AUC and pantoprazole concentration at end of the 15 min infusion (C_{max}) increased linearly with increasing dose (see Fig. 2).

Fig. 2. Assessment of Dose Linearity of AUC Following Intravenous Doses of 10, 20, 40 and 80 mg

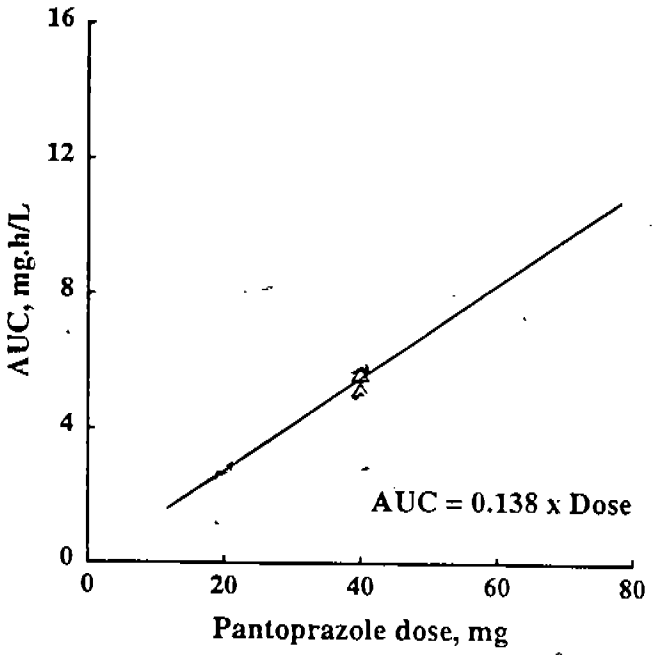


Table 2. ANOVA Assessment of Equivalence of Pantoprazole Pharmacokinetic Parameters Following Intravenous Doses of 10, 20, 40 and 80 mg with the 80 mg Dose as Reference

point estimates and 90%-confidence limits, reference: 80 mg

	Dose		
	10 mg	20 mg	40 mg
C(0.25 h)	0.91 (0.81, 1.03)	1.04 (0.92, 1.17)	1.06 (0.94, 1.20)
AUC(0-Inf)	0.85 (0.78, 0.92)	0.93 (0.85, 1.01)	0.97 (0.89, 1.06)

	Dose		
	10 mg	20 mg	40 mg
$t_{½}$	0.80 (0.71, 0.91)	0.89 (0.79, 1.01)	0.90 (0.80, 1.02)
Cl/kg	1.18 (1.08, 1.28)	1.08 (0.99, 1.17)	1.03 (0.94, 1.12)
Vdarea	0.95 (0.83, 1.08)	0.94 (0.83, 1.07)	0.91 (0.80, 1.04)

The kinetics of pantoprazole was best described by the two-compartmental model. Across dose levels, the mean Cl_T, V_d and $t_{1/2}$ were, respectively, 7.6-9.0 L/h, 11.0-12.0 L and 0.9-1.2 h and were dose independent. The inter-compartmental rate constants and the volume of distribution in the central compartment were determined by simultaneously fitting the function (Q_t /V_c) describing the pantoprazole concentration versus time for the 20, 40 and 80 mg dose groups using a two-compartmental, first order elimination intravenous infusion model. Q_t and V_c represent the amount of pantoprazole in the central compartmental and apparent volume of distribution in the central compartment, respectively. The mean values of K_{12}, K_{21}, and K_{10} were 0.40 h^{-1}, 0.91 h^{-1} and 1.12 h^{-1}, respectively. The mean V_c was 6.9 L.

Using individual subject dose normalized, log transformed values, equivalence of the C_{max} (serum concentration at the end of infusion) and AUC of for the dose range (10-80 mg was assessed using ANOVA for the 90% confidence limits, with the 80 mg dose as reference and the 10, 20 and 40 mg doses tests, (Table 2). The point estimates and confidence intervals for C_{max} for the 10, 20 and 40 mg doses were entirely within the range of ——— required for equivalence as were those for AUC for the 20 and 40 mg doses. The lower 90% confidence limit for AUC of the 10 mg dose was 78%. Overall, it could be considered that dose proportional of AUC was established in the dose range of 10-80 mg for Cmax and AUC. Similarly, equivalence of body weight normalized Cl_T and V_d was established for the dose range of 10-80 mg indicating that these parameters are dose independent in this dose range.

The pharmacokinetics of pantoprazole was also evaluated in 6 male subjects each receiving a single 40 mg dose of ^{14}C-labeled pantoprazole (37.5 uCi) by constant rate intravenous infusion over 15 min (Byk GuldenProtocol #FHP108E). The mean values of body weight normalized Cl_T and Vd_{area} (0.123 L/h/kg and 0.152 L/kg, respectively) determined in this study, were within the range of values for the dose range in Table 2 which, when expressed per kg, are as follows: Cl_T : ——— L/h/kg and Vd_{area}: ——— L/kg. The elimination half-life obtained in this study (0.89 h) also approximated 1 h. These findings suggest consistency of pharmacokinetic data across studies.

(b) **Intravenous Kinetics of Pantoprazole from Injection Concentrate and Lyophile Formulations**: The kinetics of pantoprazole was evaluated in 12 normal, male subjects each receiving a single 40 mg dose as an injection concentrate and 45.5 mg and 91 mg doses as a lyophile formulation. Each dose was administered by a 15 min constant rate intravenous infusion in a placebo controlled crossover study (Byk Gulden Protocol FHP027E; GMR-29734). The lyophile formulation is proposed for marketing for intravenous administration. The concentrate formulation was used for intravenous administration in the early clinical development. Plots of pantoprazole serum concentration versus time for the tested doses are presented in Fig. 3. The mean±SD pharmacokinetic parameters are presented in Table 3. CO and LY in parentheses represent concentrate formulation and lyophile formulation, respectively.

Fig. 3. Mean ± SD Pantoprazole Serum Concentration Versus Time For Single Intravenous Doses of 40 and 80 mg as Lyophile Formulation and 40 mg as Injection Concentrate.

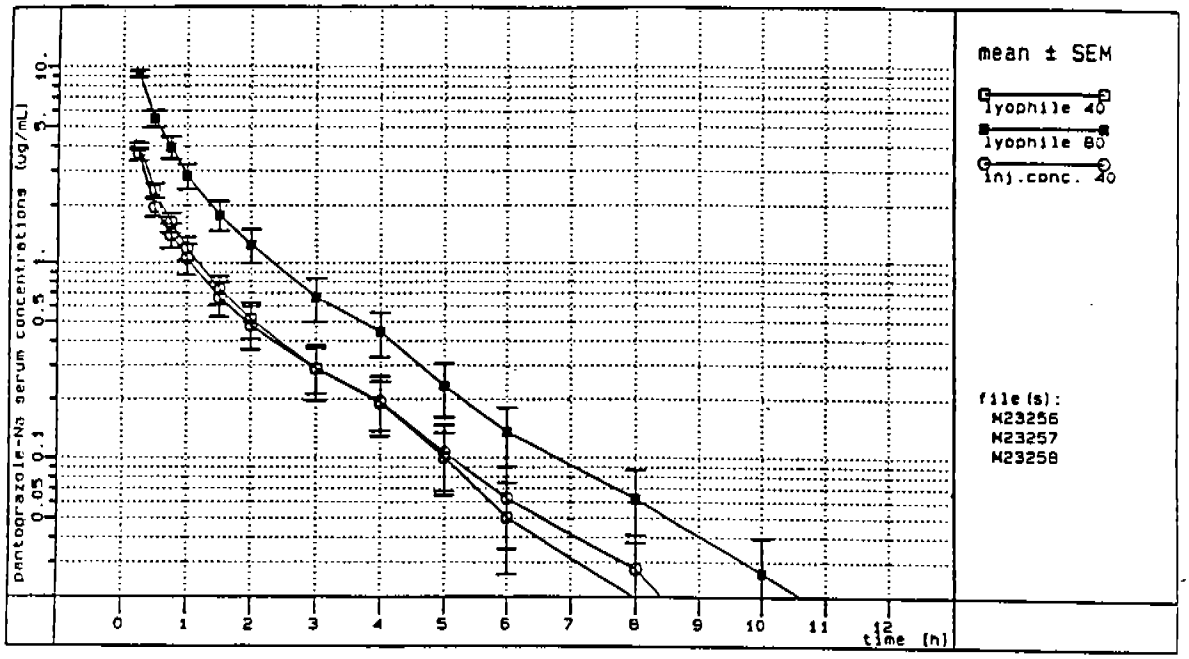


Table 3. Mean + SD Pantoprazole Pharmacokinetic Parameters in Normal Subjects Following Administration of 10, 20, 30 and 40 mg doses by Intravenous Infusion

Dose (mg)	n	C_{max} (mg/L)	t_{max} (h)	AUC ([mg/L]h)	$t_{1/2}$ (h)	Cl_T (L/h)	V_d (L)
40(CO)	12	3.67±0.95	0.25	3.6±2.2	1.3±0.3	14.0±6.4	23.6±8.8
45.5(LY)	12	4.00±0.55	0.25	4.0±1.9	1.2±0.3	11.7±4.0	19.3±6.3
91(LY)	12	9.24±1.15	0.25	9.3±4.5	1.2±0.3	10.3±4.2	17.2±5.3

Panroprazole half-life values were similar for the three treatments as were the Cl_T and V_d values for the two lyophile formulation. Cl_T and V_d values for the injection concentrate appeared to be slightly greater than those for the two lyophile formulations. C_{max} values for the 40 mg lyophile injection and the 40 mg injection concentrate were similar. In this study, for the 40 mg dose of injection concentrate, both the mean Cl_T and V_d approximately 100% higher and the mean AUC was 50% lower as compared to values obtained in Byk Gulden Protocol FHP003 (see page 3). No explanation was provided as to the observed kinetic differences between the two intravenous formulations. Since the increases in Cl_T and V_d were similar, the half-life values for both studies (1.0-1.3 h) were similar.

The results of comparison of log transformed AUC by the Two One-sided T-tests Procedure for the 90% confidence limits for (i) the 40 mg injection concentrate dose as reference versus the 45.5 mg lyophile dose (adjusted to 40 mg) as test and (ii) the 40 mg lyophile dose as reference versus the 91 mg lyophile dose (adjusted to 80 mg) as test are presented in Table 4.

Table 4. Pantoprazole AUC Equivalence: 40 mg Lyophile Formulation Versus 40 mg Injection Concentrate and 40 mg Lyophile Formulation Versus 80 mg Lyophile Formulation

Two One-sided T-Tests	Test/Reference (%)	
	Point Estimate	90% Confidence Limits
Reference: 40 mg Inj. Conc. Test: 40 mg Lyophile	100	90 – 110
Reference: 40 mg Lyophile Test: 80 mg Lyophile (adjusted)	116	107 – 125

In both cases, the point estimates and the confidence of limits of the ratio (test/reference) of the mean log transformed AUC values were in the interval of 80-125%. These findings suggest (i) that the systemic exposures for the 40 mg pantoprazole injection concentrate, that was used for the early clinical development, and the 40 mg pantoprazole lyophile formulation that is proposed for marketing for intravenous administration, are equivalent and (ii) that the systemic exposure for 40 mg pantoprazole lyophile proposed for marketing for intravenous administration and 80 mg pantoprazole lyophile are dose proportional. However, dose proportionality is not an issue of concern as only the 40 mg dose is proposed for marketing.

(c) **Oral Administration: Single Dose**: The kinetics of pantoprazole for the orally administered enteric coated tablet was characterized for the dose range of 10-80 mg (Byk Gulden Protocol #A9907-GER; GMR 29717) in 10 normal male subjects. Plots of mean ± SD pantoprazole serum concentration versus time are presented in Fig. 4. The mean ± SD pantoprazole pharmacokinetic parameters are presented in Table 5. Also presented in Table 5 are the mean ± SD pharmacokinetic parameters for the 40 mg enteric coated tablet formulations used in the bioequivalence studies submitted in this NDA (Byk Gulden Protocols FHP028E, FHP014 and FHP041).

Fig. 4. Plots of Mean ± SD Pantoprazole Serum Concentration Versus Time Following Single Oral Doses of 10, 20, 40 and 80 mg in 12 Normal Subjects

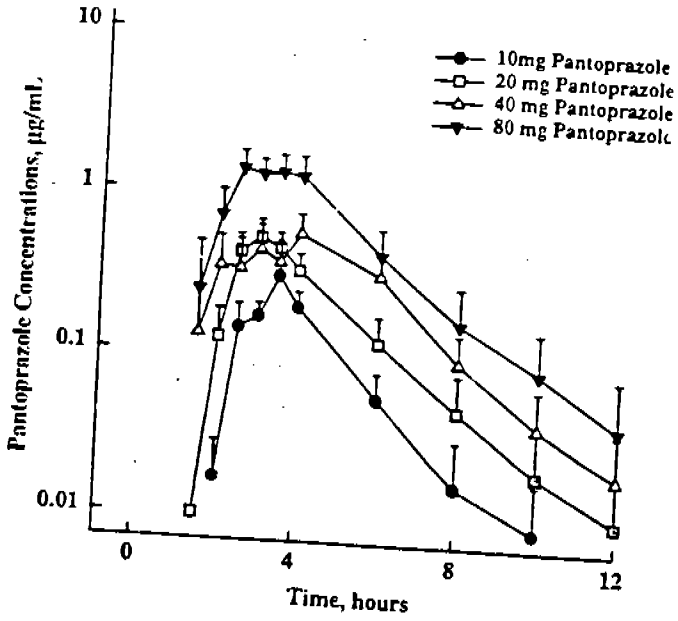


Table 5. Mean + SD Pantoprazole Pharmacokinetic Parameters in Normal Subjects Following Administration of Single Oral Doses of 10, 20, 40 and 80 mg

Protocol	n	Dose (mg)	C_{max} (ug/mL)	t_{lag} (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)
A9907-GER	9	10^{I}	0.41±0.12		3.1±0.5	0.7±0.6	0.9±0.6
GMR-2917	10	20^{I}	0.78±0.37		3.2±1.1	1.5±1.4	0.9±0.6
	9	40^{I}	1.20±0.56		3.7±1.5	2.6±1.6	1.2±0.7
	10	40^{I*}	1.39±0.62		3.2±1.2	2.8±2.1	0.9±0.3
	10	80^{I}	2.78±1.12		3.1±1.2	5.0±4.1	0.9±0.6
FHP014	35	40^{IIa}	2.30±0.7	1.8±1.0	2.8±1.1	4.3±2.0	1.2±0.3
GMR-29687	1^{pm}	40^{IIa}	2.71	2.0	3.0	27.0	10.0
	35	40^{III}	2.42±0.77	1.4±0.7	2.5±0.8	4.4±2.1	1.2±0.3
	1^{pm}	40^{III}	3.59	1.0	2.0	32.0	9.1
FHP028	35	40^{III}	2.50±1.06	1.5±0.8	2.6±0.9	4.9+3.2	1.2±0.4
GMR-29716	1^{pm}	40^{III}	4.03			38.4	6.7
	35	40^{mf}	2.45±0.77	1.4±0.6	2.4± 0.6	4.2±2.8	1.2±0.4
	1^{pm}	40^{mf}	4.36			34.0	8.4
FHP041	36	40^{mf}	2.51±0.67	1.7±0.8	2.6±0.9	4.6±2.0	1.2±0.3
GMR-31756	36	40^{nf}	2.58±0.84	1.4±0.8	2.5±1.1	5.1±2.4	1.3±0.4

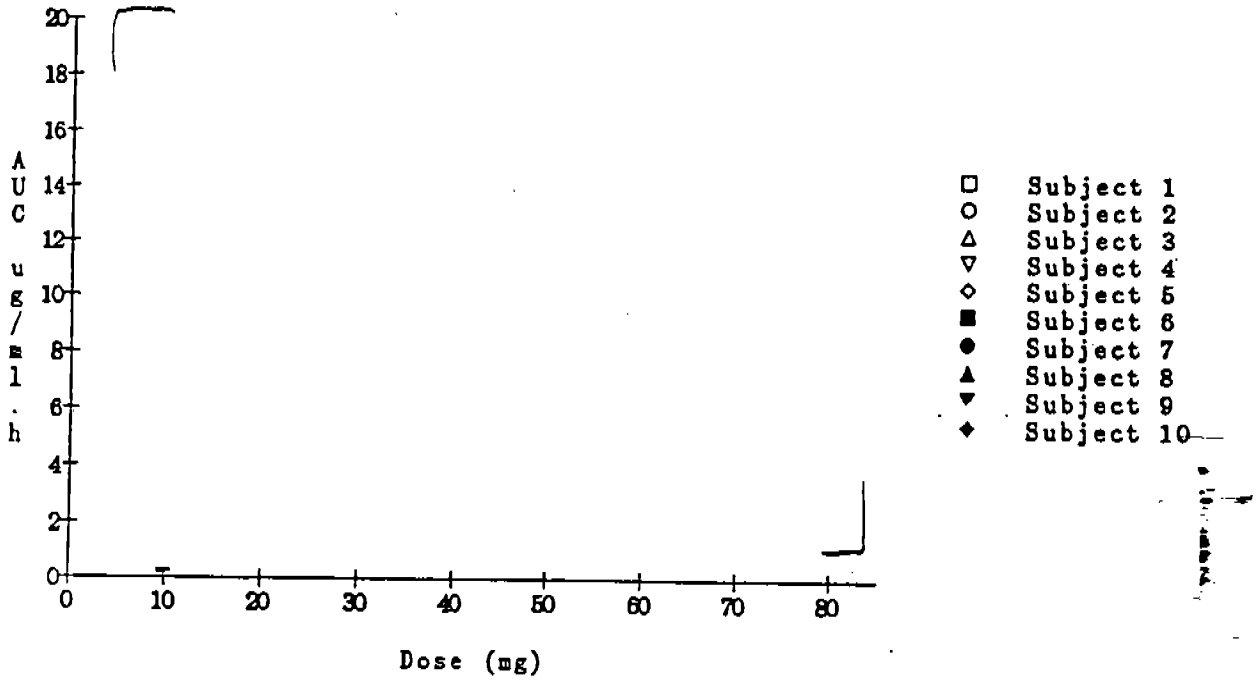
[I]Early Phase I Formulation (Formulation A), [*]Repeated; [II]Phase II formulation; [III]Phase III formulation, [mf]To-be-marketed formulation; [nf]New formulation, [pm]Poor metabolizer. [a]2 x20 mg tablet.

In extensive metabolizers of pantoprazole receiving the 40 mg dose, the pharmacokinetic parameters of pantoprazole were comparable across studies for the later formulations (Phase IIb, Phaes III, the to-be-marketed and the new enteric coated 40 mg pantoprazole tablet formulations). For this dose, the C_{max} and AUC obtained in the dose ranging study (Protocol A9907-GER) were markedly lower than the values for the Phase IIb, Phase III and the to-be-marketed formulations. This could be due to differences between the formulation used in the initial stages of drug development versus the improved, later phase and to-be-marketed formulations. Across studies, t_{max} and $t_{1/2}$ were dose independent.

In the dose ranging study (Protocol A9907-GER; GMR-2917), AUC and Cmax were dose linear in the dose range of 10-80 mg (Fig.5). Generally, dose normalized AUC values were equivalent (Fig. 6a) suggesting its dose proportionality in this dose range except that one subject showed significant deviation from dose proportionality. Dose normalized C_{max} values were not equivalent (Fig. 6b), subsequently, C_{max} was not considered dose proportional in this dose range. However, dose proportionality is not an issue of concern as only the 40 mg dose is proposed for marketing.

Fig. 5. Assessment of Dose Linearity of AUC (a) and C_{max} (b) Following Oral Pantoprazole Doses of 10, 20, 40 and 80 mg

(a)



(b)

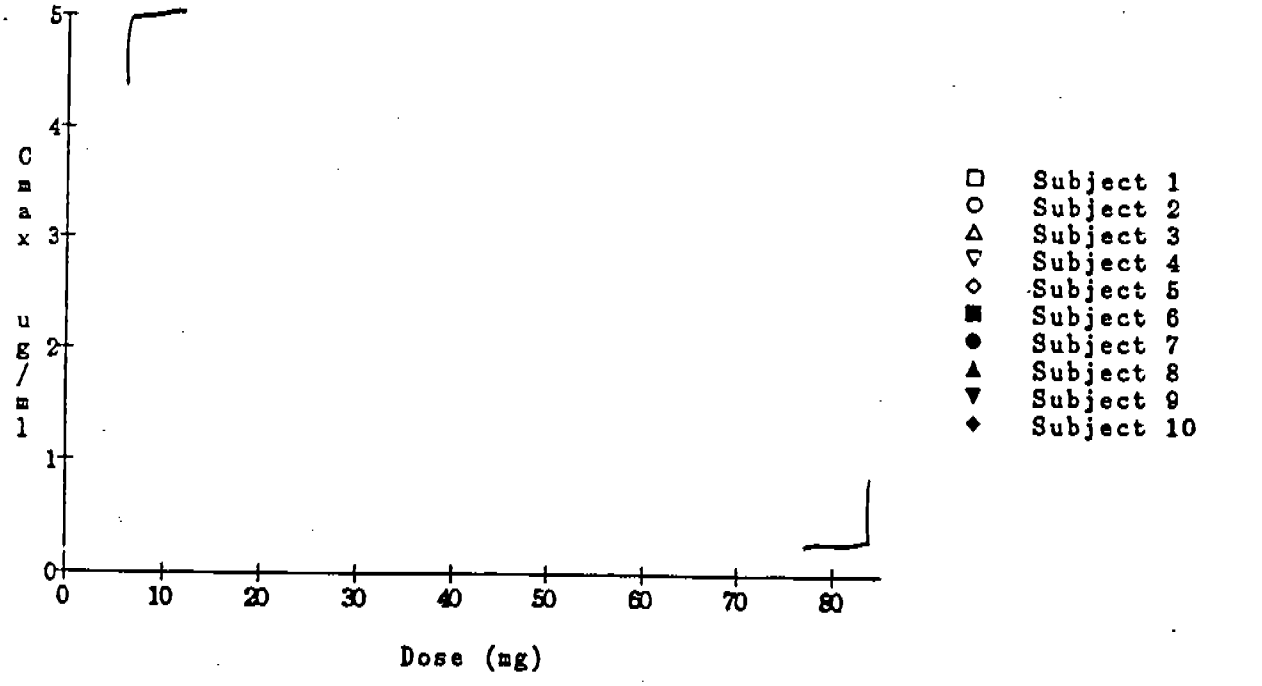
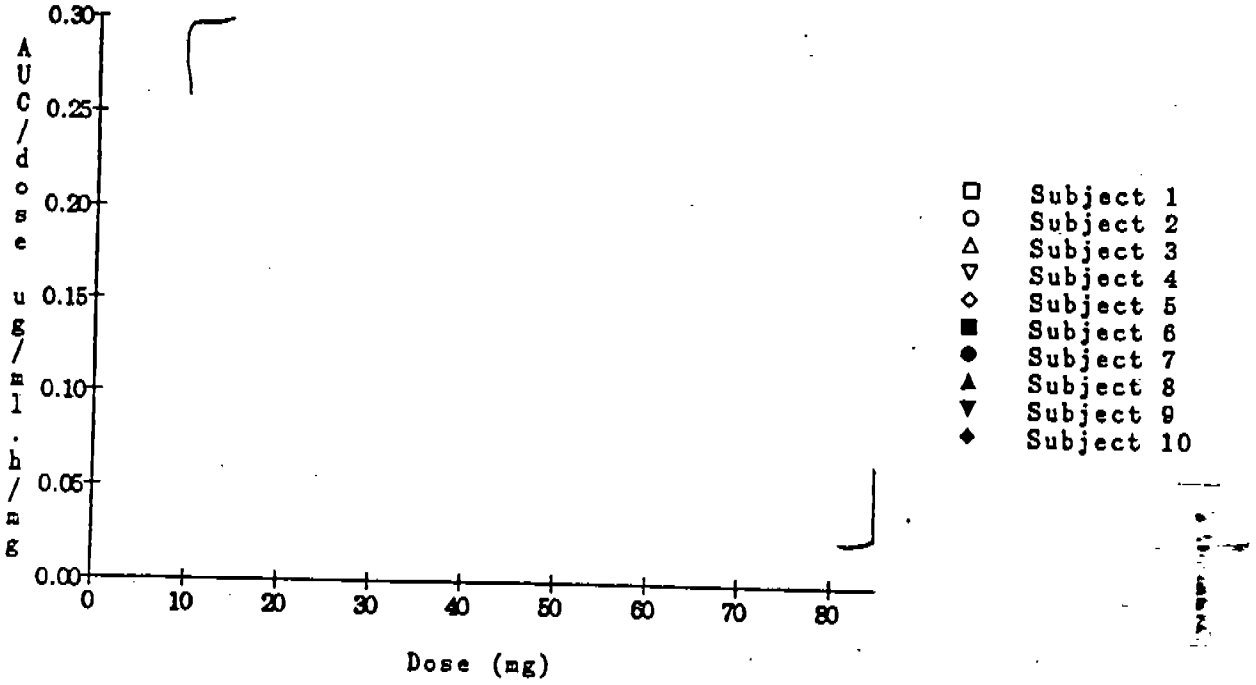
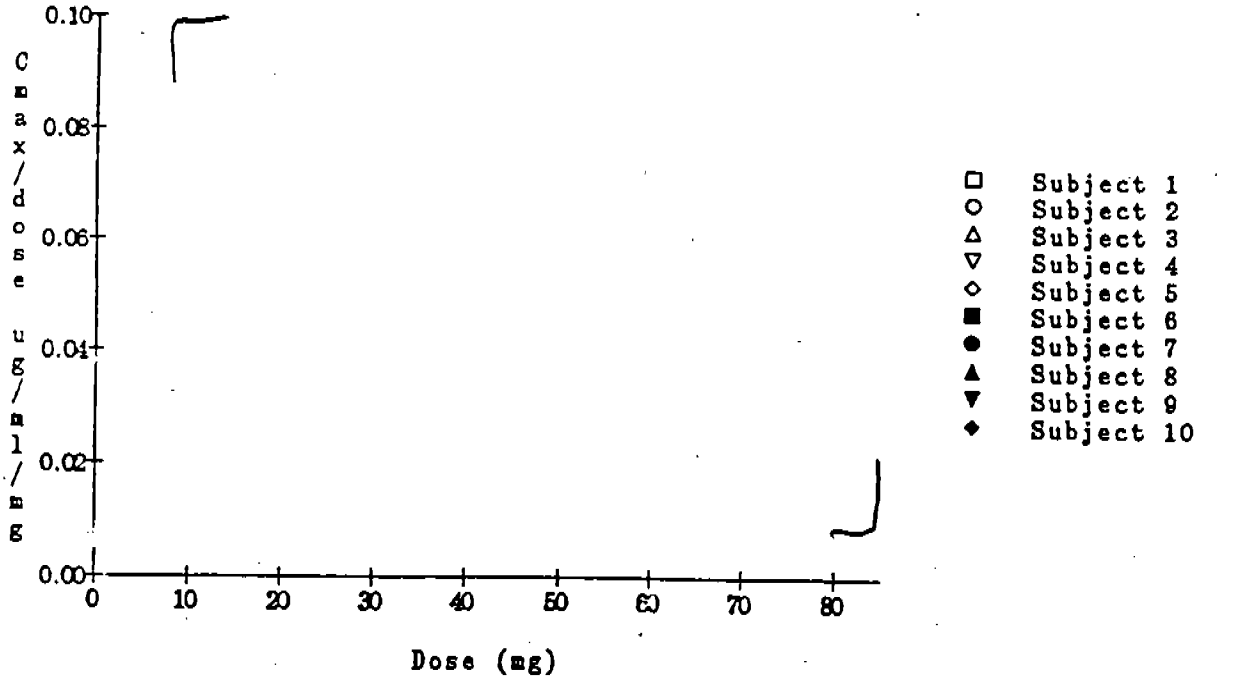


Fig. 6. Relationship between Dose normalized AUC (a) and C_{max} (b) Following Oral Pantoprazole Doses of 10, 20, 40 and 80 mg

(a)



(b)



(d) **Oral Administration: Multiple Dose**: The multiple dose kinetics of orally administered enteric coated pantoprazole tablet was determined in 16 healthy male subjects receiving the 20, 40 and 80 mg doses for 7 days (Byk Gulden Protocol #FK3029; GMR-29707) and in 12 healthy male subjects receiving the 20 and 40 mg doses also for 7 days (Byk Gulden Protocol #FHP007E; GMR-30133). In each study, the doses were administered in a crossover fashion. Plots of mean ± SEM pantoprazole serum concentration versus time for Byk Gulden Protocol FHP007E are presented in Fig. 7. The mean ± SD pharmacokinetic parameters of pantoprazole for both studies are provided in Table 6.

Fig. 7. Plots of Mean ± SD Pantoprazole Serum Concentration Versus Time for Days 1 and 7 Following Multiple Oral Doses of 20 and 40 mg in 12 Normal Subjects

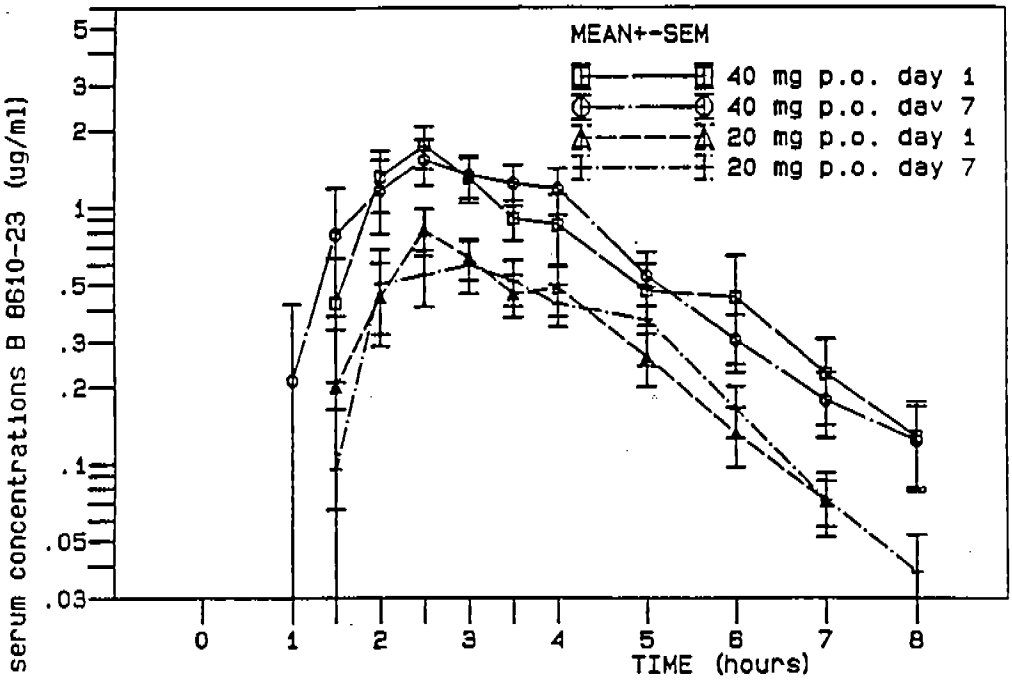


Table 6. Mean + SD Pantoprazole Pharmacokinetic Parameters in Normal Subjects Following Multiple Oral Doses of 20 and 40 mg

Protocol	n	Day	Dose (mg)	C_{max} (ug/mL)	tlag (h)	t_{max} (h)	AUC (mg/L)h	$t_{1/2}$ (h)
FK3029	15	7	20	1.02±0.30	—	2.1±1.4	1.7±0.6	1.2±0.2
GMR-29707	1[pa]	7	20	1.54	—	2.43	12.8	6.1
	15	7	40	2.16±0.85	—	1.9±0.5	3.2±1.1	1.0±0.2
	1[pa]	7	40	3.80	—	2.43	26.2	5.8
	15	7	80	4.08±1.25	—	1.9±10.6	7.2±2.8	1.3±0.6
	1[pa]	7	80	5.91	—	2.43	50.7	5.6
FHP007E	11	1	20	1.19±0.31	—	2.7±0.7	2.2±0.8	1.1±0.3
GMR-30133	12	7	20	1.23±0.30	—	3.0±0.9	2.1±0.6	1.0±0.5
	12	1	40	2.61±0.76	—	2.8±1.2	4.9±1.9	1.1±0.5
	11	7	40	2.52±0.77	—	2.5± 0.9	4.7±1.1	1.1±0.5

The multiple dose pharmcokinetic parameters of orally administered enteric coated pantoprazole tablets were similar to its single dose values for the 20 and 40 mg tablets (Byk Gulden Protocol FHP007E). T_{max} and $t_{1/2}$ were dose independent in both studies. In extensive metabolizers, $t_{1/2}$ values for both studies were similar. For the 40 mg dose, the mean C_{max} values for Protocol FHP007E were slightly (17-21%) higher. The mean AUC for this study (Protocol FHP007E) was 47-53% higher.

(e) **Systemic Accumulation in Normal Metabolizers upon Multiple Oral Dosing**: The results of Byk Gulden Protocol FHP007E in Table 7 above show that in extensive metabolizers, pantoprazole C_{max} for Day 1 and Day 7 were similar. These results suggest that in normal, metabolizers (all subjects in this study were normal metabolizers), pantoprazole would not accumulate in the serum upon multiple dosing.

(f) **Systemic Accumulation in Poor Metabolizers upon Multiple Oral Dosing**: In Byk Gulden Protocols FHP014 and FHP028, some poor metabolizers of pantoprazole, with dramatically high AUC and $t_{1/2}$ values, were identified (see Table 5). It was noted that the C_{max} values for these poor metabolizers were not equally dramatically higher than those of the normal metabolizers. Steady state C_{max} values were not determined since these were single dose studies. This reviewer has, therefore, predicted the potential of steady state accumulation of pantoprazole in poor metabolizers using the following standard pharmacokinetic equation:

$$R = 1/(1-e^{-K\tau})$$

where R is the accumulation ratio (factor), K is the terminal elimination rate constant and τ is the dosing interval for pantoprazole (24 h). The worst case scenario is the subject with the half-life of 10 h. In this subject, the accumulation ratio is only 1.23 (i.e., the ratio, $C_{max[ss]} : C_{max[dose\ \#1]}$ would be 1.23: 1.00). This finding suggests that even in poor metabolizers with pantoprazole half-life as long as 10 h (half-life is approximately 1 h in extensive metabolizers), there would be no significant steady state drug accumulation upon multiple dosing. This is due to the long dosing interval (24 h) of the drug.

2. BIOAVAILABILITY: The absolute bioavailability of pantoprazole enteric coated tablet was studied in 12 healthy male subjects each receiving a single oral dose of 40 mg (2x20 mg tablets) and a single 40 mg dose by intravenous infusion over 15 min in a crossover fashion (Byk Gulden Protocol #A9915-GER; GMR-29728). The mean absolute bioavailability (AUC_{oral}/AUC_{IV}) was 77% (range= ———. Excluding the single poor pantoprazole metabolizer ($t_{1/2}$>3.5 h for both routes of administration) did not significantly affect the mean absolute bioavailability (76% in this case).

APPEARS THIS WAY
ON ORIGINAL

3. BIOEQUIVALENCE:

(a) Bioequivalence of the To-be-marketed Formulation and the Phase III Clinical Safety and Efficacy Study Formulation: The bioequivalence of the to-be-marketed enteric coated 40 mg pantoprazole tablet formulation (Formulation E: test) and the enteric coated 40 mg tablet that was used in the Phase III clinical safety and efficacy trials (Formulation C: reference) was assessed in 36 healthy male subjects (Byk Gulden Protocol #FHP028E). Plots of the mean + SEM serum concentration of pantoprazole versus time for both formulations are presented in Fig. 8. The mean + SD of all pharmacokinetic parameters have already been presented (see Table 5).

Fig. 8. Plots of Mean ± SEM Pantoprazole Serum Concentration Versus Time Following a Single Oral Dose 40 mg of Phase III Clinical Study Formulation or the Proposed Market Formulation in 36 Normal Subjects

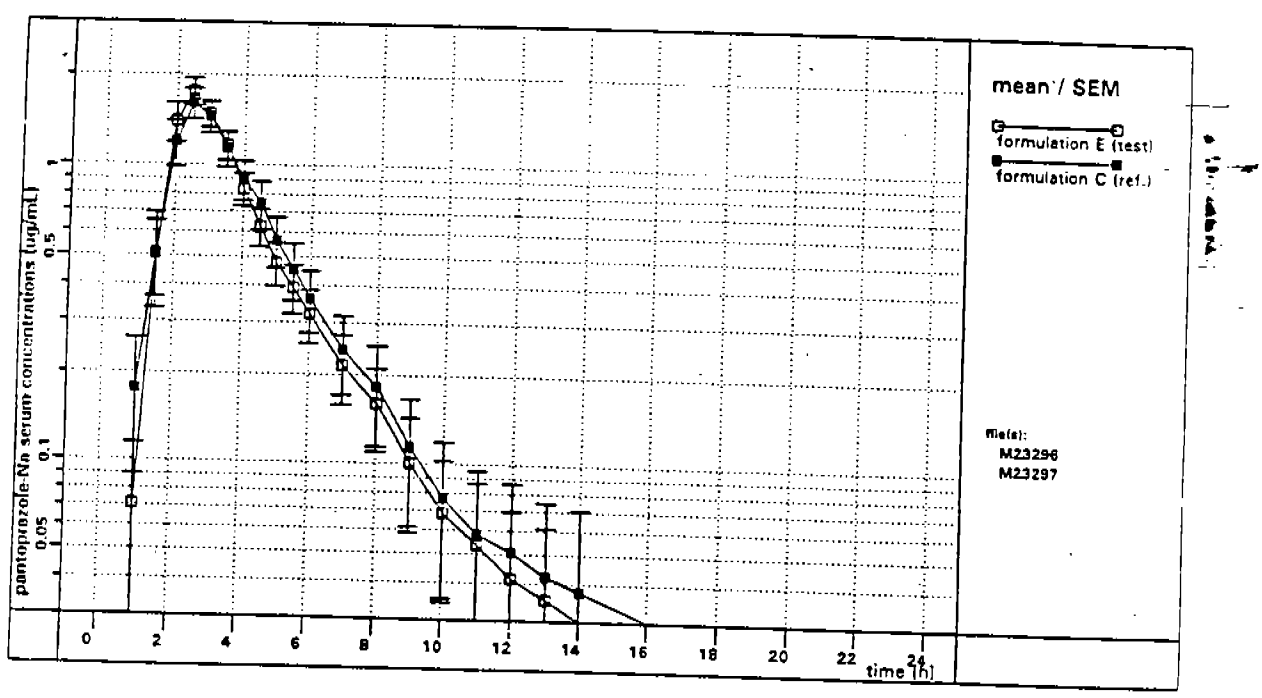


Table 7. Assessment of Bioequivalence Phase III clinically Tested Formulation and the Proposed Market Formulation

Pantoprazole 40 mg p.o. Pharmacokinetic characteristic	Reference: formulation C	Test: formulation E	Equivalence ratio (Test/Reference) Point estimate	90%-confidence interval
	Geometric mean, n = 36 exp (mean(ln) ± SD (ln)) $)		after logarithmic transf.$)	
AUC(0,Inf.)(µg/mLxh)	4.37 (2.25, 8.47)	4.35 (2.21, 8.56)	1.00	0.92 1.07
Cmax (µg/mL)	2.28 (1.41, 3.68)	2.32 (1.65, 3.27)	1.02	0.91 1.15
t1/2 (h)	1.17 (0.77, 1.79)	1.23 (0.76, 1.90)	1.05	1.00 1.11
tmax-tlag (h)	1.19 (0.74)	1.00 (0.34)	-0.19	-0.43 +0.04

$) mean (SD) for tmax-tlag, additive model (no transformation), confidence interval in hours

The bioequivalence of the the test formulation (Formulation E) and the reference formulation (Formulation C) was assessed using the Two One-sided Test Procedure for the 90% confidence limits. The ratios (test/reference) of the mean values of log transformed C_{max} and AUC were within the interval of 0.80-1.25 required for bioequivalence (Table 7). Therefore, the bioequivalence of the to-be-marketed enteric coated 40 mg pantoprazole tablet and the enteric coated 40 mg tablet that was used in the Phase III clinical safety and efficacy studies has been demonstrated.

(b) **Bioequivalence of Two 20 mg Enteric Coated Phase IIb Tested Pantoprazole Tablets (Formulation B: test) and One Phase III Tested 40 mg Enteric Coated Tablet (Formulation C: reference):** The bioequivalence of the 2x20 mg enteric coated tablets that were used in the Phase IIb clinical safety and efficacy trials (Formulation B:test) and the 1x40 mg enteric coated pantoprazole tablet that was used in the Phase III clinical safety and efficacy trials (Formulation C: reference) was assessed in 36 healthy male subjects (Byk Gulden Protocol #FHP014; GMR-29687). The mean plots of mean serum concentration of pantoprazole versus time for these formulations were not provided; therefore typical individual subject plots are presented in Fig. 9. The mean + SD pharmacokinetic parameters for this study have already been presented (see Table 5).

Fig. 9. Typical Plots of Individual Subject Pantoprazole Serum Concentration Versus Time Following a Single Oral Dose 40 mg of Phase III Clinical Study Formulation or the 2 x 20 mg Phase IIb Formulation in 36 Normal Subjects

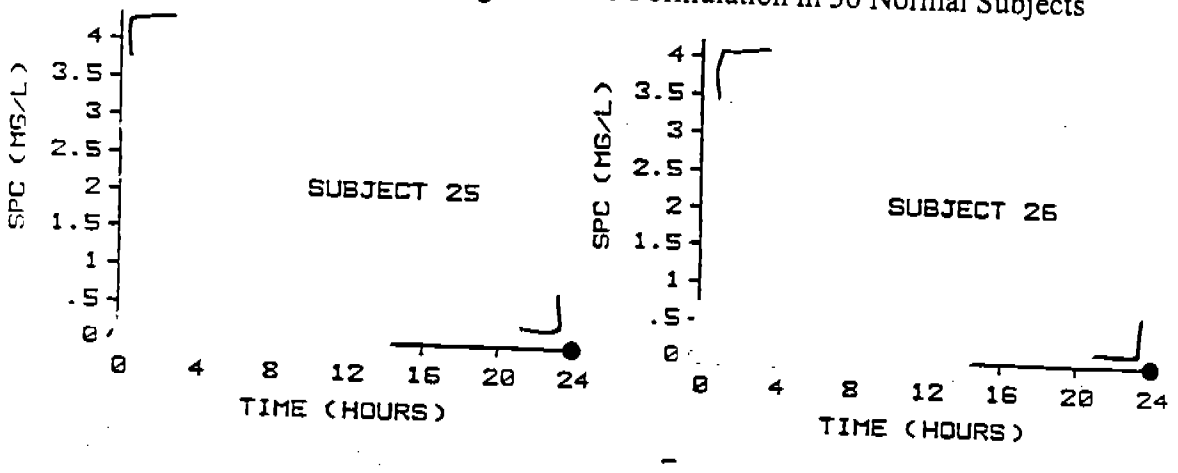


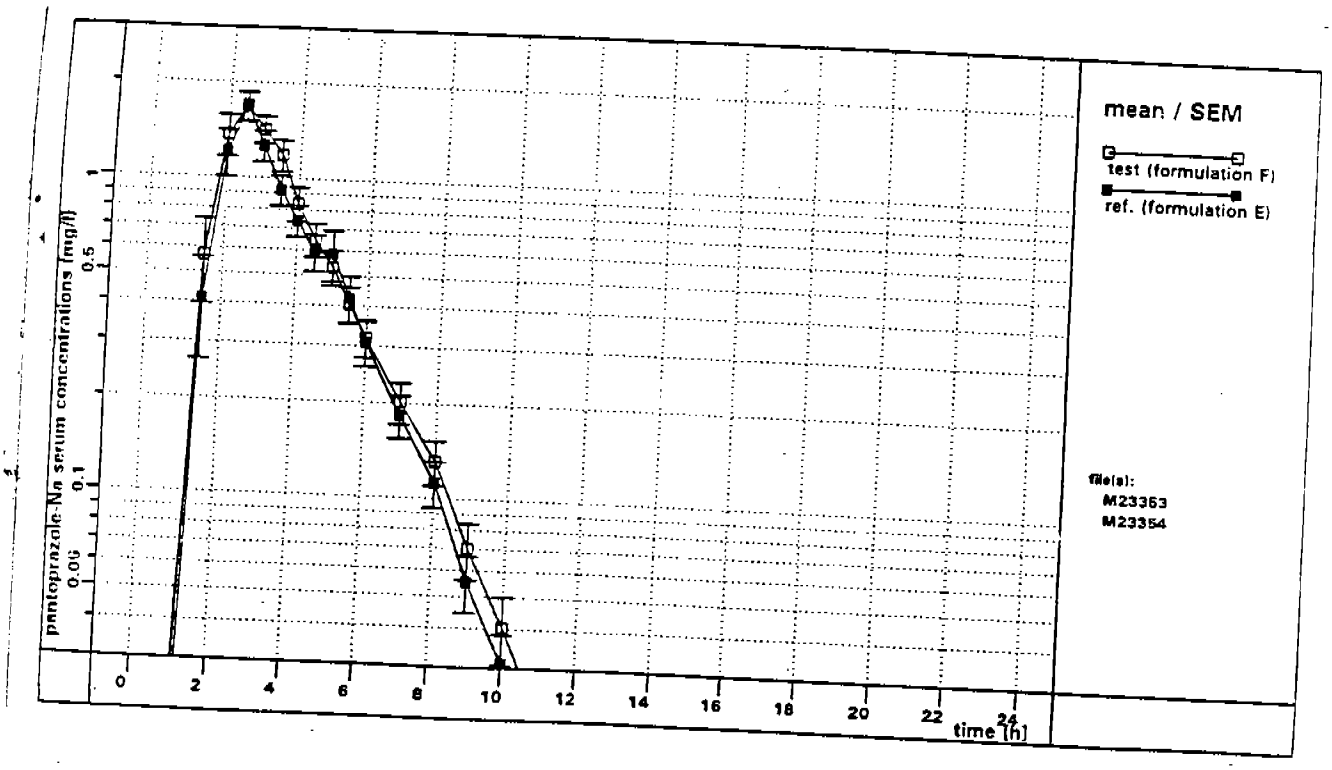
Table 8. Assessment of Bioequivalence Phase III clinically Tested Formulation and the Phase IIb Clinically Study Formulation

Pantoprazole a single oral dose of 40 mg in each period Pharmacokinetic Characteristic	Reference: 40 mg tablet (Phase III form.) Geometric mean, n = 36 (exp(mean(ln) ± sd(ln))	Test: 2 x 20 mg tablets in a capsule (Phase IIb form.) Geometric mean, n = 36 (exp(mean(ln) ± sd(ln))	Bioequivalence ratio (Test/Reference) Point estimate after logarithmic transformation	Bioequivalence ratio (Test/Reference) 90%-confidence interval after logarithmic transformation
AUC(0,∞) (mg/l h)	4.22 (2.43, 7.32)	4.14 (2.44, 7.04)	0.98	0.94, 1.02
Cmax (mg/l)	2.31 (1.70, 3.15)	2.20 (1.65, 2.94)	0.95	0.89, 1.01
Half-life (h)	1.28 (0.85, 1.92)	1.27 (0.82, 1.96)	0.99	0.96, 1.03

The bioequivalence of the test formulation (Formulation B) and the reference formulation (Formulation C) was assessed using the Two One-sided Test Procedure for the 90% confidence limits. The ratios (test/reference) of the mean log transformed Cmax and AUC were within the interval of 0.80-1.25 that is required for bioequivalence (Table 8). Therefore, the bioequivalence of the Phase IIb 2x20 mg enteric coated pantoprazole tablets and the 40 mg enteric coated pantoprazole that was used in the Phase III clinical safety and efficacy studies has been demonstrated.

(c) **Bioequivalence of a New Formulation and the To-be-marketed Formulation:** The bioequivalence of new enteric coated 40 mg pantoprazole tablet formulation (Formulation F: test) and the to-be-marketed enteric coated 40 mg pantoprazole tablet formulation (Formulation E: reference) was assessed in 36 healthy male subjects (Byk Gulden Protocol #FHP041, GMR-31756). Plots of the mean ± SEM plots of serum concentration of pantoprazole versus time for both formulations are presented in Fig.10. The mean ± SD pharmacokinetic parameters for this study have already been presented (see Table 5).

Fig. 10. Plots of Mean ± SEM Pantoprazole Serum Concentration Versus Time Following a Single Oral Dose 40 mg of a Enteric Formulation or the Proposed Enteric Coated Market Formulation in 36 Normal Subjects



The bioequivalence of the test formulation (Formulation F) and the reference formulation (Formulation E) was assessed using the Two One-sided Test Procedure for the 90% confidence limits. The ratios (test/reference) of the mean log transformed AUC and Cmax were within the interval of 0.80-1.25 that is required for bioequivalence (Table 9).

Table 9. Assessment of Bioequivalence Phase III Clinical Study Formulation and the Phase IIb Clinical Study Formulation

Pharmacokinetic characteristic of pantoprazole-Na	Reference: geometric mean (N=36) (68%-range)	Test: geometric mean (N=36) (68%-range)	Equivalence ratio (Test/Reference) Point estimate (90% confidence interval)
AUC (mgxh/l)	4.11	4.51	1.10 (1.03, 1.16)
C_{max}/AUC (1/h)	0.577	0.516	0.89 (0.83, 0.96)
$t_{1/2}$ (h)	1.18	1.26	1.07 (1.02, 1.12)
C_{max} (mg/l)	2.37	2.33	0.98 (0.90, 1.07)

The ratio (test/reference) of the mean values of log transformed Cmax/AUC, which the sponsor also used as an indicator of bioequivalence was within the interval of 0.80-1.25. Therefore, the bioequivalence of the new enteric coated 40 mg pantoprazole tablet formulation (Formulation F) and the to-be-marketed enteric coated 40 mg pantoprazole tablet formulation (Formulation E) has been demonstrated.

4. METABOLISM:

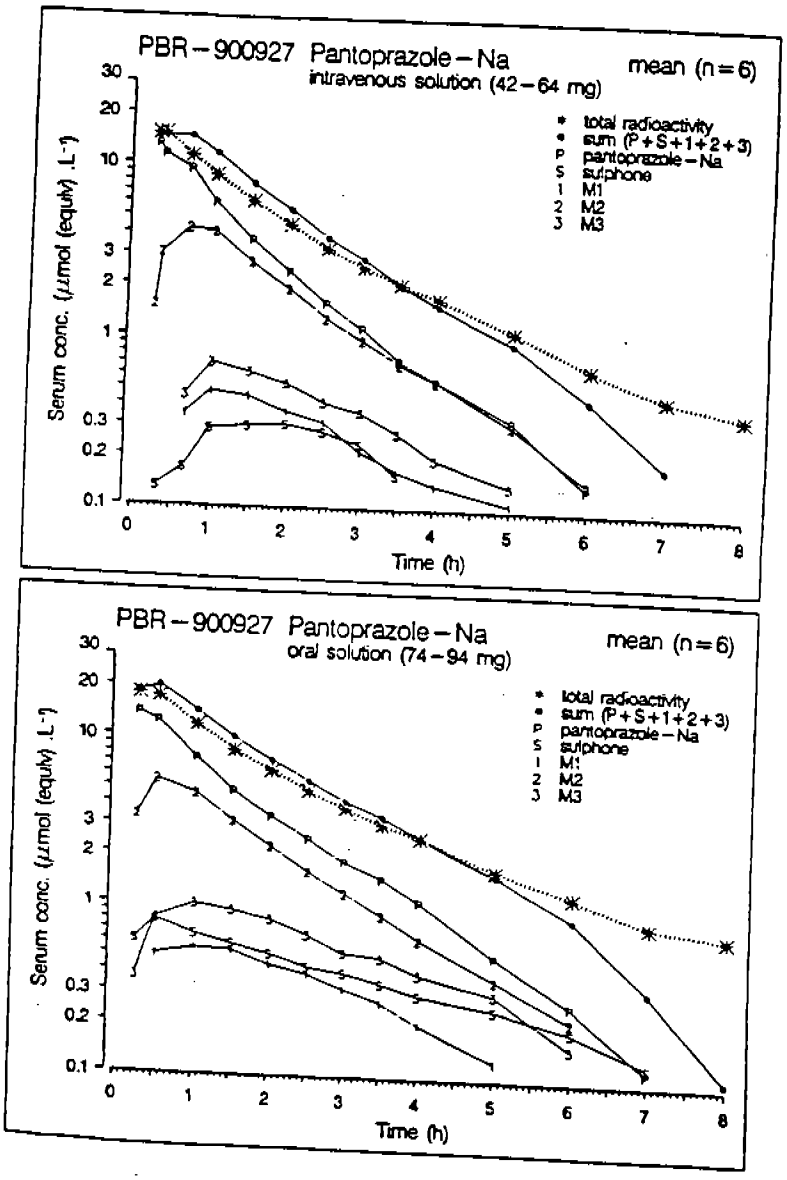
(a) **Metabolic Pathways**: The metabolism of pantoprazole was evaluated in 6 healthy male volunteers who received a single 60 mg dose of the ^{14}C-labeled drug (37.5 uCi) as an intravenous injection over 15 min and a single 80 mg dose of the labeled drug (50 uCi) as an oral solution in a crossover fashion (Byk Gudlden Protocol #FHP018E, GMR-29693). The main pathways of pantoprazole metabolism are presented in Fig. 11.

Fig. 11. Pathways of Pantoprazole Metabolism

Three primary metabolic pathways were identified: (a) demethylation by CYP2C19 with subsequent sulfate conjugation to a p-O-desmethyl-O-sulfate derivative designated as M2, (b) oxidation by CYP3A4 to a sulfone and (c) reduction at the sulfur atom and demethylation to a p-O-desmethyl-sulfide derivative designated as M3-deconjugate, a portion of which undergoes sulfate conjugation to a p-O-desmethyl-O-sulfate sulfide derivative designated as M3, as well as glucuronic acid conjugation to a p-O-desmethyl-O-glucuronyl sulphide derivative designated as M4. M2 is further oxidized by CYP3A4 to a p-O-desmethyl-O-sulfate sulphone derivative designated as M1. The sulfone metabolite is demethylated by CYP2C19 with subsequent sulfate conjugation aiso to M1. The sponsor states that CYP2C9 and CYP2D do play minor roles in pantoprazole metabolism. However, the metabolic pathways mediated by these two isozymes have not been specified.

An unidentified metabolite, designated as MX, was also formed from pantoprazole. In this study, the sulfone metabolite was not detected in urine whereas M4 and MX were not detected in serum. Plots of the serum concentration of pantoprazole and its main metabolites are presented in Fig. 12.

Fig 12. Plots of Mean Serum Concentrations of Total Radioactivity, Pantoprazole and its Metabolites Following Administration of ^{14}C-labeled Pantoprazole as an Intravenous Injection (60 mg) and as an Oral Solution (80 mg) in Six Normal Subjects



The serum concentrations of pantoprazole metabolites were in the order of M2 > > M3 (in all forms) > M1 > sulfone following intravenous infusion and M2 > > M3 (in all forms) > sulfone > M1 following oral solution administration .

Pantoprazole was eliminated mainly in urine, as its metabolites, and to a minor extent in feces. No unmetabolized pantoprazole was excreted in urine The mean cumulative percentages of the administered doses ultimately eliminated in urine and feces, were, respectively, 70.9% and 18.5% for the intravenous dose and 72.4% and 18.45% for the dose of oral solution (Table 10).

Table 10. Renal and Fecal Excretion of Total Radioactivity Following Administration of ^{14}C-labeled Pantoprazole as an Intravenous Solution (60 mg) and as an Oral Solution (80 mg) in Six Normal subjects

Characteristic		Mean	SD	Median	Range
A^e_{urine}	i.v.	70.9	7.6	68.7	
(% of actual dose)	oral	72.4	6.4	74.8	
A^e_{faeces}	i.v.	18.5	4.8	19.2	
(% of actual dose)	oral	18.4	6.3	15.0	
A^e_{total}	i.v.	89.4	5.1	91.2	
(% of actual dose)	oral	90.7	1.4	90.8	

The mean cumulative renal excretion was 29.3% of the intravenous dose versus 37.7% of the oral dose at 8 h postdose and 37.9% for the intravenous dose versus 46.1% for the oral dose at 24 h postdose. The higher cumulative metabolite values for the oral route at 8 and 24 hours postdose is likely to be related to pre-systemic metabolism. At 24 h postdose pantoprazole metabolites ultimately excreted in urine were in the following order of M2 > > M3-decongugate > M1 > M4 = MX > M3 for the intravenous dose and M2 > > M3-deconjugate > M1 > M4 > MX > M3 for the oral dose. Based on these findings, M2 is the major metabolite of pantoprazole and CYP2C19 is the predominant isozyme for its metabolism. The roles of the other isozymes (CYPs 3A4, 2C9 and 2D6) are relatively minor.

CYP2C19 exhibits a genetic polymorphism and is deficient in some individuals (e.g., 3-5% of Caucasians and 15-20% of Indians). It is expected that some patients (those deficient in this isozyme) would be poor metabolizers of pantoprazole as compared to those with normal amounts of the isozyme (normal metabolizers) who would metabolize the drug more efficiently. This would result in pantoprazole kinetic differences between these two sub-populations.

In a study evaluating the kinetics of a 50:50, racemate of pantoprazole in poor metabolizers ($n=4$), the mean elimination half-lives of the unresolved pantoprazole and

the (+)- and (-)- enantiomers, were 5.4 h, 8.0 h and 3.0 h, respectively (Byk Gulden Report 227/92; GMR-30131 [see Item 5 below]). Furthermore, 2-3 half-lives following dose administration, 80-90% of pantoprazole in the serum was in the form of the (+)-enantiomer in these subjects. These findings suggest that only the metabolism of the (+)- enantiomer of pantoprazole is significantly affected by the genetic polymorphism exhibited by CYP2C19.

(b) **Metabolite Kinetics**: The pharmacokinetic parameters of pantoprazole, M2 and the sum of pantoprazole and its serum metabolites following an intravenous dose of 60 mg and an oral dose of 80 mg in normal volunteers are presented in Table 11.

Table 11. Pharmacokinetic Parameters of Pantoprazole and Metabolites Following Administration of ^{14}C-labeled Pantoprazole as an Intravenous Solution (60 mg) and as an Oral Solution (80 mg) in Six Normal subjects

Characteristic		Mean	SD	Median	Range
PANTOPRAZOLE					
C_{max} ($\mu mol.L^{-1}$)	oral	14.25	1.50	13.88	
t_{max} (h)	oral			0.25	
AUC_{0-inf} ($\mu mol.h.L^{-1}$)	i.v. oral	16.15 20.96	2.95 8.05	16.00 17.00	
$t_{½}$ (h)	i.v. oral	0.89 1.07	0.25 0.16	0.88 1.05	
Cl ($L.h^{-1}.kg^{-1}$)	i.v.	0.123	0.021	0.119	
$V_{d_{area}}$ ($L.kg^{-1}$)	i.v.	0.152	0.026	0.152	
METABOLITE M2					
C_{max} ($\mu moleq.L^{-1}$)	i.v. oral	4.29 5.53	0.98 0.81	4.54 5.41	
t_{max} (h)	i.v. oral			0.67 0.50	
AUC_{0-inf} ($\mu moleq.h.L^{-1}$)	i.v. oral	8.95 11.24	1.69 1.74	9.12 11.48	
$t_{½}$ (h)	i.v. oral	1.20 1.18	0.24 0.17	1.20 1.08	
SUM OF PANTOPRAZOLE AND METABOLITES					
C_{max} ($\mu moleq.L^{-1}$)	oral	20.34	2.36	20.19	
t_{max} (h)	oral			0.50	
AUC_{0-inf} ($\mu moleq.h.L^{-1}$)	i.v. oral	29.41 40.53	5.48 10.38	30.61 37.20	
$t_{½}$ (h)	i.v. oral	1.04 1.28	0.30 0.20	1.02 1.21	

Like the parent drug, the metabolites of pantoprazole are rapidly cleared from the serum.

(c) **Confirmation of Metabolic Pathways**: In *in vitro* studies with human liver microsomes, pantoprazole metabolism was significantly inhibited by ketoconazole, quinidine and sulfaphenazole, confirming the participation of CYP3A4 and/or CYP2C19, CYP2D6 and CYP2C9, respectively, in the metabolic process (Byk Gulden Protocol 120/96; GTR 31216). Lower rates of pantoprazole metabolism were observed for CYP2C19 poor metabolizers and CYP3A4 medium metabolizers but not for CYP2D6 poor metabolizers. These findings confirm the participation of CYP2C19 in pantoprazole and suggests this isozyme (CYP2C19) and/or CYP3A4 to be the major isozyme(s) responsible for pantoprazole metabolism. The results of the above *in vivo* metabolism study (Byk Gudlden Protocol #FHP018E, GMR-29693) indicates that CYP2C19 is the major isozyme responsible for the metabolism of the drug.

5. PHARMACOKINETICS OF PANTOPRAZOLE ENANTIOMERS: Pantoprazole is a racemic compound with the center of optical activity at the sulfur atom. In the NDA, it is stated the pharmacologic activities of its enantiomers are "indistinguishable. However, toxicology studies in animals have shown that the (-)-enantiomer is more toxic than the (+)-enantiomer and that only the (+)-enentiomer converts to the (-)-enantiomer. The kinetics of the (+)- and (-)-enantiomers was evaluated in (i) 8 extensive metabolizers (selected from Protocol HFP016) receiving a single 80 mg dose of pantoprazole by intravenous bolus injection, (ii) 9 extensive metabolizers (selected from Protocol FHP014) receiving a single 40 mg (2x20 mg enteric coated tablets) oral dose and (iii) one poor metabolizer (Subject 1 from Protocol HFP006, pantoprazole $t_{1/2}$=6.4 h) receiving a single 30 mg dose by intravenous bolus injection and three poor metabolizers (Subject 22 from HFP014 with pantoprazole $t_{1/2}$=6.3 h and Subjects 9 and 12 from Protocol FHP017 with pantoprazole $t_{1/2}$ values of 4.2 h and 4.6 h, respectively) each receiving a single oral dose of the enteric coated 40 mg tablet (Byk Gulden Report 227/92; GMR-30131). Mean plots were not provided. Typical individual subject plots of serum concentration versus time for the racemic (±) [unresolved] pantoprazole and its (+)- and (-)-enantiomers are presented in Figs. 13-16 for these subject groups. The mean ± SD pharmacokinetic parameters of these moieties in these sub-populations are presented in Table 12. IV, PO, NM and EM, represent intravenous administration, oral administration, normal metabolizer and poor metabolizer, respectively.

Fig 13. Typical Individual Subject Plots of Serum Concentrations of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Intravenous Administration of 80 mg Racemic Pantropazole in Normal Metabolizers

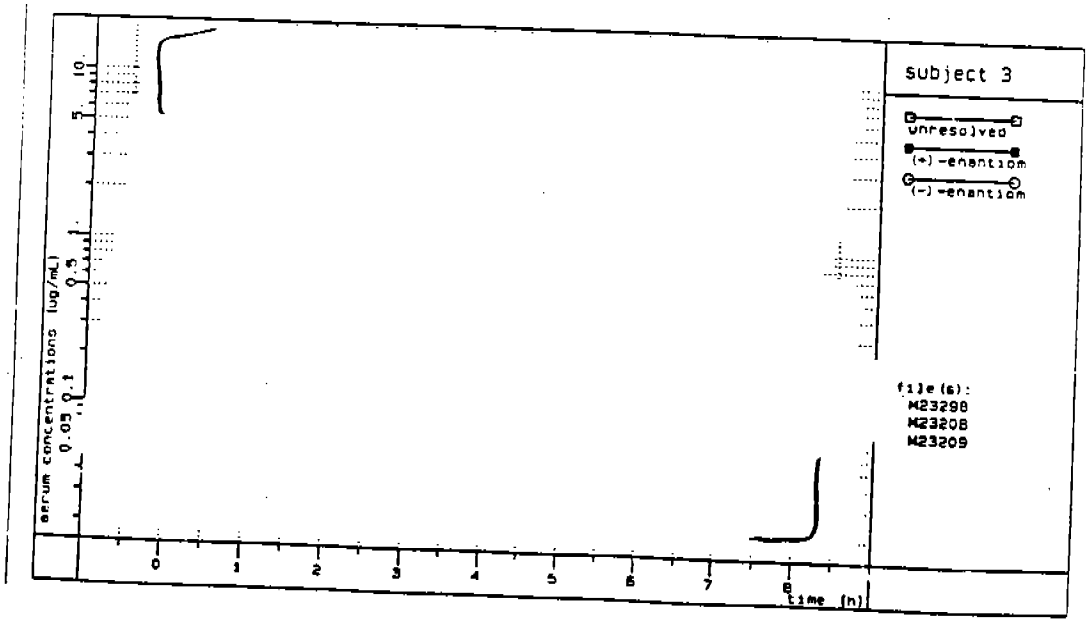


Fig 14. Typical Individual Subject Plots of Serum Concentrations of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Oral Administration of 40 mg Racemic Pantropazole in Normal Metabolizers

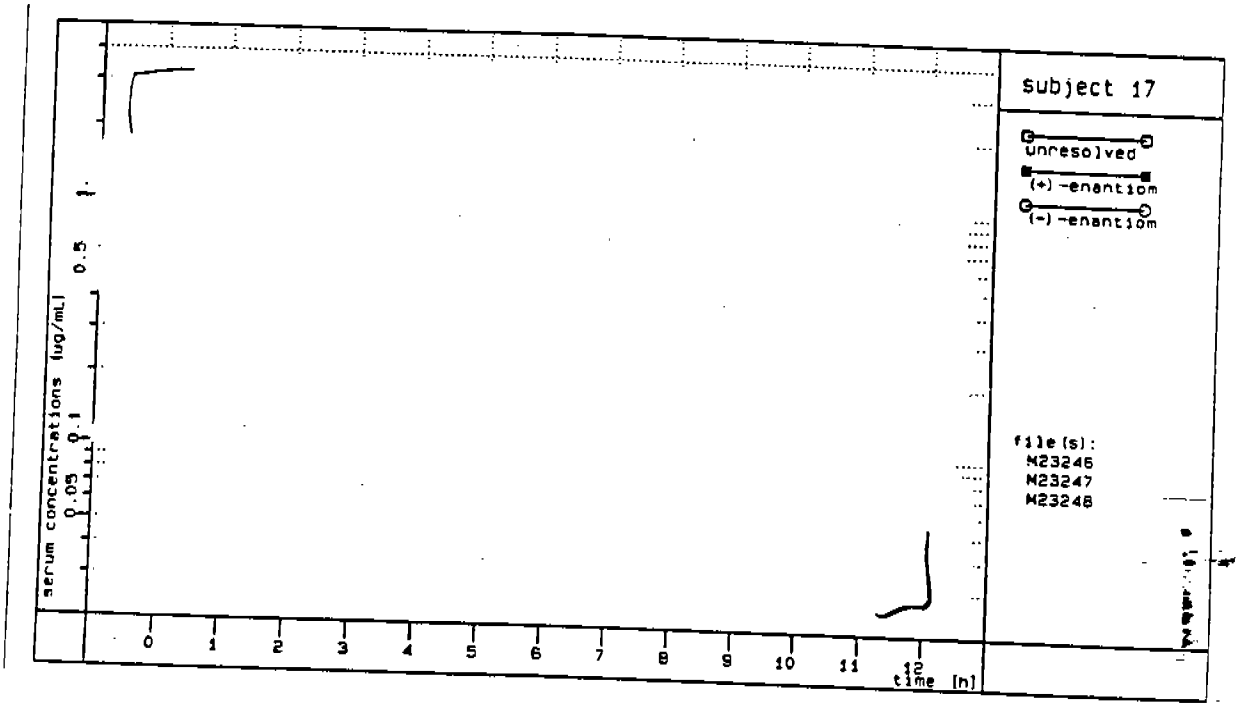


Fig 15. Typical Individual Subject Plots of Serum Concentrations of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Intravenous Administration of 30 mg Racemic Pantropazole in Poor Metabolizers

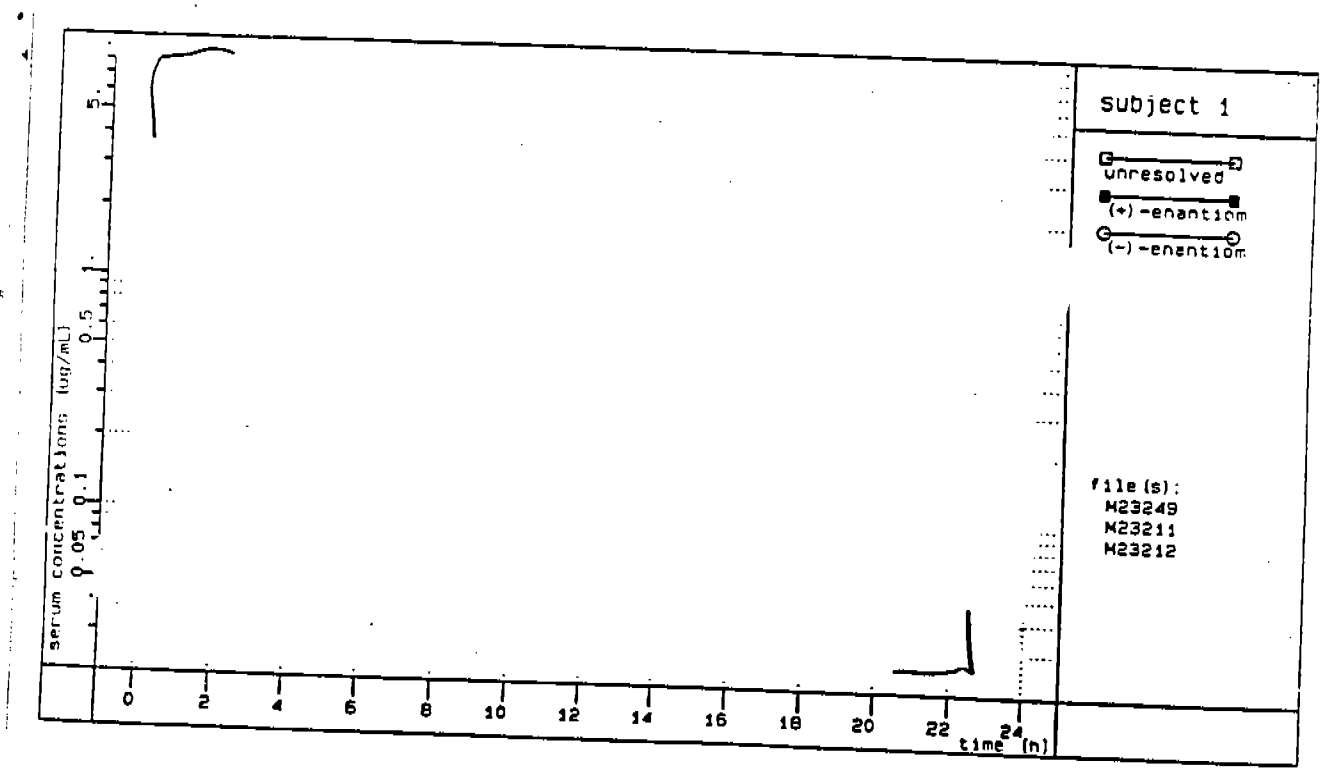


Fig 16. Typical Individual Subject Plots of Serum Concentrations of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Oral Administration of 40 mg Racemic Pantropazole in Poor Metabolizers

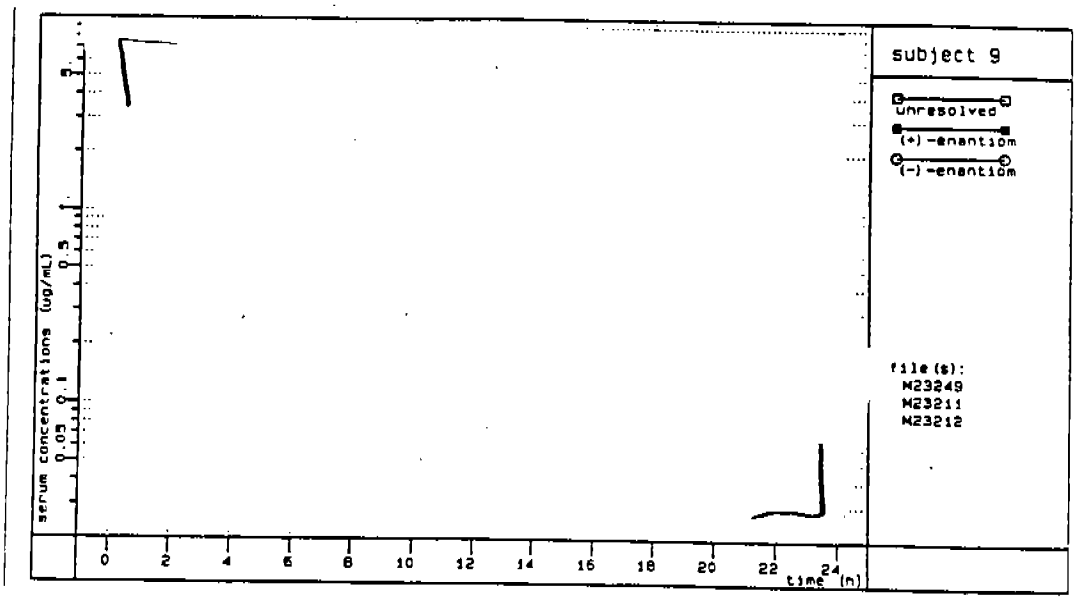


Table 12. Pharmacokinetic Parameters of Racemic Pantoprazole and its (+)- and (-)-Enantiomers Following Intravenous and Oral Administration in Normal Metabolizers and Poor Metabolizers

Moiety	n	Dose (mg)	C_{max} (mg/L)	t_{max} (h)	t_{max} (h)	AUC ([mg/L]h)	$t_{1/2}$ (h)	Cl_T (L/h)	V_d (L)
±	8(EM)	80(IV)	—	—	—	9.3±3.8	1.2±0.6	10.0±4.1	17.5±12.4
(+)-	8(EM)	—	—	—	—	4.3±2.0	0.9±0.5	22.3± 10.0	28.7±21.4
(-)-	8(EM)	—	—	—1	—	4.8± 3.2	1.1±0.5	19.4±8.2	29.4±22.9
±	9(EM)	40(PO)	2.7+1.1	—	2.4+1.1	5.8±3.0	1.3±0.3	—	—
(+)-	9(EM)	—	1.4+0.5	—	2.8+1.0	3.1±1.8	1.0±0.5	—	—
(-)-	9(EM)	—	1.4+1.1	—1	2.4+1.1	3.1± 1.4	1.1±0.4	—	—

In extensive metabolizers, regardless of the route of administration (intravenous or oral), the elimination of the (+)-enantiomer ie essentially the same as the (-)-enantiomer but in general, the pharmacokinetic parameters of both species were comparable. In poor metabolizers, the elimination half-life for the (+)- enantiomer more than doubled and its AUC (where determined) more than tripled the values for the (-)-enantiomer. In three of the four poor metabolizers, the elimination half-life values for the (-)-enantiomer (2.5-2.8 h) were within the range ($\leq$ 3.5 h) specified in the NDA for extensive metabolizers of pantoprazole. The value for the remaining one subject (3.9 h) was close to this range. It was further noted that in the serum of extensive metabolizers, the percentage of pantoprazole in the form of the (+)-enantiomer generally decreased with time and was less than 50% of total pantoprazole by 7 h postdose regardles of the route of administration (Figs. 17 and 18). The reverse was true of poor metabolites, with the percentage of pantoprazole in the form of the (+)-enantiomer being approximately 80-90% of total pantoprazole in serum in the interval of 12-24 h postdose (Fig. 19).

Fig. 17. Percentage of (+)-Enantiomer in Serum Following Intravenous Administration of 80 mg Racemic Pantoprazole in Extensive Metabolizers

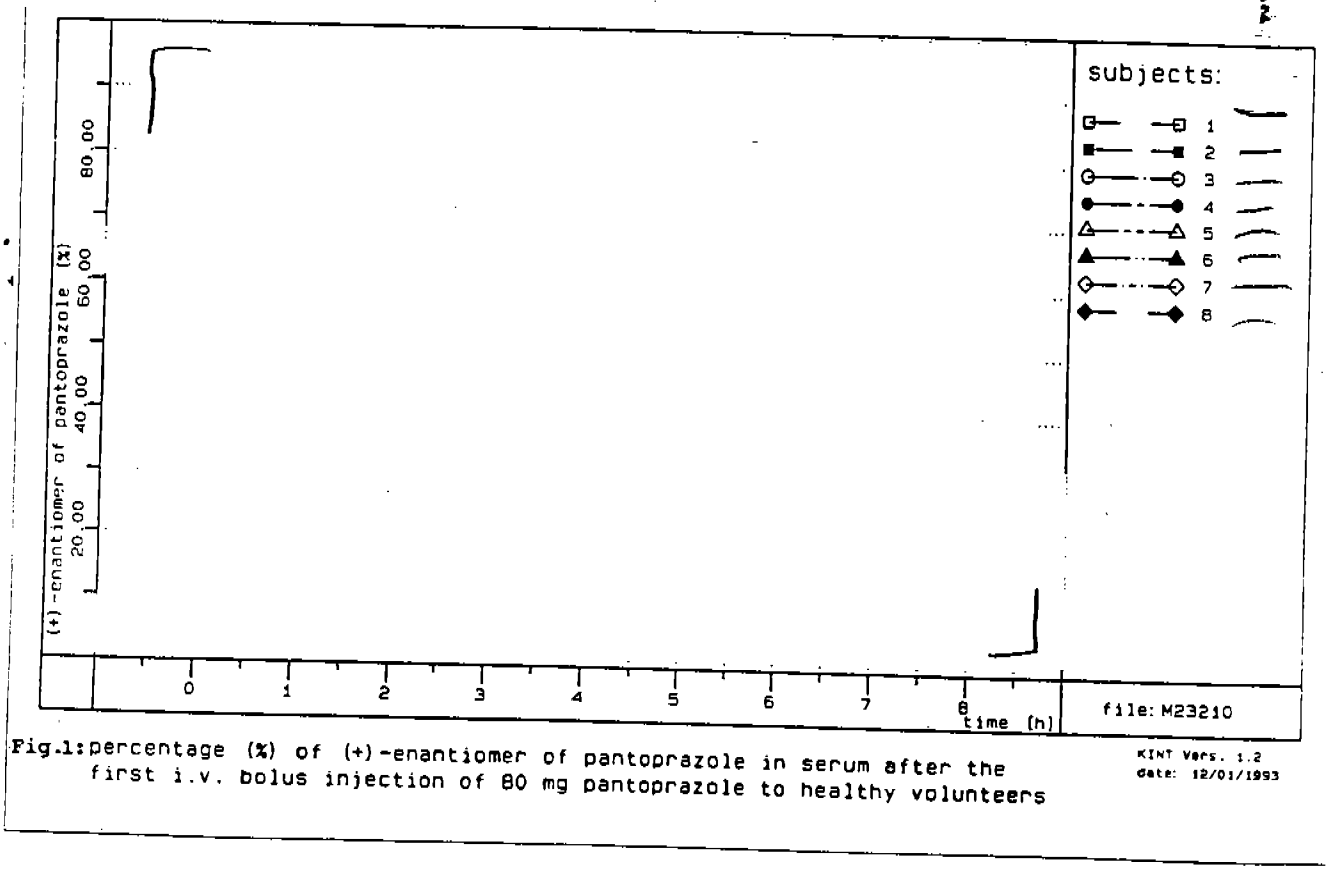


Fig.1: percentage (%) of (+)-enantiomer of pantoprazole in serum after the first i.v. bolus injection of 80 mg pantoprazole to healthy volunteers

Fig. 18. Percentage of (+)-Enantiomer in Serum Following Intravenous Administration of 40 mg Racemic Pantoprazole in Extensive Metabolizers

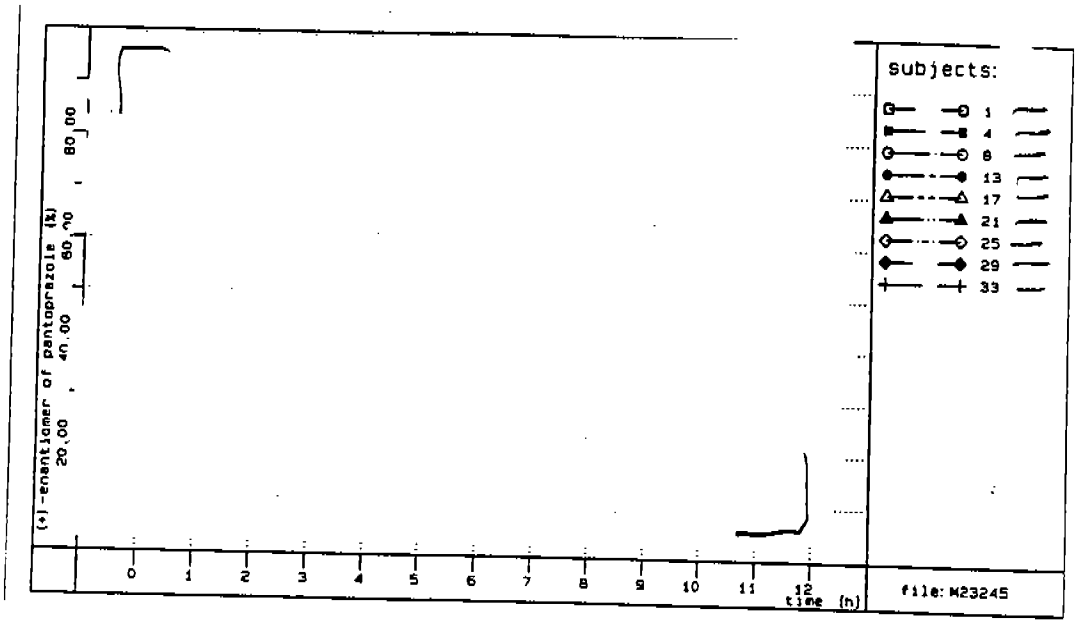
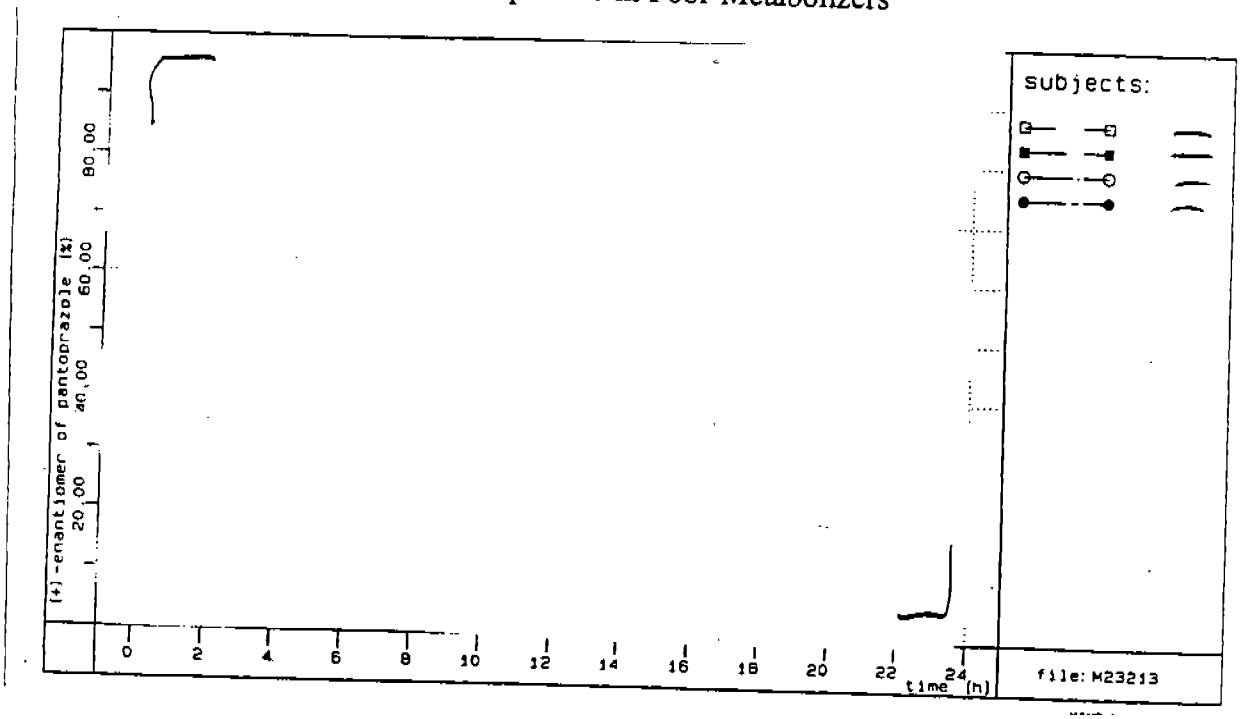


Fig. 19. Percentage of (+)-Enantiomer in Serum Following Intravenous 30 mg and Oral 40 mg Racemic Pantoprazole in Poor Metabolizers



These findings suggest that only the metabolism of the (+)-isomer of pantoprazole is significantly affected by the genetic polymorphism exhibited by CYP2C19, the major isozyme for pantoprazole metabolism.

6. PRE-SYSTEMIC ELIMINATION: In a crossover study of intravenous and oral solution doses of ^{14}C-pantoprazole in six healthy volunteers (Byk Gudlden Protocol #FHP018E, GMR-29693), the absolute bioavailability of pantoprazole for the oral solution was 81% whereas 96% of the dose was absorbed. It is reasonable to infer that the difference in the absorbed and bioavailable amounts (15% of the oral dose) is due pre-systemic metabolism. The higher amounts of pantoprazole metabolites at 8 and 24 h postdose for the oral dose as compared to the intravenous dose (see item 4 [page 19]) also suggests the occurrence of pre-systemic metabolism.

7. BINDING TO ERYTHROCYTES: In the above crossover study of intravenous and oral solution doses of ^{14}C- pantoprazole in six healthy volunteers (Byk Gudlden Protocol #FHP018E, GMR-29693), the geometric mean $\pm$ SD ratio ($AUC_{serum}/AUC_{whole\ blood}$) of total radioactivity was high (1.66 ± 0.66 for oral solution and 1.59 ± 0.15 intravenous administration). These results suggest that erythocyte binding or penetration of pantoprazole is minimal to negligible as compared to it binding to serum components. These findings are supported by the 98% binding to serum components determined in the serum protein binding studies (see item 8).

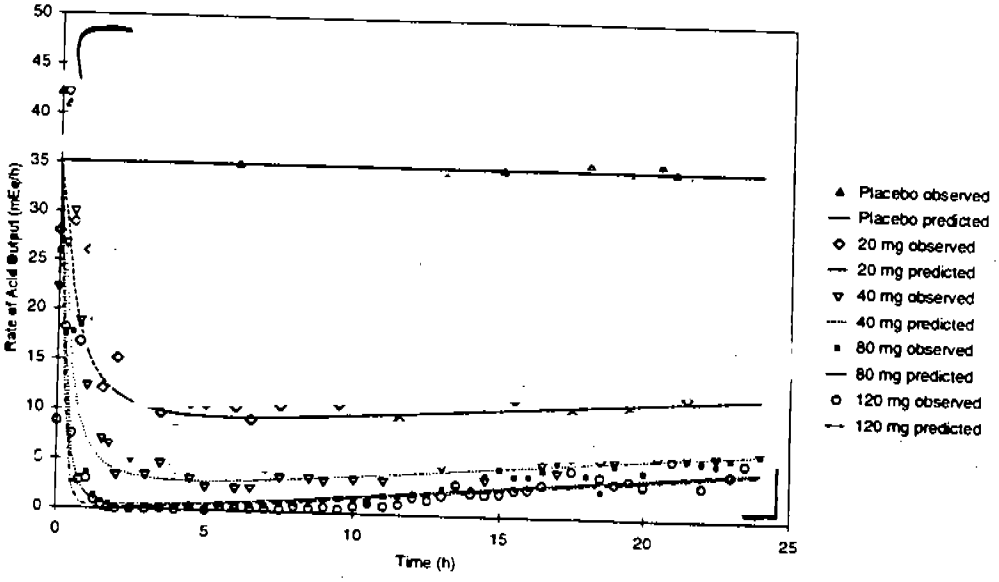
8. SERUM PROTEIN BINDING: The serum protein binding of pantoprazole was determined (i) in serum obtained from five healthy male subjects injrcted with ^{14}C-labeled pantoprazole (^{14}C-pantoprazole), (ii) in 3.5% human albumin and (iii) in 0.2% alpha1-acid glycoprotein at pantoprazole concentrations ranging from 0.23 ug/mL to 100.23 um/mL. The method of equilibrium dialysis was utilized (Byk Gulden #RZ93002/BY1023). Pantoprazole was 97% bound to serum proteins at all concentrations tested, 94% bound to serum albumin in the concentration range of 0.23 - 20.23 um/mL and 91% bound to serum albumin at a concentration of 100.23 ug/mL. Pantoprazole binding to $alpha_1$-glycoprotein (64%, 50%, 31% and 15% at concentrations of 0.23, 2.23, 20.23 and 100.23%, respectively) was drug concentration dependent. These results suggest the presence of multiple pantoprazole binding sites on $alpha_1$-glycoprotein. *In vitro* study of pantoprazole binding to human serum proteins by the method of equilibrium dialysis was estimated in two other studies, Byk Gulden Report #244E/88 (five pantoprazole concentrations in the range of 0.9-9.8 umol per liter) and Byk Gulden Report #90E/96 (pantoprazole concentrations of 0.5 and 3.0 ug/mL) . In both studies pantoprazole was 98% bound to human serum proteins. Pantoprazole was also 98% bound to serum proteins of renally impaired patients receiving a single dose of the 40 mg enteric coated tablet (Byk Gulden Protocol FHP023).

Based on these findings, (i) pantoprazole is highly bound to human serum proteins, (ii) the primary serum binding protein is serum albumin and (iii) $alpha_1$-glycoprotein plays only a minor role in the binding of pantoprazole and may have multiple binding sites for it.

9. PHARMACODYNAMICS: Pantoprazole is a non-competitive inhibitor of the proton pump which suppresses the final step in gastric acid secretion by binding covalently to the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell.

10. PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) RELATIONS: The relationship between the pharmacokinetics and pharmacodynamics of pantoprazole was evaluated for the 0 (placebo), 20, 40, 80 and 120 mg doses of pantoprazole administered by intravenous infusion, over 15 min, to normal subjects in whom gastric acid secretion was induced using pentagastrin (Protocol 3001k1-100-US). The irreversible effect pharmacodynamic model was utilized. Since drug concentrations were not measured in this study, the pantoprazole concentrations obtained for the 20, 40 and 80 mg doses in another study (Byk Gulden Protocol FHP003) and those predicted for the 120 mg dose using the data from Byk Gulden Protocol FHP003 (assuming dose proportionality in the pantoprazole dose range of 20-120 mg) were used to build the model The results are presented in Fig. 20.

Fig. 20. Pharmacodynamic Profile of Pantoprazole



In Byk Gulden Protocol FHP003, dose proportionality of Cmax and AUC for single dose administration was demonstrated for the dose range of 20-80 mg. The 120 mg dose was not evaluated. Therefore, in this review, the assumption of dose proportionality in the dose range of 20-120 mg is not considered to be tenable. Accordingly, the data for the 120 mg dose is not considered in discussing the results.

The 20 mg and 40 mg doses of intravenous pantoprazole reduced pentagastrin induced gastric acid output from the placebo value of 35 MEq/h to approximately 10 mEq/h and 2.5 mEq/h, respectively. With the 80 mg dose, pentagastrin induced acid secretion

was completely eliminated within 2 h of dosing. In this study, pantoprazole reduced pentagastrin induced acid secretion in a dose dependent fashion.

The effect of pantoprazole on gastric acid reduction lasts about 24 h which supports the dosing interval of 24 h.

In a placebo controlled, clinical efficacy trial that used enteric coated pantoprazole tablets at doses of 20, 40 and 80 mg, the median intragastric pH values for the 40 and 80 mg doses were similar but were significantly lower than the values for the 20 mg dose (Table 13). These findings suggest that the 80 mg dose would have no significant therapeutic advantage over the 40 mg dose, which was ultimately selected for marketing.

Table 13. Effects of Single 20, 40 and 80 mg Doses of Pantoprazole On Intragastric pH as Compared to Placebo

	Median pH			
Time	placebo	20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.9*	3.8*#	3.9*#
8 a.m. - 10 p.m. (Daytime)	1.6	3.2*	4.4*#	4.8*#
10 p.m. - 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo
\# Significantly different from 20 mg

11. EFFICACY END POINT: HEALING OF EROSIVE ESOPHAGITIS ASSOCIATED WITH REFLUX DISEASE (GERD): The rate of GERD healing was assessed at the end of 4 and 8 weeks of treatment in 541 patients receiving the enteric coated 10, 20 and 40 mg pantoprazole tablets for 8 weeks in a placebo controlled efficacy trial (n=68, 153, 158 and 162 for placebo, 10, 20 and 40 mg doses, respectively). The healing rates for 4 and 8 weeks of treatment are presented in Table 14.

Table 14. Erosive Esophagitis Healing Rates for Oral 10, 20 and 40 mg Oral Pantoprazole Treatment of Patients with GERD as Compared to Placebo

Erosive Esophagitis Healing Rates				
	PROTONIX			Placebo
Week	10 mg QD (n = 153)	20 mg QD (n = 158)	40 mg QD (n = 162)	(n =68)
4	45.6%+*	58.4%+#	75.0%+*	14.3%
8	66.0%+*	83.5 %+#	92.6%+*	39.7%

+($p < 0.001$) PROTONIX versus placebo.
*($p < 0.05$) versus 10 mg. or 20 mg PROTONIX
#($p < 0.05$) versus 10 mg PROTONIX

For the evaluated dose range of pantoprazole, erosive esophagitis healing rate increased significantly with increasing pantoprazole dose. The healing rate for the 40 mg dose was considered optimal.