to increased exposure after oral administration. The high variability in the bioavailability with the 40 mg dose (50-157%) may be explained with the irregular diet (c) another reason could be non linearity at the lower doses (with three doses this could not accurately be ruled out).

- It is not clear why the bioavailability reduces with increase of dose. The high bioavailability cannot be explained by merely the plasma levels being close to the LLOQ, because basing bioavailability calculations on AUC0-t also gave bioavailabilities greater than 100.
- The results of this study should be treated with caution and is best not used for any labeling purposes.
- This study should be repeated in a controlled setting to accurately characterize the absolute bioavailability of memantine.

Dose Proportionality:

- A power analysis showed that the pharmacokinetic parameters were proportional in the range of 10-40 mg memantine.

APPEARS THIS WAY
ON ORIGINAL

Study: 1E1801/SunY7017: Safety and Pharmacokinetic Study of a single oral dose of SUN Y7017 in Healthy Adult Males

The study design is as follows:

Study Design	Placebo controlled, single blind, single dose study
Study Population	N=32 subjects Age: 21-35 years Gender: males and females Weight: NA Race: Japanese
Treatment Group	Memantine or placebo was administered as follows: Group 1: 1 x 5 mg memantine tablet (N=6) or placebo (N=2) Group 2: 1 x 10 mg memantine tablet (N=6) or placebo (N=2) Group 3: 2 x 10 mg memantine tablet (N=6) or placebo (N=2) Group 4: 4 x 10 mg memantine tablet (N=6) or placebo (N=2) Doses administered stepwise after confirming safety.
Dosage and Administration	All subjects received a single dose of the assigned dosing of memantine under fasting conditions administered with 150 ml water. 5 mg tablet lot no: 8Y22 10 mg tablet lot no: 8Y23 Placebo lot no. 8715
Sampling: Blood	At 0 (pre-dose), 1, 2, 4, 6, 8, 13, 24, 72, 168, 336, and 504 hours post-dose following administration of 5, 10, and 40 mg memantine and At 0 (pre-dose) 1, 2, 4, 6, 8, 13, 24, 72, 96, 120, 144, 168, 336, and 504 hours post-dose following administration of 20 mg memantine. At pre-dose and every 24 hours until Day 3 for the 5, 10, and 40 mg doses and until Day 7 for the 20 mg dose.
Urine	At pre-dose and every 24 hours until Day 3 for the 5, 10, and 40 mg doses (up to 72 hour post dose) and until Day 7 for the 20 mg dose (up to 168 hours post dose)
Feces	none
Analysis	— for memantine samples Lower Limits of Quantitation Plasma Urine Memantine — Plasma: — — from nominal concentration. quality control concentrations, — Urine: — quality control concentrations, — Stability complete Assay validation complete and acceptable
PK Assessment	AUC, Cmax, Tmax, t1/2, MRT

Safety Assessment	Blood pressure, pulse rate respiratory rate, ECG, Laboratory tests, hematology, blood chemistry

Pharmacokinetic Results:

The pharmacokinetic parameters of memantine in plasma and in urine are summarized in the following Table:

Table:
Pharmacokinetic Parameters (Mean ± SD) of Memantine in Plasma and Urine Following Single Oral Doses of 5, 10, 20, and 40 mg in Healthy Male Japanese Subjects

Parameter	*Group 1: 5 mg (n=6)*	*Group 2: 10 mg (n=6)*	*Group 3: 20 mg (n=6)*	*Group 4: 40 mg (n=6)*
^{C}max (ng/mL)	6.86 ± 0.66	12.18 ± 1.68	28.98 ± 3.65	60.11 ± 13.08
^{T}max (h)	5.3 ± 2.1	5.3 ± 1.6	6.0 ± 3.8	4.5 ± 2.3
^{AUC}0-t (ng h/mL)	431.9 ± 52.7	924.4 ± 155.0	2362.2 ± 476.4	4708.3 ± 538.7
^{AUC}0-∞ (ng h/mL)	489.4 ± 51.0	1091.7 ± 172.7	2497.6 ± 482.8	4794.0 ± 572.3
^{T}1/2 (h)	55.3 ± 6.4	63.1 ± 11.8	71.3 ± 12.6	57.3 ± 8.0
MRT (h)	75.7 ± 8.7	86.7 ± 15.7	96.7 ± 14.9	77.4 ± 10.2
%Dose*	42.39 ± 3.80	34.84 ± 3.37	59.21 ± 3.30	37.40 ± 3.30
^{CL}r (mL/min)	107.2 ± 15.2	84.3 ± 16.7	84.0 ± 12.0	78.7 ± 7.4

*% excreted in urine up to 72 hours post-dose in Groups 1, 2, and 4 and up to 168 hours post-dose in Step 3

The Table shows that AUC and Cmax did increase with dose. The Tmax, T1/2, urinary excretion and renal clearance minimally changed with dose.

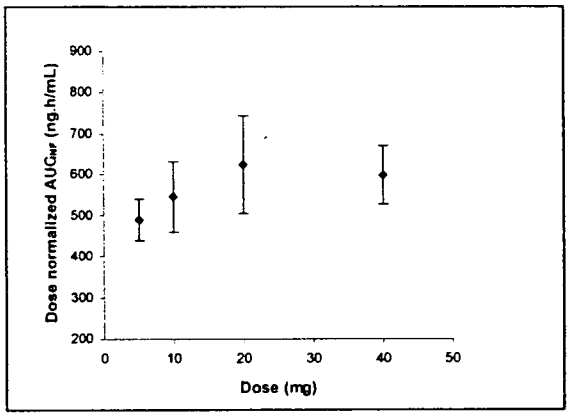
Dose proportionality:

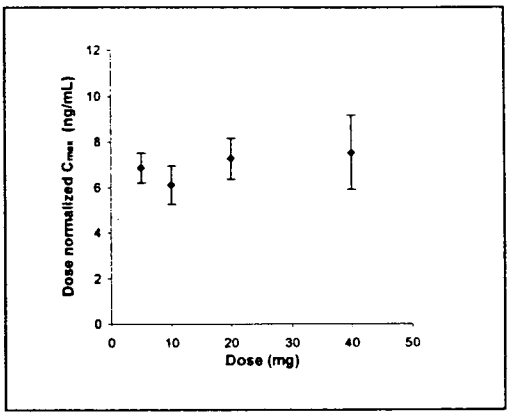
Dose proportionality was evaluated although this study was a parallel group study. The following Table shows dose normalized AUCo-∞ and Cmax for the four doses:

Dose	Dose normalized AUCo-∞	Dose normalized Cmax
5	489.40 ±51	6.86 ± 0.7
10	545.85 ± 86.35	6.09 ± 0.8
20	624.4 ± 120.7	7.24 ±0.9
40	599.25 ± 71.5	7.51 ± 1.6

The sponsor has evaluated dose proportionality by pairwise comparison and Pearson's correlation coefficient and concludes that the pharmacokinetic parameters were dose proportional. An ANOVA conducted by the reviewer using power model shows that the AUCo-∞ and Cmax are approximately dose proportional as shown in the Table below. The 95% CI does not contain 1, but is very close. Graphical representation is also given below:

Parameter	Estimate	95% CI
AUCo-∞	1.105	1.06-1.25
Cmax	1.059	1.01-1.19





Safety: Dizziness and Sleepiness developed significantly at the 40 mg dose.

Conclusions:

- Following single oral doses of 5, 10, 20 and 40 mg memantine the doses increased approximately in a dose proportional manner in this parallel group study. Since this is a parallel study, it is not a very robust way of assessing dose proportionality. The differences observed may be due to the parallel study design.
- Tmax and t1/2 were similar between the doses.
- Percent of the doses excreted in the urine as unchanged drug was relatively similar across doses.

Study: MEM-PK-04: An Open Label. Randomized, Three –Way Crossover, Bioavailability Study Comparing Memantine Modified Release to Immediate Release Tablets in Human Subjects

Objectives:

- To compare the bioavailability of memantine modified release tablets to an immediate release tablet.

Only bioavailability data from the immediate release tablet will be discussed here. This has been reviewed because memantine was detected by a more sensitive method using a lower limit of quantification with a complete assay validation report.

The study design is as follows:

Study Design	Open-label, randomized, single dose, 3-way crossover study
Study Population	N=23 subjects, 19 completed, 3 discontinued Age: 18-35 years , meam age 22.4 years Gender: 12 males and 11 females Weight: 52.3-90.5 kg, mean 70.1 kg Race: 19 Caucasians, 3 Black and 1 Other
Treatment Group	Treatment A: 2 x 10 mg immediate release tablet at 0800 and 1200 hours, for one day Treatment B: 1 x 20 mg modified release formulation I Treatment C: 1 x 20 mg modified release formulation II
Dosage and Administration	All subjects received a single dose of 20 mg (2x10 mg) memantine under fasting conditions with 240 ml water Memantine 10 mg IR tablet: Lot 5007 All treatments separated by a 21 day washout period Diet: Standardized low fat meals were provided to all subjects while institutionalized. No caffeine, grapefruit juice and alcohol allowed
Sampling: Blood	On Days 1, 22, and 43 after the 0800 hour drug administration at: 0.0-hour (pre-dose), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 24, 36, 48, 72, 96, 144, 192, 240, 288, and 336 hours post dose.
Urine	none
Feces	none
Analysis	for memantine samples Lower Limits of Quantitation Plasma Memantine Quality control concentrations, Stability:

	Assay validation complete and acceptable.
PK Assessment	AUC, Cmax, Tmax, t1/2,
Safety Assessment	Adverse events, vital signs, laboratory tests, ECG

Pharmacokinetic Results:

The mean pharmacokinetic parameters after the administration of a single dose of 20 mg (given in divided doses 4 hours apart) memantine IR tablets is given in the following Table:

Table:
Pharmacokinetic Parameters of Memantine (Mean ± SD) Following 20 mg Memantine as Immediate Tablet Formulation

Parameter	*Treatment A IR Formulation I (2x10 mg) (n = 20)*
C_{max} (ng/mL)	24.92 ± 4.82
T_{max} (h)	8.2 ± 2.0
AUC_{0-24} (ng h/mL)	435.7 ± 87.0
AUC_{0-t} (ng h/mL)	1898.2 ± 453.0
$AUC_{0-\infty}$ (ng . h/mL)	1969.0 ± 455.8
$T_{1/2}$ (h)	57.4 ± 14.2
MRT (h)	83.9 ± 17.8

Evaluation of the effect of gender on memantine PK parameters following administration of the IR formulation (Treatment A) showed no statistically significant differences between male and female subjects in Cmax, AUC0-t and AUC0-∞ after accounting for weight differences. In addition, gender had no effect on the terminal elimination half-life. These results are presented in the Table below.

Table: Evaluation of Gender Effect on Weight-Adjusted Pharmacokinetic Parameters of Memantine Following Administration of the IR Formulation

Parameter	*Males (n=11)*	*Females (n=9)*	*p-Value*
C_{max} adjusted (ng/mL)	24.64 ± 3.59	24.34 ±2.38	0.8941
AUC_{0-t} adjusted (ng h/mL)	1744.4 ± 294.7	1970.6 ± 341.9	0.2482
$AUC_{0-\infty}$ adjusted (ng h/mL)	1855.6 ± 285.7	2034.6 ± 361.9	0.3197
$T_{1/2}$ (h)	53.4 ± 13.1	62.0 ± 14.4	0.1773

Conclusions:

This study gives the PK parameters of a single 20 mg dose (given in divided doses 4 hours apart) in 20 subjects. The assay validation for this study is complete, hence PK parameters from this study are reliable.

- The T1/2 is about 57 hours
- Time to peak is about 8 hours
- No gender related difference in the PK parameters was observed in this study.

Study: MRZ 90001-9506: ***Comparative Bioavailability of Two Galenical Formulations of Memantine in Elderly Subjects***

Objective:

To compare the pharmacokinetics of memantine from a sustained release (SR) tablet and an immediate release (IR) tablet. The SR tablet is not a subject of this application, hence only the IR component in this study will be reviewed. This study was reviewed as it was the only study conducted in the elderly population.

A brief overview of some essential components of the study design pertaining to only the IR arm of the study is given below:

Study Design	Open label, 2-way crossover, randomized study with single dosing
Study Population	N=22 Healthy subjects, Age: 51-69 years (mean age 57 years for men and 57.4 years for females) Gender: 12 males and 11 females Weight: 63-90 kg for mean (mean 76.6 kg) 50-80 kg for females (mean 61.7 kg) Race: NA
Treatment Group	Single group
Dosage and Administration	Each subject received the following dosing regimen: 2x10 mg IR tablets single dose, lot# 50701 and SR tablets in the 2nd arm Diet: Subjects requested to fast on the pre-kinetic days since 7 pm and received standardized meal 2, 5 and 10 hours after dosing. Volunteers abstained from alcohol for the duration of the study. Also abstained from coffee or tea.
Sampling: Blood	At 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 192, 240, and 288 hours post-dose.
Urine	none
Feces	none
Analysis	Lower Limits of Quantitation Plasma Memantine
PK Assessment	AUC0-t, Cmax, Tmax, C/F, T1/2
Safety Assessment	clinical laboratory safety assessments

PD Assessment	None

Pharmacokinetic Results:

The following Table shows the pharmacokinetic parameters after a single dose of 2x10 mg memantine tablets in elderly subjects:

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following a Single Dose of 2 x 10 mg Immediate Release Tablet in Healthy Elderly Subjects

Parameter	*2 x 10 mg IR Tablets*		
	All (n=22)	*Males (n=12)*	*Females (n=10)*
C_{max} (ng/mL)	23.80 ± 6.10	21.69 ± 4.05	26.33 ± 7.34
Wt Adjusted Cmax			22.09 ± 4.45
T_{max} (h)	6.55 ± 7.99	7.00 ± 9.37	6.00 ± 6.41
AUC_{0-t} (ng h/mL)	1998 ± 514	1928 ± 421	2082 ± 621
$AUC_{0-\infty}$ (ng h/mL)	2174 ± 564	2126 ± 512	2232 ± 644
Wt Adjusted AUC0-∞			2130 ± 374
$T_{1/2}$ (h)	77.79 ± 20.74	82.21 ± 21.96	70.50 ± 18.89
CL/F (L/h)	9.82 ± 2.57	9.94 ± 2.45	9.68 ± 2.82

- Higher mean Cmax and AUC were observed in female than in male subjects. The female subjects had a 5% higher mean $AUC_{0-\infty}$ value and a 21% higher mean Cmax value than male subjects. Mean T1/2 value was shorter in female subjects as compared to male subjects by 14%.
- After adjusting for differences in weight between male and female subjects, mean Cmax and AUC0-∞ values were similar in the two subject groups.

Conclusions:

- There were no differences in pharmacokinetic parameters between male and female subjects after adjusting for weight differences.
- Although this study was done in the elderly population, it did not include subjects greater than 69 years in age and is not representative of the true elderly age range for the Alzheimer's disease. Only two subjects in this study were ≥ 65 years of age.
- The mean t1/2 was 78 hours.
- Mean time to peak was 6.55 hours.

Study: MRZ 90001-9604: ***Pharmacokinetic and Relative Bioavailability of Memantine Tablets and Memantine Slow-Release Tablet in a Cross-Over Design in Healthy Subjects***

Only the immediate release arm of the study will be discussed here. This study was done with young subjects

A brief overview of some essential components of the study design pertaining to only the IR arm of the study is given below:

Study Design	open label, controlled, single dose
Study Population	N=24 Healthy subjects, Age: 24-36 years (mean 30.6 years) Gender: 12 males Weight: 64-103 kg for males (mean 77.3 kg) Race: NA
Treatment Group	Single group 2 x 10 mg Tablets
Dosage and Administration	Each subject received the following dosing regimen: 2 x 10 mg IR tablets QD Diet: Subjects requested to fast overnight and received standardized meal 2, 5 and 10 hours after dosing.
Sampling: Blood	At 0 hour (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 216 hours following drug administration.
Urine	none
Feces	none
Analysis	Lower Limits of Quantitation Plasma Memantine not clear at what temperature they were stored.
PK Assessment	Total plasma clearance, AUC0-t, Cmax, Tmax, T1/2
Safety Assessment	General adverse events
PD Assessment	None

Pharmacokinetic Results:

The pharmacokinetic parameters after single dose of 20 mg memantine are shown in the following Table:

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following a Single Dose of 2 x 10 mg IR Tablet in Healthy Young Subjects	
Parameter	***2 x 10 mg IR Tablet (n = 12)***
C_{max} (ng/mL)	23.8 ± 5.3
T_{max} (h)	3.3 ± 1.7
AUC_{0-t} (ng h/mL)	1568.7 ± 300.7
$AUC_{0-\infty}$ (ng h/mL)	1716.2 ± 358.0
$T_{1/2}$ (h)	63.7 ± 12.6
CL_{tot} (mL/min)	167.7 ± 33.2

Reviewer's Comment:

- *It seems the sponsor has attempted to characterize the long term stability. The study was conducted in November-December 1996. The samples arrived for analysis on the 6th and 18th December. Stability samples were prepared on 10th December and stored till the analysis. It does seem that the duration of analysis has been covered. The stability samples were stored along with the standard solution and plasma samples. However, the temperature of storage is not clear. As such no mention has been made on the room termperature storage. The assay validation is minimally acceptable as such.*
- *Based on the sponsor's response, processed sample stability was evaluated and samples were shown to be stable for 3 days.*

Conclusions:

The results obtained from this study are similar to the previous studies.

- The mean time to peak is somewhat shorter than the other studies, averaging about 3.3 hours.
- The mean t1/2 is 64 hours.

Study: MRZ 90001-8201: Human Pharmacokinetic Studies with Memantine

This was a pilot study conducted very early in the development of this drug.

Objectives:

- To characterize the pharmacokinetics of memantine and evaluate dose proportionality after single oral and intravenous administration in a small number of healthy volunteers.
- A secondary objective was to evaluate whether the pharmacokinetics of memantine in healthy subjects were predictive of memantine steady-state concentrations in patients.

The study design is as follows:

Study Design	open-label, single dose, cross-over study in healthy subjects and in patients, performed in two stages.
Study Population	N=6 Healthy subjects, Age: 30-43 years Gender: All males Weight: N/A Race: N/A
Treatment Group	Treatment A: 20 mg intravenous dose Treatment B: 20 mg oral solution Treatment C: 1 x 20 mg oral tablet Treatment D: 2 x 20 mg oral tablet
Dosage and Administration	Treatment A-D separated by a washout period of 3 months Diet: Fasted for 12 hours prior to dosing Volunteers abstained from alcohol for the duration of the study. Also abstained coffee or tea.
Sampling: Blood	At 0 (pre-dose), 1, 2, 4, 8, 15, 26, 32, 50, 78, and 146 hours post dose.
Urine	over 24-hour periods for a total of 13 days
Feces	none

Analysis	Lower Limits of Quantitation Plasma Urine Memantine

	No other parameters provided Providing a range of LLOQ seems odd.
PK Assessment	AUC0-t, Cmax,
Safety Assessment	none
PD Assessment	None

Pharmacokinetic Results:

Pharmacokinetic parameters were calculated using the compartmental approach. After oral administration, two maxima were observed at 3.2 ± 0.6 and 19.8 ± 8.8 hr.

The pharmacokinetic parameters are shown in the following Table:

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following Administration of Memantine as a 20 mg Intravenous Dose, 20 mg Oral Solution, 1 x 20 mg Tablet and 2 x 20 mg Tablets in Healthy Subjects

Parameter	*20 mg Intravenous Dose (n= 4)*	*20 mg Oral Solution (n = 3)*	*1 x 20 mg Tablet (n = 6)*	*2x 20 mg Tablets (n=3)*
$^{AUC}0\text{-}\infty$ (^{ng}h/mL)	2116 ± 832	3099 ± 528	2892 ± 848	4163 ± 181
$T1/2,\alpha$ (h)	0.6 ± 0.1	4.8 ± 2.6	10.2 ± 5.1	11.2 ± 5.4
$T1/2,\beta$ (h)	61.1 ± 24.9	58.5 ± 27.8	65.4 ± 29.4	54.3 ± 5.6
F (%)	-	146	136	98

Memantine was more than completely absorbed from the oral formulations. Absolute bioavailability values were 146%, 136%, and 98% for the 20 mg oral solution, the 20 mg oral dose, and the 40 mg oral dose, respectively.

Elimination of memantine was described by a biexponential model with mean half-lives of 10 ± 5 hr and 65 ± 29 hr for the α -phase and β -phase, respectively.

Looking at the AUC0-∞ for the 20 and 40 mg doses, they are not dose proportional.

The sponsor has conducted the second stage of the study in 5 patients from the clinical trial, however they do not mention the disease of the patients. After repeated IV administration of 10 mg in the morning and evening for 7 days, in the second stage of the study in patients, the mean plasma levels of 63 ng/ml were measured in these patients. The sponsor's secondary objective of evaluating whether the pharmacokinetics of memantine in healthy subjects were predictive of memantine steady-state concentrations in patients could not successfully be estimated by this study.

Reviewer's Comment:

This study was conducted very early in the drug development. The LLOQ is given as a range. This study gave information on the 20 mg tablet strength, given as 1x20 mg and 2x20 mg doses. All other previous studies were conducted with the 10 mg tablet strength.

This study although a pilot was reviewed to gain insight on the higher strength and had information on the absolute bioavailability. The absolute bioavailability is greater than 100 in this study too. The assay validation in this study is also not complete and uses a different ..... in the other). This study was also intended to evaluate dose proportionality between the 20 and 40 mg doses. Statistical analysis was not conducted. The number of subjects are few, but the doses do not appear to be dose proportional. This study should only be treated as a supportive study at the best.

APPEARS THIS WAY
ON ORIGINAL

Study: PAZ 1983: Orienting Pharmacokinetic Studies on ^{14}C-Memantine in Healthy Subjects

Objective:

To determine the pharmacokinetic parameters of ^{14}C- memantine after single intravenous and oral administration.

This study is only a pilot supportive study. The study design is as follows:

Study Design	Pilot study
Study Population	N=2 Healthy subjects, Age: 52 and 39 years Gender: males Weight: NA Race: Caucasians
Treatment Group	Subject 1 (52 years): 20 mg IV Subject 2 (39 years): 20 mg Oral
Dosage and Administration	Subject 1 (52 years): 20 mg SD intravenous dose of ^{14}C- memantine, total activity of 86.20 μCi Subject 2 (39 years): 20 mg SD oral ^{14}C- memantine capsule, total activity of 86.04 μCi, taken with 100 ml water Diet: Fasted for 12 hours prior to dosing, meals given 4 and 12 hours post-dosing Volunteers abstained from alcohol for the duration of the study. Also abstained coffee or tea. Only mineral water allowed as a drink
Sampling: Blood	After IV Dose: at 0 (pre-dose), 5, 10, 20, and 40 minutes and at 1.5, 3, 5, 8, 12, 24, 32, 48, 56, 72, and 96 hours post-dose. After Oral Dose: at 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 32, 48, 56, 72, and 120 hours post-dose.
Urine	After IV Dose: at time intervals 0-6, 6-12, 12-24, 24-32, 32-48, 48-74, and 74-96 hours post-dose. After Oral Dose: at time intervals 0-6, 6-12, 12-24, 24-32, 32-48, 48-74, 74-96, 96-120, and 360-384 hours post-dose.
Feces	At time intervals 0-24, 24-48, 48-72, and 72-96 hours.
Analysis	Liquid scintillation for plasma samples Radio –scanning for urine samples Lower Limits of Quantitation Plasma Urine Memantine NA NA NA=not available
PK Assessment	AUC0-t, Cmax, t1/2, Vd, Cltot
Safety Assessment	none

PD Assessment	none

Pharmacokinetic Results:

Pharmacokinetic parameters were calculated using the two-compartment open model. The following Table presents the pharmacokinetic parameters in blood and plasma obtained following memantine intravenous and oral administration in the two male subjects.

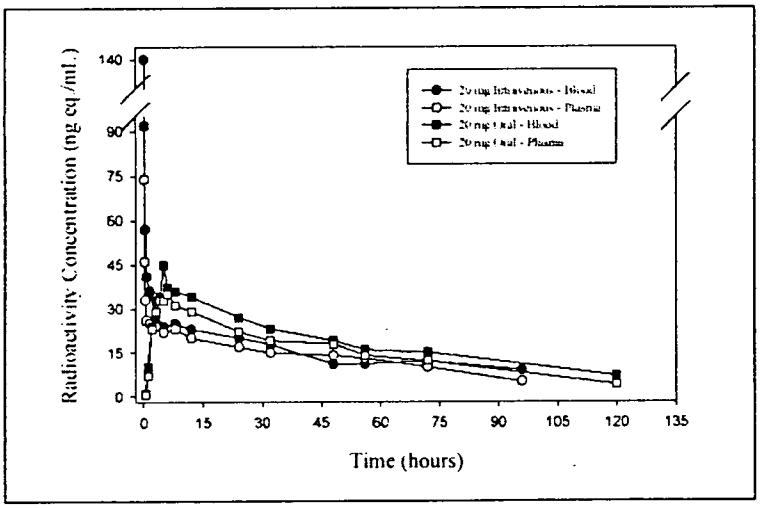
Table: Radioactivity Pharmacokinetic Parameters Following an Intravenous and an Oral Dose of ^{14}C-Memantine in Two Healthy Male Subjects

Parameter	*20 mg Intravenous ^{14}C-Memantine*		*20 mg Oral ^{14}C-Memantine*	
	Plasma	*Blood*	*Plasma*	*Blood*
C_{max} (ng eq./mL)	74[a]	140.0[a]	34	39
T_{max} (h)	0.083	0.083	5.5	6.0
AUC_{0-t} (ng eq h/mL)	1341	1519	1885	2193
$AUC_{0-\infty}$ (ng eq h/mL)	1797	1795	2440	2705
$T_{1/2,\alpha}$ (h)	0.075	0.117	2.15	2.24
$T_{1/2,\beta}$ (h)	49	39	58	52
$T_{1/2,ka}$ (h)	-	-	2.1	2.2
Vd (L)	-	-	300	270
Cl tot (L/hr)	-	-	8.2	7.4

[a] First post-dose measured concentration

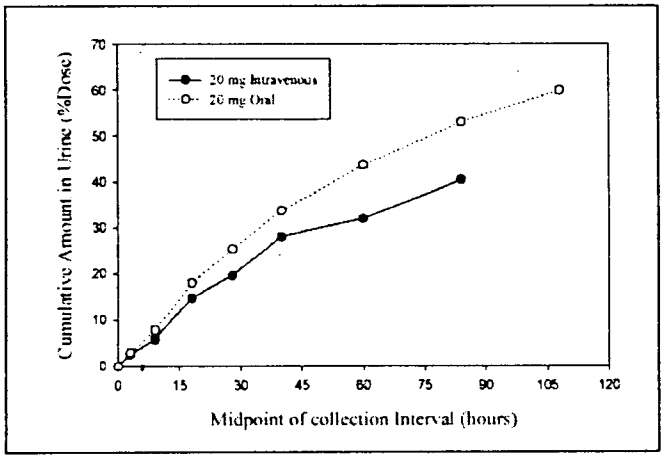
Cmax and AUC parameters were greater in blood than in plasma except for AUC0-∞ of the intravenous dose which was similar in blood and plasma.

The following figure shows the blood and plasma radioactivity concentration profiles after intravenous and oral administrations.



For each subject, memantine concentrations were higher in blood compared to plasma. When comparing intravenous to the oral dose, peak radioactivity concentration was higher following intravenous administration but plasma concentrations were higher after oral administration from around 3 hours post-dose until the end of collection period.

The urinary excretion of radioactivity data is shown in the following figure:



By 96 hours post-dose, 53% and 40% of the administered radioactivity was excreted in urine following oral and intravenous administration, respectively. Fecal excretion represented 4.2% and 2.4% of administered radioactive dose for the oral and intravenous dose, respectively. By 120 hours post-dose, 59.9% of the administered radioactivity was excreted in urine for the oral dose. Renal radioactivity elimination had not been terminated even after 15 days.

Reviewer's comment:

No assay validation was given for this study. The results should only be treated as pilot and preliminary and no conclusions for labeling purposes should be drawn from this study.

Preliminary Conclusions:

- ^{14}C-memantine is eliminated mainly via the renal route, with approximately 60% of the administered oral dose being eliminated in the urine at the end of 120 hours, and 4.2% in the feces during the 96-hour post-dose collection period.
- Elimination of radioactivity was biphasic.
- This study also provides the observation that absolute bioavailablity of memantine tablets is 135%.

Study: MRZ 90001-9201: ***Pharmacokinetics and Relative Bioavailability of Three Galenic Formulations of Memantine (Tablet, Slow Release Tablet and Solution) in a 3-Way Crossover Trial***

This study was not reviewed because the slow release tablet and the solution are not the subject of this application. The conventional tablet is the subject of this application. However, the dose studied was 2 x 10 mg single dose which has already been evaluated in other studies as well. This study would not give any additional information for this application.

APPEARS THIS WAY
ON ORIGINAL

Study: HUK-610/5: Memantine: Safety, Tolerance and Pharmacokinetics after Single Intravenous Infusions of 30 and 40 mg Given at a Rate of 10mg/h to Healthy Male Volunteers

This study was not reviewed since IV infusion is not the to be marketed mode of administration.

APPEARS THIS WAY
ON ORIGINAL

MULTIPLE DOSE STUDY

Study: HUK 610/13: (^{14}C)-Memantine: A Study of the Absorption, Metabolism and Excretion Following Oral Administration to Healthy Human Volunteers

Objectives:

(a) To measure the radioactivity associated with drug product in blood and plasma following oral administration of ^{14}C-memantine to healthy male volunteers under steady-state conditions,
(b) To obtain a mass balance by quantifying the urinary and fecal excretion of radioactivity, and
(c) To examine the pattern of metabolites in plasma, urine and feces.

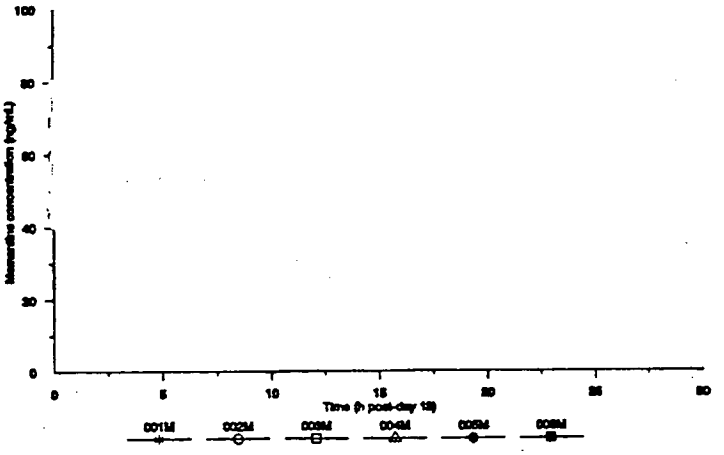
The study design is as follows:

Study Design	Open label, single oral dose of ^{14}C-memantine under steady state conditions
Study Population	N=6 Healthy subjects, Age: 34-49 years (mean 44 years) Gender: males Weight: 53.5-92 kg (mean 73 kg) Race: Caucasians
Treatment Group	Single group
Dosage and Administration	Each subject received the following dosing regimen (3x5 mg for 19 days): Days 1-12: 5 mg oral memantine at 0900, 1400, and 1900 hours each day Day 13: A single oral administration of ^{14}C-memantine as an aqueous solution (50 ml) at 0900 (radioactivity 90.35 μCi/mg), ingested via a drinking straw and 5 mg oral memantine at 1400 and 1900 hours The container was rinsed with 150 ml water, and the washings ingested via a straw. Days 14-19: 5 mg oral memantine at 0900, 1400, and 1900 hours each day Tablets administered with 150 mL of water Diet: Following an overnight fast a light breakfast provided 0.5 hour prior to dosing. Lunch, afternoon snack, evening meal and evening snack were provided 4.5, 7, 9.5 and 14 hour after radiolabeled dose administration. Volunteers abstained from alcohol 48 hours prior to and for the duration of the study. Also abstained from xanthine containing food or drinks 48 hours prior to until 168 hours after administration of radiolabeled dose.
Sampling: Blood	Days 1 to 13: prior to the morning dose

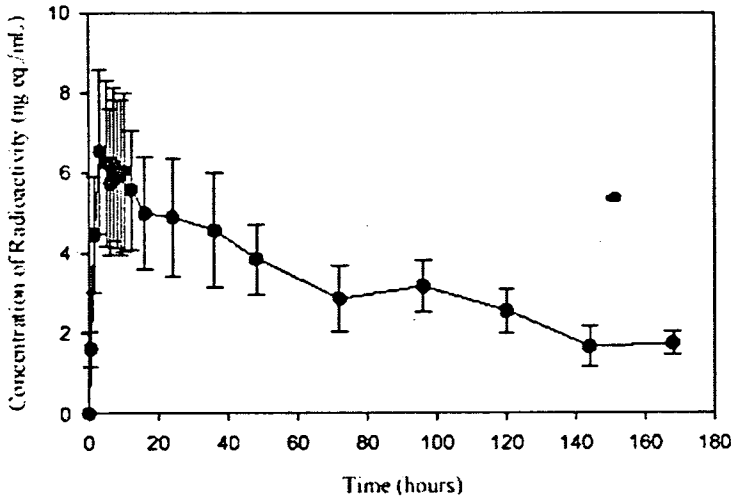
	Day 13: At 0.5, 1.5, 3, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 78, 96, 120, 144, and 168 hours.
Urine	Day 13: At 0-6, 6-12, 12-24, and at 24-hour intervals thereafter up to 480 hours.
Feces	Day 13: At 24-hour intervals for 480 hours following administration of the radiolabeled dose.
Sweat	Day 13: From 0-24 and 24-48 hours post the radiolabeled dose.
Analysis	Liquid Scintillation Counting for memantine in plasma radiodetection radioactivity in urine for memantine cold Lower Limits of Quantitation Plasma / Urine Memantine (cold) Memantine (hot) Mean background Disintegration rate x 3SD / Twice the background disintegrations Radioactivity measurement adequate.
PK Assessment	AUC0-t, Cmax, Tmax, t1/2 following the radioactive dose
Safety Assessment	clinical laboratory safety assessments
PD Assessment	None

Pharmacokinetic Results:

The trough concentrations show that the subjects had approached steady state by the time the radiolabeled dose was administered. From Day 12 onwards, plasma levels of memantine were approaching steady state. The plasma concentrations did not increase significantly from Day 16 onwards. The concentrations after the radiolabeled dose on Day 13 also show that the steady state was maintained in most cases as shown in the following figure:



The following figure shows the mean plasma radioactivity concentration versus time plots following a single oral administration of 5 mg ^{14}C-memantine under steady-state conditions.



The following Table summarizes the plasma radioactivity pharmacokinetic parameters. A mean maximum plasma radioactivity concentration of 7.032 ng eq./mL was obtained within 3 to 10 hours after administration of the radiolabeled dose. Mean terminal elimination half-life of radiolabeled material was 98.5 hours (68-125 hours).

Table: Plasma Radioactivity Pharmacokinetic Parameters Following a Single Oral Dose of ^{14}C Memantine Under Steady-State Conditions in Healthy Subjects

Parameter	*Subject*						*Mean ± SD*
	1	*2*	*3*	*4*	*5*	*6*	
C_{max} (ng eq./mL)							7.03 ± 1.57
T_{max} (h)							5.2 ± 2.9
$T_{1/2}$ (h)							98.48 ± 22.20
AUC_{0-t} (ng eq h/mL)							547.7 ± 126.9
$AUC_{0-\infty}$ (ng eq h/mL)							785.1 ± 146.4

In a separate addendum to the report plasma samples were reanalyzed to assess the cold memantine concentrations on Day 13 from predose up to 16 hours post dose. AUC calculations up to a dosing interval of 8 hours is given below. The sponsor has reported AUC for sampling up to 16 hours. AUC0-8 was calculated by the reviewer for the cold memantine for comparison at equivalent doses.

Table: Plasma AUC Following a Single Oral Dose of 5 mg Memantine Under Steady-State Conditions in Healthy Subjects (post hoc analysis)

Parameter	*Subject*						*Mean ± SD*
	1	*2*	*3*	*4*	*5*	*6*	
$AUC_{0-\tau}$ (ng h/mL)							467.6 ± 89.79

A very crude comparison could be made between AUC (AUC0-8 cold/AUC0-∞ hot) based on radioactivity and that of cold memantine. This suggests that about 68 % of the radioactivity is due to the parent memantine in plasma.

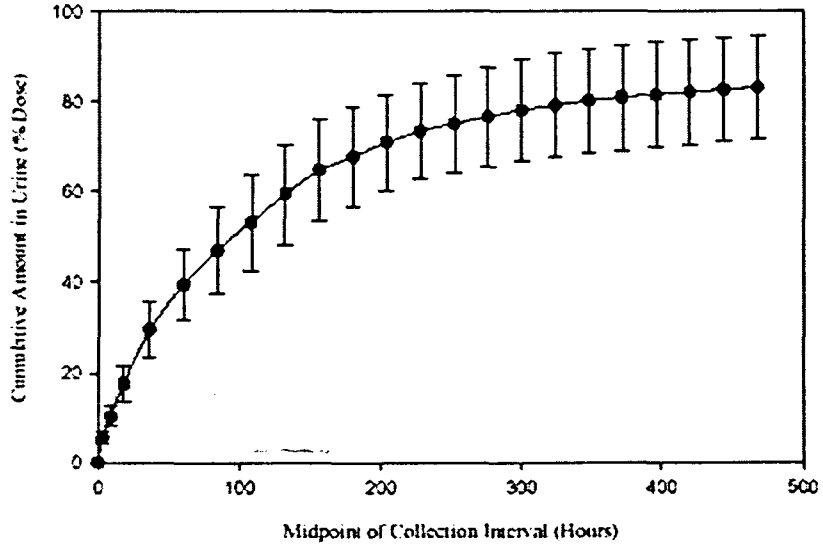
The recovery of radioactivity in the urine and feces is shown in the following Table. Recovery in the sweat was analyzed in two subjects and was undetectable.

Table: Recovery of Radioactivity in Urine and Feces (%Dose) Following a Single Oral Dose of ^{14}C-Memantine Under Steady-State Conditions in Healthy Subjects

Tissue	*Subject*						*Mean ± SD*
	1	*2*	*3*	*4*	*5*	*6*	
Feces							0.539 ± 0.407
Urine							83.16 ± 11.66
Total							83.70 ± 11.77

- The majority of the radioactivity was excreted in urine, representing a mean (SD) of 83.16±11.77% of the administered radioactive dose within a 480 h period.
- The mean excretion in the urine for subjects 1,2,4 and 5 was 90.36 ± 1.09%.
- The lowest amount of radioactivity excreted in urine was observed in the two subjects (3 and 6) who displayed the longest elimination half-life in plasma hours, respectively). This suggests that the urine collection period might not have been sufficient for these 2 subjects, which could contribute to the lower % dose excreted in urine. There was a protracted rate of excretion in urine (with 0.1-0.7% of the administered dose still being eliminated at 480 hours).
- Minimal radioactivity was detected in feces which averaged 0.54%.

The mean cumulative amount (% of dose) of radioactivity excreted in the urine following a single 5 mg dose of ^{14}C memantine under steady state conditions is shown in the following figure:



Protein Binding:
In vitro protein binding of ^{14}C-memantine ranged from 41.9 to 45.3% over the concentration range of 0.5 to 10 µM. No relationship between plasma concentration and the degree of binding was observed.

Metabolic profiling:
Metabolic profiling of memantine was performed only in urine due to the low levels of radioactivity in plasma and feces. — metabolic profiling showed that the proportion of intact memantine excreted in urine increased over the first 12 hour post dose, rising from 30-67% of the radioactivity in the 0-6 h samples to 42-82% in the 6-12 h samples. The amount of radioactivity associated with the metabolites decreased with time, falling from 19-26% in the 0-6 h samples to <15% in the 216-240 h samples. An ——— analysis on urine of subject 2 showed that memantine is poorly metabolized in man forming small quantities of oxidative metabolites. Memantine the major radiolabeled component accounted for approximately 68% of the characterized material. Two other components amounted to approximately 15%and 17% of the radioactivity. This corroborates well with the rough estimation that the mean % of radioactivity due to memantine alone was 68%.

Inter-individual variations in the absorption, metabolism and excretion of memantine were found. Two subjects (3 and 6), for whom lower mass balance was achieved, exhibited greater Tmax values (7 & 10 hours, as compared to 3 and 5 hours), longer terminal elimination half-life (122 and 125 hour as compared to ~80-90 hours) and reduced metabolic clearance of memantine, resulting in more intact memantine being renally eliminated (77-82%), when compared to the other 4 subjects (57-67% intact). These numbers correlate well with the rough calculation showing that 68% of the radioactivity is due to the intact memantine in plasma. This also corroborates well with Study 610/4 that suggested that about 44% of the drug is cleared non renally based on the values for the total clearance (122 ml/min) and renal clearance (68 ml/min).

Based on these results, greater than 57% of ^{14}C memantine was determined to be excreted as intact drug by renal elimination. The predominant route of memantine metabolism was via hydroxylation to form 1-amino-3- hydroxymethyl-5-methyladamantane (MRZ 2/373, 11-hydroxy memantine), 1-amino-3,5-dimethyl-7- hydroxyadamantane (MRZ 2/544, 7-hydroxy memantine), and MRZ 2/374 (6-hydroxy memantine).

Conclusions:

- Radioactivity was recovered primarily in the urine (83% of the administered dose).
- Recovery in feces was minimal (0.54% of the administered dose).
- Recovery in sweat was undetectable.
- Memantine was cleared by both metabolic and renal routes, with greater than 57% of ^{14}C memantine excreted as intact drug by renal elimination.
- The predominant route of memantine metabolism was via hydroxylation to form 1-amino-3- hydroxymethyl-5-methyladamantane (11-hydroxy memantine), 1-amino-

3,5-dimethyl-7- hydroxyadamantane (7-hydroxy memantine), and MRZ 2/374 (6-hydroxy memantine).

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Study: MRZ 90001-9601: ***Pharmacokinetic Study to Investigate the Influence of Urinary pH and Urine Flow on Renal Clearance of Memantine***

Objectives:

To evaluate possible pharmacokinetic influences of urine pH and urinary flow on renal clearance of memantine, an alkaline substance with pKa of 10.27.

As plasma concentration is dependent on elimination, it is necessary to evaluate possible influences of the elimination kinetics of memantine which is predominantly excreted via the kidneys. Major determinants of renal elimination of alkaline drugs are urinary pH and flow. The excretion of weak base memantine (pKa=10.27) was investigated in this study under conditions of alkaline (pH 8) and acidic (pH 5) urine pH and high and low urinary flow rates.

The study design is as follows:

Study Design	Open label, four-way crossover, randomized study with multiple dosing
Study Population	N=13 Healthy subjects, Age: 22-31 years (mean 26.7 years) Gender: NA Weight: 53.5-92 kg (mean 78.3 kg) Race: Caucasians
Treatment Group	Single group
Dosage and Administration	Each subject received the following dosing regimen: Days 1-43: 10 mg memantine once daily Tablets administered with 150 mL of water Day 1-21: Administered under conditions of normal urine pH and flow Day 22: Kinetic period A: acidic urine pH, low urinary flow Day 29: Kinetic period B: acidic urine pH, high urinary flow Day 36: Kinetic period C: alkaline urine pH, low urinary flow Day 43: Kinetic period D: alkaline urine pH, high urinary flow These kinetic periods were separated by 1 week interval. pH Adjustment: In order to alkalize the urine, subjects received 4 g of sodium bicarbonate every 4 hours from the pre-kinetic day (Days 21, 28, 35, and 42) at 2:00 PM until 10:00 PM on the kinetic day (Days 22, 29, 36, and 43). In order to acidify the urine, subjects received 1 g of ammonium chloride every 3 hours starting on the pre-kinetic day at 2:00 PM until 11:00 PM on the kinetic day. Urinary Flow Adjustment: For low urinary flow, subjects received 600 mL water during one

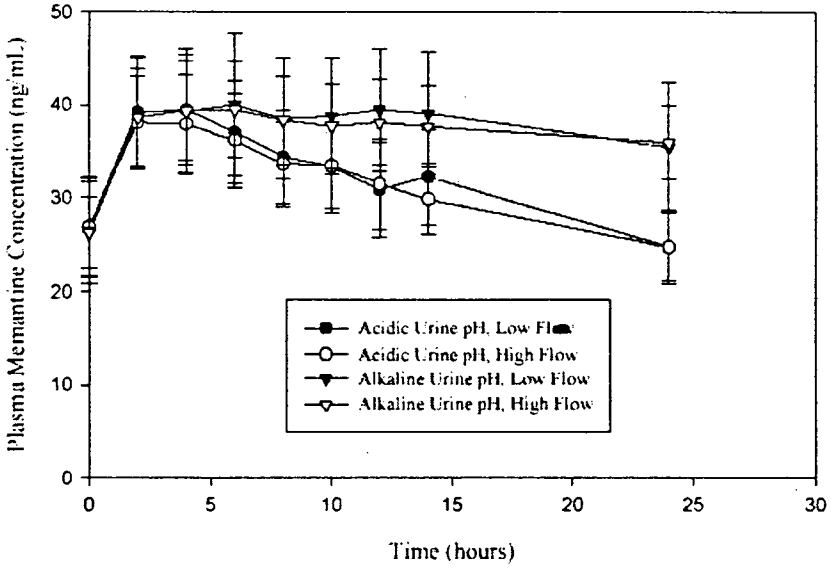
	kinetic period (pre-kinetic day and kinetic day). For increased urinary flow, subjects received 6000 mL water during the kinetic period (pre-kinetic day and kinetic day). Diet: Subjects requested to fast on the pre-kinetic days since 7 pm and received standardized meal 2, 5 and 10 hours after dosing. Volunteers abstained from alcohol for the duration of the study. Also abstained coffee or tea.
Sampling: Blood	Days 22, 29, 36 and 43: at 0 (pre-dose), 2, 4, 6, 8, 10, 12, 14, and 24 hours post-dose. Days 1, 10 and 15: pre-dose in order to evaluate steady-state concentrations under normal urinary conditions.
Urine	At 0-2, 2-4, 4-6, 6-8, 8-10, 10- 12, 12-14, and 14-24 hour intervals.
Feces	none
Analysis	Lower Limits of Quantitation Plasma Urine Memantine ng/ml Plasma: Linear range: ng/ml Inter-day precision: Inter-day accuracy: % of the nominal value Urine: Linear range: ng/ml Inter-day precision: %CV Inter-day accuracy: % of the nominal value
PK Assessment	Total plasma clearance, renal clearance, amount of memantine excreted into the urine. AUC0-t, Cmax, Tmax, urinary flow
Safety Assessment	clinical laboratory safety assessments
PD Assessment	None

Pharmacokinetic Results:

The mean±SD plasma concentration on Day 10 and 15 were 25.82±4.5 ng/ml and 27.57±4.37 ng/ml, suggesting steady state was approached by Day 10.

The mean plasma concentration versus time profiles in each kinetic period are presented in the following Figure. Similar peak plasma concentrations were observed under all urinary conditions. However, plasma concentrations after Tmax were higher under alkaline conditions than acidic conditions. Differences in urine flow did not appear to

substantially affect the plasma memantine concentration levels.



The pharmacokinetic parameters of memantine in plasma following administration of memantine under conditions of acidic/alkaline urine pH and low/high urinary flow are summarized in the following Table:

Pharmacokinetic Parameters (Mean ± SD) of Memantine Following Multiple Dose Administration of 10 mg Tablets Under Conditions of Altered Urine pH and Urinary Flow

Parameter	*Kinetic Period*			
	A (Acidic/Low) (n=12)	*B (Acidic/High) (n=12)*	*C (Alkaline/Low) (n=12)*	*D (Alkaline/High) (n=12)*
C_{max} (ng/mL)	40.20 ± 5.50	38.84 ± 4.75	41.32 ± 7.30	40.31 ± 5.04
T_{max} (h)	3.50 ± 1.24	3.33 ± 1.30	8.00 ± 4.82	7.00 ± 3.46
AUC_{0-24} ng h/mL)	766.1 ± 111.8	751.0 ± 102.1	908.2 ± 156.2	894.7 ± 104.9

- Statistical comparison of memantine pharmacokinetic parameters in plasma showed no significant differences with respect to the Cmax parameter.
- AUC0-24 values were significantly higher (~20%) under alkaline than acidic conditions, regardless of urinary flow.
- Tmax values were significantly higher (2-fold) under alkaline than acidic conditions, regardless of urinary flow.
- Plasma samples were not taken under normal urine pH and flow.
- Urinary flow did not have a significant effect on memantine plasma pharmacokinetic parameters.

The following Table summarizes clearance parameters of memantine (total, renal and extrarenal clearance) as well as the amount of memantine excreted in urine during a 24-hour dosing interval. Due to changes in total clearance with changes in urine pH and urinary flow, this parameter could not be calculated using a non-compartmental approach

(D/AUC). The changes in the urine pH and flow caused a deviation from the steady state conditions that existed under normal conditions. Since dosing of memantine during altered urinary pH/flow did not continue for a sufficient time to allow attainment of new steady state (only one memantine dose was administered per kinetic period), evaluation of memantine pharmacokinetics on the four kinetic days did not occur under steady state conditions. Deviation from steady state will be more under alkaline conditions. Plasma and urinary data were analyzed using a one-compartment model with first-order absorption with memantine elimination being attributed to a renal component and a nonrenal component.

Pharmacokinetic analysis was performed using NONMEM. The renal component (k_R) was described as a function of urine pH and urinary flow while the extrarenal component was independent of urine pH and urinary flow. Data included in the compartmental pharmacokinetic analysis consisted of plasma and urine data from the four kinetic periods as well as pre-dose plasma concentration data obtained during normal urine conditions (Days 1, 10, and 15). Inclusion of the plasma data from Days 1, 10, and 15 allowed the model to provide predictions for the total, renal and extrarenal clearances under conditions of normal urine pH and urinary flow. In addition, model-predicted values were obtained for the amount of memantine excreted unchanged in urine during steady-state conditions prior to altering urine pH and urinary flow.

Table: Excretion Parameters (Mean ± SD) of Memantine Following Multiple Dose Administration of 10 mg Tablets in Healthy subjects Under Conditions of Altered Urine pH and Urinary Flow

Parameter	*Kinetic Period*				
	Control (n=12)	*Acidic/Low (n=12)*	*Acidic/High (n=12)*	*Alkaline/Low (n=12)*	*Alkaline/High (n=12)*
^{CL}T (mL/min)	182.09 ± 23.03	226.87 ± 25.36	237.00 ± 27.37	39.41 ± 16.96	49.53 ± 13.88
^{CL}R (mL/min)	163.81 ± 27.50	208.60 ± 25.62	218.72 ± 28.94	21.13 ± 7.80	31.25 ± 6.42
^{CL}R (%)[a]	89.81 ± 7.66	92.00 ± 6.19	92.26 ± 6.07	59.67 ± 25.42	67.37 ± 21.61
^{CL}XR (mL/min)	18.28 ± 14.09	18.28 ± 14.09	18.28 ± 14.09	18.28 ± 14.09	18.28 ± 14.09
^{CL}XR (%)[a]	10.19 ± 7.66	8.00 ± 6.19	7.74 ± 6.07	40.33 ± 25.42	32.63 ± 21.61
$^{Ae}0$-24 (mg)	7.62 ± 0.65[b]	9.61 ± 1.62 [b]	9.70 ± 1.95 [b]	1.33 ± 0.52 [b]	1.70 ± 0.37 [b]

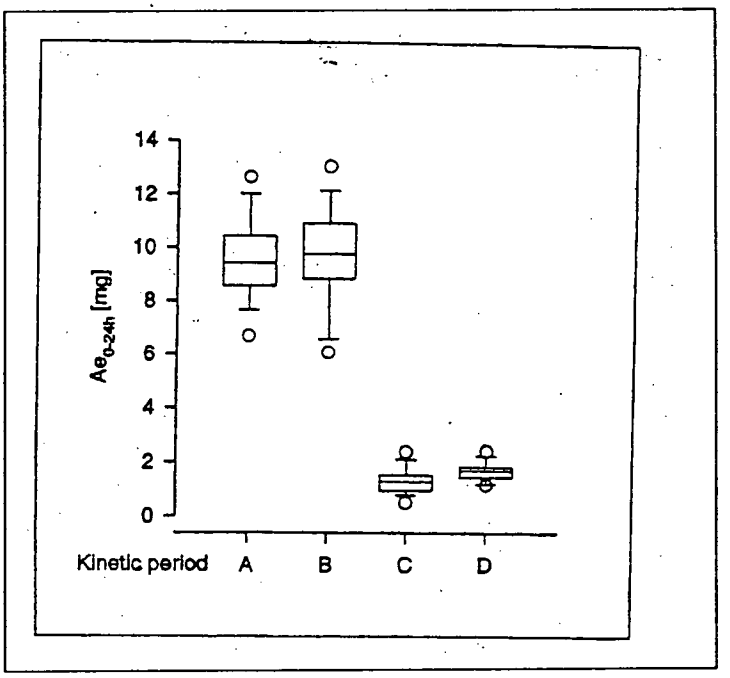
[a] % of CL_T

[b] $^{Ae}0$-24 values represent actual amount excreted in urine for the four kinetic periods but model-predicted value for control conditions.

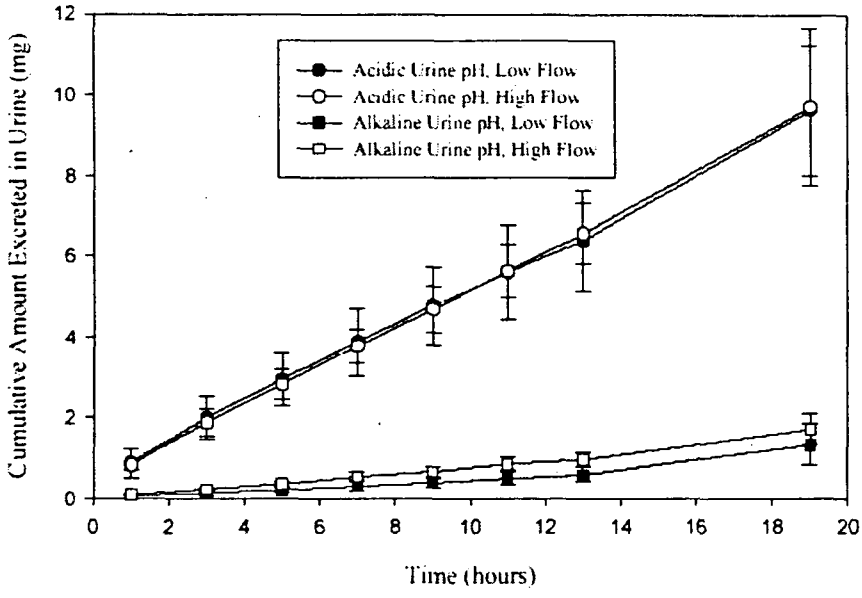
- Statistical comparisons demonstrated statistically significant differences ($p < 0.001$) in the total (CL_T) and renal (CL_R) clearance values between treatments indicating an influence of urine pH and urinary flow on the renal excretion of memantine.
- Differences in urine pH led to substantially greater differences in total and renal clearance than differences in urinary flow. CL_R was 7-9 fold higher in the acidic kinetic periods compared to the alkaline kinetic period indicating that urine pH is a major factor influencing renal clearance of the drug.
- Mean CL_T values increased by 25% and 30% and CL_R values increased by 27% and 34% under acidic conditions of low and high flow, respectively, compared to their respective values under normal conditions. Under alkaline conditions, mean CL_T

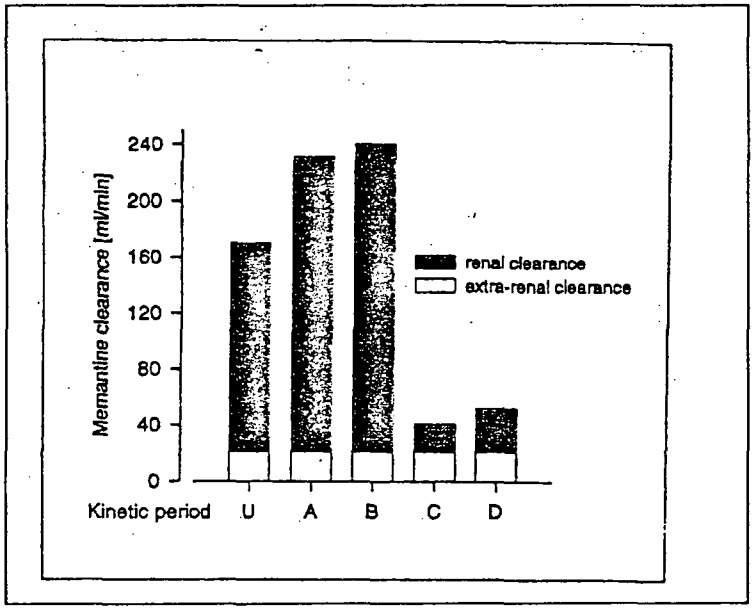
values decreased by 73% and 78% and CL_R values decreased by 80 % and 87%, under low and high flow conditions, respectively, compared to normal conditions. The reduced CL_R at alkaline urine pH can be explained by pH dependent tubular reabsoprtion under these conditions because the ratio of nonionized memantine in alkaline solution (pH 8) is considerably higher (0.005), than in acidic urine (pH 5), where the ratio of nonionized drug is very low (0.00005). Under these conditions tubular reabsorption seems unlikely, in contrast tubular secretion must be taken into account, as the renal clearance of memantine at acidic pH exceeds the expected glomerular filtration rate.

- High urinary flow resulted in an increase in CL_R of only about 9 ml/min under both acidic and alkaline conditions. Even though this difference between high and low urinary flow was statistically significant, it does not seem to be clinically relevant.
- The renal component of total memantine clearance was similar between normal and acidic conditions, as urine tends to be acidic under normal conditions, and was the primary route of memantine elimination averaging between 90% to 92% of total clearance under normal and acidic conditions (low and high flow), respectively. Renal clearance of memantine under alkaline conditions was 60% and 67% of total clearance for low flow and high flow, respectively.
- Significantly higher values (6-7 fold) of the amount of memantine excreted in the urine during the 0-24 hour interval were observed under acidic conditions than alkaline conditions, regardless of urinary flow as shown in the following Figure. Urinary flow did not have significant effect on renal excretion of memantine.



The mean cumulative amount of memantine excreted in the urine following multiple dose administration of 10 mg tablets under conditions of altered urine pH and urinary flow is shown in the following Figure:





Absolute Bioavailability from CLr:

Based on discussions with Dr. Peter Hinderling, Lalka-Felman method was used to estimate oral absolute bioavailability for drugs with pH dependent renal elimination (J. Phar, Sci, 1974; 63: 1812-1815) based on the following equation 2:

$\Delta CL = \Delta CLr = fD/AUC - fD/AUC' \ldots\ldots\ldots\ldots\ldots\ldots (1)$

$f = \Delta CLr/D. \{AUC.AUC'/AUC' - AUC)\} \ldots\ldots\ldots\ldots (2)$

Where AUC and AUC' are AUCs under acidic and alkaline conditions respectively and ΔCLr is the change in CLr between the acidic and renal clearances.

The calculations showed that the absolute bioavailability for the 10 mg dose based on AUCs under acidic and alkaline conditions is 159% and is comparable to the results of the other studies. This high absolute bioavailability cannot be explained.

Conclusions:

- Since changes in urine pH could cause deviation from steady state, this study can give qualitative estimates of the effect of urinary pH and flow. Quantitative estimates may not be very robust.
- Under normal and acidic conditions, the majority of the memantine is excreted renally. The renal CL averaged between 90-92% of the total clearance under normal and acidic conditions.
- Acidic urinary conditions caused an increase in the memantine total and renal clearance of up to 30% and 34%, respectively.
- Alkaline conditions had a greater impact on memantine excretion, leading to higher exposure (AUC0-24) under alkaline conditions. There was a 78% and 87% reduction in the total and renal clearance of memantine, respectively.
- Under alkaline conditions, the renal clearance was 60% and 67% of the total clearance under low and high urinary flow, respectively.
- Urinary flow did not have a substantial effect on renal elimination in either alkaline or acidic conditions.
- Plasma Cmax was similar under acidic and alkaline conditions. AUC0-24 values were significantly higher (~20%) under alkaline than acidic conditions Urinary flow did not have substantial effect on plasma Cmax and AUC0-24.

Therefore, alterations of urine pH towards alkaline conditions may lead to an accumulation of the drug with a possible increase in side effects. Urine pH is altered by diet, drugs and clinical state of the patient. Hence, memantine should be used with caution under these conditions.

Reviewer's Comment:

- *Data suggests that possibly the calculation of the pKa is not accuarate, since all the drug at pH 8 under alkaline conditions would still be ionized or some process other than reabsorption could also be taking place.*

Study: HUK 610/6: Memantine: Pharmacokinetic Study With Repeat Doses of 5, 10, and 20 mg Every 8 h for 12 Days

Objectives:

- To describe the steady-state pharmacokinetics of memantine given as 5, 10, and 20 mg oral doses every 8 h for 12 days and
- To provide further pharmacokinetic information on the absorption and disposition of memantine after repeated oral dosing.

The study design is as follows:

Study Design	Open label, multiple dose study in three groups
Study Population	N=20 Healthy subjects, 8 in each group with 4 subjects participating in both Group A and C Age: Group A: 20-46 years (mean 27 years) Group B: 20-45 years (mean 29 years) Group C: 20-30 years (mean 25 years) Gender: 20 males Weight: Group A: 64.9-77.6 kg (mean 70.7 kg) Group B: 65.5-79.6 kg (mean 71 kg) Group C: 67.4-89.9 kg (mean 76.9 kg) Race: Caucasians
Treatment Group	A: 1/2 x 10 mg memantine tablet every 8 hours for 12 days with a single dose in the morning of Day 12: 15 mg/day (actual dose of memantine free-base 4.08 mg) B: 1 x 10 mg memantine tablet every 8 hours for 12 days with a single Dose in the morning of Day 12 : 30 mg/day (actual dose of memantine free-base 8.14 mg) C: 2 x 10 mg memantine tablet every 8 hours for 3 days: 60 mg/day (actual dose of memantine free-base 16.29 mg)
Dosage and Administration	Tablets administered with 150 mL of water 10 mg memantine tablets, batch 90101 Diet: Following an overnight fast a light breakfast provided 0.5 hour prior to dosing. Lunch, afternoon snack, evening meal and evening snack were provided 4, 7.5, 11 and 15.5 hour after oral administration. Fluids were allowed ad libitum. No caffeine was allowed.
Sampling: Blood	For Groups A and B: Days 1 to 13:prior to the morning dose Days 1, 10, and 13: At 1, 2, 3, 4, 5, 6, 7, and 8 hours post-morning dose. Day 13: at 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours post-last dose. For Group C: Days 1 to 3: prior to the morning dose Days 1: At 1, 2, 3, 4, 5, 6, 7, and 8 hours post-morning dose.

	Day 3: After the second dose at 8, 16, 24, 32, 40, 48, 56, 64, 72, 80, 88, 112, and 136 hours relative to the morning dose.
Urine	For Group A and B: prior to the morning dose on Day 1 and from 0 to 8 hours after the morning dose on Days 1, 10, and 13. For Group C: At predose (-1-0 hr) and 0-8 hr after the morning dose on Day 1
Feces	none
Analysis	Lower Limits of Quantitation Plasma Urine Memantine Plasma: Linear Range: Inter-day precision: Inter-day accuracy: Quality control concentrations: ng/ml, highest concentration diluted Urine: Linear Range: Inter-day precision: Inter-day accuracy: Quality control concentrations: 150, 400 and 900 ng/ml, highest concentration diluted 10 folds
PK Assessment	AUC0-8, Cmax, Tmax, t1/2, Kel, CL, MRT, Ae(0-8), F, accumulation ratio Molecular weight ratio for calculating memantine free base=0.831
Safety Assessment	clinical laboratory safety assessments
PD Assessment	None

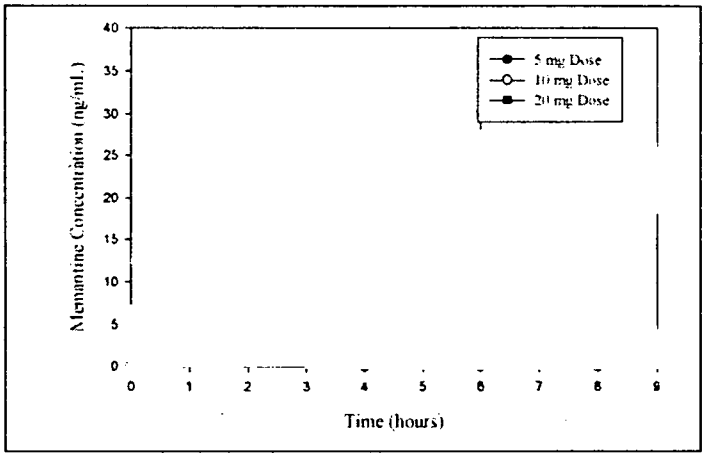
Pharmacokinetic Results:

Group A and B:

Day 1:

Cmax and AUC0-8 could not be calculated on Day 1 for the 5 and 10 mg dose groups. For a large number of subjects the plasma concentrations were below the LLOQ. Only 10 and 34 samples out of the 64 plasma concentration values were above the LLOQ for the 5 and 10 mg doses respectively. As can be seen in the following figure, memantine plasma concentrations were close to or below the LLOQ ~ ng/mL) on Day 1 after single doses of 5 and 10 mg.

The initial protocol had 10 and 20 mg dose groups, 5 mg was later added because the 20 mg dose group had to be dropped due to poor tolerance. Reducing the dose resulted in quantification problems with the plasma and urine samples.



Day 10 & 13:

The pharmacokinetic parameters of memantine in plasma and urine on Days 10 and 13 following multiple doses of 5 and 10 mg every 8 hours are shown in the following Table:

Parameter	*Day 10*		*Day 13*	
	5 mg Dose (n=8)	*10 mg Dose (n=8)*	*5 mg Dose (n=8)*	*10 mg Dose (n=8)*
C_{max} (ng/mL)	64.33 ± 9.13	128.70 ± 14.31	76.63 ± 11.21	139.50 ± 20.31
C_{max} (adjusted) [a]	15.77 ± 2.24	15.81 ± 1.76	18.78 ± 2.75	17.14 ± 2.50
T_{max} (h)	5.4 ± 2.1	3.7 ± 2.7	5.4 ± 1.6	4.0 ± 2.4
AUC_{0-8} (ng h/mL)	461 ± 73	880 ± 109	516 ± 86	977 ± 127
AUC_{0-8} (adjusted)[a]	113.0 ± 17.8	108.05 ± 13.35	126.40 ± 21.05	120.07 ± 15.58
C_{min} (ng/mL)	49.83 ± 8.45	90.91 ± 17.54	57.46 ± 11.16	102.06 ± 16.85
C_{min} (adjusted)[a]	12.21 ± 2.07	11.17 ± 2.16	14.08 ± 2.74	12.54 ± 2.07
T_{min} (h)	4.0 ± 2.6	3.6 ± 2.2	3.9 ± 2.0	5.0 ± 2.7
C_{av} (ng/mL)	57.61 ± 9.08	109.94 ± 13.58	64.66 ± 10.74	122.17 ± 15.85
C_{av} (adjusted)[a]	14.12 ± 2.22	13.51 ± 1.67	15.80 ± 2.63	15.01 ± 1.95
$T_{1/2}$ (h)	-	-	91.1 ± 27.8	72.6 ± 11.8
MRT (h)	-	-	123.1 ± 27.3	96.6 ± 18.5
Ae_{0-8} (mg)	0.942 ± 0.247	1.714 ± 0.451	1.169 ± 0.354	1.207 ± 0.608
Ae_{0-8} (adjusted)[a]	0.231 ± 0.060	0.211 ± 0.055	0.286 ± 0.087	0.148 ± 0.075
fe (%)	23.1 ± 6.0	21.1 ± 5.5	28.6 ± 8.7	14.8 ± 7.5
CL_r (mL/min)	35.16 ± 13.02	32.91 ± 9.96	38.92 ± 14.60	20.96 ± 10.26

[a] Pharmacokinetic parameter values divided by free-base dose

- After multiple dosing the half-life was 91 and 73 hours for the 5 and 10 mg respectively.

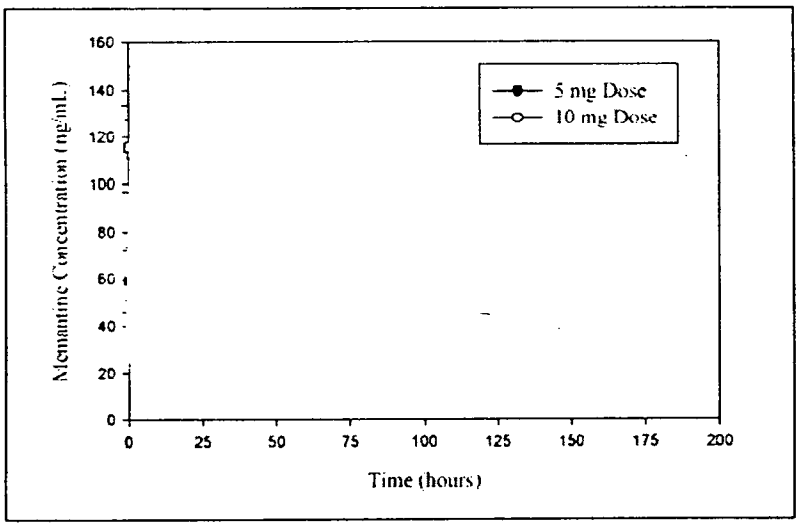
Assessment of steady state:

Assessment of steady-state was performed by comparison of memantine pharmacokinetic parameters on Day 10 and Day 13, of memantine morning pre-dose plasma concentrations on Days 8 to13, and of memantine morning pre-dose plasma concentrations on Days 10 and 13 using an ANOVA model which included treatment,

subject and day effects. There were significant differences between days for the dose adjusted parameters AUC0-8 and Cmax ($p<0.001$) regardless of treatment. In addition, there were significant differences between the morning pre-dose plasma concentrations of memantine on Days 9-13 ($p<0.001$) and on Days 10 and 13 ($p=0.047$). This shows that steady state was not established by Day 10, as indicated by the half-life of 91.1 hours (range 58.9-146.4 hours) and 72.6 hours (range 61.8-96.5 hours) for the 5 and 10 mg doses, respectively.

Assessment of dose-proportionality after multiple doses:
No significant differences were found between the dose adjusted AUC0-8 and Cmax for the 5 and 10 mg dose groups at Days 10 and 13, suggesting dose proportionality at these doses following repeat oral dosing.

The plasma concentration-time profile on Day 13 for the 5 and 10 mg dose is shown in the following figure:



Accumulation:
Accumulation could not be directly calculated as the Day 1 concentrations were unreliable for the 5 and 10 mg doses as they were close to or below the LLOQ (~ng/ml). However, looking at the Cmax at Day 10 and 13 for these doses there appears to be significant accumulation upon multiple doses. AUC0-8 could not be estimated at Day 1. The mean Cmax accumulation ratio appears to be approximately 10 for the 5 mg dose group and 15 for the 10 mg dose group. Since Day 1 Cmax values were based on plasma concentrations that were close to the limit of quantitfication, these accumulation ratios should be treated as an approximation. However, data does suggest that there is significant accumulation upon multiple dosing. Based on the half-life and proposed dosing, an accumulation factor of approximately 15 can be predicted upon multiple dosing.

Urinary excretion:

Day 1:
The fraction of unchanged drug excreted in the urine during the 8 hour after the first dose was about 2% for the 10 mg dose group and below or close to the LLOQ for the 5 mg dose group.
Day 10: The fraction of unchanged drug excreted in the urine increases to about 23% and 21% for the 5 and 10 mg dose group respectively. No significant difference was found between the dose groups on Day 10 for the dose adjusted Ae(0-8h) and CLR(0-8h), however, values for the 10 mg dose were lower than the 5 mg dose.
Day 13: The fraction of unchanged drug excreted in the urine were about 29% and 15 % for the 5 mg and 10 mg dose group respectively. The fraction of dose excreted by Day 13 for the 10 mg dose group was approximately two-thirds of the value determined on Day 10. The reason for this is unclear. The CLr was 39 and 21 ml/min for the 5 and 10 mg dose groups. This difference cannot be explained.

The urinary excretion of unchanged drug appears to be low in this study. This suggests that between 71-85% of the parent drug is cleared non-renally from the plasma after repeat dosing. However, the reason for low urinary excretion of unchanged drug could be that subjects were not asked to void their bladder prior to the 8-hour urine sampling period on Days 10 and 13. These results are contrary to that obtained from the single dose studies.

Dose adjusted Ae(0-8h) and CLr(0-8h) values were significantly different between dose groups on Day 13 (p=0.0042 and 0.013, respectively) with values being lower for the 10 mg dose group. This was not the case on Day 10.

Group C:

Subjects in Group B were supposed to receive multiple oral doses of 20 mg memantine every 8 hours (60 mg/day) until Day 13 but dosing was discontinued after the second dose on Day 3 due to poor tolerability at this dose level. The protocol did not allow for dose titration. By Day 3 adverse events originated from the nervous and musculo skeletal systems that were absent at the lower doses. These included ataxia, muscular discomfort, numbness.

The pharmacokinetic parameters following the initial 20 mg dose are shown in the following Table:

Parameter	*20 mg Dose Mean (SD)*
$AUC_{0\text{-}8}$ (ng .h/mL)	154 (34)
C_{max} (ng/mL)	27.86 (7.48)
T_{max} (h)	5.5 (2.4)
$Ae_{0\text{-}8}$ (mg)	0.664 (0.821)
$CL_{r\ (0\text{-}8)}$ (mL/min)	65.38 (62.10)

Reviewer's Comment:

The sponsor has provided additional data for the long term stability and benchtop stability of the samples. The assay validation appears adequate with these added information.

Conclusions:

- There is significant accumulation following multiple dosing. The Cmax accumulation ratio was approximately 15 for the 10 mg dose.
- The Cmax and AUC increased in a dose proportional manner following multiple dosing of 5 and 10 mg memantine.
- Steady state did not appear to have reached after 10 days of dosing.
- The results of renal elimination of unchanged drug are contrary to that obtained from the single dose studies. Only 29% and 15% of unchanged drug was excreted renally at Day 13 suggesting that 71-85% of the parent is excreted non renally.

APPEARS THIS WAY
ON ORIGINAL

Study: MRZ 90001-9402: ***Study of the Bioequivalence of the New Slow Release Tablet of Memantine and a Reference Tablet Formulation***

Only the immediate release arm of the study will be discussed here. This study was also done with elder subjects

A brief overview of some essential components of the study design pertaining to only the IR arm of the study is given below:

Study Design	Randomized, single-blind, controlled, multiple dose
Study Population	N=24 Healthy subjects, Age: 50-69 years (mean 56 years for men and 56.5 years for females) Gender: 12 males and 12 females Weight: 63-90 kg for males (mean 80.1 kg) 50-85 kg for females (mean 67.8 kg) Race: NA
Treatment Group	Single group 2 x 10 mg Tablets
Dosage and Administration	Each subject received the following dosing regimen: Day 1-5: 1 x 10 mg IR tablets QD Day 6-26: 1 x 10 mg IR tablets BID Day 27: 2 x 10 mg IR tablets Memantine tablets lot# 40401 Diet: Subjects requested to fast overnight and received standardized meal 2, 5 and 10 hours after dosing. Volunteers abstained from alcohol for the duration of the study. Also abstained coffee or tea.
Sampling: Blood	Day 6, 13 and 20: prior to morning dose Day 27: At (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours post-dose. Day 28: One sample between 16:00 and 20:00 hours Day 29-41: Between 8:00 and 10:00 hours
Urine	Day 27: 24 hour interval
Feces	none
Analysis	 Lower Limits of Quantitation Plasma Urine Memantine — Linear range ( ) in plasma Linear range ( ) in urine

	Precision — Accuracy — — No QC data provided.
PK Assessment	AUC0-t, Cmax, Tmax, Cmin, Cav, % fluctuation, T1/2, % of dose excreted in urine
Safety Assessment	General adverse events
PD Assessment	None

Pharmacokinetic Results:

The pharmacokinetic parameters after multiple doses of 20 mg memantine are shown in the following Table:

Table: Pharmacokinetic Parameters (Mean ± SD) of Memantine Following Multiple 20 mg Doses of an Immediate Release Formulation in Healthy Elderly Subjects

Parameter	*IR Formulation (n = 24)*
C_{max} (ng/mL)	91.3 ± 18.7
T_{max} (h)	4.5 ± 1.5
AUC_{0-24} (ng h/mL)	1848.5 ± 408.7
AUC_{0-t} (ng h/mL)	8162.9 ± 3655.9
$AUC_{0-\infty}$ (ng h/mL)	8836.9 ± 4048.5
C_{min} (ng/mL)	63.0 ± 15.8
C_{av} (ng/mL)	77.0 ± 17.0
%Fluctuation	37.51 ± 9.19
T_{Cav} (h)	11.53 ± 1.14
$T_{1/2}$ (h)	72.26 ± 19.55

- An ANOVA conducted showed that gender did not have a significant effect on the pharmacokinetic parameters except on % fluctuation (p=0.036).
- Pharmacokinetic samples were not obtained on Day 1, hence degree of accumulation cannot be obtained from this multiple dose study.

Rewiewer's Comment:

- *Quality control samples were not provided for the analytical runs. However, standard curve was generated each Day. The accuracy and precision for the standard curves were good. The sponsor has followed the ICH guidelines for assay validation for some of the studies. This does not meet the FDA guidance of bioanalytical validation. These studies with minimal validation can be accepted based on two reasons:*
  - *(a) No drift in data was observed in studies with quality controls using the same methodology*
  - *(b) The Pharmacokinetic parameters obtained at same doses were very similar across studies.*

- *ANOVA output not provided for the gender analysis.*
- *Lot no's used for SR and IR treatment arm are the same, is it possible. This is probably a typographical error*
- *The project was performed 8/94-3/95, plasma samples arrived to the analytical Department June-Aug 1994. How is this possible? Again this must be a typographical error.*
- *This study should only be used as a supportive multiple dose study.*

BIOEQUIVALENCE AND FOOD EFFECT STUDY

Study: MEM-PK-01: *A Single-Dose Open Label, Randomized, Three-Way Crossover Bioequivalence and Bioavailability Study Comparing 10 mg Memantine Tablets Manufactured by Forest Laboratories and Merz in Human Subjects*

Objectives:

(a) To assess the extent of absorption of 10 mg memantine tablets manufactured by Forest Laboratories and Merz given as a 20 mg dose and determine whether these products are bioequivalent and
(b) To assess the effect of food on the pharmacokinetics of the Forest memantine tablet.

The study design is as follows:

Study Design	Open label, single dose, three-way crossover study
Study Population	N=23 subjects Age: 18-35 years, mean 25 years Gender: 17 males and 6 females Weight: 55.7-99.7 kg, mean 77.4 kg Race: Caucasians
Treatment Group	Memantine was administered in a crossover manner as follows: Treatment A: 20 mg (2 x 10 mg) SD of memantine tablets (Forest) under fasted conditions Treatment B: 20 mg (2 x 10 mg) of memantine tablets (Forest) under fed conditions Treatment C: 20 mg (2 x 10 mg) of memantine tablets (Merz) under fasted conditions Washout period: 21 days between treatments
Dosage and Administration	All subjects received a single dose of the assigned dosing of memantine administered with 240 ml water. For Treatment A and C subjects fasted for at least 10 hours prior to dosing and 4 hours after dosing. For Treatment B subjects fasted for 10 hours and were then given standardized high fat breakfast. Memantine was given after 30 minutes of breakfast and then subjects fasted for another 4 hours. Water was permitted as desired except 1 hour before and after dosing. Forest Lot# 5007 Diet: High Fat breakfast: 2 eggs fried in butter, 2 bacon strips, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk 150 protein calories, 250 carbohydrate calories, 500-600 fat calories Other times all subjects were given standardized low fat meals.

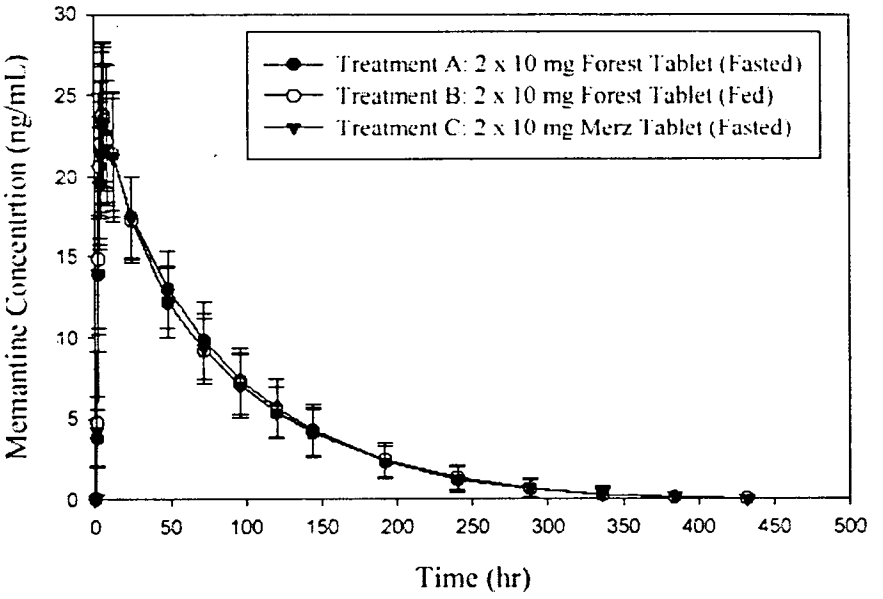
	No alcohol or grapefruit juice was allowed 72 hours prior and through out the study.
Sampling: Blood	On Days 1, 22, and 43 at: 0.0 hour (pre-dose), 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 192, 240, 288, 336, 384, and 432 hours post dose.
Urine	none
Feces	none
Analysis	— for memantine samples Lower Limits of Quantitation Plasma Memantine — Linear Range — Inter and Intraday Precision Inter and Intraday Accuracy Quality control concentrations Stability: Human plasma for 24 hours at RT Specificity: No interference Recovery: — Assay complete and acceptable
PK Assessment	AUC, Cmax, Tmax, t1/2, CL/F, Vz/F
Safety Assessment	Blood pressure, pulse rate, respiratory rate, ECG, Laboratory tests, hematology, blood chemistry

Formulation differences between the Forest and Merz formulations (RP1 and RP3) are shown in the following Table for the 5 mg tablets.

Compositional Code	A1		A2		A3	
Lot Number of Drug Product	Forest Commercial Product		Rp1		Rp3	
Ingredients (Core)	*mg/tablet*	*%w/w*	*mg/tablet*	*%w/w*	*mg/tablet*	*%w/w*
Memantine HCl	5.00		5.00		5.00	
Lactose Monohydrate, NF						
Microcrystalline Cellulose, NF						
Colloidal Silicon Dioxide, NF						
Talc, USP						
Magnesium Stearate, NF						
Subtotal Weight (mg)						
Ingredients (Film Coat)						
Tan			-	-	-	-
	-	-			-	-
	-	-			-	-
	-	-				
	-	-	-	-		
	-	-	-	-		
	-	-	-	-		
	-	-	-	-		
	-	-	-	-		
Total Coated Tablet Weight (mg)	128.75		101.24		252.00	

Pharmacokinetic Results:

The mean plasma concentrations of memantine are shown in the following Figure. Mean plasma concentrations were similar following administration of the Forest formulation under fasted and fed conditions and the administration of the Merz formulation under fasted conditions.



The pharmacokinetic parameters of memantine following administration of the Forest tablets under fasted and fed conditions and the Merz tablets under fasted conditions are tabulated in the following Table.

Table:
Pharmacokinetic Parameters of Memantine Following Administration of 2 x 10 mg Forest Tablets Under Fasted and Fed Conditions and 2 x 10 mg Merz Tablets Under Fasted Conditions in Healthy Male and Female Subjects

Parameter	*Treatment A Forest, fasted (n=23)*	*Treatment B Forest, Fed (n=23)*	*Treatment C Merz, Fasted (n=23)*
C_{max} (ng/mL)	24.4 ± 4.4	24.7 ± 4.4	23.7 ± 3.6
T_{max} (h)	5.6 ± 0.8	5.0 ± 2.0	5.8 ± 0.7
AUC_{0-t} (ng h/mL)	1878.5 ± 468.1	1840.4 ± 435.9	1824.3 ± 450.2
$AUC_{0-\infty}$ (ng h/mL)	1939.7 ± 472.1	1898.7 ± 444.3	1881.2 ± 453.3
$T_{1/2}$ (h)	55.6 ± 10.3	55.9 ± 10.7	57.2 ± 10.9
CL/F (mL/min)	151.0 ± 36.0	153.7 ± 29.1	155.1 ± 38.8
Vd/F (L)	846.7 ± 123.3	868.1 ± 143.7	899.4 ± 155.9

Statistical comparisons for Treatment B versus Treatment A and Treatment A versus Treatment C are presented in the following Table.

Table:
Comparison of Memantine Pharmacokinetic Parameters (90% CI) Following Administration of 2 x 10 mg Forest Tablets Under Fasted and Fed Conditions and 2 x 10 mg Merz Tablets Under Fasted Conditions in Healthy Male and Female Subjects

Parameter	*Treatment B vs. Treatment A (Fed vs. Fasted)*	*Treatment A vs. Treatment C (Forest vs. Merz)*
C_{max} (ng/mL)	99 – 106	98 – 105
AUC_{0-t} (ng h/mL)	99 – 107	95 – 102

$AUC_{0-\infty}$ (ng h/mL)	100 - 107	95 - 102

There were no statistically significant differences in terms of Cmax and AUC parameters following administration of the Forest tablets under fasted and fed conditions. Similarly, there were no statistically significant differences between the Forest and Merz tablets.

Safety:

Most common side effects were malaise, light headed feeling, headache, pharyngitis. There were no clinically relevant changes in mean laboratory, vital signs and ECG values.

Conclusions:

- Food had no effect on the rate and extent of absorption of memantine following administration of 2 x 10 mg memantine tablets manufactured by Forest Laboratories, Inc.
- Memantine 10 mg tablets manufactured by Forest were bioequivalent to the 10 mg tablets manufactured by Merz.

Study: MRZ 90001-9704/MKL 2745: Study of the Influence of Food on the Bioavailability of Memantine from a New Memantine SR Formulation and on the Relative Bioavailability of This Formulation Versus an IR Formulation Following Repeated Peroral Doses

This study has not been reviewed completely because a single dose food effect study has been conducted with the to-be-marketed formulation. The food effect portion in this study was conducted with the SR formulation, which is not the to-be-marketed dosage form for this application.

Only the immediate release arm of the study was reviewed as multiple doses of the IR tablet were given. This study was also done with elder subjects.

A brief overview of some essential components of the study design pertaining to only the IR arm of the study is given below:

Study Design	Open label, parallel group, multiple dose
Study Population	N=24 Healthy subjects, Age: 51-71 years (mean 56.5 years for men and 59.4 years for females) Gender: 18 males and 6 females Weight: 59-94 kg for males (mean 81.9 kg) 52-87 kg for females (mean 67.8 kg) Race: Caucasians
Treatment Group	Treatment D: 1 x 10 mg commercial IR tablet once daily on Days 4 to 8 followed by 1 x 10 mg commercial IR tablet twice daily on Days 9 to 27 and 2 x 10 mg commercial IR tablet on Day 28.
Dosage and Administration	Each subject received the following dosing regimen: Day 4-8: 1 x 10 mg IR tablets QD Day 9-27: 1 x 10 mg IR tablets BID Day 28: 2 x 10 mg IR tablets In house Days 4-8 Diet: Standardized meals on Day 28 Volunteers abstained from alcohol from 36 hours before drug administration to Day 9 and Day 27 till end of study. Also abstained coffee or tea.
Sampling: Blood	Day 7, 14 and 21: prior to morning dose Day 28: At (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours post-dose.
Urine	Day 28: over a period of 24 hours
Feces	none
Analysis	[redacted]

	Lower Limits of Quantitation Plasma Urine Memantine Linear range Linear range Accuracy NO QC data provided
PK Assessment	AUC0-t, Cmax, Tmax, Cav, PTF, T1/2, % of dose excreted in urine
Safety Assessment	General adverse events
PD Assessment	None

Pharmacokinetic Results:

The following are the trough plasma concentrations (ng/ml) after 20 mg doses of memantine

Subject	Day 7	Day 14	Day 21	Day 28
N	24	24	24	24
Mean (% CV)	22.91 (22.9)	56.51 (22.2)	65.66 (24.6)	62.51 (29.4)

This shows that steady state has almost reached by Day 14.

The pharmacokinetic parameters after multiple doses of 20 mg memantine are shown in the following Table:

Table:
Pharmacokinetic Parameters (Mean ± SD) of Memantine Following Multiple 20 mg Doses of Immediate Release Tablets in Healthy Elderly Male and Female Subjects

	Treatment D:2 x 10 mg IR Tablet		
Parameter	*All Subjects*	*Males*	*Females*
	(n=24)	*(n = 18)*	*(n = 6)*
C_{max} (ng/mL)	85.83 ± 22.87	76.73 ± 15.73	113.13 ±1 9.30
Wt Adjusted Cmax		87.96 ± 17.63	104.02 ± 18.53
T_{max} (h)	5.15 ± 2.93	5.15 ± 3.21	5.17 ± 2.14
$AUC_{0-\infty}$ (ng h/mL)	1803 ± 492	1620 ± 373	2352 ± 397
Wt Adjusted AUC0-∞		1856 ± 418	2164 ± 390
PTF	0.349 ± 0.078	0.338 ± 0.080	0.383 ± 0.070
T_{Cav} (h)	12.66 ± 1.31	12.79 ± 1.26	12.25 ± 1.48
Ae_{0-24} (mg)	8.81 ± 2.44	8.63 ± 2.64	9.29 ± 1.94
%Dose	44.1 ± 12.2	43.2 ± 13.2	46.4 ± 9.7

- Accumulation could not be estimated as plasma levels were not taken after a single dose. However, this study gives the pharmacokinetic parameters after multiple doses of 2x10 mg memantine given in the proposed BID regimen.

- Mean Cmax and AUC0-24 values were higher in female than in male subjects by 47% and 45%, respectively, following administration of the IR formulation. Statistical evaluation showed that weight, but not gender, had a significant effect on AUC0-24 and Cmax. After accounting for weight differences, Cmax and AUC0-24 values were higher in female subjects by 18% and 17%, respectively but these differences were not statistically significant.

Reviewer's comment:

This study can be accepted due to previous mentioned reasons for accepting studies with lack of QC data, but good precision and accuracy for the standard curves generated each day of the analytical runs and also no drift in analytical data from studies that had QC data.

ADDITIONAL PILOT STUDIES

Study MRZ 90001-8609: ***Open Pilot Study to Assess the Penetration of Akatinol Memantine Tablets in the Cerebrospinal fluid.***

Objective:

To demonstrate the presence of memantine in the cerebrospinal fluid (CSF) following a 20 mg intravenous dose of memantine as a 50 mL solution administered over 10 minutes.

This was an open-label study in two groups of 5 male patients each. The first group (Group A) consisted of Parkinsonian patients who underwent stereotactic surgery (mean age of 50 years). The second group (Group B) consisted of patients who exhibited involuntary movements and pain syndromes of different origins (mean age of 66.4 years). Patients received 20 mg memantine as a 10-minute intravenous infusion. Memantine concentration was determined in plasma and CSF once for each subject. No pharmacokinetic profiling was performed.

The concentrations of memantine in plasma and CSF of the patients in the two groups are presented in the following Table:

Memantine Concentrations in Plasma and CSF Following a 20 mg Infusion in Patients Suffering from Parkinson's Disease or from Pain Syndromes and Involuntary Movements

Subject No.	*Sampling Time (min)*	*Concentration in Plasma (µg/L)*	*Concentration in CSF (µg/L)*	*Plasma to CSF Ratio*
Group A 1	26		6.6	
2	62		5.2	
3	89		9.5	
4	122		10.1	
5	141		11.3	
Group B 6	23		4.9	
7	59		4.9	
8	84		6.1	
9	119		7.1	
10	165		4.0	

Reviewer's comment:

— method was used for the detection of memantine in plasma and CSF. The limit of quantitation was — ng/mL in both. No validation parameters were listed. Providing a range for LOQ is unclear. Therefore, any conclusions cannot be drawn from this study. This study just indicates that memantine was detected in the CSF within 26 minutes after the infusion. However, quantitative estimation of the concentration is not viable from this study. The sponsor has used information from this study in the labeling. Any information from this study should be deleted from the label.

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commercial

information

Study MRZ 90001-8610: Partial Evaluation and Tolerability of Akatinol Memantine in Healthy Volunteers under Mental Stress Using Pharmaco-EEG after IV administration

The objective of this study was to clarify the time course of the qualitative and quantitative effects of memantine on pharmaco-EEG.

This was a double-blind, placebo-controlled, parallel group trial in 16 healthy male volunteers (age range 22 – 40 years). Seven subjects received a single 30 mg intravenous dose of memantine and 9 subjects received placebo.
Criteria for evaluation were: medical history data, list of physical symptoms (LPS), sleep questionnaire form (SF-A), ECG heart rate and QT interval, blood pressure, body temperature, EEG (total power and absolute power of the EEG bands δ , θ 1, α 1, α 2, β 1, β 2) and plasma memantine concentrations. EEG data were available for a total of 12 subjects (6 subjects from each group).
Statistical analyses (Mann-Whitney U-test) indicated no significant differences between the memantine and placebo groups in terms of the list of physical symptoms and the sleep questionnaire form. In addition, no significant treatment differences were observed for blood pressure, heart rate, QT interval, and body temperature. Nonparametric analyses of the variables from the pharmaco-EEG at different time-points following dosing indicated possible treatment effects, primarily in the total power and absolute power of the δ and α 1 bands. No clear correlation between plasma concentrations and total power in EEG could be demonstrated.

IN VITRO METABOLISM

To identify the role of CYP 450 enzymes in the metabolism of memantine HCl immortalized human liver epithelial cells (THLE) which were genetically manipulated to express specific CYP genes, parent Neo cells and 293 cells were incubated with memantine. Parent Neo cells are without any CYP and are used as control cells (they do not express any CYP at all). Human kidney cell line 293 was introduced as a second negative control because of first results (loss of parent compound in neo cells).

The metabolism was measured by loss of parent compound (LPC).

Parent Neo cells, 293 and CYP expressing cells (the following CYPs were tested: 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4) were incubated for 2 and 24 hours with memantine HCl (intended concentrations:10 µM and 30 µM). A 20 mM stock solution of both compounds in PBS was prepared. The specific CYP activity in each cell line as control of the functionality of the cells (positive control) were measured.

CYP	substrate	metabolite	activity [pmol/minxmg cell prot]
1A2	methoxyresorufin	resorufin	3.55
2E1	chlorzoxazone	6-hydroxychlorzoxazone	39.1
3A4	testosterone	6ß-hydroxytestosterone	146.2
2B6	benzoxyresorufin	resorufin	3.5
2A6	coumarin	7-hydroxylase Coumarin	77.6
2C9	diclofenac	4-hydroxydiclofenac	343.8
2D6	dextromethorphan	dextrorphan	55.8
2C19	mephenytoin	4-hydroxymephenytoin	10.5

Results:

The results from the incubation of memantine with the THLE cell line and the controls Neo cells and 293 cell line are given in the following Table:

Intended Concentration [µM]	Cell Type	LPC (2 h)	LPC (24 h)
10	CYP2B6	20.9 %	24.7 %
30	CYP2B6	17.1 %	28.5 %
10	neo	25.3 %	28.0 %
30	neo	19.2 %	34.3 %
10	CYP2E1	18.2 %	28.0 %
30	CYP2E1	17.7 %	20.3 %
10	CYP3A4	16.3 %	25.3 %
30	CYP3A4	12.5 %	16.5 %
10	CYP1A2	17.6 %	23.8 %
30	CYP1A2	9.7 %	29.3 %
10	CYP2C19	15.0 %	22.4 %
30	CYP2C19	13.5 %	21.2 %
10	CYP2C9	20.7 %	27.7 %
30	CYP2C9	19.5 %	41.3 %
10	CYP2D6	22.0 %	25.8 %
30	CYP2D6	21.5 %	26.3 %
10	CYP2A6	22.1 %	24.6 %
30	CYP2A6	15.1 %	21.6%
10	CYP2C9	15.1 %	21.1 %
30	CYP2C9	20.3 %	15.7 %
10	CYP2D6	16.5 %	13.4 %
30	CYP2D6	17.2 %	15.1 %
10	neo	16.0 %	15.7 %
30	neo	17.6 %	14.7 %
10	293	21.3 %	26.3 %
30	293	21.4 %	24.4 %

This table demonstrates that similar loss of parent compound was observed with the controls as well as memantine. The loss of parent compound (LPC) being in the range of 19-34%. Incubations with 2C9 and 2D6 were repeated and the LPC was again in the range of 13-26% as given in the above table. This loss of parent compound was independent of the concentration of memantine in the incubation mixture.

The data from individual experiments is given in the following Table:

Intended Concentration [µM]	Cell Type	Control (2 h)	Control (24 h)	Cells (2 h)	Cells (24 h)	LPC (2 h)	LPC (24 h)
10	CYP2B6	1,966.8 ± 0.9	2,082.1 ± 42.2	1,556.3 ± 49.2	1,567.9 ± 17.7	20.9 %	24.7 %
30	CYP2B6	5,893.2 ± 69.4	6,787.8 ± 124.9	4,884.3 ± 78.0	4,854.7 ± 51.2	17.1 %	28.5 %
10	neo	1,966.8 ± 0.9	2,082.1 ± 42.2	1,469.1 ± 6.0	1,499.4 ± 2.3	25.3 %	28.0 %
30	neo	5,893.2 ± 69.4	6,787.8 ± 124.9	4,759.8 ± 38.5	4,460.9 ± 144.1	19.2 %	34.3 %

Intended Concentration [µM]	Cell Type	Control (2 h)	Control (24 h)	Cells (2 h)	Cells (24 h)	LPC (2 h)	LPC (24 h)
10	CYP2E1	19,540.2 ± 151.8	20,358.8 ± 270.5	15,990.0 ± 57.1	14,652.7 ± 761.6	18.2 %	28.0 %
30	CYP2E1	55,251.8 ± 324.5	55,566.7 ± 508.6	45,455.6 ± 101.3	44,259.0 ± 285.9	17.7 %	20.3 %
10	CYP3A4	19,540.2 ± 151.8	20,358.8 ± 270.5	16,352.6 ± 283.3	15,205.2 ± 352.5	16.3 %	25.3 %
30	CYP3A4	55,251.8 ± 324.5	55,566.7 ± 508.6	48,365.9 ± 245.1	46,413.3 ± 103.3	12.5 %	16.5 %

Indended Concentration [µM]	Cell Type	Control (2 h)	Control (24 h)	Cells (2 h)	Cells (24 h)	LPC (2 h)	LPC (24 h)
10	CYP1A2	21,433.3 ± 230.9	22,962.9 ± 8.7	17,665.6 ± 518.6	17,497.8 ± 195.0	17.6 %	23.8 %
30	CYP1A2	61,544.9 ± 1,013.6	64,751.5 ± 401.4	55,549.9 ± 679.3	45,772.2 ± 16,047.9	9.7 %	29.3 %
10	CYP2C19	21,433.3 ± 230.9	22,962.9 ± 8.7	18,223.0 ± 148.9	17,824.5 ± 378.2	15.0 %	22.4 %
30	CYP2C19	61,544.9 ± 1,013.6	64,751.5 ± 401.4	53,257.1 ± 191.2	51,021.1 ± 7,928.4	13.5 %	21.2 %

Intended Concentration [µM]	Cell Type	Control (2 h)	Control (24 h)	Cells (2 h)	Cells (24 h)	LPC (2 h)	LPC (24 h)
10	CYP2A6	19,464.7*	-	15,156.6 ± 59.6	14,674.3 ± 271.2	22.1 %	24.6 %
30	CYP2A6	57,960.4*	-	49,181.4 ± 850.6	45,464.6 ± 293.4	15.1 %	21.6%

* 0 h-control (2 h, 24 h control values are missing)

Intended Concentration [µM]	Cell Type	Control (2 h)	Control (24 h)	Cells (2 h)	Cells (24 h)	LPC (2 h)	LPC (24 h)
10	CYP2C9	19,195.9 ± 442.5	18,330.3 ± 275.9	15,229.6 ± 237.4	13,254.2 ± 48.9	20.7 %	27.7 %
30	CYP2C9	55,226.1 ± 621.8	54,043.8 ± 2,768.2	44,471.2 ± 321.8	31,746.8 ± 10,926.4	19.5 %	41.3 %
10	CYP2D6	19,195.9 ± 442.5	18,330.3 ± 275.9	14,979.1 ± 332.4	13,598.2 ± 819.7	22.0 %	25.8 %
30	CYP2D6	55,226.1 ± 621.8	54,043.8 ± 2,768.2	43,336.5 ± 1,809.1	39,806.6 ± 911.8	21.5 %	26.3 %

Concentration [µM]	cell type	control (2 h)	control (24 h)	cells (2 h)	cells (24 h)	LPC* (2 h)	LPC (24 h)
10	CYP2C9	2,168.4 ± 57.6	2,117.3 ± 26.0	1,840.2 ± 10.1	1,670.5 ± 82.0	15.1 %	21.1 %
30	CYP2C9	5,898.1 ± 49.0	5,725.7 ± 110.9	4,701.0 ± 78.1	4,824.0 ± 143.7	20.3 %	15.7 %
10	CYP2D6	2,168.4 ± 57.6	2,117.3 ± 26.0	1,809.9 ± 64.2	1,834.3 ± 62.0	16.5 %	13.4 %
30	CYP2D6	5,898.1 ± 49.0	5,725.7 ± 110.9	4,881.2 ± 25.4	4,860.6 ± 83.2	17.2 %	15.1 %
10	neo	2,168.4 ± 57.6	2,117.3 ± 26.0	1,820.8 ± 64.6	1,784.4 ± 60.6	16.0 %	15.7 %
30	neo	5,898.1 ± 49.0	5,725.7 ± 110.9	4,859.6 ± 37.6	4,882.2 ± 126.7	17.6 %	14.7 %

Concentration [µM]	cell type	control (2 h)	control (24 h)	cells (2 h)	cells (24 h)	LPC (2 h)	LPC (24 h)
10	293	1,751.7 ± 9.3	1,699.1 ± 4.5	1,379.4 ± 23.3	1,252.3 ± 10.7	21.3 %	26.3 %
30	293	5,046.5 ± 5.0	5,079.0 ± 69.2	3,966.0 ± 58.2	3,838.0 ± 138.9	21.4 %	24.4 %

Conlcusions:

These results show that CYP isoenzymes are not involved in the metabolism of memantine at the concentrations studied.