CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-224

Clinical Pharmacology and Biopharmaceutics Review

COMPLETED MAY

MAY 19 2000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDAs: 21-169 and 21-224	Submission Dates: October 23, 1998 September 29, 1999 January 31, 2000 February 8, 2000 February 18, 2000 February 25, 2000 April 10, 2000
Generic Name:	**Galantamine**
Brand Name:	**REMINYL®**
Formulations:	**IR Tablets (4, 8, and 12 mg) (NDA #21-169)** **Solution (4 mg/ml) (NDA# 21-224)**
Indication:	**Alzheimer's disease**
Sponsor:	**Janssen**
Type of Submission:	**NDA (NME)**
Reviewer:	**Sayed Al-Habet, Ph.D.**
Date of Review:	**February 24, 2000**

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Synopsis:

Galantamine hydrobromide , a tertiary alkaloid extracted from several species of Amaryllidaceae, is a competitive and reversible acetylcholinesterase inhibitor and modulates the neuronal nicotinic acetylcholine receptor. Galantamine has been developed for the treatment of patients with mild or moderate Alzheimer's disease. The recommended dose range is 12-16 mg galantamine b.i.d. after dose-titration by weekly increments of 4 mg b.i.d. Galantamine is a weak base with one ionization constant due to the azepine moiety (pKa = 8.2). The molecular weight of galantamine hydrobromide is 368.27. Galantamine is slightly lipophilic as demonstrated by a partition coefficient between n-octanol/buffer solution (pH 12.0) of 1.1. The solubility of galantamine in water (pH 6.0) is 31 mg/mL.

RECOMMENDATION

Based on the information submitted to us, this NDA is ACCEPTABLE to the Office of Clinical Pharmacology and Biopharmaceutics.

COMMENTS TO THE CLINICAL DIVISION

1) In patients with moderate hepatic impairment, AUC increased by about 33%, associated with an increase in half- life of about 30% (8 vs 10.5 h) and a reduction in apparent plasma clearance of 23%. There was no adequate information on the PK of galantamine in patients with severe hepatic impairment. Exposure is expected to increase further with increasing degree of impairment. See also OCPB Labelling.

2) The pharmacokinetics of galantamine were statistically significantly different in moderately and severely renally impaired patients. AUC was 37% and 67% higher in the moderate and severe group as compared to normals. See also OCPB Labelling.

3) Paraxetine at 20 mg once daily dosing for 12 days increased the AUC of galantamine by 40% at steady-state. The effect of paroxetine on galantamine disposition could be more pronounced at the commonly administered paroxetine maintenance dose of 30 mg. See also OCPB Labelling.

4) Ketoconazole 200 mg b.i.d. increased the AUC of galantamine by 30%. Dose adjustment may be necessary when ketoconazole is co-administered with galantamine. See also OCPB Labelling.

COMMENTS TO LABELLING:

The sponsor is requested to adopt OCPB labeling as outlined in Appendix II.

COMMENT TO THE SPONSOR:

The sponsor is requested to adopt the following dissolution methodology for all strengths of galantamine tablets.

Apparatus II:	USP (Paddles)
Speed:	50 rpm
Medium:	500 mL water
Specification:	Not less than [redacted] % (Q), in 20 minutes

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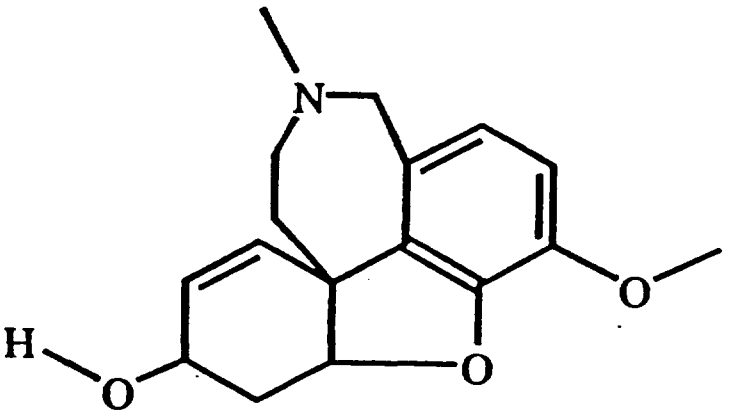
SUMMARY REVIEW
OF PHARMACOKINETICS AND BIOAVAILABILITY
(Question Based Review, QBR)

A) BACKGROUND:

What are the Physico-Chemical Properties of Galantamine?

Galantamine is a weak base with one ionization constant due to the azepine moiety (pKa = 8.2). The molecular weight of galantamine hydrobromide is 368.27. Galantamine is slightly lipophilic as demonstrated by a partition coefficient between n-octanol/buffer solution (pH 12.0) of 1.1. The solubility of galantamine in water (pH 6.0) is 31 mg/mL. According to the Biopharmaceutics Classification System (BCS), galantamine would be considered to be a category I drug as it is both highly soluble and highly permeable.

What is the Structural Formula of Galantamine?



What is the Indication of Galantamine?

REMINYL (galantamine) has been developed for the treatment of patients with mild or moderate Alzheimer's disease.

What is the Mechanism of Action of Galantamine?

Galantamine is a competitive and reversible acetylcholinesterase inhibitor. It modulates the neuronal nicotinic acetylcholine receptor.

How Will Galantamine be Supplied?

REMINYL (galantamine) will be available as oral IR tablets in the following strengths: 4 mg, 8 mg; and 12 mg, and also as an oral solution in a single 4 mg/ml strength.

What is the Proposed Dosage and Administration of Galantamine?

The recommended dose range is 12-16 mg galantamine b.i.d. after dose-titration by weekly increments of 4 mg b.i.d. The recommended starting dose is 8 mg per day (4 mg BID) for at least one week, followed by 16 mg/day (8 mg BID) for at least another week before proceeding to the recommended maintenance dose of 24 mg/day (12 mg BID). In some patients slower titration may result in improved tolerability.

What Assay Method Was Used?

[redacted] was the method employed in most of the formal studies. This method uses a [redacted] with [redacted] determine galantamine and norgalantamine (also known as N-desmethyl-galantamine) in biological samples. The lower limits of quantification in plasma were [redacted] ng/ mL for galantamine and [redacted] ng/ mL for norgalantamine. The mean coefficients of variation for independently prepared quality control samples were ~8.00% for galantamine and ~ 11.00% for norgalantamine.

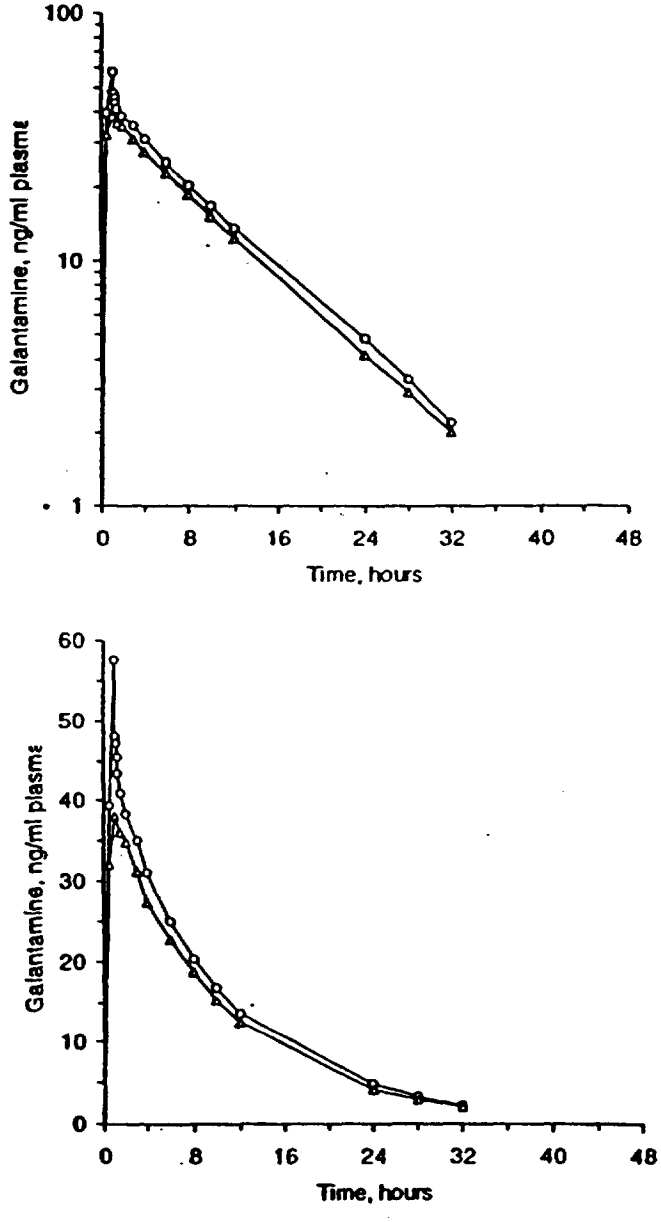
B) CLINICAL PHARMACOLOGY STUDIES:

What is the Bioavailability of Galantamine?

The absolute bioavailability of galantamine was investigated after a single dose of 8 mg administered as either oral solution or IV infusion over 1 hour in 12 healthy subjects (study# N130723). Galantamine was rapidly absorbed with peak plasma concentrations generally attained in about 1 hour after oral administration. The absolute oral bioavailability of galantamine was 88.5% and was comparable between PMs and EMs. After IV administration of 8 mg galantamine, the mean (±sd) steady-state volume of distribution was 175 ± 23 L and the total body clearance was 297 ± 70 ml/min. This shows that galantamine is a low clearance drug. On average, renal clearance accounted for about 23% of the total plasma clearance. **Attachments 1 and 2** show the mean PK data. Norgalantamine (also known as N-demethylgalantamine, one of the active metabolites of galantamine) was not quantifiable in plasma in this study (see metabolism section). The urinary excretion of galantamine and norgalantamine was comparable after oral and i. v. administration.
The relative bioavailability of galantamine is discussed below.

JRF—Galantamine i.v. vs oral : GAL-BEL-4 / Part I : Pharmacokinetics 30

Display 5: Semilogarithmic (upper) and linear-linear (lower) plot of the mean plasma concentrations of galantamine as a function of time



○ : Treatment A: 20 ml of a 0.4 mg/ml i.v. solution of galantamine as a 1-hour infusion

△ : Treatment B: 16 ml of a 0.5 mg/ml oral solution of galantamine

Pharmacokinetics			
Plasma data			
Galantamine Compartmental analysis		Treatment A 1-hour i.v. infusion	
$t_{1/2\alpha}$	min	8 ± 4	
$t_{1/2\beta}$	h	7.4 ± 1.7	
V_c	l	57.4 ± 17.3	
Vd_{ss}	l	175 ± 23	
Vd_{area}	l	182 ± 23	
Cl	ml/min	297 ± 70	
Galantamine Non-compartmental analysis		Treatment A 1-hour i.v. infusion	Treatment B Oral solution
t_{max}	h	1.0 ± 0.0	1.2 ± 0.6
C_{max}	ng/ml	58.3 ± 13.4	42.6 ± 13.1
$t_{1/2term}$	h	7.4 ± 1.7	7.3 ± 1.7
AUC_{last}	ng.h/ml	462 ± 108	408 ± 93
AUC_{∞}	ng.h/ml	482 ± 112	427 ± 102
F_{abs}	%	100	88.5 ± 5.4
Norgalantamine		Plasma concentrations of norgalantamine were below the lower limit of quantification at each time point (quantified in 2 subjects after each treatment).	
Urine data			
		Treatment A 1-hour i.v. infusion (n = 11)	Treatment B Oral solution (n = 10)
Galantamine			
Ae_{24h}	µg	1751 ± 518	1467 ± 454
Ae_{24h}	% of dose	21.9 ± 6.4	18.3 ± 5.7
Cl_{renal}	ml/min	68.4 ± 22.0	65.5 ± 14.9
Norgalantamine			
Ae_{24h}	µg	123 ± 25	143 ± 23
Ae_{24h}	% of dose	1.62 ± 0.32	1.88 ± 0.30

Conclusions
Galantamine is a low-clearance drug with a moderate volume of distribution. Elimination of galantamine is bi-exponential, with a mean terminal half-life of 7.4 hours. The absolute oral bioavailability is high (88.5%). Norgalantamine is not detectable in plasma after single dosing. The main pharmacokinetic parameters of galantamine in poor and extensive metabolisers of dextromethorphan were generally within the same range.

Is There Any Effect of Food of Galantamine Absorption and Bioavailability?

The effect of food was investigated in 24 healthy elderly subjects (23 completed) after a single dose of 10 mg (study # N122056/1). Under fed conditions (standard breakfast), the extent of galantamine absorption was not altered, but the rate of absorption was somewhat slower than in fasting condition. Galantamine peak plasma concentration was attained after about 2.5 hours when given with food and at about 1 hour after fasting. The Cmax was reduced by about 25% after food relative to fasting (43 vs 58 ng/ml). **Attachments 3 and 4** show the mean data.

Is There Bioequivalence Among Formulations Used During Galantamine Development?

Oral Tablets:

i) The 4 mg US to-be-marketed tablet formulation was shown to be bioequivalent to both the 4 mg research tablet, and the 8 mg research tablet at a dose of 8 mg in 29 healthy subjects (study # N137034).

ii) The 12 mg US to-be-marketed tablet was shown to be bioequivalent to the 12 mg research tablet when both were administered as 12 mg bid in 30 healthy subjects (Study # N137007). This study used the 8 mg US to-be-marketed tablets in escalating doses from 4 mg bid to 12 mg bid. The research tablets were used in the Phase III pivotal trials. The 90% CI for both Cmax and AUC in all studies were within the range of 80% and 125%.

This bioequivalence study was conducted as a multiple dose, dose escalation study, as 12 mg as a 'stat' initial single dose cannot being given to either healthy subjects or to patients.

Based on the fact that the to be marketed 4, 8, and 12 mg tablets are compositionally proportional, the drug follows linear kinetics, and that it falls in BCS category I (highly soluble/highly permeable drug), the sponsor could have requested a 'waiver for a biostudy' for the 12 mg tablets, based on dissolution.

iii) In addition, the mean bioavialability of the 12 mg US to-be-marketed tablets relative to oral solution (12 mg dose) in 27 healthy subjects was approximately 100% (study #N130883). The CI for both Cmax and AUC in this study was also within 80% to 125%, with a comparable Tmaxs (1 hour).

FIGURE S1

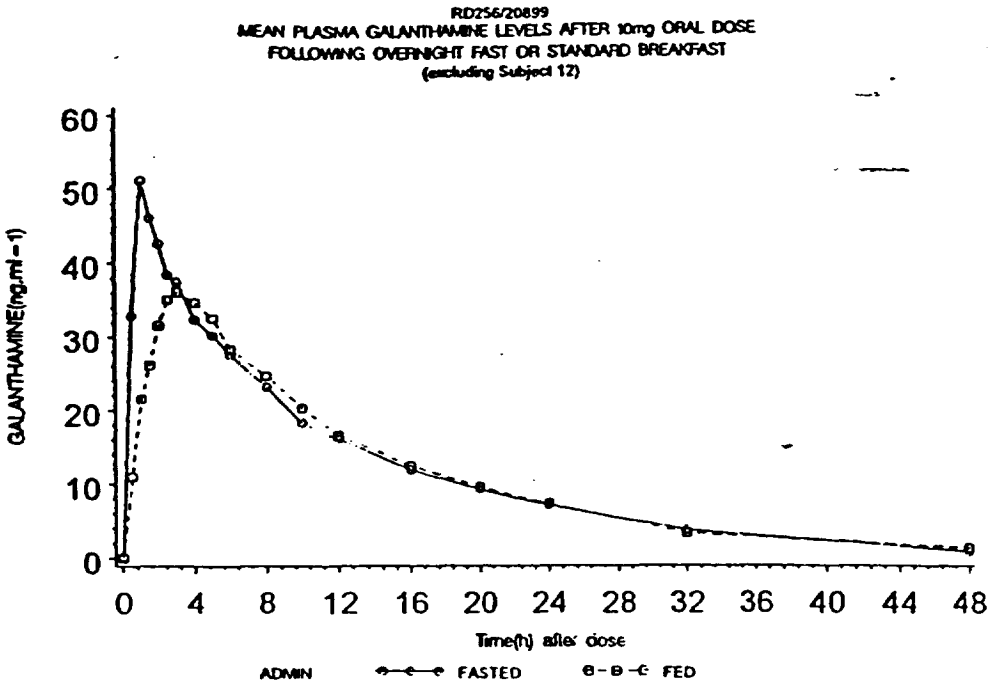


FIGURE S2

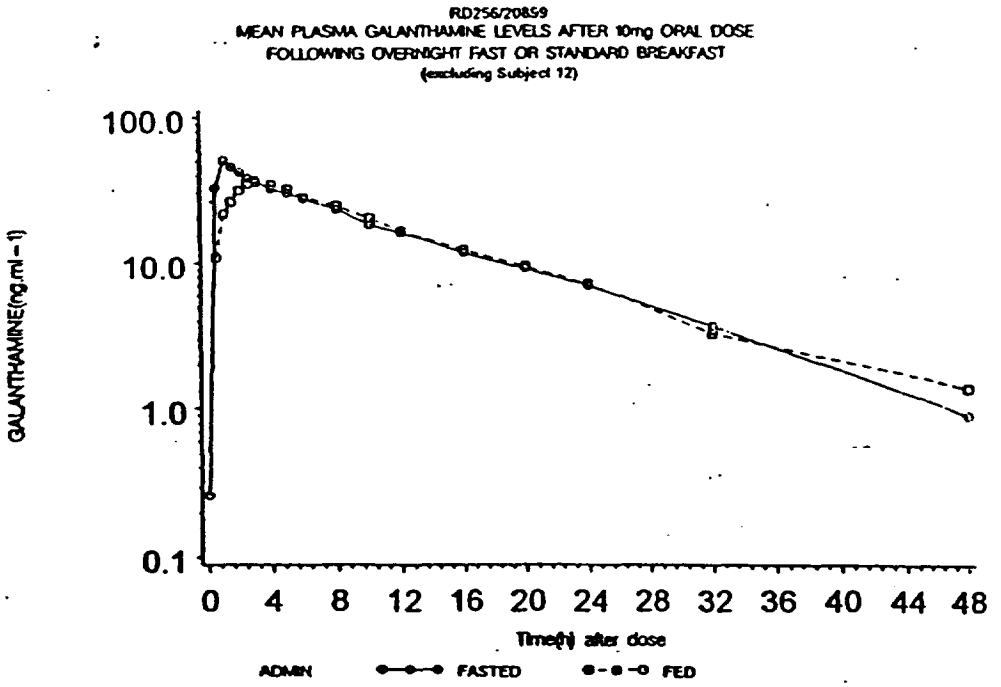


TABLE S1

RD 256/20899

Summary Galanthamine Pharmacokinetic Parameters and Statistical Analysis (excluding Subject 12).

	Treatment A: Fasted	Treatment B: Fed	ANOVA	Ratio Test/Reference (90% Confidence Intervals)
Cmax: Mean (± SD) $ng.ml^{-1}$	57.5 (±15.8)	42.5 (±7.5)	S	0.76 (0.69 : 0.83)
Tmax: Mean (± SD) h	1.1 (±0.5)	2.6 (±1.4)	S*	-
Thalf: Mean (± SD) h	9.7 (±0.5)	9.7 (±3.3)	NS	-
AUC_t : Mean (± SD) $ng.ml^{-1}.h$	507.4 (±175.5)	491.2 (±166.9)	NS	-
AUC_i: Mean(± SD) $ng.ml^{-1}.h$	562.3 (±179.9)	543.2 (±175.9)	NS	0.96 (0.93 : 0.99)

NS = No significant difference

S = Significant difference

* = Wilcoxon Scores Probability

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Oral Solution:

The oral solution of galantamine (12 mg) was bioequivalent to the US tablet formulation (12 mg) in the rate and extent of absorption. This bioequivalence study for oral solution (study #130883) was also submitted in NDA# 21-224 - the NDA for oral solution.

A summary of the data for the two pivotal studies for the tablets (#N137034 and N137007) and a pivotal study for the oral solution (#130883) are shown in **Attachments 5-8.**

What is the Elimination Pathways of Galantamine (Metabolism and Excretion)?

In Vivo Metabolism:

The metabolism and excretion of galantamine were investigated in four healthy subjects, 2 poor metabolizers (PM) and 2 extensive metabolizers (EM) of CYP2D6 after a single oral dose of 4-mg ^{3}H-galantamine in an aqueous solution (study# N137227). The oral dose of galantamine was well absorbed (**Attachment 9**). Based on the AUC ratio, unchanged galantamine accounted for 32% of the total radioactivity in the plasma. Seven days after dosing, 93-99% of the administered radioactivity had been excreted: 90-97% was recovered in urine and 2.2-6.3% in the feces (**Attachment 10, 10B**). The total amount of radioactivity excreted was similar in PM and EM (**Attachment 10B**).

The major metabolic pathways were glucuronidation, O- demethylation, N- demethylation, N-oxidation and epimerization (**Attachment 11**). The O-demethylation route was far more important in EM than in PM. The O-desmethyl-galantamine metabolite is rapidly glucuronidated. The lower extent of O-demethylated metabolite excreted in PM was primarily compensated by a greater excretion of unchanged galantamine and its N -oxide and secondarily by increased excretion of metabolites formed by glucuronidation, epimerization and N - demethylation. In both EM and PM, unchanged galantamine and its glucuronide accounted for most of the plasma radioactivity.

In Vitro Metabolism:

The biotransformation of galantamine was studied in cultures of human liver microsomes. ^{14}C-Galantamine with the ^{14}C-label on either the O-methyl or the N-methyl moiety was used to allow identification of metabolites formed by O-demethylation and N-demethylation. CYP3A4 and CYP2D6 were the major enzymes involved in the phase-1 metabolism of galantamine. CYP3A4 mediated the formation of galantamine-N-oxide, whereas CYP2D6 was involved in the formation of O-desmethyl-galantamine. Overall, it appears that there are at least five pathways for the metabolism of galantamine in humans and therefore no single pathway is likely to be affected or be able to predominate.

N #137034

Table 8-4: **Pharmacokinetic parameters of galantamine and summary of the bioequivalence analysis after single oral intake of one 8-mg research tablet, two 4-mg research tablets and two 4-mg non-US/US market tablets in 29 healthy subjects[PK 21].**

Parameter	8 mg tablet research (F8) Mean ± SD	2 x 4 mg tablets research (F5) Mean ± SD	2 x 4 mg tablets non-US/US market (F13) Mean ± SD
t_{max}, h	1.1 ± 0.6	0.9 ± 0.5	1.0 ± 0.5
C_{max}, ng/ml	46.3 ± 10.1	47.9 ± 10.3	45.8 ± 8.4
$t_{1/2term}$, h	7.9 ± 1.9	8.1 ± 1.7	7.9 ± 1.8
AUC_{last}, ng.h/ml	433 ± 113	436 ± 129	432 ± 129
AUC_{∞}, ng.h/ml	451 ± 118	454 ± 129	449 ± 133
Geometric mean treatment ratio and associated 90% confidence interval			
Parameter	2x4mg F5/8mg F8	2x4mg F13/8mg F8	2x4mg F13/2x4mg F5
AUC_{last},	100.1 (97.1-103.2)	98.9 (95.9-102.0)	98.8 (95.8-101.9)
AUC_{∞},	100.0 (96.9-103.2)	98.6 (95.6-101.8)	98.7 (95.6-101.8)
C_{max},	103.7 (97.9-110.0)	99.7 (94.0-105.7)	96.1 (90.7-101.9)

Table 8-5: **Pharmacokinetic parameters of galantamine and summary of the bioequivalence analysis at steady state of galantamine 12 mg b.i.d. given as 12 mg non-US market tablets, 12 mg US market tablets and as 12 mg research tablets in 30 healthy male subjects[PK 22].**

#N137007

Parameter	12 mg tablet non-US market (F16) Mean ± SD	12 mg tablet US market (F19) Mean ± SD	12 mg tablet Research (F9) Mean ± SD
t_{max}, h	0.9 ± 0.4	1.0 ± 0.5	1.0 ± 0.6
C_{min}, ng/ml	25.9 ± 8.9	25.2 ± 8.5	25.0 ± 8.9
C_{max}, ng/ml	89.7 ± 19.9	86.4 ± 18.7	90.2 ± 19.2
AUC_{τ}, ng.h/ml	567 ± 146	566 ± 144	562 ± 147
$C_{ss,av}$, ng/ml	47.2 ± 12.0	47.2 ± 12.0	46.9 ± 12.0
Geometric mean treatment ratio and associated 90 % confidence interval			
Parameter	12 mg non-US/12 mg Research	12 mg US/12 mg Research	
AUC_{τ}, ng.h/ml	100.8 (97.8-104.0)	101.0 (97.9-104.1)	
C_{min}, ng/ml	100.8 (95.7-106.2)	98.1 (93.1-103.4)	
C_{max}, ng/ml	99.1 (93.9-104.6)	95.7 (90.7-101.1)	

Table 8-6: **Pharmacokinetic parameters of galantamine and summary of the bioequivalence analysis at steady state of galantamine 12 mg b.i.d. given as a 12 mg US market tablets and as 3 ml of the 4 mg/ml oral solution in 27 healthy male subjects[PK 23].**

#N130883

Parameter	12 mg tablet US (F19) Mean ± SD	12 mg oral solution (4 mg/ml) (F20) Mean ± SD	Geometric mean treatment ratio and associated 90% confidence interval
t_{max}, h	1.02 ± 0.56	1.08 ± 0.47	
C_{min}, ng/ml	30.7 ± 10.3	29.8 ± 10.2	97.2 (93.4-101.1)
C_{max}, ng/ml	89.4 ± 18.3	87.6 ± 20.5	97.5 (90.5-104.9)
AUC_{τ}, ng.h/ml	623 ± 147	606 ± 156	97.0 (91.3-102.9)
$C_{ss,av}$, ng/ml	51.9 ± 12.2	50.5 ± 13.0	

[ ] Study # N137034

REPORT : CP/98/0861
TRIAL : GAL-NED-3

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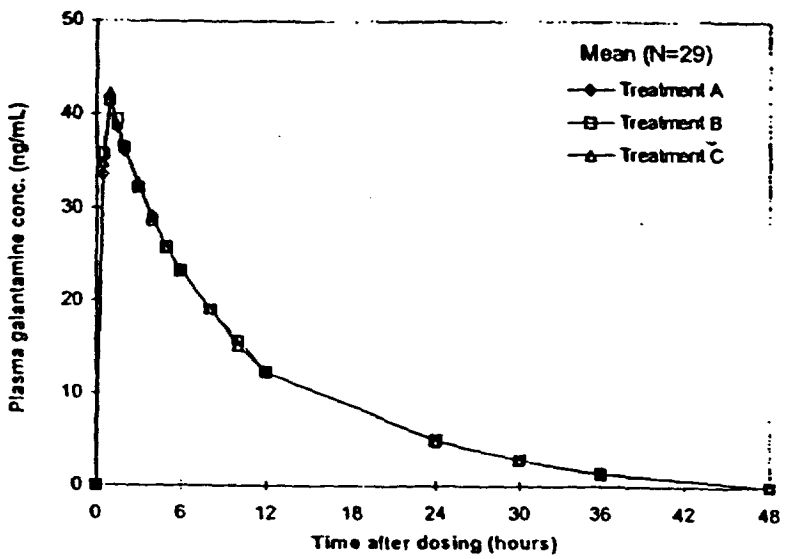
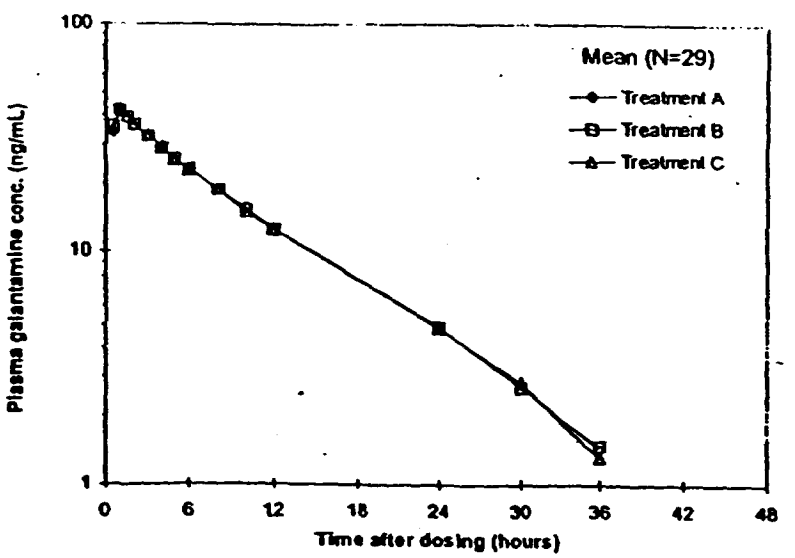
Display 6: Comparative plot of the mean plasma concentration-time profiles of galantamine.

Treatment A: 8 mg galantamine as one 8 mg research tablet (F8).
Treatment B: 8 mg galantamine as two 4 mg research tablets (F5).
Treatment C: 8 mg galantamine as two 4 mg market tablets (F13).

Upper panel: linear co-ordinates; lower panel: log-linear co-ordinates.





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[ ] Study # 137007

REPORT : CP/98/0507
TRIAL : GAL-NED-4

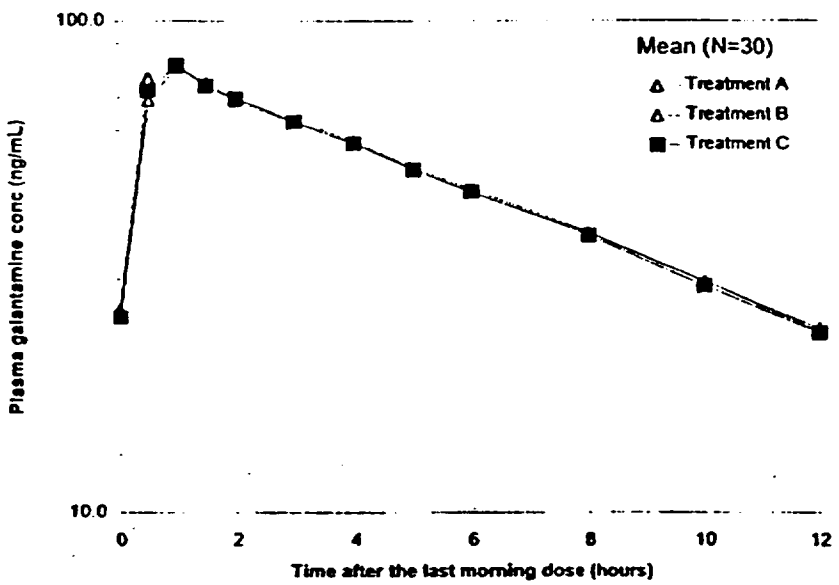
Display 8: (continued) Comparative plot of the mean plasma concentration-time profiles of galantamine at steady-state.

Treatment A: b.i.d. treatment with 12 mg galantamine for 7 days as the IRF market tablet formulation.

Treatment B: b.i.d. treatment with 12 mg galantamine for 7 days as the US market tablet formulation.

Treatment C: b.i.d. treatment with 12 mg galantamine for 7 days as the research tablet formulation.

Semilogarithmic co-ordinates.



Study #N130883

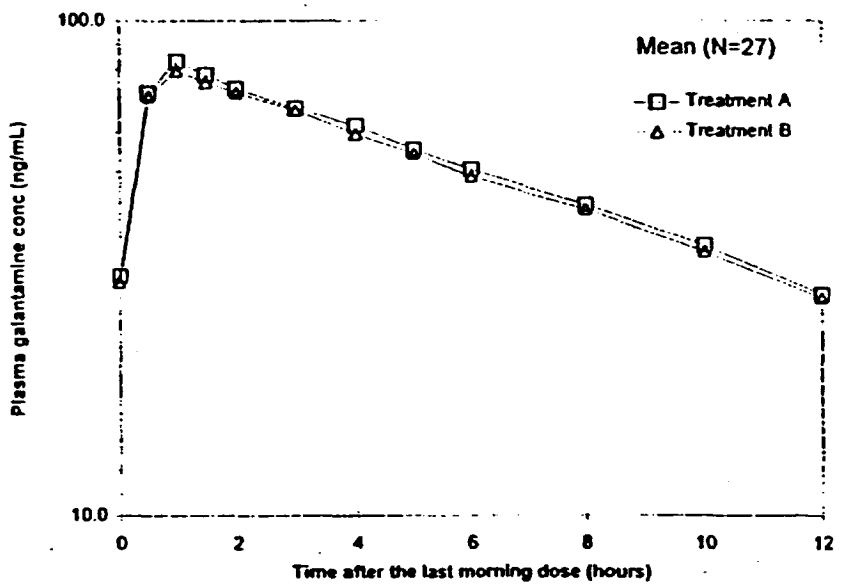
REPORT : CP/98/0548
TRIAL : GAL-NED-5

Display 8: (continued) Comparative plot of the mean plasma concentration-time profiles of galantamine at steady-state: days 21 and 28.

Treatment A: b.i.d. treatment with 12 mg galantamine for 7 days as the US market tablet formulation.

Treatment B: b.i.d. treatment with 12 mg galantamine for 7 days as the oral solution (3 mL/dose).

Semilogarithmic co-ordinates.



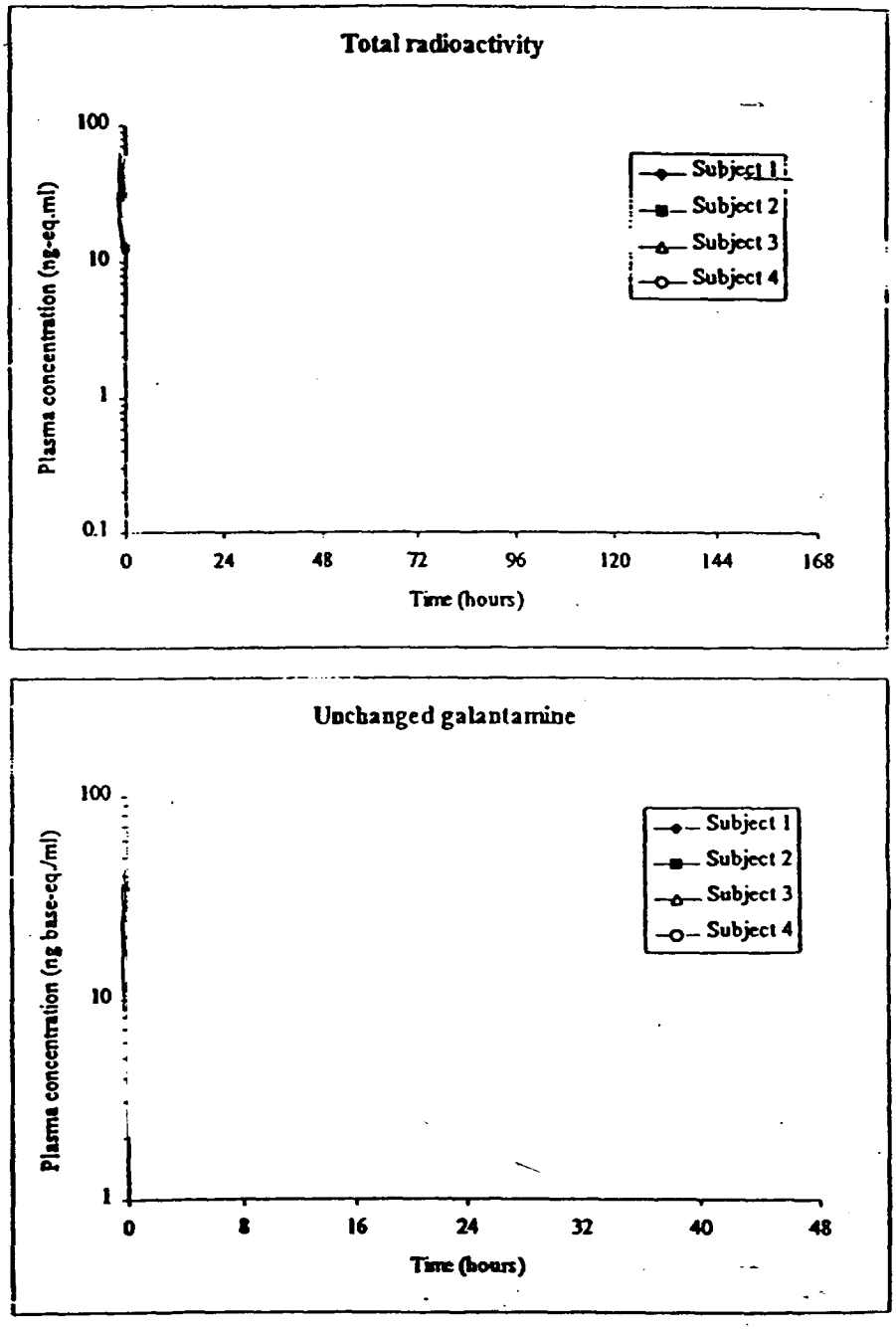
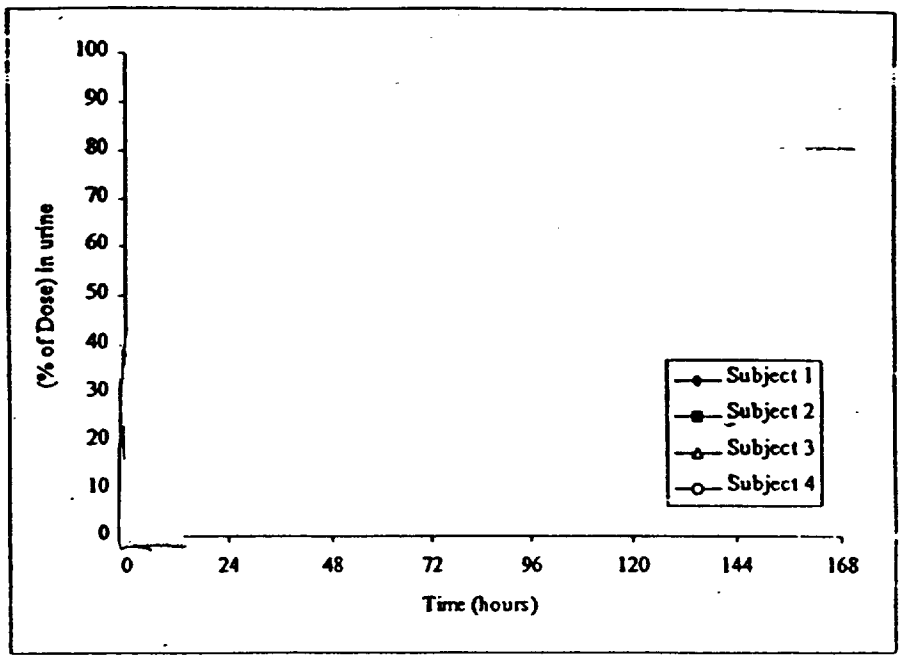


Figure 3: Semilogarithmic plot of the plasma concentrations of total radioactivity (upper chart) and unchanged galantamine (lower chart) as a function of time in four healthy male subjects after a single oral dose of 4 mg base-eq. ^{3}H-galantamine hydrobromide. Plasma levels of total radioactivity are expressed as ng-eq. to galantamine per ml.



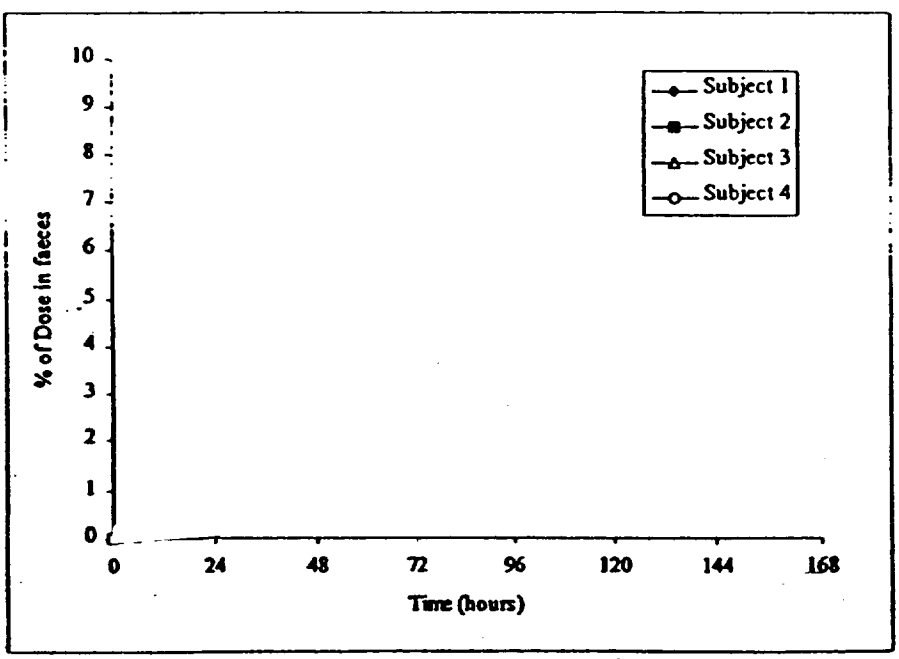


Figure 4: Cumulative excretion of the total radioactivity in urine (upper chart) and faeces (lower chart) after a single oral dose of 4 mg base-eq. ^{3}H-galantamine hydrobromide in four male subjects as a function of time.

Table 7: Excretion of galantamine and its metabolites in urine of healthy male subjects after a single oral dose of 4 mg base-eq. ^{3}H-galantamine hydrobromide, separately presented for poor metabolizers (subjects 1 and 2) and extensive metabolizers (subjects 3 and 4). Values were determined by a [redacted] assay. Figures represent the % of the sample radioactivity and the underlined figures represent the % of the dose radioactivity accounted for by unchanged galantamine and by the various metabolites.

	Subjects 1 and 2										Subjects 3 and 4									
Code	0-4 h[a] (20.78 %)		4-8 h[b] (16.84 %)		8-24 h (33.99 %)		24-72 h[c] (19.92 %)		0-72 h[d] (91.53 %)		0-4 h[a] (23.48 %)		4-8 h[b] (17.95 %)		8-24 h (33.07 %)		24-72 h[c] (17.43 %)		0-72 h[d] (91.93 %)	
2											14.7	3.45	16.5	2.97	20.4	6.75	22.9	3.98		17.15
3											2.2	0.51	3.4	0.62	4.9	1.61	6.3	1.10		3.84
23							2.2	0.43		0.43	9.7	2.27	7.5	1.34	10.6	3.51	10.5	1.82		8.94
5	18.0	3.74	16.9	2.85	14.7	4.99	9.1	1.81		13.39	9.8	2.29	12.9	2.31	12.8	4.22	7.8	1.35		10.17
6							0.6	0.11		0.11	0.9	0.22	1.2	0.21	1.5	0.48	1.2	0.21		1.12
20	4.1	0.86	5.0	0.85	5.7	1.94	5.3	1.05		4.70	0.4	0.10	2.8	0.50	3.1	1.02	2.9	0.50		2.12
8	3.6	0.74	4.0	0.67	6.5	2.22	4.2	0.83		4.46	2.3	0.55	3.4	0.61	4.1	1.36	2.6	0.46		2.98
10	23.6	4.90	20.6	3.47	14.8	5.01	15.8	3.14		16.52	12.4	2.92	11.9	2.14	7.6	2.50	6.1	1.07		8.63
UD	51.1	10.62	44.8	7.54	40.6	13.78	36.1	7.19		39.13	34.2	8.03	23.3	4.17	28.1	9.29	16.9	2.95		24.44
16	1.6	0.34	1.7	0.29	2.6	0.89	4.9	0.97		2.49	0.7	0.17	1.5	0.27	1.8	0.61	2.4	0.42		1.47
17	2.0	0.42	2.8	0.47	2.8	0.95	4.3	0.86		2.70			0.9	0.17						0.17
13	1.4	0.29	1.7	0.29	4.1	1.40	7.5	1.50		3.48										
Sum	105.4	21.91	97.5	16.43	91.8	31.18	90.0	17.89		87.41	87.3	20.51	85.3	15.31	94.9	31.35	79.6	13.86		81.03

Subjects 1 and 2 are poor metabolizers, subjects 3 and 4 are extensive metabolizers.

a % of the dose was obtained by summation of the average percentage of the dose in the 0-2 h and 2-4 h individual urine samples.

b % of the dose was obtained by summation of the average percentage of the dose in the 4-6 h and 6-8 h individual urine samples.

c % of the dose was obtained by summation of the average percentage of the dose in the 24-32 h, 32-48 h and 48-72 h individual urine samples.

d % of the dose was obtained by summation of the average percentage of the dose in the 0-2 h, 2-4 h, 4-6 h, 6-8 h, 8-24 h, 24-32 h, 32-48 h and 48-72 h individual urine samples.

Figure 12: Metabolic pathways of galantamine after a single oral dose of 4 mg base-eq. ^{3}H-galantamine hydrobromide in four healthy male subjects.

What is the Active Moiety?

The main active moiety is the parent drug, galantamine. Norgalantamine (N-desmethy-galantamine) is equally potent to galantamine, but is present in plasma at low concentrations (< 5%).

What is the Degree of the Plasma Protein Binding of Galantamine?

The plasma protein binding of galantamine is low and averaged 18% at the therapeutically relevant plasma concentration of 100 ng/mL (study # R113675). In whole blood, galantamine was mainly distributed into the blood cells (52.7%). The average blood to plasma concentration ratio of galantamine was 1.1.

What is the PK of Galantamine Relative to Dose ? (i.e., is There Dose Proportionality?)

A) Healthy Subjects

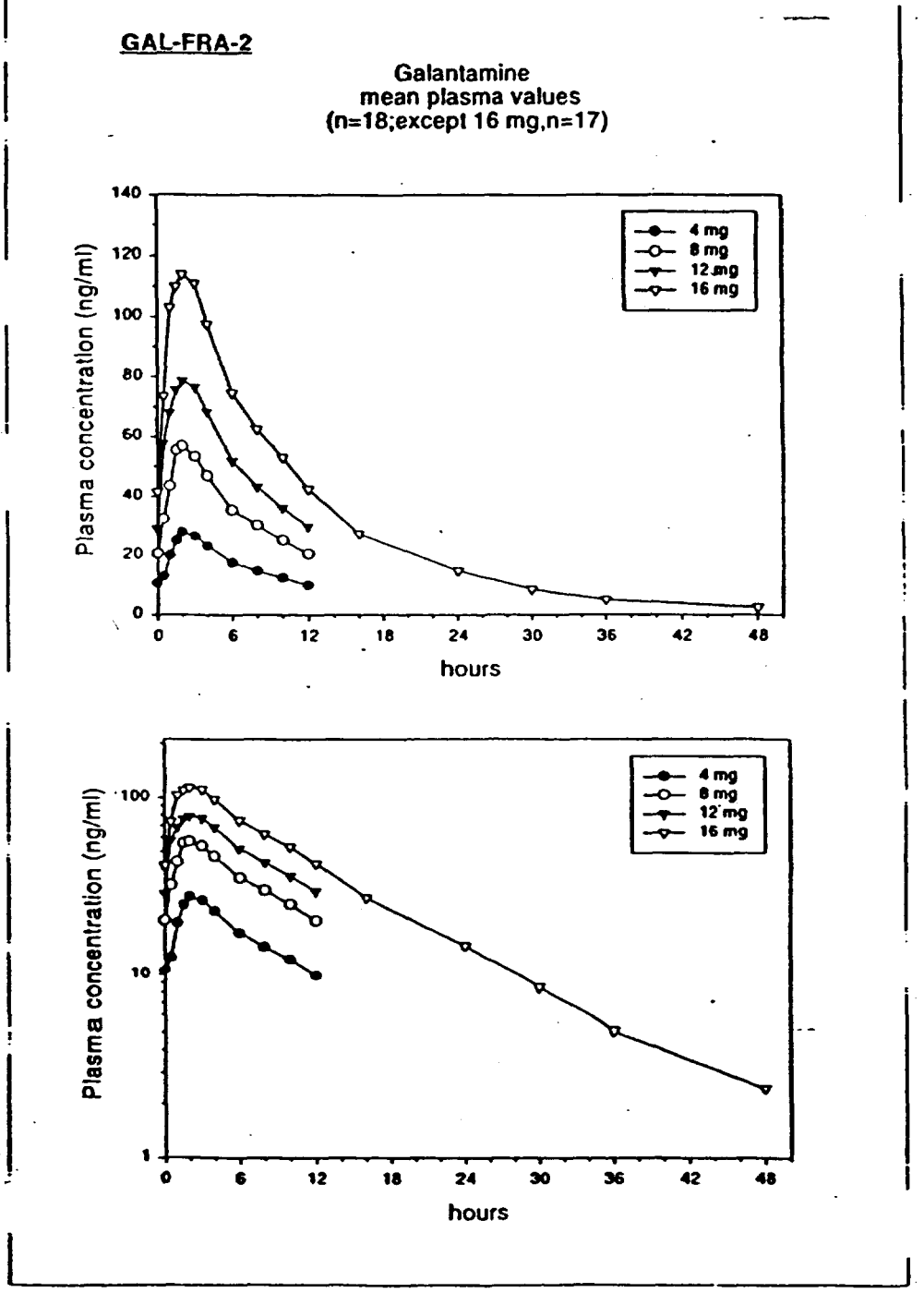
This was a multiple-dose study in 18 healthy subjects of 18 to 55 years of age (study # N137375). Galantamine was administered at a dose of 4 mg b.i.d. in week 1, 8 mg b.i.d. in week 2, 12 mg b.i.d. in week 3, and 16 mg b.i.d. in week 4. Galatamine PK was assessed at steady-state (day 7 of each dose) over a 12 hour dosing interval and up to 48 hours after the last 16 mg dose.
The average steady state trough and peak plasma concentrations fluctuated between and ng/ mL at steady-state of 12 mg b.i.d. and between and ng/ mL at steady-state of 16 mg b.i.d. AUC and Cmax increased proportionally with the dose. The terminal half-life after 16 mg dose was 8 hours. Steady state of galantamine was attained within 2 to 3 days, with minimal accumulation (accumulation factor of 1.5). The mean pharmacokinetic parameters of galantamine are shown in **Attachments 12-15.** Assessment of the data based on dose-normalization of the PK parameters show that the drug follows linear kinetics from 4 mg bid to 16 mg bid. The most common adverse event at high doses was nausea.

B) Alzheimer's Disease Patients

The dose proportionality of galantamine was investigated in a formal PK study in patients with Alzheimer's disease after a single and multiple dose (study# N137056). This study was found to be GCP non-complaint and the sponsor did not adhere to the protocol during the clinical conduct. Therefore, no PK conclusions could be made from this study.

However, based on five placebo-controlled trials (#N122078, #N130852, N133909, N134124, and N133910) and one uncontrolled trial (#130832), the PK of galantamine in Alzheimer's disease patients was also dose proportional (study#122078). The average steady-state trough and peak plasma concentrations fluctuated between and ng/ mL at 12 mg b.i.d. and between and ng/mL at 16 mg b.i.d (study# 130832). **Attachment 16** shows the mean data from these studies. From these results, the steady-state plasma concentrations at trough and peak in Alzheimer's disease patients appears to be about 30% to 40% higher compared to healthy

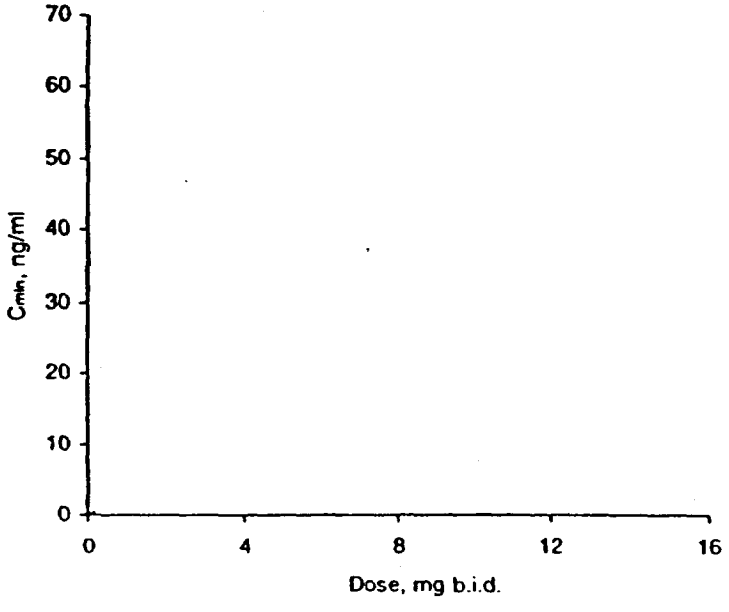
Display 4: Galantamine mean plasma concentration-time profiles



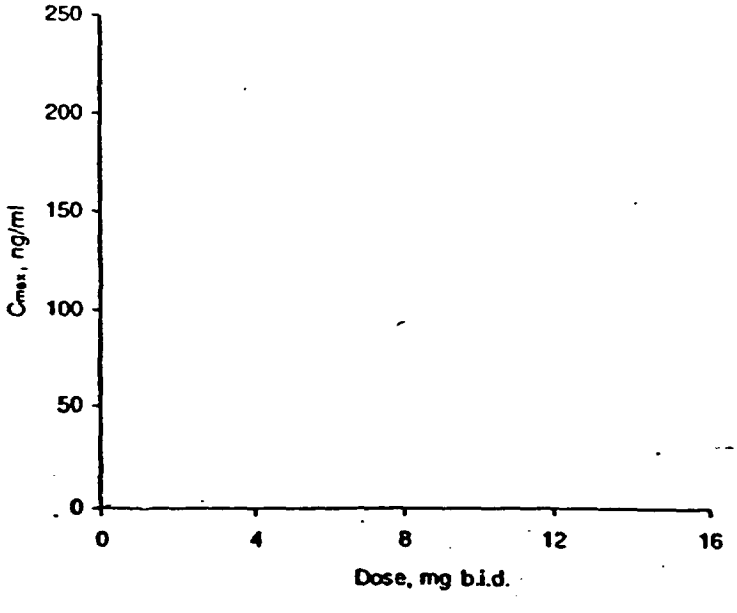
JRF--Trial GAL-FRA-02 43

Display 6: Individual pharmacokinetic parameters (C_{min}, C_{max} and AUC_t) in function of the administered dose

(Cmin)



(Cmax)

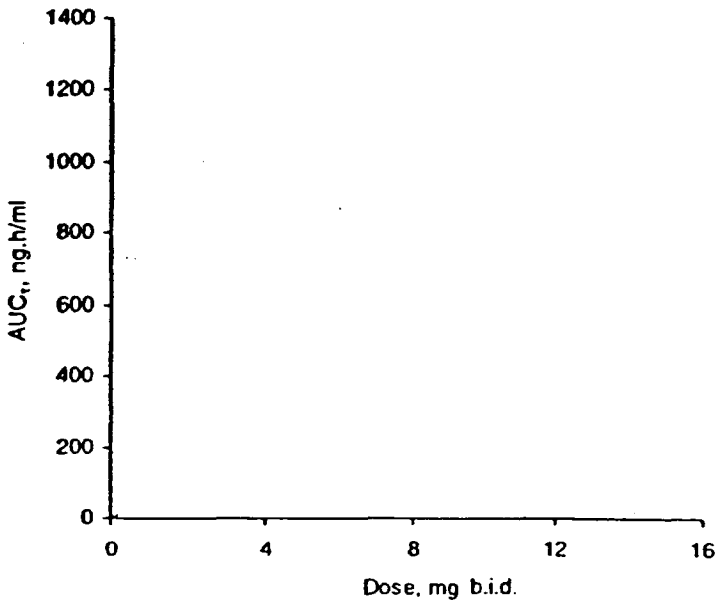


JRF--Trial GAL-FRA-02

44

Display 6: Individual pharmacokinetic parameters (C_{min}, C_{max} and AUC_τ) in function of the administered dose, cont'd

(AUC)



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Display 7: Descriptive statistics and ANOVA results comparing the steady-state pharmacokinetic parameters of galantamine after administration of 4, 8, 12 and 16 mg b.i.d.

Parameters normalized to a dose of 1 mg

Parameter	4mg bid (day 7) (A)	8mg bid (day 14) (B)	12mg bid (day 21) (C)	16mg bid (day 28) (D)	ANOVA results (p-value)[3]	Multiple comparison [4]
Log-transformed [1]						
$C_{min,ss}$, ng/ml	2.51 (2.18 - 2.89)	2.46 (2.14 - 2.83)	2.32 (2.01 - 2.66)	2.46 (2.14 - 2.83)	0.18	-
C_{max}, ng/ml	7.54 (6.89 - 8.25)	7.77 (7.10 - 8.50)	7.77 (6.89 - 8.76)	8.25 (7.32 - 9.30)	0.16	-
$C_{ss,av}$, ng/ml	4.26 (3.86 - 4.71)	4.39 (3.90 - 4.95)	4.31 (3.90 - 4.76)	4.62 (4.10 - 5.21)	0.0024	AD, BD, CD
AUC_τ, ng.h/ml	51.4 (46.5 - 56.8)	53.0 (47.0 - 59.7)	51.4 (46.5 - 56.8)	55.7 (49.4 - 62.8)	0.0026	AD, BD, CD
Original scale [2]						
t_{max}, h	1.89 ± 0.76	1.78 ± 0.67	1.97 ± 1.05	1.74 ± 0.89	0.56[5]	-
$C_{min,ss}$, ng/ml	2.66 ± 1.00	2.58 ± 0.85	2.43 ± 0.77	2.60 ± 0.89	0.25	-
C_{max}, ng/ml	7.69 ± 1.55	7.98 ± 1.77	8.13 ± 2.62	8.55 ± 2.26	0.20	-
$C_{ss,av}$, ng/ml	4.42 ± 1.16	4.57 ± 1.22	4.42 ± 1.06	4.78 ± 1.27	0.0030	AD, BD, CD
FI	119 ± 28	122 ± 25	131 ± 44	127 ± 29	0.44	-
AUC_τ, ng.h/ml	53.0 ± 13.9	54.8 ± 14.7	53.1 ± 12.7	57.4 ± 15.3	0.0032	AD, BD, CD

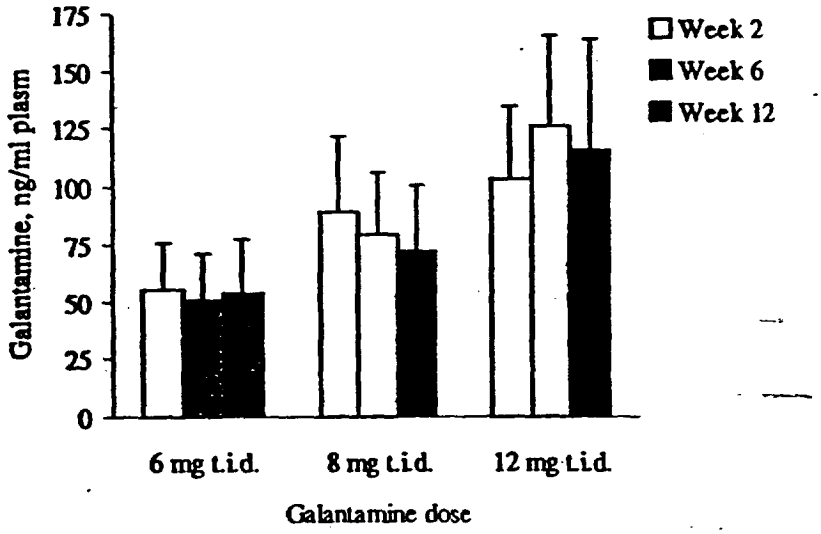
[1] Results presented as geometric mean (90% confidence interval)

[2] Results presented as mean ± SD

[3] p-value for the overall comparison

[4] Treatment pairs are statistically different ($p \leq 0.05$)
(only reported if overall p-value ≤ 0.05)

[5] Friedman result



Study # N122078

Figure 9-1: Mean (± SD) galantamine plasma concentrations per dose and per visit in Alzheimer patients treated with galantamine 6 mg t.i.d., 8 mg t.i.d. and 12 mg t.i.d.[PK 24].

Table 9-1: Mean (± SD) near-peak plasma concentrations and pharmacokinetic parameters in Alzheimer patients treated with galantamine 12 mg b.i.d. or 16 mg b.i.d.[PK 25].

	12 mg b.i.d.		16 mg b.i.d.	
Near-peak plasma concentrations				
	n	Mean ± SD	n	Mean ± SD
Week 2[1]	14	76.3 ± 27.8	13	95.3 ± 33.4
Week 4	13	105 ± 27	14	147 ± 61
Week 8	13	105 ± 32	13	166 ± 46
Week 16	9	106 ± 31	9	146 ± 64
Mean pharmacokinetic parameters at Week 8				
	n	Mean ± SD	n	Mean ± SD
C_{min}, ng/ml	10	55.0 ± 18.1	10	69.7 ± 32.0
t_{max}, h	10	2.6 ± 0.4	10	2.6 ± 0.4
C_{max} ng/ml	10	126 ± 29	10	172 ± 51
AUC_{0h}, ng.h/ml	10	611 ± 145	10	815 ± 248

[1] The actual dose at Week 2 (*i.e.*, end of the titration period) is 8 mg b.i.d.

Study #N130832

Table 9-2: Mean galantamine plasma concentrations (ng/ml) taken at predose and > 0h - ≤ 3h during long-term treatment of Alzheimer patients from GAL-USA-1, GAL-INT-1 and GAL-INT-2[PK 27, PK 28, PK 29].

	GAL-USA-1 Mean ± SD (min - max)	n	GAL-INT-1 Mean ± SD (min - max)	n	GAL-INT-2 Mean ± SD (min - max)	n
12 mg b.i.d. Pre-dose (near-trough)	40.3 ± 22.3 (NQ - 135)	132	46.0 ± 24.4 (2.4 - 160)	140	49.6 ± 34.1 (NQ - 271)	194
> 0 - ≤ 3h (near-peak)	96.5 ± 34.8 (16.0 - 217)	148	106 ± 36 (23.7 - 202)	145	102 ± 42 (NQ - 292)	217
16 mg b.i.d. Pre-dose (near-trough)	53.1 ± 31.5 (NQ - 146)	107	57.4 ± 25.8 (NQ - 130)	136	ND[1]	
> 0 - ≤ 3h (near-peak)	121 ± 51 (NQ - 310)	123	137 ± 44 (32.1 - 252)	139		

[1] ND : No data : at week 3, all galantamine-treated patients were on a 12 mg b.i.d. dose

Study # N133909 N134124 N133910

subjects (see above section). This could be explained by the age of the Alzheimer population. The average terminal half-life is about 11 hours versus 8 hours in healthy subjects.

What is the Pharmacokinetics of Galantamine in Special Populations?

A) Gender: Galantamine clearance was 20 % lower in females compared to males, and this can be explained by body weight differences (see Population Pharmacokinetics below).

B) Race: Based on the population PK analysis race had no effect on the pharmacokinetics of galantamine (**Attachment 17**).

C) Liver Disease

This was a two-center, open label, single oral 4 mg dose study in normal healthy male volunteers and hepatically impaired patients (study # N137239). The demographics of this study were as

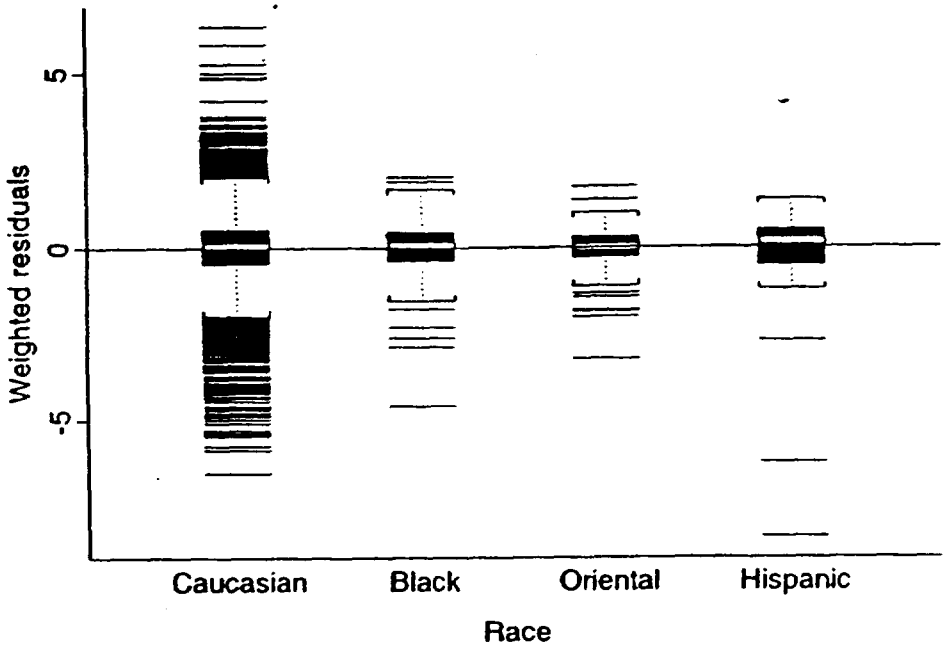
follows: normal healthy subjects (n=8), mild (n=8, Child-Pugh score of 5-6), moderate (n=8, Child-Pugh score of 7-9) and severe (n=1, Child-Pugh score of 10-15) hepatic impairment patients. The pharmacokinetic parameters of subjects with mild hepatic impairment were comparable to those of healthy subjects. In patients with moderate hepatic impairment, AUC increased by about 33%, associated with an increase in half- life of about 30% (8 vs 10.5 h) and a reduction in apparent plasma clearance of 23% (**Attachment 18**). Exposure is expected to increase further with increasing degree of impairment. This is in line with the observed parameters in one subject with severe hepatic impairment. The most common adverse event was headache in some subjects.

D) Renal Impairment

The PK of galantamine after a single oral dose of 8 mg was studied in subjects with moderate (n=8, CLcr =30-60 ml/min) and severe (n=9, CLcr =5-29 ml/min) renal insufficiency and in age and weight matched healthy subjects (n= 8, Clcr > 70 ml/min/1.73m^2). The pharmacokinetics of galantamine was modified in subjects with renal impairment (study # N130996).

The PK parameters were statistically significantly different in the group with severe renal insufficiency as compared to healthy subjects: AUC(0-infinity) of galantamine was increased by 67% and renal clearance was reduced by 72% and the half life was increased from approximately 7.6 to 12 hours (**Attachment 19**). However, the peak plasma concentrations were not changed. In moderate renal impairment, AUC was 37% higher, half life 3 hours longer, and renal clearance was 45% lower in the moderate group compared to normals.

The increase in galantamine exposure could be clinically significant in chronic treatment in patients with severe renal impairment.



Display 4. Weighted residuals *versus* race plot illustrating the lack of race on galantamine pharmacokinetics.

GAL-USA-2

HEPATIC IMPAIRMENT

Figure 2. Semi-log plots of mean plasma concentrations versus time

Display PK.6. Semi-log plot of mean plasma concentration versus time for different hepatic groups

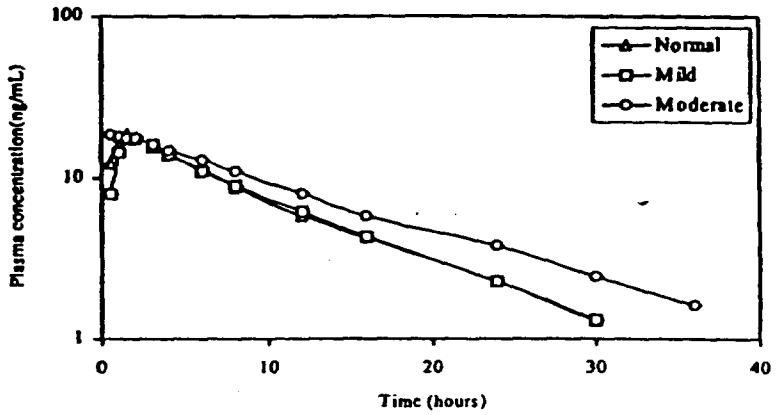


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Table 6. Pharmacokinetic parameters (mean ± SD)

	Hepatic function group			
Pharmacokinetic parameter mean ± SD	Normal n=8	Mild impairment n=8	Moderate impairment n=8	Pairwise comparisons
C_{max} (ng/mL)	22.3 ± 6.8	19.0 ± 5.0	22.8 ± 7.6	>0.05
t_{max} (h)	1.19 ± 0.59	1.70 ± 0.75	1.44 ±1.16	>0.05
$t_{½term}$ (h)	8.08 ± 1.47	8.23 ± 0.98	10.53 ± 1.46	0.003[a]
AUC_{last} (ng·h/mL)	194 ± 46	189 ± 37	255 ± 70	>0.05
AUC_{∞} (ng·h/mL)	208 ± 47	205 ± 40	277 ± 74	0.051[a]
Cl/f (mL/min)	334 ± 66	336 ± 63	258 ± 65	0.061[a]
Vd_{area}/f (L/kg)	2.90±0.44	2.87±0.66	2.80±0.30	>0.05
$Ae_{48\,h}$ (mg)	1.02 ± 0.27	0.94 ± 0.26	1.21 ± 0.54	>0.05
Cl_R (mL/min)	80.8 ± 23.8	85.5 ± 25.3	72.5 ± 25.3	>0.05

Source: Displays 7, 8, 9, 10

Severe hepatic impairment subject results: t_{max} = 1 hour; C_{max} = 20.90 ng/mL; $t_{½term}$ = 12.02 hours; AUC_{∞} = 358 ng·h/mL; Cl/f = 186.2 mL/min.

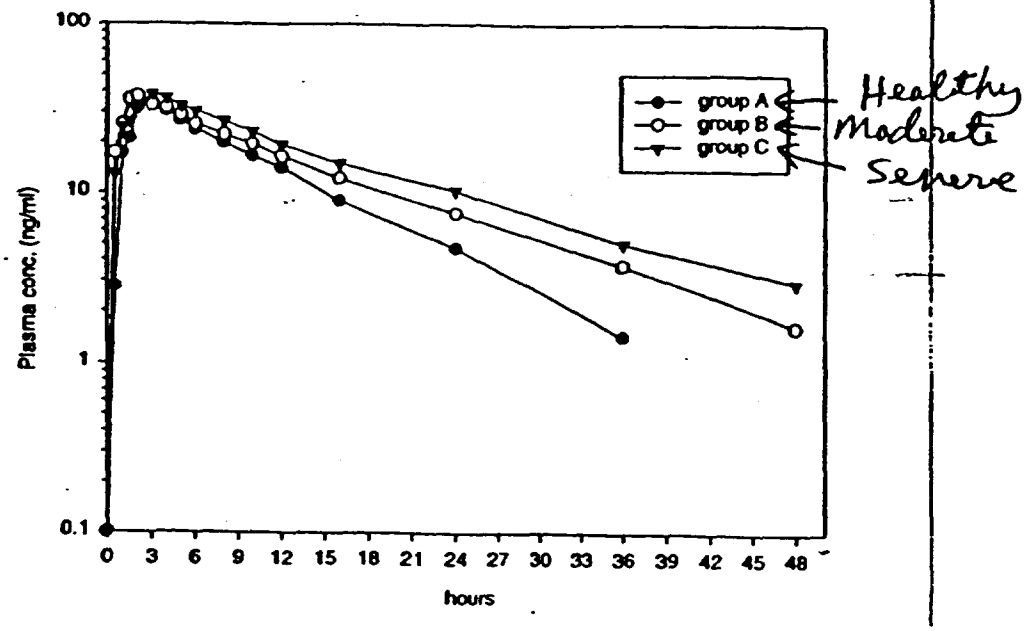
The Ae_{48h} and the Cl_R values were derived by the formula calculation described in Section 3.7.2.2. Pharmacokinetics.

[a] Pairwise comparison of normal and moderate hepatic impairment subjects.

Mild hepatic impairment versus normal: Galantamine pharmacokinetic parameters for subjects with mild hepatic impairment did not differ significantly from those with normal hepatic function.

RENAL IMPAIRMENT

Display 5 **Time course of the mean galantamine plasma concentrations**



Mean (± SD) - Pharmacokinetic parameters of galantamine and norgalantamine					
Parameter (mean ± SD)	Group A Healthy subjects	Group B Moderate insufficients	Group C Severe insufficients	Statistics p-values (ANOVA)[a] B vs A	C vs A
Galantamine					
t_{max}, h	2.4 ± 0.9	3.5 ± 0.6	2.5 ± 1.6	NS*	NS*
C_{max}, ng/ml	38.7 ± 8.1	42.0 ± 8.5	43.0 ± 11.6	NS	NS
AUC_{∞}, ng.h/ml	419 ± 94	577 ± 212	698 ± 247	NS	<0.01
$t_{1/2el}$, h	7.67 ± 1.67	10.5 ± 4.1	11.9 ± 2.6	NS	<0.01
Cl_{tot}, ml/min	71.8 ± 21.5	39.7 ± 18.0	19.9 ± 5.5	<0.01	<0.001
[a]: on original scale * Kruskal-Wallis test					
Norgalantamine					
Ae_{48h}, % of dose	2.00 ± 0.55	0.60 ± 0.62	0.25 ± 0.52	—	—

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E) Population pharmacokinetics

Population analysis integrating galantamine single and multiple dose pharmacokinetics was performed using the NONMEM software (see detailed analysis in Appendix I). Galantamine plasma concentration data from 15 clinical trials were incorporated in the database: Twelve trials were formal pharmacokinetic studies with frequent plasma sampling, and three were clinical efficacy Phase III trials with sparse sampling . In total, 7534 plasma concentration measurements from 1089 subjects were included in the analysis. The following covariates were tested as potential factors affecting the above parameters: age, gender, race, body weight, body surface area, lean body mass, ideal body weight, renal function (creatinine clearance), hepatic function, dose, duration of treatment, study, CYP2D6 genotype, co- medication.

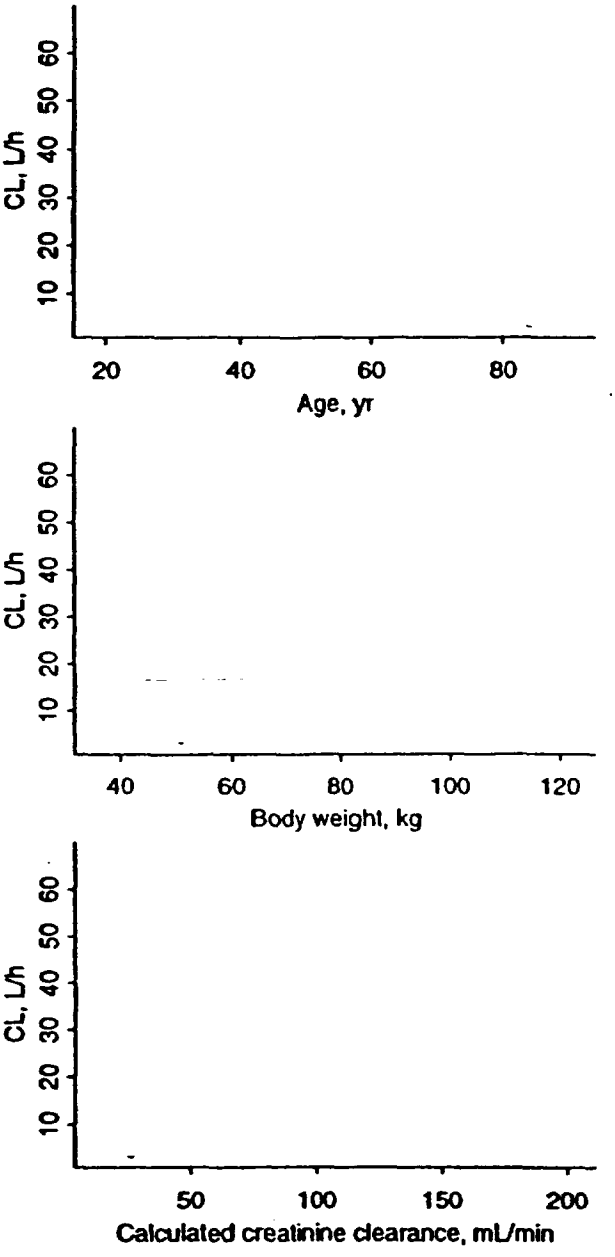
Galantamine clearance increased with body weight but decreased with age (**Attachment 20**). Clearance in females was about 20% lower than in males, explained by lower creatinine clearance and body weight differences (**Attachment 21**). Clearance in Alzheimer patients and healthy volunteers is shown in **Attachment 22**. This difference can be explained by the age difference and by the higher proportion of females in the studied Alzheimer population. This difference should not be of any major clinical significance. Galantamine clearance in poor metabolizers was about 25% lower than in extensive metabolizers, however no bimodality was detected. There was no effect of the race of patients on the pharmacokinetics of galantamine.

What Drugs Could Potentially Interact with Galantamine?

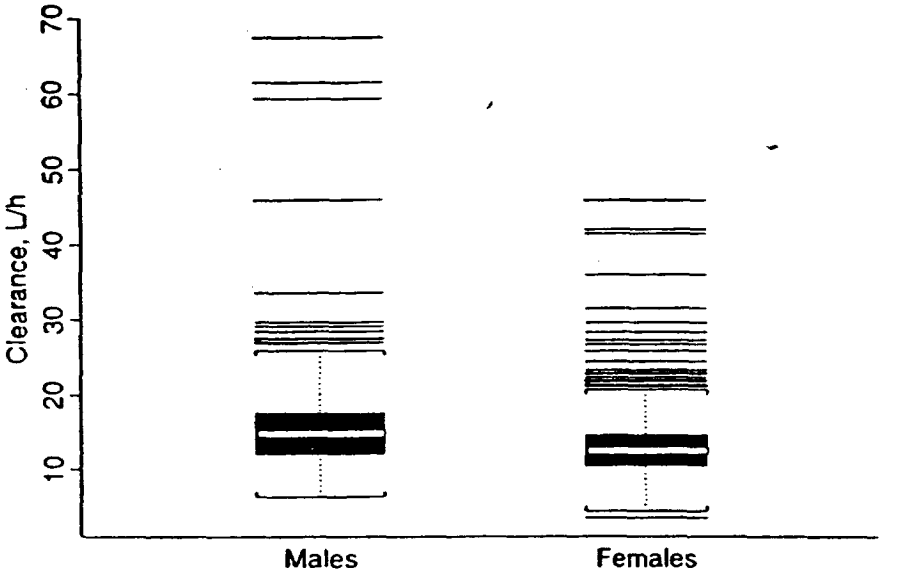
A) *In vitro:*

The inhibitory properties of galantamine on the metabolism of isoenzyme specific substrates were studied to estimate the inhibitory potential of galantamine towards the metabolism of other drugs. Human liver microsomes were incubated with galantamine (0.1, 1 and 10 μg/mL) and a number of cytochrome P450 model substrates. Galantamine, at a concentration of 10μg/mL, did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. The concentration of 10 µg/ml is 100 fold greater than therapeutically observed peak concentration seen in humans. Thus, the inhibitory potential of galantamine on other drugs is unlikely.

It should be noted that since the plasma protein binding of galantamine is only 17%, changes in the plasma protein binding of galantamine will not result in relevant effect on its free fraction. Therefore, specific interactions on the level of protein binding were not investigated by the sponsor.



Display 6. Effects of subjects' age, body weight and creatinine clearance on galantamine clearance. Each point represents an individual Bayesian estimate of clearance. Open circles: males; filled circles: females. Dashed lines are smoothing curves.



Display 7. Boxplots of galantamine clearance in male and female Alzheimer's disease patients.

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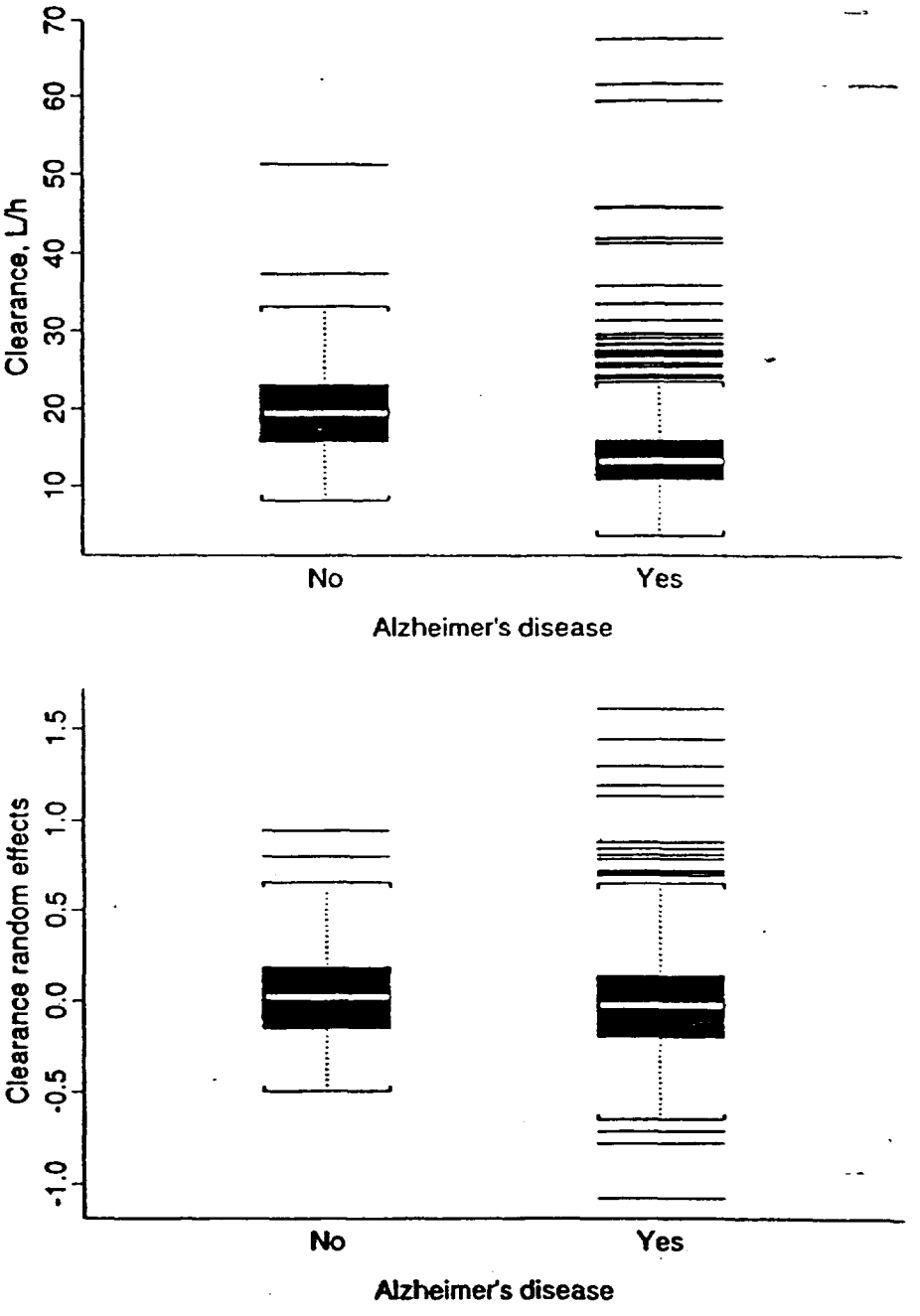


Display 8. Galantamine clearance in patients with Alzheimer's disease and in normal subject (upper plot) and clearance random effects (bottom plot).

B) *In vivo* Drug-Drug Interaction Studies:

i) Is There Any Effect of Galantamine on Other Drugs?

Warfarin (study # N137054): This was a double-blind, randomized, placebo-controlled, two-period cross-over trial in normal healthy male subjects (n=16). Galantamine was titrated from 4 mg b.i.d. to 12 mg b.i.d. at increments of 4 mg b.i.d/week. On the 5th day of dosing with 12 mg b.i.d. galantamine or placebo, a single oral dose of 25 mg warfarin was administered. Galantamine had no effect on the pharmacokinetic parameters of R-and-S-warfarin or on the PD parameters of warfarin as shown by comparable prothrombin times (20 seconds) **(Attachment 23)**.

Digoxin (study # N137055): This was a double-blind, randomized, placebo-controlled, two-period cross-over trial in normal healthy subjects (n=10). Galantamine was titrated from 4 mg b.i.d. to 12 mg b.i.d. at increments of 4 mg b.i.d/week. Digoxin dose was also titrated from 0.25 mg t.i.d. to 0.375 mg daily with its titration starting on day 15 until day 21. Galantamine had no effect on the pharmacokinetics of digoxin **(Attachment 24)**.

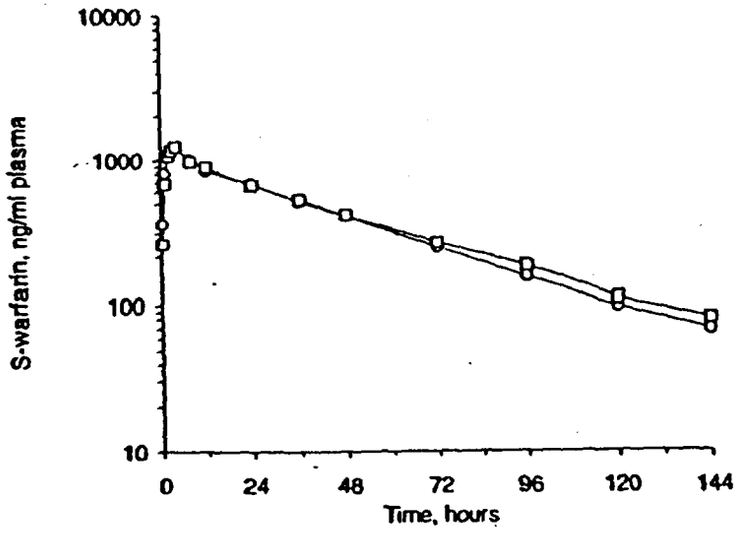
ii) Is There Any Effect of Other Drugs on Galantamine?

Cimetidine and Ranitidine (study # N130526): This was an open-label, three-way cross-over study in 12 healthy subjects (6 males/6 females). Galatamine was administered as a single dose of 4 mg on day 2 of a 3-day treatment with either cimetidine (800 mg daily for 3 days) or ranitidine (300 mg daily for 3 days), or no cotreatment. Cimetidine increased the bioavialability of galantamine by approximately 15% which is not clinically significant. Ranitidine had no effect on the PK of galantamine **(Attachment 25)**.

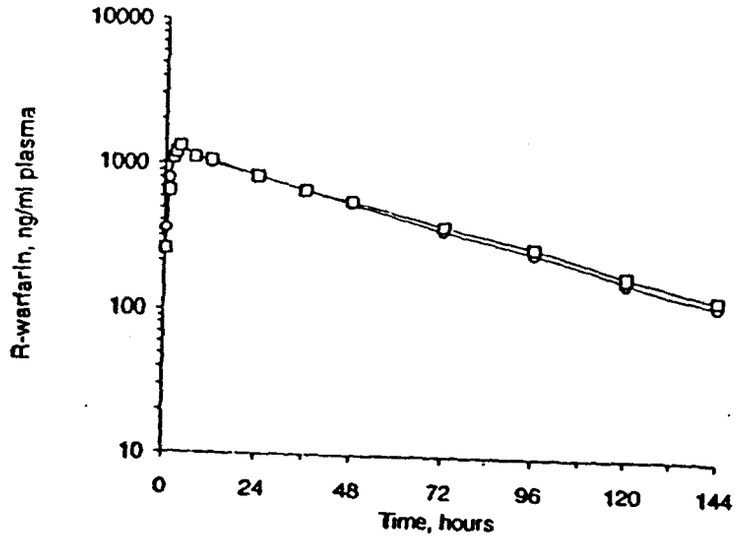
Ketoconazole (study # N130280): This was a double-blind, placebo-controlled, two-period cross-over trial in normal healthy subjects (n=16, 8 males and 8 females). During both periods each subject was treated with galantamine 4 mg b.i.d. for 8 days. Ketoconazole 200 mg b.i.d. or placebo b.i.d. was co-administered on days 6-9 in a crossover design. On co-treatment with ketoconazole, the oral bioavailability of galantamine was increased by approximately 30% **(Attachments 26 and 27)**. The amount of galantamine excreted in urine was not changed on ketoconazole co-treatment.

Erythromycin (study # N130868): This was an open-label, randomized, two-period cross-over study in 16 healthy males and females. Galantamine was administered for 6 days at a dose of 4 mg b.i.d. and a final dose of 4 mg was taken on the morning of day 7. On days 5-8 either erythromycin 500 mg q.i.d. or no-co-treatment was given. Erythromycin increased the bioavailability of galantamine by approximately 10% which is not clinically significant **(Attachment 28)**.

Display 7: Time course of the mean S-warfarin plasma concentrations (upper linear-linear plot; lower semi-logarithmic plot)
○ warfarin + galantamine □ warfarin + placebo



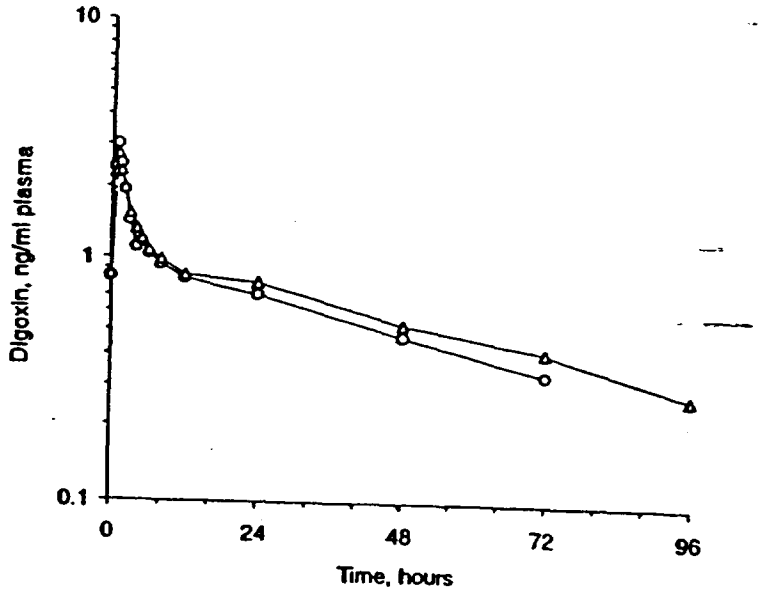
Display 6: Time course of the mean R-warfarin plasma concentrations (upper semi-logarithmic plot; lower linear-linear plot)
○ warfarin + galantamine □ warfarin + placebo



Parameter	Treatment A[1] (warfarin-galantamine)	Treatment B[1] (warfarin-placebo)	treatment ratio A/B (90% CI)[2]
R-warfarin			
C_{max}, ng/ml	1348 ± 192	1367 ± 224	99 (95-103)
AUC_{last}, ng.h/ml	66763 ± 14934	69484 ± 16564	96 (93-100)
AUC_{∞}, ng.h/ml	74415 ± 19814	78619 ± 25117	95 (91-100)
S-warfarin			
C_{max}, ng/ml	1300 ± 173	1296 ± 217	101 (97-105)
AUC_{last}, ng.h/ml	50829 ± 20123	52773 ± 22404	97 (93-102)
AUC_{∞}, ng.h/ml	55012 ± 25310	58429 ± 30315	96 (91-101)
Prothrombin times			
PT_{max}, s	20.5 ± 4.5	19.7 ± 3.4	103 (101-106)
$AUC_{PTO\text{-}144h}$, s.h	2213 ± 338	2159 ± 269	102 (100-104)

[1]Mean ± S.D. on original scale
[2]Based on log-transformed data

Display 6: Time course of the mean digoxin plasma concentrations on day 21
○ digoxin + galantamine Δ digoxin + placebo



Pharmacokinetics			
Mean (± S.D.) pharmacokinetic parameters and treatment ratios of digoxin (n = 10)			
Parameter	Treatment A[1] (digoxin - galantamine)	Treatment B[1] (digoxin - placebo)	treatment ratio A/B (90% CI)[2]
t_{max}, h	1.0 ± 0.3	1.0 ± 0.5	-
C_{min}, ng/ml	0.84 ± 0.16	0.85 ± 0.23	101 (90-114)
C_{max}, ng/ml	3.06 ± 0.81	2.85 ± 0.93	108 (99-119)
$C_{ss,av}$, ng/ml	1.02 ± 0.19	1.06 ± 0.20	95 (91-101)
$t_{1/2\ term}$, h	56.6 ± 14.1	58.5 ± 13.6	-
AUC_τ, ng.h/ml	24.4 ± 4.5	25.5 ± 4.8	96 (91-101)

[1]Mean ± S.D. on original scale
[2]Based on log-transformed data

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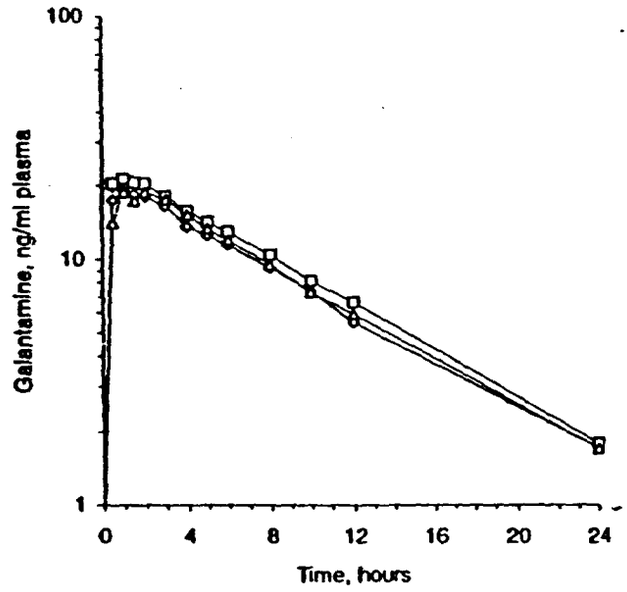
Display 5: Time course of the mean galantamine plasma concentrations
(upper, linear-linear plot; lower, semi-logarithmic plot)
◇ Galantamine only □ Cimetidine co-treatment △ Ranitidine co-treatment



Mean (± S.D.) pharmacokinetic parameters of galantamine			
Parameter	Treatment A (gal-none)	Treatment B (gal-cim)	Treatment C (gal-ran)
t_{max}, h	1.3 ± 0.9	1.3 ± 0.8	1.5 ± 0.9
C_{max}, ng/ml	23.4 ± 5.7	25.1 ± 7.3	22.4 ± 5.1
$t_{1/2\ term}$, h	6.3 ± 1.6	6.7 ± 2.1	6.5 ± 2.1
AUC_{last}, ng.h/ml	187 ± 61	215 ± 68	195 ± 76
AUC_{∞}, ng.h/ml	199 ± 63	231 ± 71	213 ± 78

Parameter	treatment ratio B/A (90% CI)[1]		treatment ratio C/A (90% CI)[1]	
C_{max}, ng/ml	106	(95 - 118)	97	(86 - 107)
AUC_{last}, ng.h/ml	116	(106 - 127)	102	(94 - 112)
AUC_{∞}, ng.h/ml	116	(109 - 126)	105	(98 - 114)

[1] Based on log-transformed data

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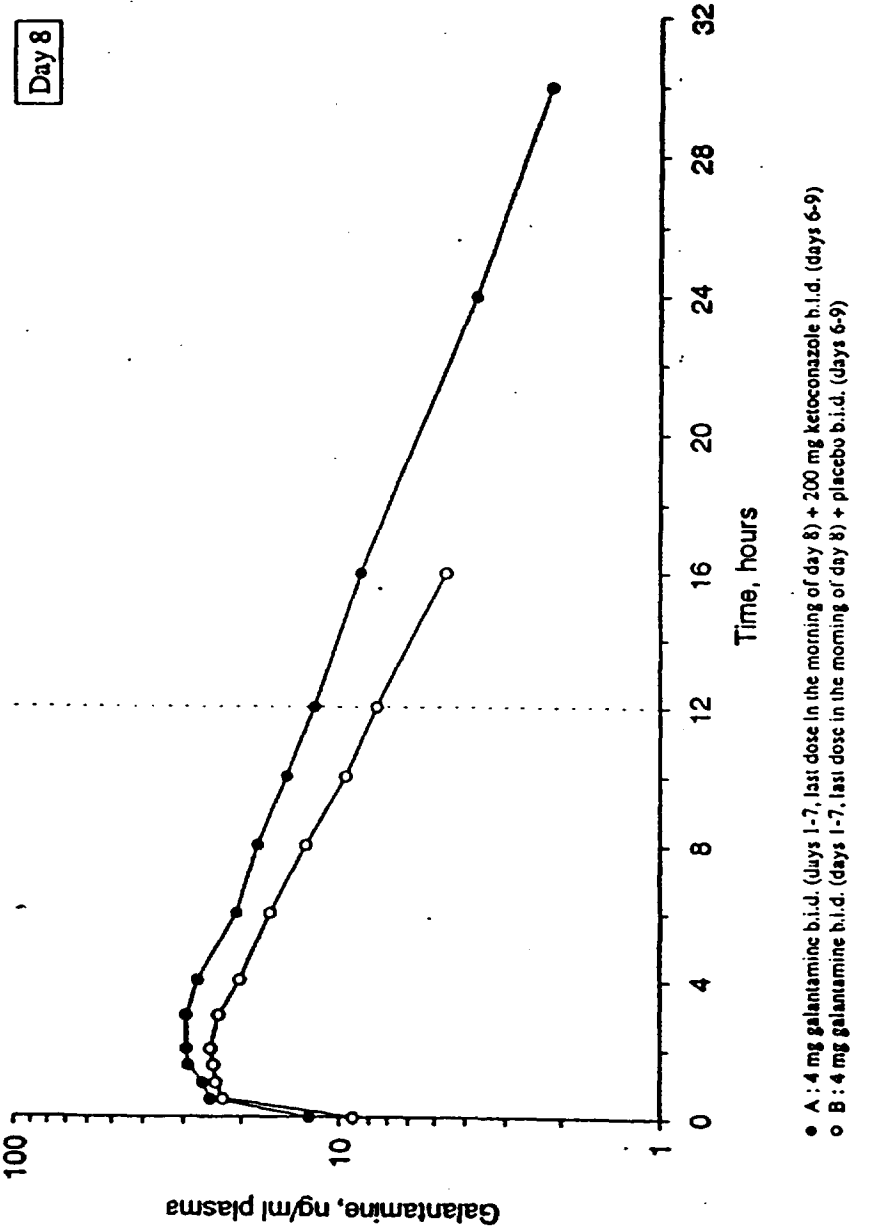
JRF--Trial GAL-BEL-7

Display 5: Semi-logarithmic (day 8) and linear-linear (day 1-10) plot of the mean galantamine plasma concentrations



(9e)

Mean (± S.D.) pharmacokinetic parameters of galantamine and norgalantamine			
Parameter	Treatment A[1] (galantamine-ketoconazole)	Treatment B[1] (galantamine-placebo)	treatment ratio A/B (90% CI)[2]
galantamine			
t_{max}, h	1.9 ± 1.2	1.3 ± 0.7	-
C_{min}, ng/ml	12.4 ± 5.3	9.0 ± 4.1	139 (123-157)
C_{max}, ng/ml	35.4 ± 7.5	30.4 ± 8.8	117 (105-134)
AUC_t, ng.h/ml	253 ± 73	195 ± 55	131 (122-140)
$C_{ss,av}$, ng/ml	21.1 ± 6.1	16.2 ± 4.6	-
$t_{1/2\ term}$, h	7.8 ± 1.7	5.9 ± 1.5	-
Ae_{12}, % of dose	26.6 ± 9.4	25.9 ± 7.9	-
Cl_{ren}, ml/min	72.6 ± 27.7	92.3 ± 31.5	-
norgalantamine			
Ae_{12}, % of dose	2.31 ± 0.61	2.69 ± 0.64	-
Plasma concentrations of norgalantamine, measured in a selection of subjects (n=4), were below or very close to the quantification limit in all samples.			

[1]Mean ± S.D. on original scale
[2]Based on log-transformed data

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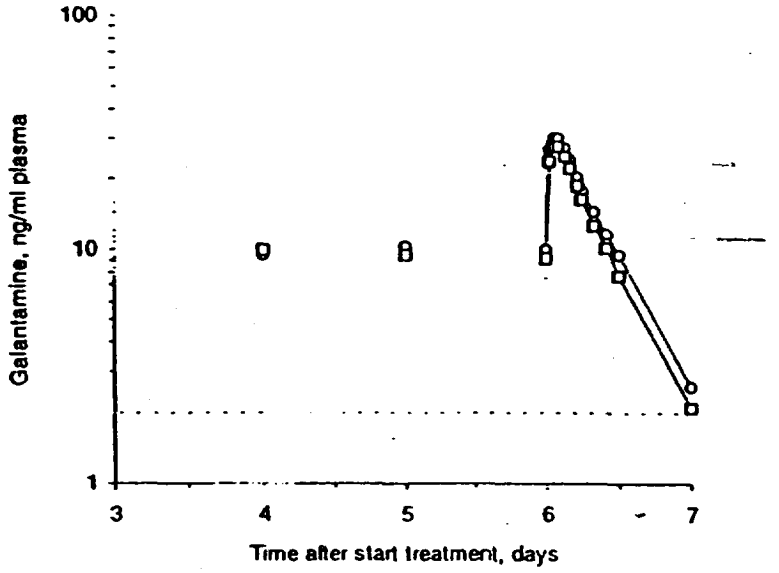
Display 6: Time course of the mean galantamine plasma concentrations

□ Galantamine only ○ Erythromycin co-treatment



Pharmacokinetics			
Mean (± S.D.) pharmacokinetic parameters and treatment ratios of galantamine			
Parameter	Treatment A[1] (galantamine-erythromycin)	Treatment B[1] (galantamine only)	treatment ratio A/B (90% CI)[2]
t_{max}, h	1.2 ± 0.9	1.4 ± 1.0	-
C_{min}, ng/ml	9.7 ± 2.0	9.1 ± 3.4	113 (101-125)
C_{max}, ng/ml	35.4 ± 4.2	33.0 ± 5.6	108 (102-115)
$C_{ss,av}$, ng/ml	18.9 ± 3.5	17.1 ± 3.7	110 (106-116)
AUC_τ, ng.h/ml	227 ± 42	205 ± 44	112 (106-116)
$t_{1/2\,term}$, h	6.7 ± 1.6	6.1 ± 1.8	-

[1]Mean ± S.D. on original scale
[2]Based on log-transformed data

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Paroxetine (study # N137171): This was an open-label, randomized, two-period cross-over study in 12 healthy male and female subjects. Paroxetine was dosed 10 mg b.i.d. on days 1-3, followed by 20 mg once daily in the morning on days 4-16 in one period (treatment A) and no co-treatment in the other period (treatment B). In each session, subjects were treated with galantamine 4 mg b.i.d. on days 10-14, with a last dose taken in the morning on day 15. During treatment with paroxetine 20 mg once daily, the AUC of galantamine was increased by approximately 20% after its first dose of galantamine and by about 40% at its steady-state **(Attachments 29 and 30)**. It should be noted that the maintenance dose of paroxetine is 30 mg daily, therefore, the effect of paroxetine of galantamine disposition could be more pronounced at 30 mg dose.

Is There any PK/PD Relationship With Galantamine?

A) Relationship Between Galantamine Plasma Concentration and AChE inhibition:

From literature, the extent and the time course of ex vivo inhibition of AChE activity in human erythrocytes after administration of galantamine is predictable from the plasma concentrations of the parent compound. The putative mechanism of galantamine in the symptomatic treatment of Alzheimer's diseases was investigated *in vivo* by measuring the ex vivo inhibition of AChE activity in human erythrocytes. Different oral (10 mg as an oral solution and as a tablet formulation) and intravenous (5 and 10 mg infused over 30 minutes) doses of galantamine in healthy male volunteers were studied. Plasma concentrations and ex vivo AChE inhibition in red blood cells were measured at the same time points. The time course of the AChE inhibition and plasma concentration time profiles were in good accordance. The maximum inhibition of AChE activity (I max) and Cmax were closely correlated independent of the dosing route. The maximum inhibition was observed at the end of the 30- minute infusion period or at the peak time (0.5 and 1.5 hours) after the oral administration. *In vitro* and ex vivo concentration response curves were superimposable, indicating that no metabolites of galantamine exert additional inhibition of acetylcholinesterase activity.

B) Relationship Between Plasma Concentration and Clinical Response/Effect:

The relationship between plasma concentrations (Css,av) and efficacy (i.e., change in ADAS-Cog-11 and CIBIC-plus at month 6) and safety parameters (i. e., incidence of syncope) was investigated in the pivotal phase III-trials GAL- USA- 1, GAL- INT- 1 and GAL- INT- 2 (dose range: 12 mg and 16 mg galantamine b.i.d.).

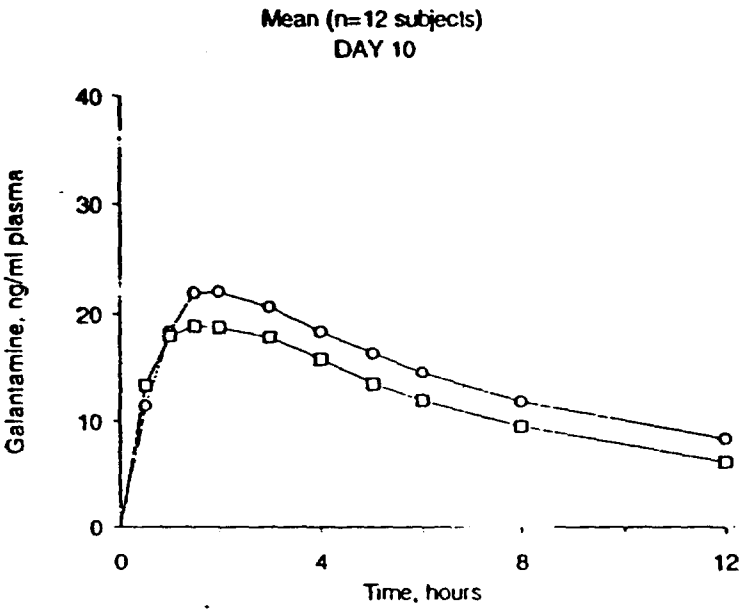
In all three trials, a small but statistically significant trend for a decrease in change in ADAS-cog/11 scores at month 6with increasing galantamine concentrations compared to placebo, could be observed **(Attachments 31 and 32)**. However, there was no dose response between galantamine steady-state concentrations and the various responder groups **(Attachment 33)**. No relationship between CIBIC- plus scores at month 6 and galantamine Css,av was observed **(Attachment 34)**. There was no relationship between steady-state concentration and the occurence of syncope **(Attachment 35)**.

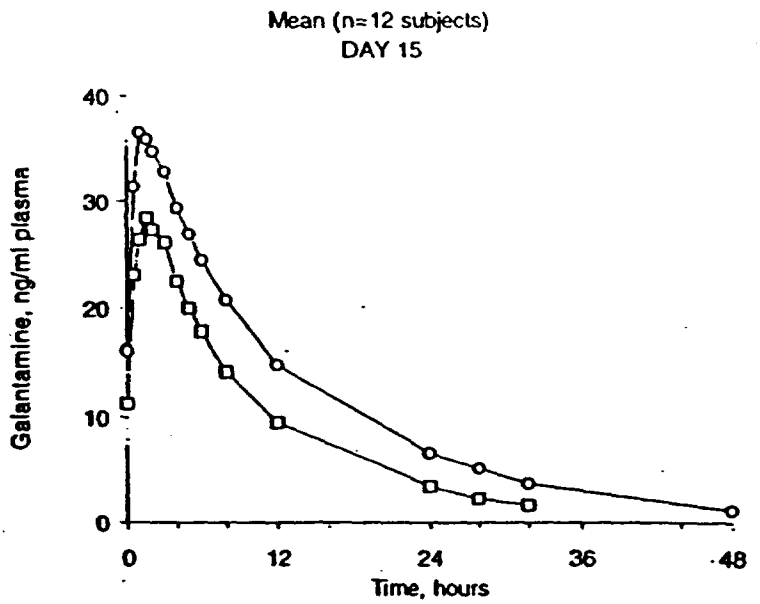
JRF--Trial GAL-BEL-22 44

Display 5: Time course of the mean galantamine plasma concentrations, cont'd

Detail (linear-linear plots)

o galantamine + paroxetine □ galantamine only





Clinical Research Report (final version, 27/01/99) Janssen Research Foundation

Pharmacokinetics			
Mean (± S.D.) pharmacokinetic parameters and treatment ratios of galantamine			
Parameter	Treatment A[1] (galantamine-paroxetine)	Treatment B[1] (galantamine only)	ratio A/B (90% CI)[2]
Day 10 (first dose galantamine 4 mg b.i.d.)			
t_{max}, h	1.8 ± 0.7	1.6 ± .1.0	-
C_{max}, ng/ml	23.7 ± 4.1	22.2 ± 4.8	107 (103-112)
AUC_τ, ng.h/ml	170 ± 27	144 ± 20	118 (111-126)
Day 15 (steady-state of galantamine 4 mg b.i.d.)			
t_{max}, h	1.2 ± 0.7	1.5 ± 0.9	-
C_{0h}, ng/ml	16.1 ± 2.7	11.2 ± 4.2	152 (124-186)
C_{max}, ng/ml	39.9 ± 8.1	31.8 ± 6.8	126 (111-143)
AUC_τ, ng.h/ml	298 ± 43	219 ± 50	138 (120-159)
$t_{1/2\ term}$, h	9.8 ± 1.6	7.5 ± 1.9	-

[1]Mean ± S.D. on original scale (n = 12 subjects)
[2]Based on log-transformed data

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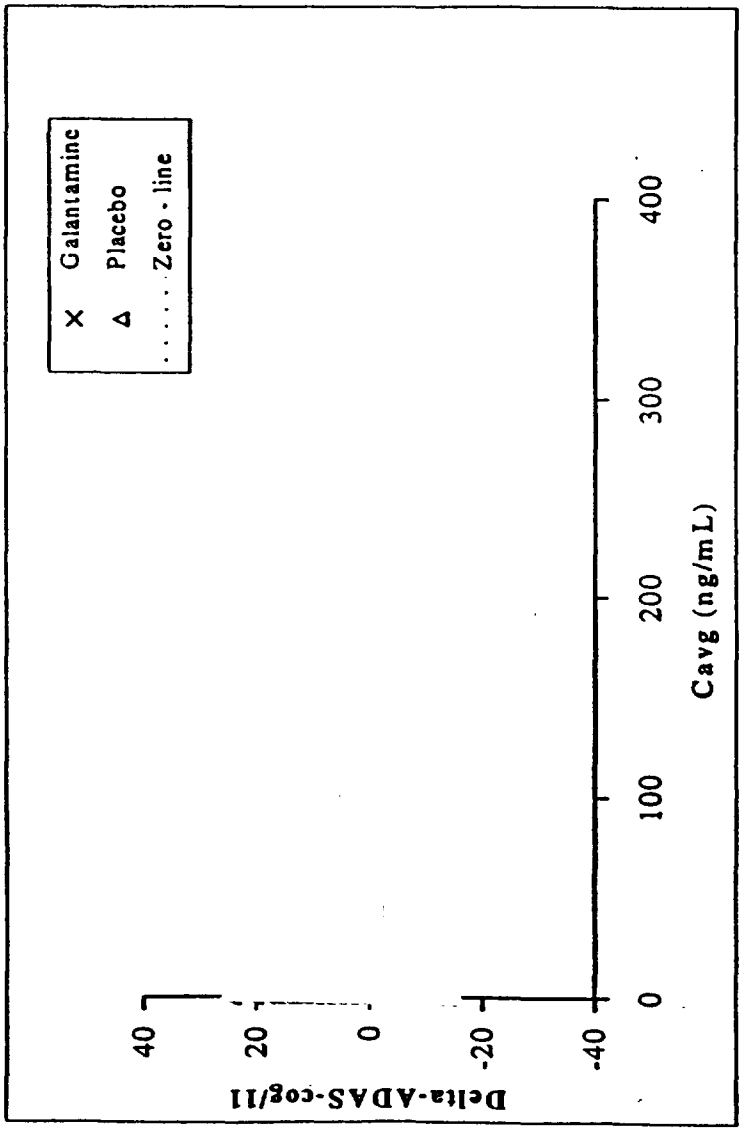
Display 2: Changes of ADAS-cog/11 from baseline at Month 6 versus galantamine average plasma concentrations at steady state

Placebo patients included



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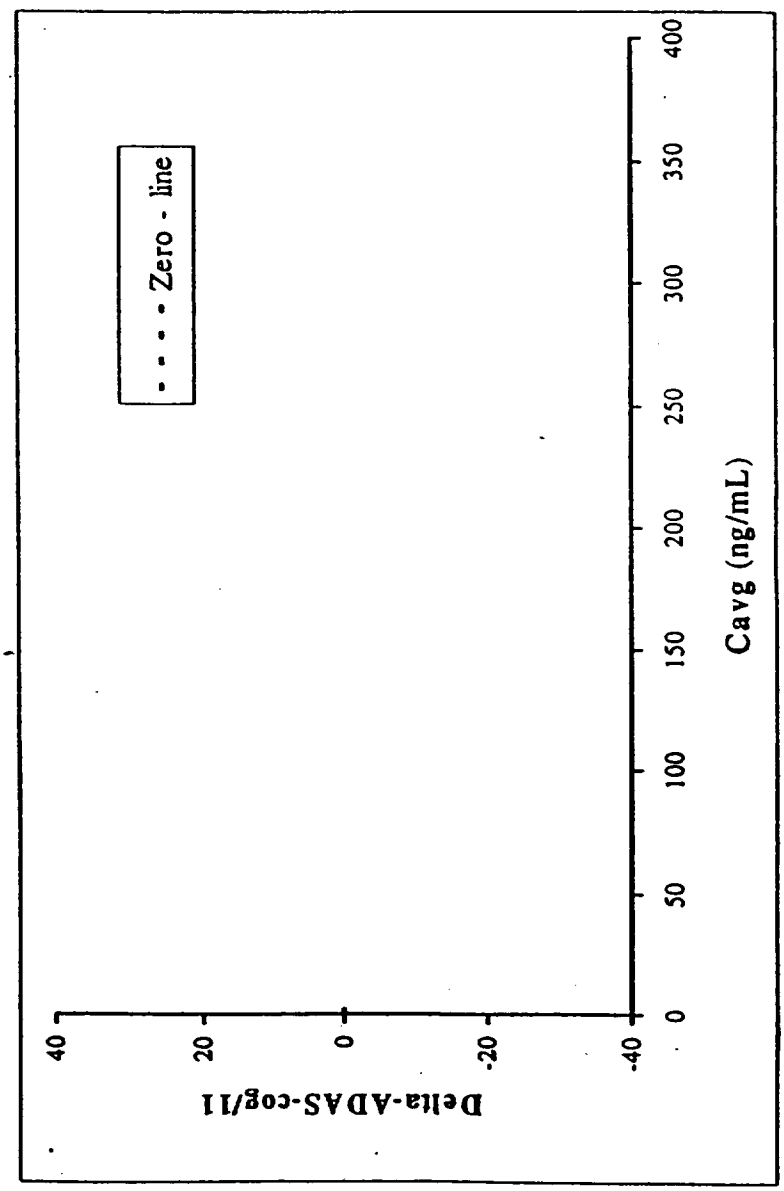
08/31/99

Display 2: Changes of ADAS-cog/11 from baseline at Month 6 versus galantamine average plasma concentrations at steady state. (cont'd)

Placebo patients excluded



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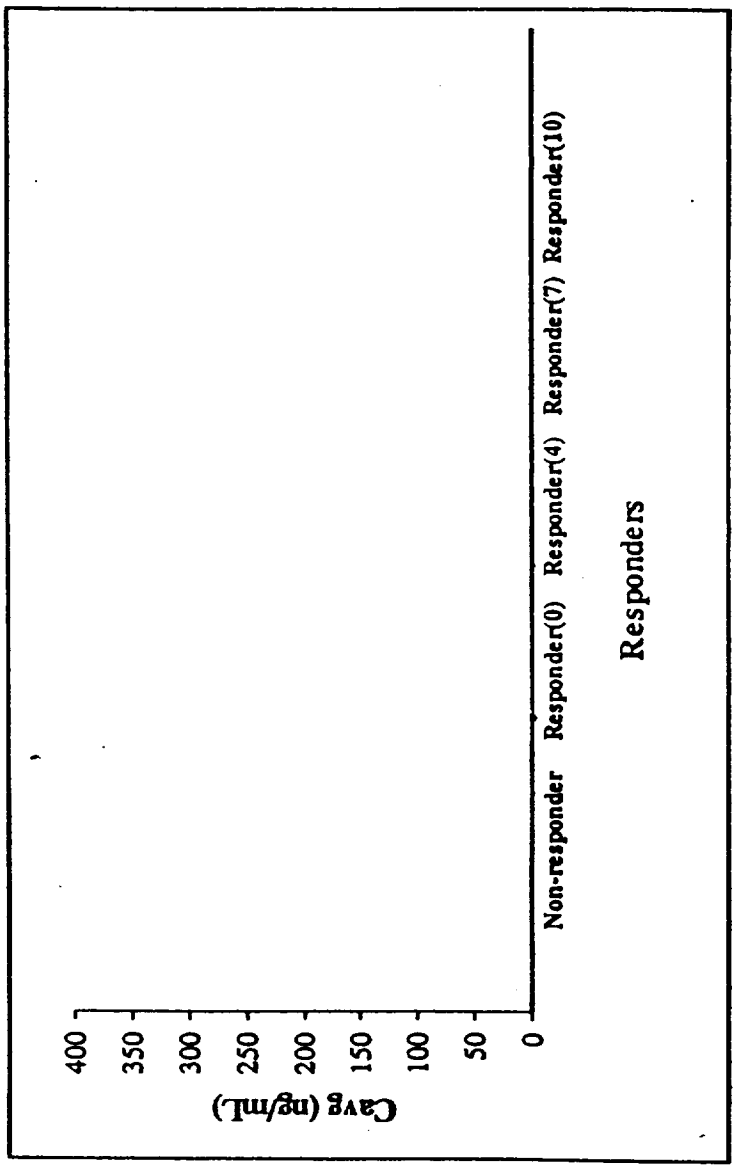
Display 4: Galantamine average plasma concentrations at steady state versus responders based on ADAS-cog/11



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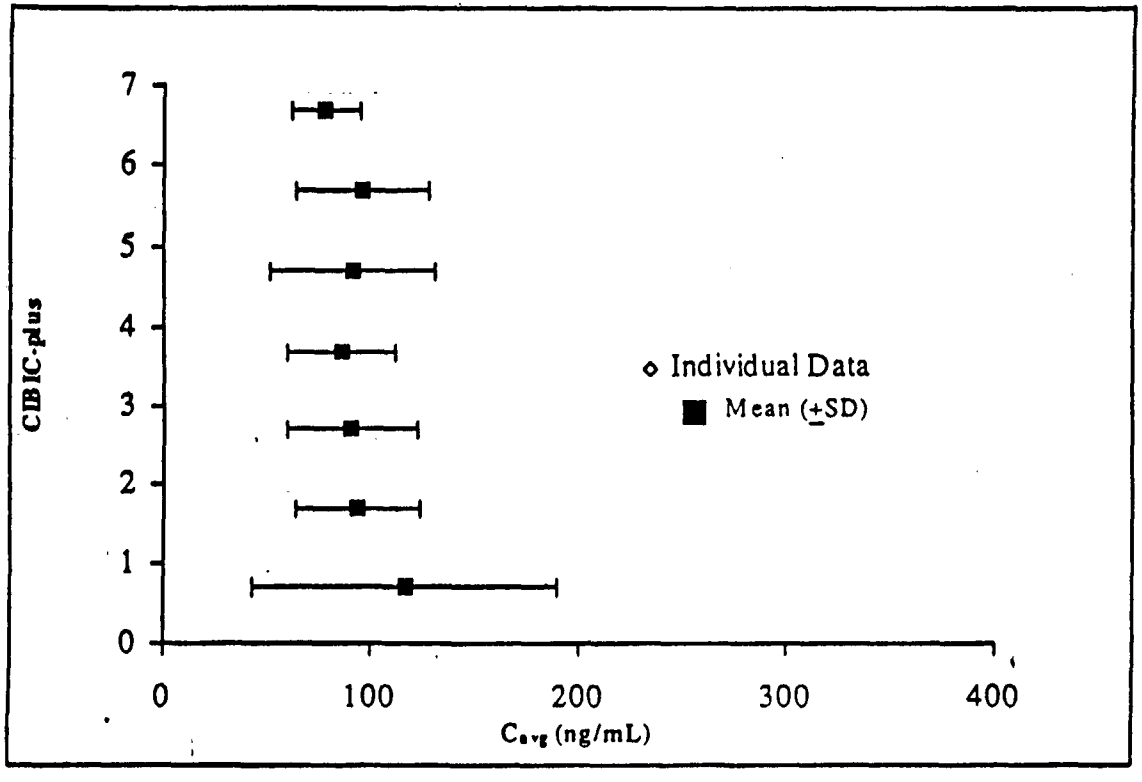
Display 3: CIBIC-plus at Month 6 versus galantamine average plasma concentrations at steady state



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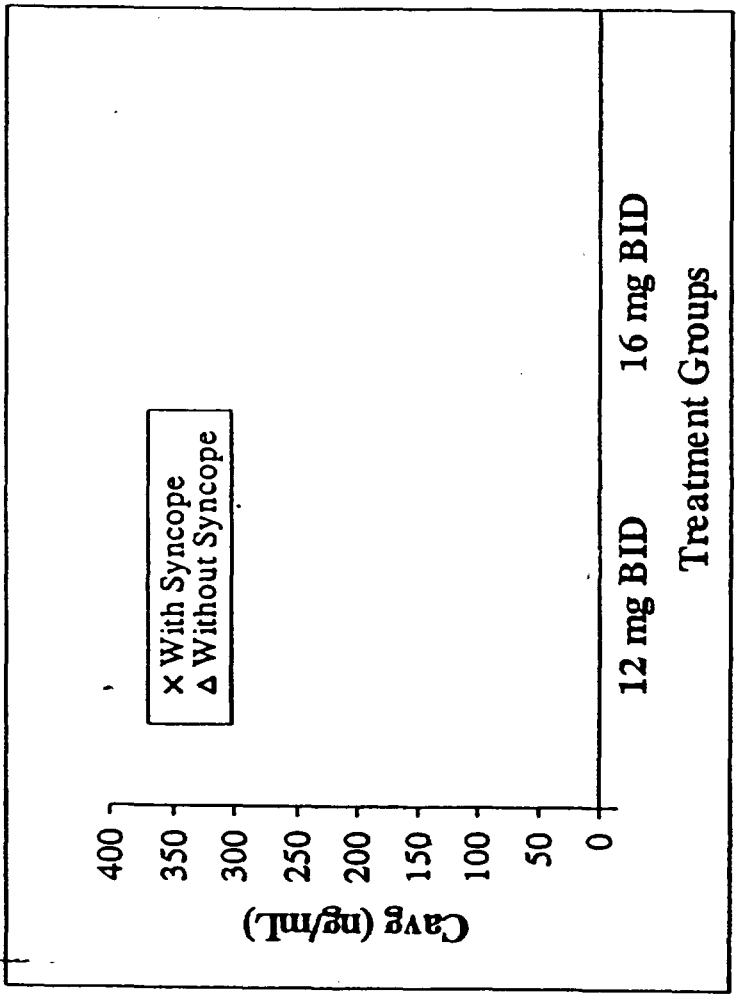
Display 6: Galantamine average plasma concentrations at steady state versus syncope



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What is the Dissolution Profile of Galantamine Tablets?

Galantamine is very soluble in water (31 mg/ml). In various aqueous buffers covering a wide range of pH's (1-8), the solubility of galantamine ranged from 34 mg/ml to 64 mg/ml. The sponsor has performed dissolution testing in water using paddles rotated at 50 rpm. The US to-be-marketed bio-batches for 4, 8, and 12 mg tablets showed very rapid dissolution profile. For all strengths individual tablet dissolution data showed that almost % of the drug had dissolved in minutes, and that % had dissolved in minutes (**Attachments 36-38**).

Based on the rapid dissolution of all galantamine tablet strengths the sponsor is requested to adopt the following dissolution methodology for all strengths of galantamine tablets.

Apparatus II:	USP (Paddles)
Speed:	50 rpm
Medium:	500 mL water
Specification:	Not less than % (Q), in 20 minutes

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Table 9: Dissolution profiles of lot I127 used in GAL-NED-4, eq. 12 mg market tablet for USA - F019

	% Dissolved at				
	10 min.	20 min.	30 min.	45 min.	60 min.
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	90.5	98.6	100.1	101.0	100.6
SD	3.3	1.2	0.8	1.0	0.8

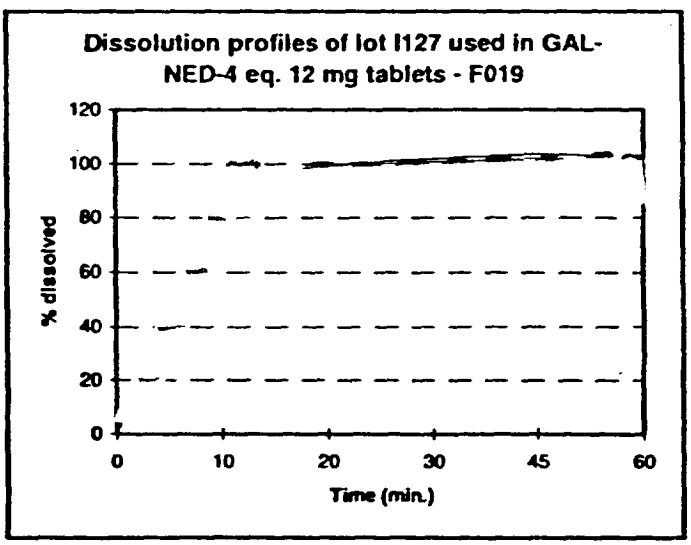


Table 8: Dissolution profiles of lot I296 used in GAL-NED-4, eq. 8 mg market tablet - F014

	% Dissolved at				
	10 min.	20 min.	30 min.	45 min.	60 min.
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean	94.1	97.4	97.7	98.6	99.2
SD	3.3	2.3	2.3	2.0	2.2

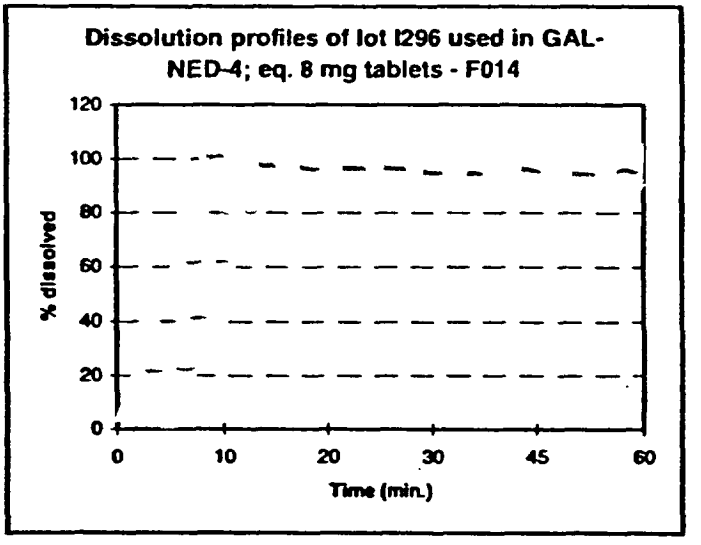
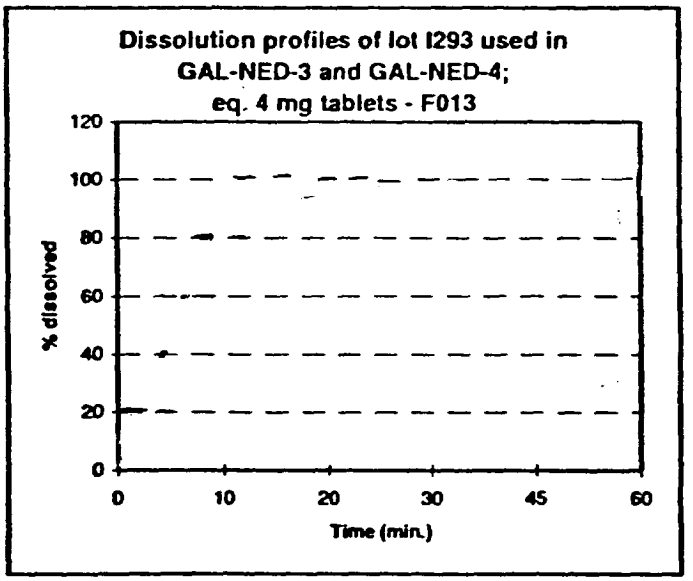


Table 6: Dissolution profiles of lot I293 used in GAL-NED-3 and GAL-NED-4, eq. 4 mg market tablet - F013

	% Dissolved at				
	10 min.	20 min.	30 min.	45 min.	60 min.
1					
2					
3					
4					
5					
6					
7					
9					
10					
11					
12					
Mean	95.4	97.6	97.9	98.0	98.1
SD	2.6	1.5	1.3	1.3	1.4



ClinPharm/Biopharm Briefing on: **May 12, 2000.**

Briefing Attendees: Drs.S-M. Huang, M. Mehta, V. Sekar, T. Fadiran, G. Robbie, J. Gobburu, E. Mishina, B. Rosloff, R. Mani, S.Al-Habet, R. Baweja.

Reviewed by:

/S/ May 19, 2000

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

RD/FT initialed by Raman Baweja, Ph.D /S/ 5/19/2000.

cc: NDAs # 21-169 and 21-224: HFD-120, HFD-860 (Al-Habet, Baweja, Mehta), and Drug files (Biopharm File, CDR).

Acknowledgment: We are grateful to Dr. Elena Mishina for her assistance in the pharmacometric portion of the NDA review.

APPENDIX I

(Pharmacometric Review)

CLINICAL PHARMACOLOGY &BIOPHARMACEUTICS REVIEW
PHARMACOMETRICS REVIEW

NDA 21,169 **Submission Date:** September 29, 1999

Drug Name:	Reminyl (galantamine)
Formulation:	Oral tablets
Applicant:	Janssen Research Foundation
Consult:	Reports: "Population Analysis of Galantamine Pharmacokinetics in Healthy Subjects and Patients with Alzheimer's Disease" and "Pooled Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Analyses of the Efficacy and Safety of Galantamine in Alzheimer's Disease"
Pharmacometrics Specialist:	Elena V. Mishina, Ph.D.

Preamble/Background:

Galantamine, a tertiary alkaloid extracted from several species of Amaryllidaceae, is an established competitive acetylcholinesterase inhibitor and modulates the neuronal nicotinic acetylcholine receptor. The applicant proposed Galantamine for the treatment of patients with mild or moderate Alzheimer's disease. The proposed dosage is 12 mg galantamine b.i.d. after dose-titration with 4 mg b.i.d. weekly increments.
The applicant has conducted 12 formal pharmacokinetic studies after oral administration of Galantamine (GAL-BEL-2, GAL-BEL-4, GAL-BEL-7, GAL-BEL-12, GAL-BEL-15, GAL-BEL-22, GAL-NED-3, GAL-NED-4, GAL-NED-5, GAL-FRA-1, GAL-FRA-2, GAL-USA-2). Galantamine plasma concentrations were also monitored in Phase III clinical efficacy trials with sparse sampling (GAL-USA-1, GAL-INT-1, GAL-INT-2) in patients with Alzheimer's disease.
A population analysis of galantamine pharmacokinetics after single and multiple dosing was performed using the NONMEM software.

The objectives of this analysis were

- to obtain estimates of basic pharmacokinetic parameters of galantamine in healthy subjects and in the target population of patients with Alzheimer's disease;
- to assess effects of subject's demographic characteristics and other covariates on galantamine clearance and distribution parameters;
- to estimate plasma concentration margins in Alzheimer patients receiving various doses of galantamine.

The primary efficacy parameters evaluated in the phase-III pivotal studies GAL-USA-1 and GAL-INT-1 were the change from baseline at Month 6 in Alzheimer's Disease

Assessment Scale-cognitive sub-scale (ADAS-cog/11) and the Clinician's Interview-Based Impression of Change - plus caregiver input (CIBIC-plus) at Month 6. Disability Assessment for Dementia (DAD) was used as the secondary efficacy variable. Safety was also assessed during the treatment, and SAEs (severe adverse events) were monitored until 30 days after the cessation of medication.
The applicant performed a pooled PK/PD analysis of the data from these two studies. The objective of this analysis was to investigate the relationship between galantamine plasma concentrations and the effect on psychometric testing, weight change, syncope, fall, anorexia, muscle weakness, bradycardia, SAEs during the trial and within 30 days after the cessation of galantamine medication, and mortality.

Questions:

Are the gender differences estimated by the population pharmacokinetics data analysis of Galantamine acceptable?
Are the PK/PD relationships of Galantamine plasma concentrations and ADAS-cog scores and syncope properly justified?

The first question related to the report "Population Analysis of Galantamine Pharmacokinetics in Healthy Subjects and Patients with Alzheimer's Disease"

Methods:

The data subjected to the population pharmacokinetic analysis were from 15 clinical trials named above. The numbers of subjects and their demographic characteristics are shown in Table 1.
Galantamine plasma levels were assayed by[ ]. The limit of quantification was( )ng/mL.
The applicant presented a complete list of covariates. Abbreviations used in NM-TRAN control files and data sets, and units are given in the parenthesis.

Continuous variables

- Age (AGE, years)
- Body weight (WT, kg)
- Height (HT, cm)
- Body surface area (BSA, m^2) calculated from WT and HT using the height-weight formula: $BSA=WT^{0.5378}*HT^{0.3964}*0.024265$
- Lean body mass (LBM, kg) calculated from WT and HT:
  Males: $LBM=1.10*WT-(128*(WT^2/HT^2))$
  Females: $LBM=1.07*WT-(148*(WT^2/HT^2))$
- Ideal body weight (IBW, kg) calculated according to:
  Male: IBW=50+1/2.5*(HT-150)
  Female: IBW=45+1/2.5*(HT-150)

- Serum creatinine (SCR, mg/dL)
- Creatinine clearance (CLCR, mL/min) calculated using Cockroft-Gault equation
  Males: CLCR=WT*(140-AGE)/72/SCR
  Females: CLCR=0.85*WT*(140-AGE)/72/SCR
- Dose (DOSE, mg)
- Duration of treatments (DUR, days)
- Time since therapy initiation (TIME)

Categorical covariates

- Gender (SEX)
- Race (RACE)
- Hepatic function (HEP)
- Study (STU)

The applicant included in data sets only basic covariates (derived covariates were calculated within NM-TRAN control streams). The genotype and concomitant medication data were also not included in the data sets as covariates. The effects of genotype and comedication on galantamine clearance were analysed using posterior Bayesian estimates and population residuals produced by the NONMEM program after fitting a final model to the data.

The applicant created two combined data sets: the first one (set A) consisted of the data from 12 formal pharmacokinetic studies (GAL-BEL-2, GAL-BEL-4, GAL-BEL-7, GAL-BEL-12, GAL-BEL-15, GAL-BEL-22, GAL-NED-3, GAL-NED-4, GAL-NED-5, GAL-FRA-1, GAL-FRA-2 and GAL-USA-2). The second data set (data set B) comprised Phase III trial pharmacokinetic data (GAL-USA-1, GAL-INT-1, GAL-INT-2).

Data set A was used during the initial steps of population pharmacokinetic model development (structural and residual error model selection, the structure of variance-covariance matrix for random effects, etc.). Before building a model for covariate effects, data sets A and B were randomly split into index (50-60 % of subjects) and validation data sets. Index data sets A and B were combined and used in the model development. Validation data sets A and B were also combined for the validation purpose.

Final estimates of model parameters were obtained by fitting a final model to the complete data set including both A and B.

Examination of the original data sets revealed several data points with relatively high galantamine concentration measured long after the latest documented intake. According to the available pharmacokinetic data, the galantamine mean terminal half-life is about 10 h and the apparent volume of distribution is 200 L. Therefore, at 63 h post 16 mg single dose the concentration should be below the limit of quantification (ng/mL). Data points at sampling times exceeding 1000 h were excluded before model building. Aditional data points were diagnosed as outliers after completing the population model development.

The NONMEM program version V level 1, the NM-TRAN program version IV level 1, and the PREDPP program version III level 1 were used throughout the analysis(\Windows 95 was applied for graphical and statistical analysis.

Modeling:

1. Structural Model

The applicant selected structural model based on visual inspection of individual galantamine plasma concentration-time. Variance residual error structures were evaluated based on examination of pooled scatter plots of concentration vs time for single dose studies. Random effects for pharmacokinetic parameters were assumed to be log-normally distributed.

All pharmacokinetic models used in the current analysis were parameterized in terms of the oral clearance, apparent volumes of distributions, intercompartment exchange flow rate, absorption rate constant and lag time.

After fitting candidate models to data set A, the applicant selected a model for further development based of the skewness of individual residuals and the Akaike information criterion (AIC).

A preliminary structure of variance-covariance matrix for random effects was selected after visual inspection of pairwise plots of posterior random effects (ETAs) produced by the POSTHOC step of a NONMEM run. The applicant chose the final structure of variance-covariance matrix by comparing objective function (OBJ) values.

2. Covariate Effects Model

In the process of model building, the applicant visually inspected posterior Bayes estimates of random effects (ETAs) produced by the POSTHOC step of a NONMEM run plotted *versus* covariates. In case of an appreciable trend in ETAs *versus* a covariate, the latter was included in the model. Continuous covariates like WT and AGE were included as additive terms consisting of the regression coefficient to be estimated multiplied by the difference between an actual value and a median across a data set. The statistical significance was tested using the likelihood ratio test (the drop in OBJ should be not less than 6.6 units that corresponds to the level of significance of 0.01). The consecutive steps of model development are summarized in Table 1.

After including an effect of the covariates into the model, the applicant obtained and plotted new estimates of random effects (ETAs), and then tested next covariate. The sequence for testing effects of covariates was as following: covariates related to concomitant diseases (CLCR and HEP); DOSE; AGE; WT; SEX; RACE; TIME; Study.

Gender effect was tested after including all significant fixed effects of demographic variables in the model since almost all demographic variables were gender-dependent.

Then the applicant checked the significance of fixed effects in a final model by the common technique of backward deletion of covariates (significance was based on the increase in OBJ less than 7.9, P = 0.005), Table 2.

3. Model Validation and Diagnostics

The applicant performed the validation of the model developed with the index data set based on graphical and non-parametric analysis. In addition, a validation through parameters was performed.

The validated model was fitted to the complete data set including data sets A and B. A detailed analysis of residuals was performed to detect outlying points. The following diagnostic plots were constructed:

1. Population weighted residuals computed by the NONMEM program (WRES) *versus* population predicted concentrations
2. WRES *versus* time post first drug intake in each patient
3. WRES *versus* major covariates (age, WT, LBM, CLCR, HEP, dose, gender, race, study)
4. Histogram and probability density plots of WRES
5. Population weighted residuals computed by the NONMEM program (WRES) *versus* population predicted concentrations

After excluding the identified outliers, the model was re-fitted, and final estimates of parameters were obtained.

4. Analysis of Genotype and Co-medication Effects

Part of patients of GAL-INT-1 and GAL-INT-2 were genotyped with respect to CYP 2D6 (one of galantamine metabolic pathways). Probability densities of distribution of CL in each of three genotypes (poor metabolizers, PM; heterozygotic extensive metabolizers, hetero-EM; homozygotic extensive metabolizers, homo-EM) were computed and density curves were overlayed with the histogram of all CL values.

Most patients of the Phase III trials took also drugs other than galantamine. To explore the effect of concomitant medications, an additional analysis of population residuals was performed. Only a small part of the patients received potent inhibitors of CYP 2D6 (131 patient out of 852 or 15.4%). Thirty co-medicated drugs were selected which might potentially affect galantamine pharmacokinetics:

1. AMITRIPTYLINE
2. AMLODIPINE
3. ATENOLOL
4. CARBAMAZEPINE
5. CIMETIDINE
6. CISAPRIDE
7. CLARITHROMYCIN
8. ERYTHROMYCIN
9. FAMOTIDINE
10. FLUOXETINE
11. FLUVOXAMINE
12. FUROSEMIDE
13. ITRACONAZOLE

14. LANSOPRAZOLE
15. METOPROLOL
16. NIFEDIPINE
17. NIZATIDINE
18. OMEPRAZOLE
19. OTHER ANTACIDS
20. PARACETAMOL
21. PAROXETINE
22. PROPRANOLOL
23. QUINIDINE
24. RANITIDINE
25. SERTRALINE
26. SOTALOL
27. THEOPHYLLINE
28. THIORIDAZINE
29. VALPROATE
30. VERAPAMIL

The list includes known inhibitors of cytochrome P-450, and also gastro-intestinal agents, in particular, antacids since they can potentially affect galantamine absorption. Furosemide was included as it could affect the renal part of galantamine clearance.

A separate database of 13 drugs known as inhibitors of cytochrome P-450 were also prepared and analysed:

1. AMITRIPTYLINE
2. ERYTHROMYCIN
3. FLUOXETINE
4. FLUVOXAMINE
5. ITRACONAZOLE
6. METOPROLOL
7. OMEPRAZOLE
8. PAROXETINE
9. PROPRANOLOL
10. QUINIDINE
11. THEOPHYLLINE
12. VALPROATE
13. VERAPAMIL

The population residuals were plotted *versus* corresponding drug names and compared with the histogram and the density curve of all population residuals obtained after fitting the final model to the complete data set. This enabled visual assessment of possible interactions between galantamine and concomitant medications.

Results:

The applicant properly explained the different steps of model building. Both one-compartmental (1CM) and two-compartmental (2CM) models with a first-order absorption and a lag time were tested as structural pharmacokinetic model.

Two residual error models were tested:

Error model 1 (EM1): Residual error modelled as a sum of a constant variance term and a term in which CV is a power function of the predicted concentration. Power was estimated as a model parameter.

Error model 2 (EM2): Constant variance model for log-transformed concentrations. The variance was assumed to be a step function of the concentration. The threshold was estimated as a model parameter.

Four combinations of structural and residual models were tested by fitting them to the data set, which included all formal pharmacokinetic trials. The differences in Akaike criteria and skewness of individual residuals (standard errors with 95% confidence intervals) were calculated for each model.

Model	OBJ	AIC	Mean skewness (SE)	95% CI
1. 1CM EM1:	15877.400		6.326 (2.44)	3.32 ↔ 11.4
2. 2CM EM1:	15288.385	-581.015	0.362 (1.23)	-1.15 ↔ -3.08
3. 1CM EM2:	-9090.985		0.696 (0.350)	-0.040 ↔ 1.32
4. 2CM EM2:	-9410.588	-311.603	-0.103 (0.126)	-0.717↔0.407

Based on this diagnostics, 2CM with EM2 was selected. Then the applicant adjusted an error variance model with the step function including just one step for the concentrations below 1 ng/mL (LOQ) where the calculated residual variance was several times higher (0.0707) than for all other concentration ranges (0.0141-0.0174).

Variance-covariance matrix structure was selected by the applicant based on the graphic diagnostics of pairwise plots of ETAs for all fixed effects. From Figure 1, it is apparent that CL, V2, and V3 may covary, and the inclusion of OMEGA matrix consisting of one non-diagonal block for these parameters led to the significant decrease in the OBJ. Another non-diagonal OMEGA block was used for the Q-KA-ALAG covariance (Figure 2). The bimodal distribution of ALAG was taken into account by applying the mixture model for the ALAG random effect. Therefore, the minimization of OBJ was improved as well as variability.

Covariate Analysis

In order to explore the covariate analysis, the applicant firstly inspected correlation of the covariates (body size parameters, other demographics, concomitant diseases, etc.) graphically. Figure 3 demonstrates that all body size parameters are mutually correlated and are gender-dependent. These parameters were not dependent on age. Due to incomplete representation of the different races in galantamine studies, race was not tested as a covariate. Creatinine clearance was much lower in the patients in comparison with the healthy subjects most likely due to the advanced age.

The data sets A and B were split and the index data from each set were combined. The applicant then fit the structural model to the index data set and plotted the random effects

vs CLCR (Figure 4). Although CLCR has an apparent influence on CL, V2 and V3, inclusion of CLCR as a predictor for only CL resulted in the significant improvement of the fit (Table 1). The applicant tested the hypothesis of decrease of the metabolic part of clearance with hepatic dysfunction and found that it is significant. Additionally, it was shown to depend on the AGE. The applicant comprehensively studied the influence of body size parameters on clearance, volume of central and peripheral distribution and showed that clearance is significantly influenced by the WT.

Table 1. Summary of building the full population model

Model #	Effect tested	MOF	ΔMOF	Comments
1	Initial model (Display 4.1)	**-7518.331**	-	Initial value
2	CL depends on CLCR (Display 4.3)	**-7544.435**	26.104	Accepted
3	CL depends on hepatic function (Display 4.5)	**-7689.108**	144.673	Accepted
4	CL at 16 mg dose differs from that at lower doses	-7685.108	-4.000	Not accepted
5	CL depends on AGE (Display 4.7)	**-7699.612**	10.504	Accepted
6	CL depends on WT	-7699.612	0	Not accepted
7	V2 depends on WT (Display 4.10)	**-7809.661**	120.553	Accepted
8	CL depends on SEX	-7810.197	0.536	Not accepted
9	V2 depends on SEX (Display 4.12)	**-7865.133**	55.472	Accepted
10	V2 depends on AGE	-7865.133	0	Not accepted
11	CL depends on WT (Display 4.13)	**-7877.241**	12.108	Accepted
12	CL depends on TIME	-7877.406	0.165	Not accepted
13	Q depends on STU	-7877.817	0.576	Not accepted
14	KA depends on STU (Display 4.17)	-7893.117	15.876	Not accepted due to run abnormal interruption
15	V3 depends on AGE (Display 4.22)	**-7886.643**	9.402	Accepted
16	CL depends on LBM	-7880.081	-6.562	Not accepted
17	CL depends on BSA	-7875.253	-11.39	Not accepted
18	CL depends on IBW	-7878.696	-7.947	Not accepted
19	V2 depends on LBM (Display 4.23)	**-7898.479**	11.836	Accepted
20	V2 depends on BSA	-7842.549	-44.094	Not accepted
21	V2 depends on IBW	-7861.265	-25.378	Not accepted
22	CL depends on STU	-7899.405	0.926	Not accepted

Gender effect was an important covariate to evaluate since there were more females in the Alzheimer disease patient's population, and it was valuable to know if the gender-dependent dose adjustment is necessary. Figure 5 shows that CL, V2 and V3 could be gender-dependent. The applicant demonstrated the significance of gender influence on V2. Due to the high correlation of gender and the body size parameters, the dependence of CL on WT was tested and found to be significant.

In order to check the final significance of the fixed effects in the model, the backward deletion test was performed. All steps of deletion are described in Table 2. When the applicant found that effect of gender on V2 is insignificant, this effect was excluded from the model.

Table 2. Summary of the backward deletion test

Model #	Effect tested	MOF	ΔMOF	Comments
1	Full model (Display 4.23)	-7898.479	-	
2	CL depends on CLCR	-7841.219	-57.26	
3	CL depends on hepatic function	-7883.937	-14.542	
4	CL depends on AGE	-7887.981	-10.498	
5	CL depends on WT	-7889.513	-8.966	
6	V2 depends on LBM	-7835.483	-62.996	
7	V2 depends on SEX	-7893.581	-4.898	Excluded
8	V3 depends on AGE	-7887.255	-11.224	

After testing of all possible covariates, the applicant performed the validation of the model for covariate effects. For this purpose, the final model was used to generate posterior population and individual predictions using validation data set and initial parameter estimates obtained from the index data file for THETAs, OMEGAs, and SIGMAs. Then the applicant plotted the measured galantamine concentrations in the validation data set *versus* population and individual predictions (Figure 6). The identity and smoothing lines drawn through the data points almost coincided. No biases were observed. Additional validation through parameters showed that the covariate model predicts the individual clearance values reasonably well (Figure 7).

Then the applicant performed model diagnostics by the analysis of residuals. For this purpose, the applicant ran the covariate model with the combined data sets A and B and plotted weighted residuals vs population predictions (Figure 8), as well as vs covariates. This diagnostics confirmed that there were no biases in WRES, and WRES were almost normally distributed (Figure 9). The points outside the 99% of all WRES could be potential outliers, which were totally 86 points. Each of these points was checked considering the galantamine concentration vs time plots for the individual patients. After exclusion of the proposed outlier points, the model was refitted and the covariance step was used to evaluate the significance of the estimates. Two variance parameters for the pairs of CL-V3 and V2-V3 had high SE (803% and 89.4%) and were considered as non-significant. After exclusion of these parameters, the final model was fitted and the complete output obtained.

Final Model

The final estimates of fixed and random effect parameters are shown in Tables 3 and 4. The covariates that affect galantamine disposition are age, body weight, lean body mass, creatinine clearance and liver function. No effects of the duration of treatment and patients' race were found.

Table 3. Final estimates of the galantamine population pharmacokinetic model (fixed effects)

Item No	Affected pharmaco-kinetic parameter	Explanation	Estimate	Asympthotic standard error of estimate (%)
1	CL	Basal metabolic clearance in a patient of median age and body weight (75 yr and 67 kg) with normal liver function	9.42 L/h	5.5
2	CL	Basal metabolic clearance in a patient of median age and body weight (75 yr and 67 kg) with moderate liver dysfunction	3.63 L/h	26.9
3	CL	Coefficient relating renal galantamine clearance to creatinine clearance	0.0715	12.3
4	CL	Coefficient relating metabolic clearance to subject's age	-0.0339 $L \cdot h^{-1} \cdot yr^{-1}$	36.3
5	CL	Coefficient relating metabolic clearance to subject's body weight	0.0493 $L \cdot h^{-1} \cdot kg^{-1}$	28.4
6	Vc	Basal Vc in a patient of median lean body mass (48 kg)	157 L	10.6
7	Vc	Coefficient characterizing the dependence of Vc on subject's lean body mass	2.85 L/kg	5.1
8	Vp	Basal Vp in a patient of median age (75 yr)	59.0 L	19.8
9	Vp	Coefficient characterizing the dependence of Vp on subject's age	0.587 L/yr	45.9
10	Q	Intercompartment exchange flow rate	2.52 L/h	12.6
11	Ka	Absorption rate constant	3.05 h^{-1}	5.4
12	Tlag	Absorption lag time	0.973 h	13.3
13	Ptlag	Proportion of subjects having zero Tlag	0.832	2.3

Table 4. Final estimates of the galantamine population pharmacokinetic model (random effects)

Item No	Relevant pharmaco-kinetic parameters	Explanation	Estimate of variance or covariance	Asympthotic standard error of estimate (%)	Coefficient of variation[1] or correlation[2] (%)
1	CL	Random interindividual variability	0.0873	8.6	29.5
2	Vc	Random interindividual variability	0.0159	15.5	12.6
3	CL,Vc	Covariance	0.0252	16.7	82.2
4	Vp	Random interindividual variability	0.460	26.9	67.8
5	Q	Random interindividual variability	0.317	43.5	56.3
6	Ka	Random interindividual variability	3.81	19.8	195
7	Q, Ka	Covariance	-0.494	48.6	-67.0
8	Tlag	Random interindividual variability	0.00826	8.4	9.1
9	-	Residual intraindividual variability in formal pharmacokinetic studies (concentration > 1 ng/mL)	0.0144	16.0	12.0
10	-	Residual intraindividual variability in formal pharmacokinetic studies (concentration <= 1 ng/mL)	0.615	31.9	78.4
11	-	Residual intraindividual variability in Phase III trials	0.0600	9.5	24.5

[1] Calculated as $(\text{variance})^{1/2}*100$

[2] Calculated as $\text{sign}(\text{covariance}_{12})*[\text{covariance}_{12}/(\text{variance}_1*\text{variance}_2)^{1/2}]*100$, where variance_1 and variance_2 are variances of random effects for adjacent parameters and covariance_{12} is their covariance

Clearance

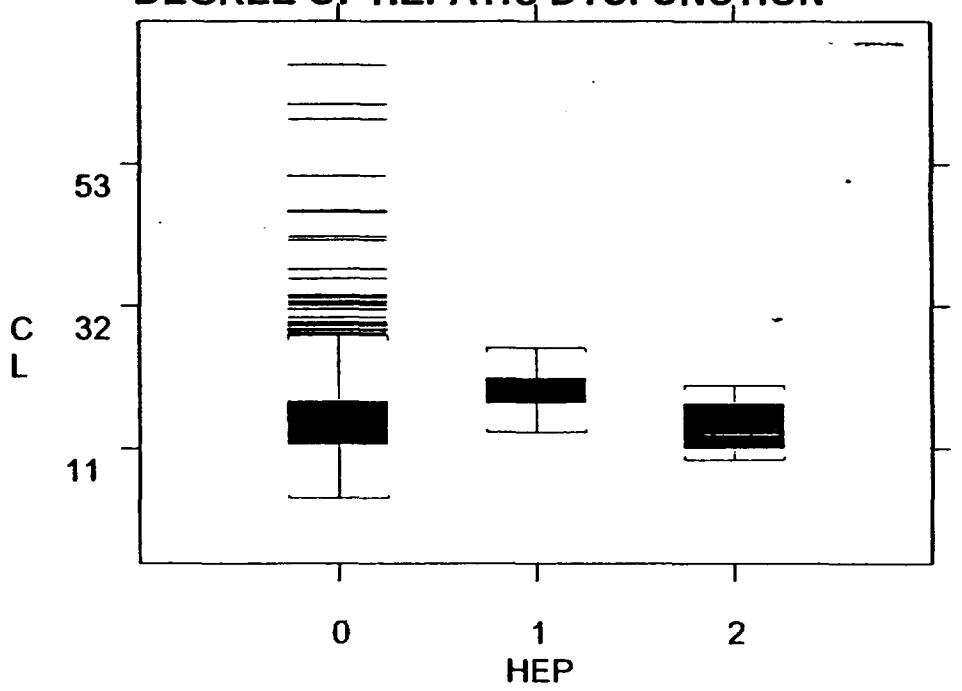
The applicant explained how clearance of galantamine was composed in the model from the metabolic and renal parts.

The metabolic clearance linearly increases with patient's body weight and decreases with age. The value of basal metabolic clearance, presented in Table 3 corresponds to the median age and body weight of the Alzheimer patients of Phase III studies (75 yr and 67 kg body weight, respectively). CL_{met} depends on the liver function (Figure 10): in patients with moderate liver dysfunction it is 62% lower than in case of normal liver function (3.63 L/h *versus* 9.42 L/h).

The renal part of clearance is proportional to creatinine clearance. The model predicts the renal galantamine clearance in a typical Alzheimer patient (calculated creatinine clearance near 60 mL/min) of 4.3 L/h. Thus one can expect the total galantamine clearance of about 9.42+4.3=13.7 L/h in Alzheimer patients with normal liver function.

The renal part is about 30% of the typical total clearance. In case of liver dysfunction the total clearance is 3.63+4.3=7.9 L/h that is 42% less as compared to patients with normal liver function. The contribution of the renal part to the overall clearance is increased to ~54.4%.

Figure 10. CLEARANCE IN PATIENTS WITH DEGREE OF HEPATIC DYSFUNCTION



Gender differences in clearance are addressed through the lower creatinine clearance and body weight (71.5% and 81.3% respectively) in females in comparison with males. The overall CL medians are 12.8 and 15.9 L/h in females and males, respectively (20% difference). The mean CL values and results of t-test are shown in Table 6 and Figure 11. The difference between the genders was very significant.

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Figure 11. BOXPLOTS OF GALANTAMINE IN MALE AND FEMALE ALZHEIMER'S DISEASE PATIENTS

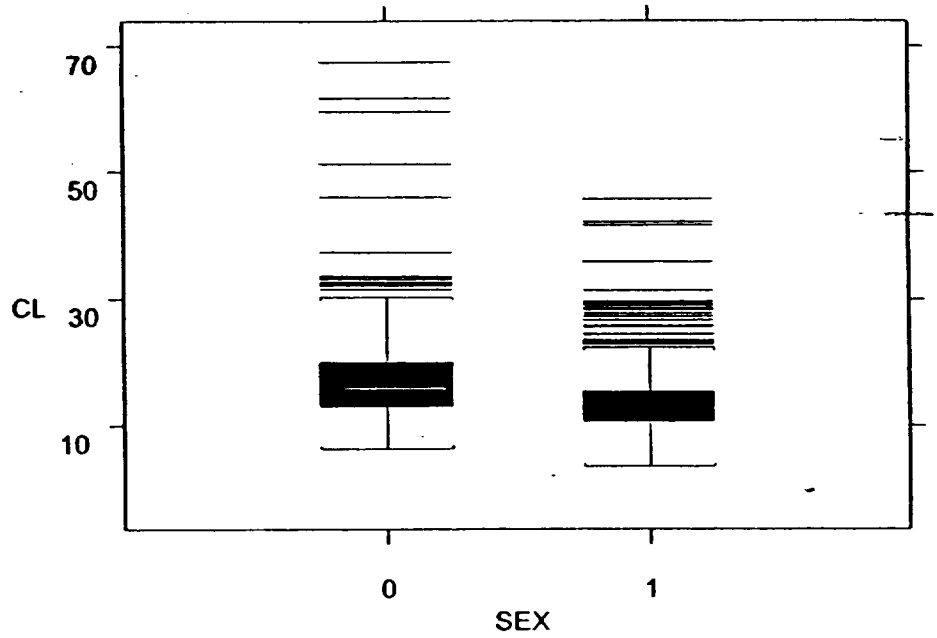
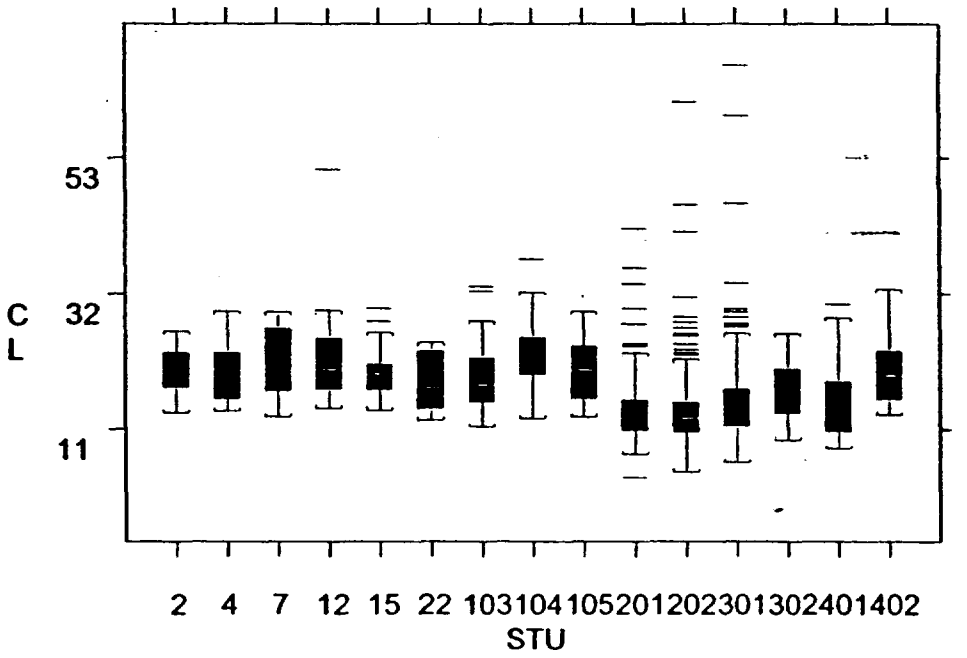


Table 6. t-Test: Two-Sample Assuming Unequal Variances

	Variable 1	*Variable 2*
Mean	17.1018733	13.75924
Variance	43.6408894	23.98687
Observations	539	550
Hypothesized Mean Difference	0	
df	992	
t Stat	9.47037331	
P(T<=t) one-tail	9.8565E-21	
t Critical one-tail	1.64639005	
P(T<=t) two-tail	1.9713E-20	
t Critical two-tail	1.9623576	

The applicant considered the other differences in the studied population. Alzheimer patients have significantly lower clearance than healthy subjects (13.2 versus 19.4 L/h) although these patients are older (median age 75 and 28 yr, respectively) and have more females (57.5% and 25.3%, respectively) than the healthy group (Figure 12).

Figure 12. CLEARANCE IN DIFFERENT STUDIES



Therefore, the applicant properly concluded that pathophysiological conditions of this disease do not alter the galantamine kinetics. Although the combination of hepatic and renal insufficiency and advanced age may result in the substantially lower clearance, the dose adjustment in females was not recommended in the Package Insert.

Effect of co-medication

Part of patients of GAL-INT-1 and GAL-INT-2 were genotyped with respect to CYP 2D6 [14, 15]. Individual Bayesian estimates of CL for those patients were isolated and the effect of genotype was investigated. The bimodality of the CL distribution in the poor metabolizers and homozygotic extensive metabolizers was not confirmed. CYP 3A4 plays also a role in galantamine metabolism, and besides that a substantial part of galantamine is excreted via renal route

The applicant plotted the histogram of all residuals and the corresponding probability density curve (the upper part of the figure) together with residuals related to 30 comedicated drugs listed above. The coadministration of inhibitors was associated with positive shift of residuals indicating a reduction in CL. This may be a result of inhibition of one or more galantamine metabolic pathways. At the same time, drugs affecting gastric acidity, furosemide and paracetamol had no appreciable effect. The most pronounced effect (25 - 33%) of co-medication was found for amitriptyline, fluoxetine, fluvoxamine, paroxetine and quinidine.

In conclusion, based on the population pharmacokinetic analysis of 15 studies, the applicant demonstrated that total clearance of galantamine depends on both metabolic and renal parts. The renal clearance is proportional to creatinine clearance. The metabolic

clearance increases with body weight and decreases with age and is lower in case of moderate liver dysfunction.
Clearance in females was 20% lower (significant difference) as compared to males, explained by lower creatinine clearance and body weight. Gender differences estimated by the population data analysis of galantamine are acceptable from the point of view of the Office of Clinical Pharmacology and Biopharmaceutics. An advanced age and a higher proportion of females in the patient population could explain the difference in clearance in Alzheimer patients as compared to healthy subjects. The galantamine clearance in patients genotyped as poor metabolizers with respect to CYP 2D6 was 25% lower as compared to extensive metabolizers, however, no bimodality in the overall distribution of galantamine clearance was detected. Concomitantly administered potent inhibitors of cytochrome P-450 2D6 reduced galantamine clearance by 25-33%. The steady-state volume of distribution was affected by lean body mass.

The second question *"Are the PK/PD relationships of galantamine plasma concentrations and ADAS-cog scores and syncope properly justified?*
related to the report "Pooled pharmacokinetic and pharmacokinetic/ pharmacodynamic (GAL-USA-1/GAL-INT-1) analyses of the Efficacy and Safety of Galantamine in Alzheimer's Disease"

Methods:

The cognitive subscale, the ADAS-cog/11, was the primary dependent variable in this trial and is the sum of the following 11 items:

1. Word Recall (score: 0 to 10)
2. Word Recognition Memory Tests (score: 0 to 12)
3. Object and Finger Naming (score: 0 to 5)
4. Commands (score: 0 to 5)
5. Constructional Praxis (score: 0 to 5)
6. Ideational Praxis (score: 0 to 5)
7. Orientation (score: 0 to 8)
8. Remembering Test Instructions (score: 0 to 5)
9. Spoken Language Ability (score: 0 to 5)
10. Comprehension of Spoken Language (score: 0 to 5)
11. Word Finding Difficulty (score: 0 to 5).

The ADAS-cog/11 was performed at Visits 1, 2, 3, 5 and 8 (screening, baseline, Week 3, Month 3, and Month 6 or termination).
Based on the change of ADAS-cog/11 from baseline at Month 6 (ΔADAS-cog/11), the patients were classified into five different responder groups:

Non-responder: ΔADAS-cog/11 > 0;

Responder (0): ΔADAS-cog/11 ≤ 0;

Responder (4): ΔADAS-cog/11 ≤ -4;

Responder (7): ΔADAS-cog/11 ≤ -7;

Responder (10): ΔADAS-cog/11 ≤ -10.

The safety parameters of interest were syncope, fall, anorexia, muscle weakness, bradycardia, and mortality occurring during the 6-month medication period and the absolute and percent body weight changes from baseline at Month 6.

Pharmacokinetics/Pharmacodynamics

The applicant obtained the individual parameter estimates for the patients enrolled in studies GAL-INT-1 and GAL-USA-1 by NONMEM as described above and then calculated the exposure over one dosing interval (AUC_τ = Dose/CL), and the corresponding average concentration ($C_{avg} = AUC_\tau/\tau$). The average galantamine plasma concentration at steady state (C_{avg}) during the plasma sampling time period was considered as a driving force for the pharmacodynamic response. The primary efficacy parameters of interest were the change in ADAS-cog/11 from baseline at Month 6 (ΔADAS-cog/11), and CIBIC-plus at Month 6. The safety parameters of interest were syncope occurring during the 6-month medication period, following titration, and the absolute and percent body weight changes from baseline at Month 6.

The pooled PK/PD assessment was based on the galantamine treated patients for whom both PK and PD data were available (placebo, 328; dose 12 mg BID, 264, dose 16 mg BID 249). For the first step, the applicant examined the concentration vs effect plots for each of the effects. Then the relationships between pharmacokinetics (C_{avg}) and pharmacodynamics (ΔADAS-cog/11, responders based on ADAS-cog/11 and other scores, and percent of body weight change) were attempted to described based on linear regression. The applicant did not indicate what software was used for the linear regression assessment.

Results

Linear regression analysis shows very weak but significant ($p<0.0001$) relationship between C_{avg} and ΔADAS-cog/11 at month 6 (R^2 0.0721, slope –0.0338) with the inclusion of placebo data results (Figure 13). This relationship could not be established when the placebo data were excluded from the analysis. The same results were observed for the relationship between C_{avg} and responders based on ADAS-cog/11 and other scores. For the weight loss, weak linear relationship was found with the inclusion of placebo data, and no correlation was observed without the placebo data.

The C_{avg} of the patients experienced syncope was graphically (Figure 14) compared with the same of the patients without this adverse effect. The applicant made a comparison based on visual examination of the scatter plots for the patients receiving 12 mg or 16 mg of galantamine BID. Although statistical comparison of these groups of patients has not been performed, the applicant concluded that C_{avg} are not different in these groups.

Comments

1. The applicant properly explained the different steps of population pharmacokinetic model building and choosing of the optimal model to fit the data based on model diagnostics. Final model to describe the pharmacokinetics of galantamine was two-compartmental model with absorption and lag-time. Covariates affecting galantamine disposition were age, body weight, lean body mass, creatinine clearance and liver function. Model validation, analysis of residuals, and detection of outliers was performed according to the requirements described in the Population PK Guidance for the industry. The reviewer verified the final run and created the main graphs for the model diagnostics graphic.

2. The clearance in females in comparison with males was estimated to be about 20% lower and was proved to be statistically significant. However, this decrease is due to lower creatinine clearance and body weight in females as compared to males (71.5% and 81.3% of those in males, respectively). After the correction by these parameters, dose adjustment based on gender is considered clinically irrelevant.

3. The applicant correctly tested the influence of the hepatic and renal insufficiency on the pharmacokinetic parameters.

4. In the Drug Interaction Section, the applicant has drawn attention to the potential interaction with the drugs, which are inhibitors of cytochrome P450 3A4 and 2D6, particularly paroxetine. Interaction with these drugs was found to be significant in the population data analysis. Proper dose adjustment in case of co-medication with cholinomimetics is under consideration for the labeling.

5. The applicant assessed PK/PD relationship between galantamine C_{avg} and ADAS-cog scores, and adverse effects, including syncope by the examination of the graphs. The applicant tested the linear relationships in each of the cases although they did not mention what software was used. Comparisons of the C_{avg} values for the patients with and without syncope were not evaluated statistically.

In conclusion, the answers on the questions for the consult:

The gender differences estimated by the population pharmacokinetics data analysis of Galantamine are acceptable.

Relationship of Galantamine plasma concentrations and pharmacodynamics measured by ADAS-cog scores shows very weak correlation. Pharmacokinetic/pharmacotoxic correlation for syncope was evaluated only based on visual comparison of the graphs.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the Reports "Population Analysis of Galantamine Pharmacokinetics in Healthy Subjects and Patients with Alzheimer's Disease" and "Pooled Pharmacokinetics and Pharmacokinetic/ Pharmacodynamic Analyses of the Efficacy and Safety of Galantamine in Alzheimer's Disease". The population analysis is acceptable from the point of view of the Office of Clinical Pharmacology and Biopharmaceutics.

[/S/]

Date MAY 19 2000

Elena Mishina, Ph. D.
Pharmacometrics Specialist

[/S/]

Raman Baweja
Neuropharmacology Team Leader

cc list: NDA 21-169
BIOPHARM - CDR

Redacted 21

pages of trade

secret and/or

confidential

commercial

information

38 pages redacted from this section of the approval package consisted of draft labeling

Barry N. Rosloff, Ph. D.
10/17/00

PHARMACOLOGIST REVIEW OF NDA 21-224
ORIGINAL SUMMARY

SPONSOR: Janssen Research Foundation
1125 Trenton-Harbourton Road
P.O. Box 200
Trenton, NJ

DRUG: galanthamine (Reminyl Oral Solution)

CATEGORY: Alzheimer's Disease

RELATED NDA: 21-169 (Reminyl Tablets)

SUMMARY AND EVALUATION:

NDA 21-169 is cross-referenced. Preclinical data in support of NDA 21-169 were reviewed by me (5/1/00 and 9/25/00). There are no new preclinical issues regarding the oral solution formulation. There are no unusual excipients.

RECOMMENDATION:

This NDA is approvable.

[/S/]

Barry N. Rosloff, Ph.D.

cc: NDA 21-224, original submission + division file
Rosloff, Fitzgerald, Fanari
GF 10/18/00