to dose for both races.

Overall Conclusions:

Pharmacokinetics:

- No meaningful pharmacokinetic differences were apparent between Japanese and Caucasian subjects.
- The statistical evaluation showed that systemic exposure to rivastigmine was slightly higher in Japanese than in Caucasians. **In contrast, for the rivastigmine's** metabolite NAP226-90, Japanese had a slightly lower systemic exposure than Caucasians. After adjusting the statistical model for body weight, Japanese subjects had a lower exposure than Caucasians for both analytes.
- With increasing doses of transdermal rivastigmine, exposure apparently increased in a slightly over proportional manner in both ethnic groups.

Pharmacodynamics:

- BChE was inhibited in plasma after a single administration of all rivastigmine patch sizes 5, 7.5, 10 and 15 cm².
- BChE inhibition in plasma started 3 hours after patch application and reached its dose dependent maximum after about 16 hours and was sustained until patches were removed.
- BChE inhibition in plasma increased as the dose/patch size increased.
- Japanese subjects exhibit higher inhibitory effect on BuChE. Although, the differences were not statistically significant. A possible reason for this finding could be the lower mean body weight for the Japanese compared to Caucasians.

EFFECT OF APLLICATION SITE:

Study 2338: ***A single-dose, open-label, crossover study evaluating the effect of application sites on the pharmacokinetics and adhesiveness properties of ENA713 FMI transdermal patch when administered to healthy subjects.***

Objectives:

- To evaluate the quality of adhesiveness of ENA713 FMI transdermal patch at different application sites (upper back, chest, abdomen, thigh, and upper arm)
- To evaluate how different patch application sites can affect the relative bioavailability of ENA713 FMI transdermal patch in elderly healthy subjects

The study design is as follows:

Study Design	Open label, randomized, single dose, crossover
Study Population	N= 39 completers (20 Healthy Caucasians and 19 healthy Japaense subjects) Age: 51-80 years (mean age 52 years) Gender: 17 males and 23 females Weight: 50.8-96.5 kg (mean 71 kg) Race: 6 Caucasian, 34 other
Treatment Group	• Group 1: ENA713 10 cm^2 (18 mg loaded dose of rivastigmine) FMI transdermal patch (N=20) • Group 2: ENA713 10 cm^2 (18 mg) FMI transdermal patch (N=20) 4 week gap between groups (two groups for site capacity reasons)
Dosage and Administration	Patch applied at five pre-selected body sites (upper back, chest, abdomen, thigh, and upper arm) of the healthy subjects. The patch application sites were defined as follows (these were the study sequences with 8 subjects per sequence: **site 1—upper back: above or over the upper part of scapula,** **site 2—chest: two to three inches below** the clavicle and lateral to the sternum, **site 3—abdomen: lower abdominal quadrant,** **site 4—thigh: outer lateral surface, and** **site 5—upper arm: over the deltoid muscle.** Both left and right side of the body were used for patch application. There was a 72 hour inter-dosing period between each site application 10 cm^2 (18 mg) FMI; KN # 3742509.00.023; Batch # 8/22063/02 Diet: all subjects had to undergo a 10 hour overnight fast prior to patch application and continue to fast for additional 2 hours post-patch application. Standard breakfast, lunch and dinner was served at 2, 5 and 10 hours post-patch application, respectively

	Washout: 72-hour washout between two treatments
Sampling: Blood	For rivastigmine and its metabolite, NAP 226-90: After patch arm: 0 hr (predose), 0.5, 1, 2, 3, 6, 8, 10, 12, 16, 22, 24, 26, 28, 32, 36 hours post-patch application.
Urine	none
Feces	none
Analysis	LC/MS/MS method Lower Limits of Quantitation Plasma / Urine Rivastigmine 0.2 ng/mL - NAP 226-90 0.2 ng/ml - Plasma: Linear Range: 0.2-30 ng/ml in plasma for both moeities Quality control concentrations: 0.4, 5.0 and 25 ng/ml Inter-day precision: < 7.91% CV Inter-day accuracy: 100-.60-105.20% of the nominal concentration
PK Assessment	AUC0-24, AUC0-∞, , Cmax, Tmax, t1/2,
Safety Assessment	Physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, hematology), and adverse event monitoring
PGx Assessment	none
PD Assessment	none
Other Assessment	Patch adhesion assessment right after application (0 hr), and 12, 24 hours post application; Skin irritation assessment at time prior to each patch application (0 hr), immediate after patch removal, and 2, 4, 8, 12, and 24 hours after patch removal

Pharmacokinetic Results:

The summary of PK parameters is given in the following Table and the concentration time profiles in the following figures:

Table: Summary of PK parameters (mean +/- SD)

Analyte	Site no.	C_{max} (ng/mL)	t_{max}* (h)	AUC_{last} (h•ng/mL)	AUC_{∞} (h•ng/mL)	$t_{½}$ (h)
rivastigmine	1 (Upper back)	6.80 ± 3.20	16.0 (8.0, 24.0)	122 ± 54.9	128 ± 51.7	3.21 ± 0.75
rivastigmine	2 (Chest)	6.34 ± 2.58	16.0 (8.0, 24.0)	123 ± 59.7	128 ± 57.7	3.35 ± 0.82
rivastigmine	3 (Abdomen)	5.44 ± 2.42	16.0 (6.0, 26.0)	101 ± 43.6	103 ± 44.0	3.37 ± 0.76
rivastigmine	4 (Thigh)	4.89 ± 1.91	22.0 (8.0, 26.0)	87.7 ± 37.6	91.0 ± 36.8	3.94 ± 2.30
rivastigmine	5 (Upper arm)	6.58 ± 2.69	16.0 (6.0, 26.0)	116 ± 41.8	118 ± 41.7	3.31 ± 0.82
NAP226-90	1 (Upper back)	2.27 ± 0.84	16.0 (8.0, 28.0)	48.7 ± 18.4	54.3 ± 15.1	5.08 ± 3.40
NAP226-90	2 (Chest)	2.26 ± 0.75	22.0 (10.0, 26.0)	49.3 ± 20.1	55.2 ± 19.0	5.08 ± 2.97
NAP226-90	3 (Abdomen)	1.99 ± 0.55	22.0 (8.0, 28.0)	43.4 ± 13.1	46.6 ± 13.5	4.78 ± 1.11
NAP226-90	4 (Thigh)	1.89 ± 0.56	22.0 (10.0, 26.0)	38.5 ± 13.9	43.8 ± 13.2	5.47 ± 1.99
NAP226-90	5 (Upper arm)	2.14 ± 0.61	22.0 (12.0, 28.0)	46.5 ± 14.6	50.3 ± 14.7	4.54 ± 1.06

* median (range)

Figure: Mean (+/- SD) plasma concentration-time plots of rivastigmine following single transdermal administration (10 cm^2, 18 mg rivastigmine) on different application sites

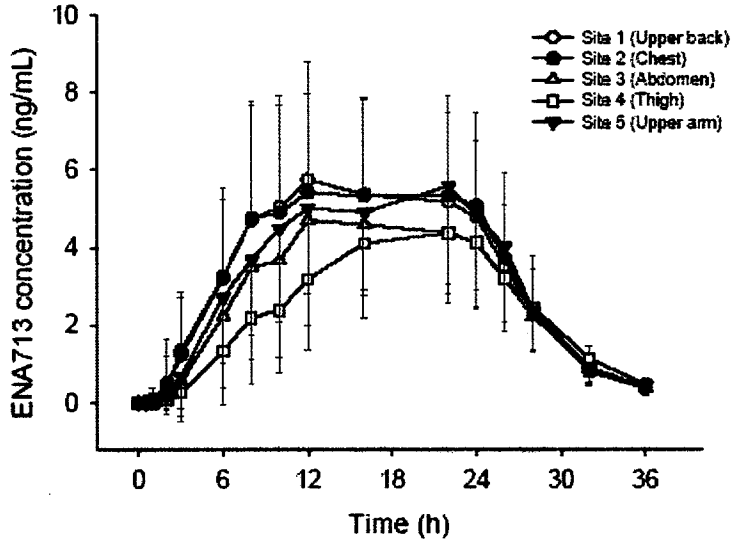
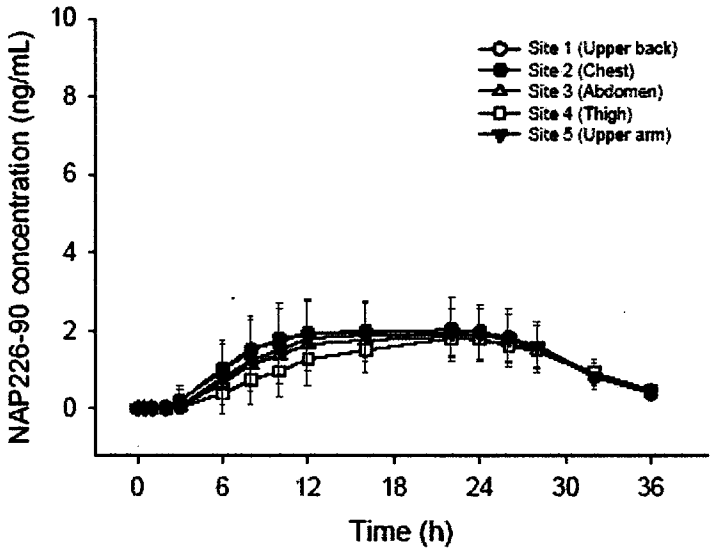


Figure: Mean (+/- SD) plasma concentration-time plots of NAP226-90 following single transdermal administration (10 cm^2, 18 mg rivastigmine) on different application sites



Rivastigmine was slowly absorbed from all application sites and reached measurable plasma levels after comparable lag time of 0.5 to 1.0 h. Visual inspection of the figure above indicates that concentrations then increased progressively reaching plateau concentrations at around 8 hours for the upper back and chest, 10 hours for upper arm, 12 hours for abdomen and 16 hours for outer thigh.

The highest exposure levels of rivastigmine (AUC∞) were obtained when the patch was applied on the upper back (site 1), chest (site 2), and upper arm (site 5), i.e. 128 ± 51.7, **128 ± 57.7, and 118 ± 41.7 h•ng/mL, respectively, vs 103 ± 44 and 91.0 ± 36.8 for the** abdomen (site 3) and thigh (site 4), respectively. Cmax were also highest for the same three application sites, i.e. 6.80 ± 3.20, 6.34 ± 2.58 and 6.58 ± 2.69 ng/mL, respectively, vs. 5.44 ± 2.42 and 4.89 ± 1.91 ng/mL for the other 2 sites, i.e. abdomen and thigh, respectively.

The mean elimination half life of rivastigmine ranged from 3.2 to 3.9 h. This apparent longer half-life after the patch as compared to oral is likely to be due to the fact that there might still be some absorption/diffusion of rivastigmine from the skin after patch removal, which may interfere with the calculation of the true elimination half-life (i.e. 1.4 to 1.7 h after iv administration.

The inter-subject variability for the exposure parameters of rivastigmine was generally moderate, as characterized by coefficients of variation (CV) of 35%–47%.

Generally, mean maximum plasma concentrations of the metabolite were 2.5-3.0 times lower than those of the parent compound. NAP226-90 appeared in plasma between 2 and 3 h after patch application for all sites of application. Plateau concentrations were reached between 12 and 16 h, except when the patch was applied to the thigh (site 4, 22 h). Similar to the parent compound, the exposure to the metabolite, NAP226-90, was highest after patch application to the upper back, chest and upper arm sites. The mean elimination half-life of NAP226-90 ranged from 5.1 to 6.5 h.

The inter-subject variability for the exposure parameters of NAP226-90 was moderate with CV ranging from 28% to 41%.

Relative Bioavailability:

Descriptively, taking the upper back application site (site 1) as the reference site (as upper back was used as the application site in other studies conducted), the chest (site 2), abdomen (site 3), outer thigh (site 4), and upper arm (site 5) application sites achieved 100%, 80%, 71%, and 97%, respectively, of exposure (AUC_∞) achieved by the upper back application site.

The descriptive results of relative bioavailability of rivastigmine from the patch was confirmed by statistical analysis is summarized in the Table below. The abdomen and outer thigh sites showed reduced bioavailability as compared to the upper arm, chest and upper arm. The chest and upper arm were bioequivalent to the upper back.

Table: Summary of statistical analysis on relative bioavailability achieved by test application sites with the upper back application site as reference

PK Parameters	Patch site	N	Geometric Mean	Ratio of geometric mean	90% CI for ratio
AUC_{last} (ng·h/mL)	1 (Upper back)	35	113.53	--	--
	2 (Chest)	39	109.36	0.963	(0.825, 1.125)
	3 (Abdomen)	40	92.54	0.815	(0.698, 0.952)
	4 (Thigh)	39	77.80	0.685	(0.584, 0.804)
	5 (Upper arm)	39	109.87	0.958	(0.829, 1.130)
AUC_∞ (ng·h/mL)	1 (Upper back)	35	117.55	--	--
	2 (Chest)	38	118.42	1.007	(0.883, 1.150)
	3 (Abdomen)	40	94.96	0.808	(0.708, 0.921)
	4 (Thigh)	39	82.69	0.703	(0.614, 0.806)
	5 (Upper arm)	39	113.60	0.966	(0.847, 1.102)
C_{max} (ng/mL)	1 (Upper back)	35	6.34	--	--
	2 (Chest)	39	5.97	0.942	(0.827, 1.073)
	3 (Abdomen)	40	5.01	0.79	(0.694, 0.900)
	4 (Thigh)	39	4.47	0.705	(0.616, 0.806)
	5 (Upper arm)	39	6.17	0.973	(0.854, 1.108)

Patch Adhesion:

Following scores was used to capture comments relating to patch adhesion:
0 = 90 % adhered (essentially no lift off of the skin)
1 = 75% to < 90% adhered (some edges only lifting off of the skin)
2 = 50% to < 75% adhered (less than half of the patch lifting off the skin)
3 = < 50% adhered but not detached (more than half the system lifting off of the skin without falling off)
4 = the patch was completely detached

Comments on additional adhesive qualities (folding, creasing, bubbling, and loosening) was also recorded during each assessment time points

The following Table shows the Patch Adeshion and Drug residuals assessment:

Table: Summary of residual rivastigmine and patch adhesion measurements

Site no.	Patch area attached (%)	Patch content (mg)	Residual content (mg)	Actual dose released (mg)	Actual dose released (%)
1 (Back)	65.9 ± 32.1	18	11.5 ± 2.0	6.54 ± 1.95	36.3 ± 0.83
2 (Chest)	70.6 ± 27.0	18	11.5 ± 1.5	6.48 ± 1.50	36.0 ± 8.34
3 (Abdomen)	83.9 ± 23.9	18	10.7 ± 1.6	7.36 ± 1.63	40.9 ± 9.07
4 (Thigh)	89.3 ± 20.1	18	11.6 ± 1.3	6.40 ± 1.25	35.6 ± 6.93
5 (Upper arm)	75.7 ± 25.6	18	11.8 ± 1.2	6.23 ± 1.16	34.6 ± 6.43

(mean ± SD)

Adhesiveness was best on the thigh with 89% of the patch area remaining attached. Whereas, in terms of amount of ENA713 released, the patch attached to the abdomen performed best with about 40% of the dose released.

The abdomen application site was the only application site with both significantly higher actual area attached and higher actual drug released than the reference upper back application site, but the absolute difference in the amount of actual drug released between the abdomen and upper back application sites was only 0.82 mg. The other test application sites (chest, outer thigh, and upper arm) did have a higher actual area attached, however, the actual amount of drug released from chest, outer thigh, and upper arm application sites were all slightly lower than the actual amount of drug released from the upper back application site.

It is also of interest to point out that abdomen application site, with the 2nd best patch adhesion performance and with the highest amount of drug released, achieved the 2nd lowest drug exposure among the five application sites. The performance of patch adhesion thus seem not to be a major factor that would influence the PK performance of the patch at various application sites.

Skin Irritation:

The following score system was used to assess skin irritation:
Dermal response:
- 0 = No erythema (normal skin)
- 1 = Erythema barely visible
- 2 = Mild erythema
- 3 = Moderate erythema
- 4 = Severe erythema
- 5 = Severe erythema with vesicles or blisters

Over all, skin irritation observed was mild to moderate erythema, and erythema generally disappeared 24 hours after patch removal. No other signs of skin irritations (i.e. edema, papules, etc.) were observed during the study.

Applications to the abdomen and the outer thigh were more likely to develop skin erythema when compared to the upper back application site (odd ratio of 13.7 and 5.9, respectively), applications to the chest and upper arm were less likely to develop skin erythema than the upper back application site (odd ratio of 0.49 and 0.35, respectively).

The odd of developing skin erythema was the highest at the time when the patches were removed from the application sites. As time elapsed, however, the odd of developing erythema also decreased.

Conclusions:

- Both the descriptive results and the statistical analysis demonstrated that similarly high plasma exposure (AUCs) to rivastigmine was obtained when the patch was applied to the chest (100%) and upper arm (97%) application sites when compared to the reference upper back (100%) application site. The 90% CI of the ratio of geometric means for the bioavailability PK parameters (AUCs & Cmax) for the chest and upper arm applications also were within the range required for showing bioequivalence (80-125%) with the upper back application site.
- The exposure to the metabolite NAP226-90 was about 1/3 of that of the parent and followed the same pattern over time as the parent.
- The chest and upper arm application site showed less skin erythema than the upper back application site. In contrast, there was more erythema on the abdomen and outer thigh than on the upper back.
- The performance of patch adhesion does not seem to be a major factor that would influence the PK performance of the patch at various application sites.

RELATIVE BIOAVAILABILITY OF DIFFERENT PATCH FORMULATIONS:

Study 155: ***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***

Objectives:

Primary Objective

- To evaluate and compare the adhesive properties of five formulations (10 cm^2 patches applied for 24 hours) of ENA 713 TDS in non-patient, male volunteers to determine the best formulation to take forward in development.

Secondary Objectives

- To evaluate and compare the pharmacokinetics of five different formulations (10 cm^2 patches applied topically for 24 hours) of ENA 713 TDS in non-patient, male volunteers.
- To evaluate and compare the local skin irritation results of five different formulations
- To evaluate and compare the safety and tolerability of these formulations.

The study design is as follows:

Study Design	Open label, single dose, randomized, five period, five treatment crossover study
Study Population	N= 20 healthy male subjects (several samples were lost and about 12-13 in each group had complete data) Age: 18-50 years (mean age 31.43 years) Gender: 20 males Weight: 55-90 kg (mean 70.95 kg) Race: all Caucasians
Treatment Group	Total Loading Dose = 18 mg, rivastigmine; ~6-12 mg rivastigmine delivered over 24 hours for all 10 cm2 patches: • Treatment A: reference TDS formulation, 10 cm^2 patch , KN # 3742509.00.006, Batch #X123 0896 • Treatment B: test TDS formulation (Test 1), 10 cm^2 patch, KN # 3742509.00.011, Batch #X042 0297 • Treatment C: test TDS formulation (Test 2), 10 cm^2 patch, KN # 3742509.00.013, Batch #X044 0297 • Treatment D: test TDS formulation (Test 3), 10 cm^2 patch, KN # 3742509.00.014, Batch #X045 0297 • Treatment E: test TDS formulation (Test 4), 10 cm^2 patch, KN # 3742509.00.015, Batch # X046 0297

<table>
<tr><td>Dosage and Administration</td><td>Patch applied for 24 hours at five pre-selected body sites (three on the left scapular back area, two on the right scapular back area) of healthy subjects.

Both left and right side of the body were used for patch application.
<table>
<tr><th>Left Scapular Back Region</th><th>Right Scapular Back Region</th></tr>
<tr><td>Application 1 (Period 1/Day 1): Test Site 1 – Top</td><td>Application 4 (Period 4/Day 1): Test Site 4 – Top</td></tr>
<tr><td>Application 2 (Period 2/Day 1): Test Site 2 – Middle</td><td>Application 5 (Period 5/Day 1): Test Site 5 – Middle</td></tr>
<tr><td>Application 3 (Period 3/Day 1): Test Site 3 – Bottom</td><td></td></tr>
</table>
<u>Diet:</u>
all subjects had to undergo a 10 hour overnight fast prior to patch application and continue to fast for additional 2 hours post-patch application.
Standard breakfast, lunch and dinner was served at 2, 5 and 10 hours post-patch application, respectively
<u>Washout:</u>
6 days washout between two treatments</td></tr>
<tr><td>Sampling: Blood</td><td>For rivastigmine and its metabolite, NAP 226-90:

At predose, 3, 6, 8, 12, 16, 20, 24, 26, 28, 32, 36, 40 and 48 hours post-dose.</td></tr>
<tr><td>Urine</td><td>none</td></tr>
<tr><td>Feces</td><td>none</td></tr>
<tr><td>Analysis</td><td>LC/MS/MS method

Lower Limits of Quantitation
<u>Plasma</u> <u>Urine</u>
Rivastigmine 0.2 ng/mL none
NAP 226-90 0.2 ng/none

<u>Plasma:</u>
Linear Range: 0.2-30 ng/ml in plasma for both moeities
Quality control concentrations: 0.4, 5.0 and 25 ng/ml
Inter-day precision: < 8.7% CV for both moieties
Inter-day accuracy: within -0.8 to11% both moieties</td></tr>
<tr><td>PK Assessment</td><td>AUC0-24, AUC0-24norm, AUC0-∞, AUC0-∞ norm, Cmax, Cmaxnorm, Tmax, t1/2, tlag</td></tr>
<tr><td>Safety Assessment</td><td>Physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, hematology), and adverse event monitoring</td></tr>
<tr><td>PGx Assessment</td><td>none</td></tr>
<tr><td>PD Assessment</td><td><u>none</u></td></tr>
<tr><td>Other Assessment</td><td><u>Patch adhesion assessment</u> right after application (0 hr), and 4, 8, 12, 24 hours post application;</td></tr>
</table>

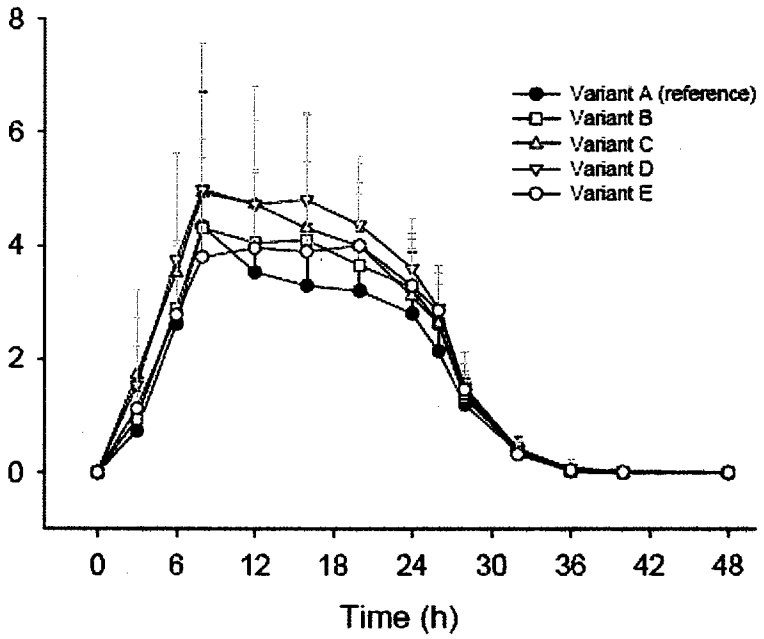
	Adhesive Strength: Patches were also assessed for adhesive strength using the Adhesive Strength Measuring Unit (ASM) using the following variables. AUC: Area under the curve (AUC) [mN*s] at 24 hours post-application. Fmax: Maximum strength (Fmax) [mN] at 24 hours post-application. Skin irritation assessment within 0.5 hour prior to and after patch application

Pharmacokinetic Results:

Rivastigmine:

The mean plasma concentration profile for rivastigmine for all five formulations is given below:

Figure: Mean (± SD) plasma concentration-time profile of rivastigmine following a single 24 hour patch application



The mean parameters of rivastigmine is given in the following Table:

Table: Mean (±SD) pharmacokinetic parameters of rivastigmine following a single 24-hour TDS application

Parameter	Arithmetic Mean ± SD Coefficient of Variation (CV%)				
	Treatment A (N=13) [Reference]	Treatment B (N=12) [Test 1]	Treatment C (N=12) [Test 2]	Treatment D (N=13) [Test 3]	Treatment E (N=14) [Test 4]
$AUC_{(0-t)}$ (ngxhr/mL)	79.48±28.02 35.3	90.70±28.77 31.7	100.31±41.65 41.5	106.84±30.76 28.8	91.30±29.58 32.4
$AUC_{(0-\infty)}$ (ngxhr/mL)	80.97±28.66 35.4	91.97±28.72 31.2	101.39±41.90 41.3	107.95±30.91 28.6	92.64±29.66 32.0
C_{max} (ng/mL)	4.53±2.29 50.6	4.71±1.41 30.0	5.54±2.34 42.3	5.65±1.77 31.4	4.65±1.72 36.9
t_{max} (hr)	12.15±4.93 40.6	12.67±5.07 40.0	12.00±4.51 37.6	12.62±5.12 40.6	14.57±4.86 33.4
$t_{1/2}$ (hr)	2.48±0.64 25.8	2.43±0.49 20.0	2.23±0.28 12.5	2.25±0.40 17.6	2.22±0.46 20.8
$AUC_{(0-t)}/D^a$ (ngxhr/mL/mg)	9.20±3.14 34.1	10.38±2.74 26.4	10.32±3.15 30.5	9.81±2.42 24.7	11.13±2.61 23.4
$AUC_{(0-\infty)}/D^a$ (ngxhr/mL/mg)	9.37±3.19 34.0	10.52±2.73 25.9	10.44±3.16 30.3	9.91±2.42 24.4	11.29±2.59 22.9
C_{max}/D^a (ng/mL/mg)	0.53±0.29 54.7	0.54±0.13 24.1	0.57±0.18 31.6	0.52±0.14 26.9	0.57±0.16 28.1

[a] Dose normalized based on residual drug content of individual patch.

All five formulations produced a sustained plasma concentration time profile of rivastigmine. Rivastigmine was slowly absorbed with an average t_{max} of about 12-hour. The average terminal elimination half-life of rivastigmine ranged from 2.22 to 2.48 hours for all the treatments.

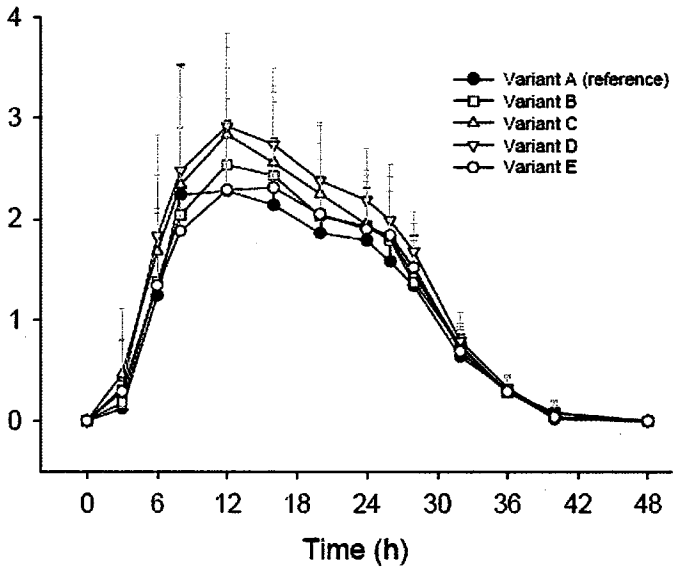
The intersubject variability for the pharmacokinetic parameters was moderate for rivastigmine (coefficient of variation, CV of 28.6-41.3% for $AUC_{0-\infty}$). However, following oral administration, the intrasubject variability is low and has been reported to be about 20% for rivastigmine (CV of 23% for $AUC_{0-\infty}$)

For dose normalized AUC and Cmax, no significant difference was found between the test Treatments B, C, D and E and the reference Treatment A.

NAP 226-90:

The mean plasma concentration profile for NAP 226-90 for all five formulations is given in the following Figure:

Figure: Mean (± SD) plasma concentration-time profile of NAP 226-90 following a single 24 hour patch application



The pharmacokinetic parameters for NAP 226-90 are given in the following Table:

Table: Mean (±SD) pharmacokinetic parameters of NAP226-90 following a single 24-hour patch application

Parameter	Arithmetic Mean ± SD Coefficient of Variation (CV%)				
	Treatment A (N=13)	Treatment B (N=12)	Treatment C (N=12)	Treatment D (N=13)	Treatment E (N=14)
$AUC_{(0-t)}$ (ngxhr/mL)	51.27±16.72 32.6	57.15±18.34 32.1	60.38±16.97 28.1	63.93±17.82 27.9	54.01±17.84 33.0
$AUC_{(0-\infty)}$ (ngxhr/mL)	53.02±16.76 31.6	58.78±18.12 30.8	61.87±16.81 27.2	65.38±17.90 27.4	55.66±17.58 31.6
C_{max} (ng/mL)	2.57±1.16 45.1	2.73±0.95 34.7	2.89±0.83 28.7	3.04±0.99 32.6	2.53±0.90 35.4
t_{max} (hr)	12.00±2.83 23.6	15.67±5.25 33.5	13.83±4.47 32.3	15.23±5.75 37.7	14.86±6.11 41.1
$t_{1/2}$ (hr)	3.90±0.87 22.3	3.99±0.59 14.8	3.80±0.54 14.1	3.44±0.24 7.0	3.63±0.51 14.1
$AUC_{(0-t)}/D^a$ (ngxhr/mL/mg)	5.93±1.82 30.7	6.54±1.66 25.4	6.33±1.54 24.3	5.88±1.41 24.0	6.66±1.94 29.1
$AUC_{(0-\infty)}/D^a$ (ngxhr/mL/mg)	6.13±1.83 29.8	6.73±1.64 24.4	6.49±1.54 23.7	6.02±1.41 23.4	6.87±1.93 28.1
C_{max}/D^a (ng/mL/mg)	0.30 ±0.15 50.0	0.31±0.08 25.8	0.30±0.07 23.3	0.28±0.08 28.6	0.31±0.10 32.3

[a] Dose normalized based on residual drug content of individual patch.

The average time to peak plasma concentrations of NAP 226-90 ranged from 12.0 to 15.67 hours. The average terminal elimination half-life of NAP 226-90 ranged from 3.44 to 3.99 hours for all the treatments.

The intersubject variability for the pharmacokinetic parameters of NAP 226-90 were smaller compared to the parent compound (coefficient of variation, CV of 27.2-31.6% for $AUC_{0-\infty}$). Also, following oral administration, the intrasubject variability has been reported to be low for NAP 226-90 and is somewhat smaller (CV of 9% for $AUC_{0-\infty}$) compared to rivastigmine.

Residual Rivastigmine remaining in the patch:

The average (±SD) residual drug in the patch for treatments A (reference), B, C, D and E were 10.0±1.2 mg, 9.3±1.4 mg, 8.4±1.5 mg, 6.8±1.0 mg and 9.6±1.3 mg, respectively. As expected, both C_{max} and $AUC_{0-\infty}$ appeared to be related to % dose available for delivery from the patch

Adhesion Assessment:

In order to measure the percent attached and detached, planimetry was performed on each patch. A transparent film was placed over the patch directly on the skin. All detached areas of the patch recorded on the transparent film and marked with a Sharpie black marker were scanned into the computer and the percent attached and detached was calculated at 12 and 24 hours post-application.

For *adhesive strength* measurements, an ASM unit, a validated measuring instrument that consists of a lifting device fixed at a post **above the subject's bed. The patch tested is** connected through a piece of nylon-thread with a strength sensor attached to the lifting device. When pedals are depressed, the lifting device moves upward and pulls the patch **off the subject's skin. The strength needed is** registered by a wire strain gauge in the force transducer and is transferred to a personal computer for downloading.

The patch attachment, strength and dose delivered are shown in the following Table: No correlation was found between the dose delivered and the patch adhesiveness ($r = 0.35$) or strength rating (AUC, $r = 0.199$ and F_{max}, $r = 0.178$).

Table: Dose Delivered, Patch Attachment and Strength Measurements

Twenty four hours post-application

Treatment	Reference A	B	C	D	E
Dose Delivered					
Mg delivered (mean ±SD) (range)	8.52±1.15 (6.8-10.6)	9.02±1.39 (7.1-11.9)	9.69±1.52 (6.6-12.8)	10.65±0.95 (8.3-12.4)	8.51±1.31 (5.8-11.4)
% delivered (mean)	47.33	50.08	53.83	59.14	47.28
Patch Attachment					
Attached (mm2) (mean ±SD)	519.30 ± 226.10	520.35 ±234.08	720.55 ±230.50	767.62 ±145.93	831.94 ±136.69
% attached (mean)	51.93	52.04	72.06	76.76	83.19
Adhesive Strength Measurements					
AUC (mean ±SD) (AUC) [mN*s}	974.89 ±921.83	1265.67 ±1143.24	2247.27 ±993.62	2415.95 ±1026.49	3265.20 ±1613.35
Maximal Force (mean ±SD) (F_{max}) [mN]	1165.34 ±1009.53	1508.38 ±1125.41	2400.18 ±1339.71	2576.09 ±1020.67	3464.71 ±1842.80

Local Skin Irritation:

Patch application sites were rated for edema, erythema, fissures and scaling at pre-dose and within 0.5 hour after patch removal (hour 24).
Edema: Very slight edema was noted for 2 subjects upon patch removal (one subject each for Treatment C and Treatment E). All other results were negative for edema.
Erythema: For each treatment, approximately one-third of the subjects (n = 6-7 per 20 subjects) had no erythema and approximately 50-60% of the subjects (n = 9-12 per 20 subjects) had very slight erythema upon patch removal. Treatment E resulted in slightly more subjects with a rating of well recognizable erythema (n = 5 vs. 2-3 per 20 subjects). No subjects were rated as having moderate erythema or strong fiery red erythema.
Fissures: All formulations were negative for producing fissures.
Scaling: All formulations were negative for producing scaling.

Conclusions:

- Sustained plasma concentrations of rivastigmine and NAP 226-90 were maintained from 8 to 24 hours after patch application. There were no statistically significant differences in dose normalized $AUC_{(0-t)}/D$, $AUC_{(0-\infty)}/D$, and C_{max}/D of rivastigmine and NAP 226-90 between the test patches (Treatments B, C, D and E) and the reference patch (Treatment A). Overall, the pharmacokinetics of rivastigmine and NAP 226-90 were essentially similar for all treatments.

- The transdermal patches used in Treatment C, D and E possessed superior adhesive properties over the 24-hour patch application period when compared to the reference patch used in Treatment A.

Study 159: ***A study to evaluate adhesiveness of five formulations of SDZ ENA713 transdermal delivery system (TDS) and two application sites, employing an Estraderm™ placebo reference, in healthy male volunteers.***

Objectives:

Primary Objective

- To evaluate and compare the adhesive properties of five formulations (10 cm^2 patches applied for 24 hours) of ENA 713 TDS in non-patient, male volunteers.

Secondary Objectives

- To evaluate and compare the pharmacokinetics of five different formulations (10 cm^2 patches applied topically for 24 hours) of ENA 713 TDS in non-patient, male volunteers.
- To evaluate and compare the local skin irritation results of five different formulations
- To evaluate and compare the safety and tolerability of these formulations.

The study design is as follows:

<table>
<tr><td>Study Design</td><td>Single-blind, single dose, randomized, 11-period, crossover study</td></tr>
<tr><td>Study Population</td><td>N= 20 healthy male subjects for phase I and II and 19 for Phase III (1 withdrew for personal reasons)
Age: 18-50 years (mean age 31.43 years)
Gender: 20 males
Weight: 55-90 kg (mean 70.95 kg)
Race: all Caucasians</td></tr>
<tr><td>Treatment Group</td><td>Total Loading Dose = 18 mg, rivastigmine; ~6-12 mg rivastigmine delivered over 24 hours for all 10 cm^2 patches:
Phase I (treatment period 1-5) : Applied to upper back using an air pressured device
<table>
<tr><th>Variant</th><th>Description</th><th>Specification</th><th>Batch number</th></tr>
<tr><td>A</td><td>New TDS Test 1 (LTS formulation J)</td><td>As variant E, with silicone oil added, double thickness acrylic layer.</td><td>8/21175/048</td></tr>
<tr><td>B</td><td>New TDS Test 2 (LTS formulation M)</td><td>As variant E, with small part of Duratak tackifier replaced by Foral tackifier in both the active matrix and acrylic layer.</td><td>8/21182/048</td></tr>
<tr><td>C</td><td>New TDS Test 3 (LTS formulation O)</td><td>As variant E, with silicone oil added.</td><td>8/21177/048</td></tr>
<tr><td>D</td><td>New TDS Test 4 (LTS formulation P)</td><td>As variant E, with different tackifier, double thickness acrylic layer.</td><td>8/21179/048</td></tr>
<tr><td>E</td><td>Reference TDS (LTS formulation N)</td><td>Round shape, 23 µm thick backing layer</td><td>8/21173/048</td></tr>
<tr><td>Estraderm™ Placebo</td><td>Currently marketed Estraderm™ (matrix) patch without active ingredient</td><td>E2 MX / placebo</td><td>8/21187/048</td></tr>
</table></td></tr>
</table>

	Phase II (treatment period 6-10) : Applied to lower back using an air pressured device Phase III (treatment period 11) : the patch that had demonstrated the best adhesiveness in Phase I (variant A) was attached to the upper back via bare-hand application, while a placebo patch was attached to a symmetrical site using the air-pressurized device.
Dosage and Administration	Patch applied for 24 hours at pre-selected body sites of healthy subjects. Diet: all subjects had to undergo a 10 hour overnight fast prior to patch application and continue to fast for additional 2 hours post-patch application. Standard breakfast, lunch and dinner was served at 2, 5 and 10 hours post-patch application, respectively Washout: 48 hours washout between two treatments
Sampling: Blood	For rivastigmine and its metabolite, NAP 226-90: At predose, 3, 6, 8, 12, 16, 20, 24, 26, 28, hours post-dose.
Urine	none
Feces	none
Analysis	GC/MS method Lower Limits of Quantitation Rivastigmine: Plasma 0.2 ng/mL; Urine none NAP 226-90: Plasma 0.2 ng/none Plasma: Linear Range: 0.2-15 ng/ml in plasma for both moeities Quality control concentrations: 0.3, 2.5 and 12.5 ng/ml Inter-day precision: < 17.6% CV for both moieties Inter-day accuracy: within -2.4 to 2.4% both moieties
PK Assessment	AUC0-24, AUC0-24norm, AUC0-∞, AUC0-∞ norm, Cmax, Cmaxnorm, Tmax, t1/2, tlag
Safety Assessment	Physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, hematology), and adverse event monitoring
PGx Assessment	none
PD Assessment	none
Other Assessment	Patch adhesion assessment right after application (0 hr), and 4, 8, 12, 24 hours post application; Adhesive Strength: Patches were also assessed for adhesive strength using the Adhesive Strength Measuring Unit (ASM) using the following variables. AUC: Area under the curve (AUC) [mN*s] at 24 hours post-application.

	Fmax: Maximum strength (Fmax) [mN] at 24 hours post-application. Skin irritation assessment: 24 hours after patch application, at patch removal

Pharmacokinetic Results:

Rivastigmine and NAP226-90:

Mean plasma levels of rivastigmine and NAP226-90 resulting from application of the five different patches were quite similar.

Figure: Mean (plus/minus SD) rivastigmine (left panel) and NAP226-90 (right panel) plasma concentration-time profiles after single 24-hr applications of rivastigmine patch variants 10 cm^2 (18 mg) in healthy male subjects

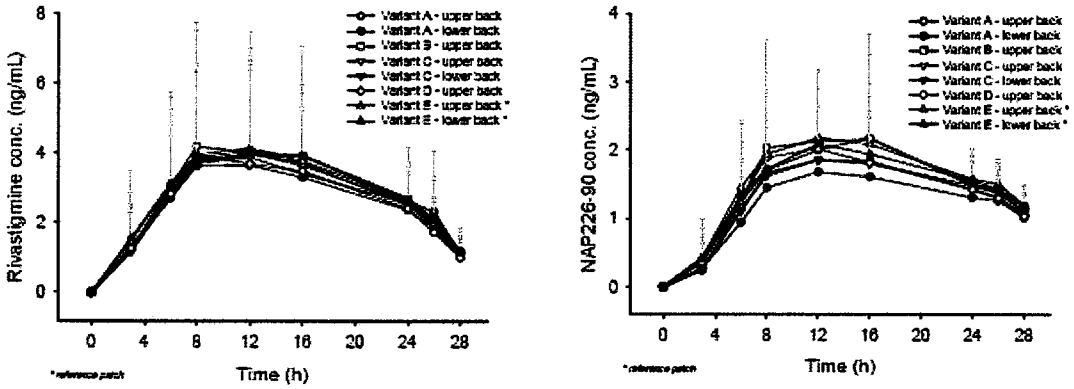


Table: Summary of pharmacokinetic parameters of rivastigmine following single 24-hr applications of rivastigmine patch variants 10 cm^2 (18 mg) on the upper or lower back in healthy male subjects

	Variant A	Variant B	Variant C	Variant D	Variant E [reference]
Upper back application site (n = 20)					
t_{lag} (h)	0.75 ± 1.92 (256%)	0.75 ± 1.65 (220%)	0.75 ± 1.65 (220%)	1.05 ± 2.01 (192%)	0.60 ± 1.57 (262%)
C_{max} (ng/mL)	4.65 ± 2.97 (63.8%)	4.76 ± 3.27 (68.6%)	4.22 ± 2.63 (62.2%)	4.43 ± 2.64 (59.5%)	4.52 ± 2.58 (57.0%)
t_{max} (h)	12.8 ± 5.17 (40.4%)	12.4 ± 3.15 (25.4%)	12.0 ± 4.10 (34.2%)	13.1 ± 5.64 (43.0%)	12.2 ± 4.20 (34.4%)
$AUC_{0\text{-}24h}$ (ng·h/mL)	70.8 ± 42.8 (60.4%)	72.3 ± 43.4 (60.0%)	68.1 ± 41.1 (60.4%)	68.2 ± 40.2 (58.9%)	74.0 ± 39.4 (53.2%)
Lower back application site (n = 20)					
t_{lag} (h)	1.05 ± 2.01 (192%)	na	0.60 ± 1.23 (205%)	na	0.75 ± 1.33 (178%)
C_{max} (ng/mL)	4.15 ± 3.71 (89.6%)	na	4.38 ± 2.97 (67.8%)	na	4.66 ± 3.57 (76.6%)
t_{max} (h)	12.4 ± 4.48 (36.1%)	na	13.5 ± 4.25 (31.5%)	na	13.2 ± 4.65 (35.2%)
$AUC_{0\text{-}24h}$ (ng·h/mL)	65.1 ± 50.6 (77.8%)	na	72.3 ± 50.1 (69.3%)	na	74.4 ± 56.8 (76.3%)

Values are arithmetic mean ± standard deviation and (CV%); na = not available.

Table: Summary of pharmacokinetic parameters of NAP226-90 following single 24-hr applications of rivastigmine patch variants 10 cm_2 (18 mg) on the upper or lower back in healthy male subjects

	Variant A	Variant B	Variant C	Variant D	Variant E [reference]
Upper back application site (n = 20)					
t_{lag} (h)	2.30 ± 2.43 (106%)	1.45 ± 2.33 (161%)	1.90 ± 2.29 (121%)	1.45 ± 2.33 (161%)	1.20 ± 2.04 (170%)
C_{max} (ng/mL)	2.39 ± 1.59 (66.5%)	2.43 ± 1.40 (57.6%)	2.04 ± 0.74 (36.2%)	2.19 ± 0.82 (37.4%)	2.33 ± 1.07 (46.0%)
t_{max} (h)	15.0 ± 3.87 (25.8%)	12.6 ± 3.25 (25.8%)	15.6 ± 6.28 (40.2%)	13.6 ± 5.86 (43.1%)	13.2 ± 5.09 (38.5%)
$AUC_{0\text{-}24h}$ (ng·h/mL)	36.1 ± 20.3 (56.2%)	38.0 ± 19.3 (50.9%)	32.6 ± 13.4 (41.1%)	34.8 ± 14.5 (41.8%)	38.4 ± 17.9 (46.6%)
Lower back application site (n = 20)					
t_{lag} (h)	2.20 ± 2.21 (101%)	na	1.81 ± 2.05 (113%)	na	1.80 ± 2.26 (126%)
C_{max} (ng/mL)	1.86 ± 0.70 (37.4%)	na	2.06 ± 0.80 (38.9%)	na	2.33 ± 1.03 (44.2%)
t_{max} (h)	15.8 ± 5.39 (34.1%)	na	15.4 ± 5.66 (36.7%)	na	15.5 ± 4.58 (29.6%)
$AUC_{0\text{-}24h}$ (ng·h/mL)	29.2 ± 11.9 (40.8%)	na	32.7 ± 13.2 (40.3%)	na	36.1 ± 17.3 (47.9%)

Values are arithmetic mean ± standard deviation and (CV%); na = not available.

Residuals in the patch:

No substantial differences were noticed regarding the percentage of drug released from the 5 patches applied to upper and lower back. The average (± SD) residual drug in the patches was in the range from 9.03 ± 1.78 mg to 9.53 ± 1.56 mg, indicating that approximately 50% of drug load (18 mg) was released from the systems.

Patch Adhesiveness:

Three methods were used to assess adhesiveness:

- The test patches were visually and mechanically inspected using a spatula and adhesiveness was assessed using a scale which measured the percentage of folding, creasing, bubbling and other unspecified patch loosening, and also the approximate percentage of the patch that was detached because of these factors. The test patches were photographed at each adhesiveness evaluation.
- As a quantitative assessment of patch attachment, the detached areas of the patches were measured by planimetric means.
- The adhesive strength of the patches was evaluated at patch removal using a validated measuring instrument.

Visual Assessment: Generally, there were no differences between the patch variants in terms of the number of subjects exhibiting loosening effects. In addition, there were no differences between active patches and placebo patches. For all variants, the number of subjects with folding observed in the patches tended to increase slightly over time, being most frequently observed at 12 or 24 hours after application. At 24 hours post-application up to 60% and 50% of the patch area for active patches and placebo patches were folded, respectively. Creasing of patches was very frequent for all active and placebo patch variants. Bubbling of patches was infrequently observed. Percentages of the patch area detached due to other loosening reasons were as high as 90%.

Plannimetric Assessment: For all patch variants, and for the placebo patches, the detached patch area (assessed by planimetric methods) increased over time following application. Mean values of the detached areas at 12 and 24 hours post-application are presented in the following table.

Table: Mean values of detached areas (cm^2), 12 and 24 hours after patch application to the upper back (Phase I)

Time post-application	Patch variant	Active (N=20)	Placebo (N=20)	Ratio of means (Active: Placebo)
12 h	A	0.25	1.03	0.24
	B	0.41	0.42	0.98
	C	0.57	0.56	1.02
	D	0.89[a]	0.62	1.44
	E	0.82	0.71	1.15
24 h	A	0.55	1.29	0.43
	B	0.93	1.65	0.56
	C	0.89	1.06	0.84
	D	3.10[a]	1.44	2.15
	E	1.49	1.47	1.01

N = Number of subjects

[a] N=19 (patch fell off for Subject 14 prior to assessment at 8 hours post-application)

In the upper back, Variant A had the smallest detachment and D the greatest at both 12 and 24 hours. This was more obvious in the active group.

Table: Mean values of detached areas (cm^2), 12 and 24 hours after patch application to the lower back (Phase II)

Time post-application	Patch variant	Active (N=20)	Placebo (N=20)	Ratio of means (Active: Placebo)
12 h	A	0.40	0.26	1.54
	B	0.41	0.18	2.28
	C	0.38	0.27	1.41
	D	0.64	0.25	2.56
	E	0.22	0.24	0.92
24 h	A	0.82	0.75	1.09
	B	0.82	0.69	1.19
	C	1.07	1.10	0.97
	D	1.99	1.09	1.83
	E	0.85	0.93	0.91

Similar trend was seen on the lower back, although the difference between placebo and active at 24 hours was less at this site.

The mean values in the three phases is given below:

Table: Mean values of detached areas (cm^2), 12 and 24 hours after application of patch variant A (Phases I to III)

Time post-application	Phase[a]	Active (N=20)	Placebo (N=20)	Ratio of means (Active: Placebo)
12 h	I	0.25	1.03	0.24
	II	0.40	0.26	1.54
	III	0.62[b]	1.13[b]	0.55
24 h	I	0.55	1.29	0.43
	II	0.82	0.75	1.09
	III	0.68[b]	1.57[b]	0.43

[a] Phase I = air-pressurized application to upper back; Phase II = air-pressurized application to lower back; Phase III = hand application to upper back (active patch only)

N = Number of subjects

[b] N = 19 for Phase III

Overall, for upper back application, patch variant A appeared to have the best adhesiveness and variant D the worse (detached area approximately 2-fold greater). Variants B and C had similar mean detached areas, which were smaller than for reference variant E. For lower back application, adhesiveness was similar for patch variants A, B, C, and E. There did not appear to be any difference between the adhesiveness of patch variant A when applied using the air-pressurized device (Phases I and II) and when applied by hand (Phase III).

Adhesive Strength:

Adhesive strength for the two phases is given in the following Table:

Table: Adhesive strength parameters (Phase I)

Parameter	Patch variant	Active (N=20)	Placebo (N=20)	Ratio of means (Active: Placebo)
t_{tot}	A	2.08	1.80	1.16
(s)	B	2.05	1.82	1.13
	C	1.93	1.82	1.06
	D	1.75[a]	1.82	0.96
	E	1.95	1.78	1.10
AUC_{0-t}	A	2446.32	2192.53	1.12
(mN*s)	B	2571.07	2347.83	1.10
	C	2274.09	2076.93	1.09
	D	1216.61[a]	2294.46	0.53
	E	1946.33	2220.21	0.88
MFT	A	1.37	1.33	1.03
(s)	B	1.40	1.40	1.00
	C	1.38	1.42	0.97
	D	1.44[a]	1.33	1.08
	E	1.40	1.30	1.08
F_{mean}	A	1202.83	1244.10	0.97
(mN)	B	1247.27	1356.67	0.92
	C	1236.80	1158.99	1.07
	D	677.15[a]	1289.38	0.53
	E	999.89	1294.40	0.77
F_{max}	A	2253.70	2145.1	1.05
(mN)	B	2474.74	2324.59	1.06
	C	2162.15	1876.5	1.15
	D	1276.01[a]	2162.17	0.59
	E	1833.81	2220.7	0.83
t_{max}	A	0.86	1.05	0.82
(s)	B	0.87	0.99	0.88
	C	0.95	0.89	1.07
	D	0.96[a]	0.92	1.04
	E	0.91	0.97	0.94

N = Number of subjects

[a] N=19 (variant D fell off for Subject 14 prior to assessment at 8 hours post-application)

Where t_{tot} =Total time.

AUC_{0-t} = Area under data.

MFT =Mean force time.

F_{mean} =Mean force.

F_{max} =Maximal force.

t_{max} =Time of maximal force.

Variant D required less force for removal, rest of the paramters were similar between active and placebo.

Table: Adhesive strength parameters (Phase II)

Parameter	Patch variant	Active (N=20)	Placebo (N=20)	Ratio of means (Active: Placebo)
t_{tot} (s)	A	1.98	1.92	1.03
	B	1.90	1.90	1.00
	C	1.95	1.96	0.99
	D	1.90	2.05	0.93
	E	2.02	1.97	1.03
AUC_{0-t} (mN*s)	A	2658.36	2678.98	0.99
	B	2595.42	2522.55	1.03
	C	2135.67	2271.04	0.94
	D	1985.63	2578.75	0.77
	E	2246.14	2732.13	0.82
MFT (s)	A	1.49	1.44	1.03
	B	1.47	1.43	1.03
	C	1.42	1.45	0.98
	D	1.37	1.54	0.89
	E	1.58	1.48	1.07
F_{mean} (mN)	A	1344.07	1387.82	0.97
	B	1356.98	1311.12	1.03
	C	1073.76	1182.88	0.91
	D	1042.97	1210.36	0.86
	E	1129.38	1385.97	0.81
F_{max} (mN)	A	2264.65	2264.68	1.00
	B	2258.62	2089.02	1.08
	C	1810.56	2019.37	0.90
	D	1782.47	2112.33	0.84
	E	1892.40	2311.15	0.82
t_{max} (s)	A	1.15	1.14	1.01
	B	1.13	1.06	1.07
	C	1.08	1.07	1.01
	D	1.08	1.09	0.99
	E	1.21	1.27	0.95

N = Number of subjects

In Phase II, for variants A, B, and C, mean values of AUC_{0-t}, F_{mean}, and F_{max} were again similar to those observed for the concurrently applied placebo patches. Variant D and the reference patch variant E required less force for removal.
Phase III also had results similar to the above two phases.

Skin Irritation:

The frequency of erythema was greater for the active patch variants compared to the concurrently applied placebo patches (Estraderm^{TM}) when skin irritation was assessed at the time of patch removal, 24 hours post-application, as seen in the following Table. The frequency and rating of erythema was similar for Patch A when applied using the airpressurized device and when applied by hand. There was little evidence of scaling and no evidence of fissures 24 hours post-application of active and placebo patches. Additional, unscheduled skin irritation assessments were performed for some subjects at 28 and 30 hours post-application (i.e. 4 and 6 hours after patch removal). There were no clinically important findings at these time points.

Table: Frequency of erythema 24 hours after patch application

		Active		Placebo	
Patch variant	Rating	Upper back	Lower back	Upper back	Lower back
A	0	1	2	11	18
[air-pressurized]	1 or 2	18	18	9	2
(N=20)	3	1	0	0	0
A	0	1		16	
[hand applied][a]	1 or 2	18	NP	3	NP
(N=19)	3	0		0	
B	0	2	0	13	15
(N=20)	1 or 2	17	19	7	5
	3	1	1	0	0
C	0	3	2	10	15
(N=20)	1 or 2	17	17	10	5
	3	0	1	0	0
D	0	5	3	13	14
(N=20)	1 or 2	15	16	7	6
	3	0	1	0	0
E	0	3	2	12	16
(N=20)	1 or 2	17	17	8	4
	3	0	1	0	0

[a] Hand application for active patch only

0 = Negative

1 = Very slight, punctiform or diffuse erythema

2 = Well recognizable, locally restricted erythema

3 = Moderately strong erythema

N = Number of subjects

NP = Not performed

Conclusions:

- In Phase I (upper back application), patch variant A appeared to have the best adhesiveness of the ENA713 TDS patch variants in terms of detached area, as

assessed by planimetric methods. The adhesiveness of ENA713 TDS patch variant D appeared to be weaker than for the other variants and for the corresponding placebo patches.

- Adhesiveness of patch variant A was compared with application by use of an airpressurized device (Phases I and II) or by hand (Phase III). Adhesiveness of patch variant A was similar for both methods.
- Adhesive strength parameters (e.g. AUC_{0-t} and F_{max}), as determined using a mechanical device, were generally similar for all variants, with the exception of patch variant D, which required less force for removal than the other variants.
- No substantial differences in pharmacokinetics were observed between upper back or lower back applications.