	40 mg	20 mg
PRIMARY	$MAO_{LI.V.}$ vs MAO_{LPO}	$MAO_{LI.V.}$ vs MAO_{LPO}
	$MAO_{FI.V.}$ vs MAO_{LPO} $MAO_{LI.V.}$ vs $MAO_{FI.V.}$	$MAO_{FI.V.}$ vs MAO_{LPO} $MAO_{LI.V.}$ vs $MAO_{FI.V.}$
SECONDARY	$BAO_{LI.V.}$ vs BAO_{LPO}	$BAO_{LI.V.}$ vs BAO_{LPO}
	$BAO_{FI.V.}$ vs BAO_{LPO} $BAO_{LI.V.}$ vs $BAO_{FI.V.}$	$BAO_{FI.V.}$ vs BAO_{LPO} $BAO_{LI.V.}$ vs $BAO_{FI.V.}$

1) Results with 40 mg PANTO

i) $MAO_{LI.V.}$ vs MAO_{LPO} (Table 6)

- The data summarized in this Table show equivalence of the I.V. Day 7 and last day oral MAO. In all three analysis populations (ITT, MITT, and VFE) the quivalence of the $MAO_{LI.V.}$ and the MAO_{LPO} was established since the hypothesis that they differed by more than 20% was rejected [p-values for the signed-rank test for the ITT, MITT and VFE were **0.004, 0.009** and **0.006,** respectively].

- The mean $MAO_{LI.V.}$ was 6.62 mEq/h compared to 6.49 mEq/h for the MAO_{LPO}. By contrast, the mean $MAO_{LI.V.}$ with I.V. placebo was 29.19 mEq/h.

ii) $MAO_{FI.V.}$ vs MAO_{LPO} (Table 7)

- The data summarized in this Table show that equivalence between MAO after one day of I.V. dosing and after oral therapy was not demonstrated with statistical significance for the 40 mg dose level. This lack of equivalence was shown regardless of the study population analyzed or the statistical test used to assess significance.

- The mean $MAO_{FI.V.}$ was 8.53 mEq/h compared to 6.49 mEq/h for the MAO_{LPO}. By contrast, the mean MAO with I.V. placebo was 14.24 mEq/h.

TABLE 6

Study 3001K1-309-US

PRIMARY EFFICACY ENDPOINT: Comparison of the mean MAO following the last dose of I.V. PANTO with that after the last oral dose of PANTO [$MAO_{LI.V.} - 1.2\ MAO_{LPO}$] for the 40 mg PANTO Treatment Groups

Study Population Analyzed →	**ITT**			**M-ITT**			**VFE**		
	I.V. PANTO		I.V. PL	I.V. PANTO		I.V. PL	I.V. PANTO		I.V. PL
Last Day Oral MAO_{LPO}		6.49±5.62 (0.0-20.3) [N=30]			6.32±5.87 (0.0-20.3) [n=26]			6.56±5.84 (0.0-20.3) [n=25]	
Last Day I.V. $MAO_{LI.V.}$	6.62±6.34 (0.0-23.1) [N=23]		29.19±13.01 (6.9-48.7) [N=7]	6.22±6.42 (0.0-23.1) [n=21]		27.44±15.50 (6.9-48.7) [N=5]	6.48±6.47 (0.0-23.1) [n=20]		27.44±15.50 (6.9-48.7) [N=5]
STATISTICS [p-values for testing $MAO_{LI.V.}$ inferior to MAO_{LPO} by 20% or more]									
Stat. Test →	t Test	Sign Test	Signed-Rank Test	t Test	Sign Test	Signed-Rank Test	t Test	Sign Test	Signed-Rank Test
p-value	0.008075	0.01330	0.004009	0.011651	0.00961	0.009041	0.009044	0.00377	0.006016

Reviewer's Table

The p-values for the ITT, M-ITT and VFE study populations were taken from sponsor's vol. 3.1, Section C, p. 015.

TABLE 7

Study 3001K1-309-US

SECONDARY EFFICACY ENDPOINT: Comparison of the Mean MAO Following the Fist Dose of I.V. PANTO With That After the Last Oral Dose of PANTO [$MAO_{FI.V.}$-1.2 MAO_{LPO}] for the 40 mg PANTO Treatment Groups

Study Population Analyzed →	ITT			M-ITT			VFE		
	I.V. PANTO		I.V. PL	I.V. PANTO		I.V. PL	I.V. PANTO		I.V. PL
Last Day Oral MAO_{LPO}		6.49±5.63 (0.0-20.3) [n=30]			6.30±5.87 (0.0-20.3) [n=26]			6.56±5.84 (0.0-20.3) [n=25]	
First Day IV $MAO_{FI.V.}$	8.53±7.66 (0.0-31.0) [n=23]		14.24±9.81 (0.2-28.0) [n=7]	8.40±7.94 (0.0-31.0) [n=21]		13.16±11.78 (0.2-28.0) [n=5]	8.76±7.96 (0.0-31.0) [n=20]		13.16±11.78 (0.2-28.0) [n=5]
STATISTICS [p-value for testing $MAO_{FI.V.}$ inferior to MAO_{LPO} by 20% or more]									
Statistical Test →	**t Test**	**Sign Test**	**Signed-Rank Test**	**t Test**	**Sign Test**	**Signed-Rank Test**	**t Test**	**Sign Test**	**Signed-Rank Test**
p-value	N.S.	N.S.	N.S.	N.S	N.S.	N.S.	N.S.	N.S.	N.S.

Reviewer's Table
The p-values for the ITT, M-ITT and VFE study populations were taken from sponsor's volume 3.1, Section C, p. 014

iii) $MAO_{LI.V.}$ vs $MAO_{FI.V.}$ (Table 8)

- Testing for equivalence between the first and last day of I.V. treatment gave inconsistent results. Except for the sign test in the M-ITT, most comparisons were either N.S. or approaching significance.

- The mean $MAO_{FI.V.}$ was 8.53 mEq/h compared to 6.62 mEq/h for the $MAO_{LI.V.}$. Both values are to be contrasted with I.V. PL ($MAO_{LI.V.}$=29.19 mEq/h).

iv) $BAO_{LI.V.}$ vs BAO_{LPO} (Table 9)

- The data summarized in this Table shows equivalence of the I.V. Day 7 and last Day oral BAO. In all three analysis populations (ITT, M-ITT and VFE) the equivalence of the $BAO_{LI.V.}$ and the BAO_{LPO} was established since the hypothesis that they differed by more than 20% was rejected [p-values for the signed-rank test for the ITT, M-ITT and VFE were 0.207, 0.009 and 0.024, respectively].

- The mean $BAO_{LI.V.}$ was 0.53 mEq/h compared to 0.80 mEq/h for the BAO_{LPO}. Both values were lower than those seen with i.v. PL: mean $BAO_{LI.V.}$ = 4.14 mEq/h.

TABLE 8
Study 3001K1-309-US

SECONDARY EFFICACY ENDPOINT: Comparison of the Mean MAO Following the Last Dose of I.V. PANTO With That After the First Dose of I.V. PANTO [$MAO_{LI.V.}$-$MAO_{FI.V.}$] for the 40 mg PANTO Treatment Groups

Study Population Analyzed →	**ITT**		**M-ITT**		**VFE**	
	I.V. PANTO	**I.V. PL**	**I.V. PANTO**	**I.V. PL**	**I.V. PANTO**	**I.V. PL**
First Day I.V. $MAO_{FI.V.}$	8.53±7.66 (0.0-31.0) [n=23]	14.24±9.81 (0.2-28.0) [n=7]	8.40±7.94 (0.0-31.0) [n=21]	13.16±11.78 (0.2-28.0) [n=5]	8.76±7.96 (0.0-31.0) [n=20]	13.16±11.78 (0.2-28.0) [n=5]
Last Day I.V. $MAO_{LI.V.}$	6.62±6.34 (0.0-23.1) [n=23]	29.19±13.01 (6.9-48.7) [n=7]	6.22±6.42 (0.0-23.1) [n=21]	27.44±15.50 (6.9-48.7) [n=5]	6.48±6.47 (0.0-23.1) [n=20]	27.44±15.50 (6.9-48.7) [n=5]

STATISTICS [p-values for testing $MAO_{LI.V.}$ inferior to $MAO_{FI.V.}$ by 20% or more]

Stat. Test →	**t Test**	**Sign Test**	**Signed-Rank Test**	**t Test**	**Sign Test**	**Signed-Rank Test**	**t Test**	**Sign Test**	**Signed-Rank Test**
p-value	N.S.	N.S.	N.S. [0.0883]	N.S.	0.04139	N.S. [0.05317]	N.S.	N.S. [0.06357]	N.S. [0.06021]

Reviewer's Table
The p-values for the ITT, M-ITT and VFE study populations were taken from sponsor's volume 3.1, Section C, p. 16.

N 0-988
Pa[illegible] 48

TABLE 9

Study 3001K1-309-US

SECONDARY EFFICACY ENDPOINT: Comparison of Mean BAO following the last dose of I.V. PANTO With That After the Last Oral Dose of PANTO [$BAO_{LI.V.}$-1.2·BAO_{LPO}] for the 40 mg PANTO Treatment Groups

Study Population Analyzed →	**ITT**			**M-ITT**			**VFE**		
	I.V. PANTO		**I.V. PL**	**I.V. PANTO**		**I.V. PL**	**I.V. PANTO**		**I.V. PL**
Last Day Oral BAO_{LPO}		0.80±1.28 (0.0-5.5) [n=30]			0.85±1.37 (0.0-5.5) [n=26]			0.88±1.38 (0.0-5.5) [n=25]	
Last Day I.V. $BAO_{LI.V.}$	0.53±0.75 (0.0-3.0) [n=23]		4.14±5.15 (0.0-15.0) [n=7]	0.54±0.78 (0.0-3.0) [n=21]		5.45±5.69 (0.0-15.0) [n=5]	0.54±0.80 (0.0-3.0) [n=20]		5.42±5.69 (0.0-15.0) [n=5]
STATISTICS [p-values for testing $BAO_{LI.V.}$ inferior to BAO_{LPO} by 20% or more]									
Stat. Test →	t Test	Sign Test	Signed-Rank Test	t Test	Sign Test	Signed-Rank Test	t Test	Sign Test	Signed-Rank Test
p-value	0.021719	0.01544	0.026928	0.029068	0.03841	0.009041	0.020632	0.01758	0.023956

Reviewer's Table
The p-values for the ITT, M-ITT and VFE study populations were taken from sponsor's vol. 3.1, Section 3, p. 015.

v) $\underline{BAO_{FI.V.} \text{ vs } BAO_{LPO}}$

- Equivalence between BAO after one day of i.v. dosing and after oral therapy was not demonstrated with statistical significance for the 40 mg dose level.

- The mean $BAO_{FI.V.}$ was 0.99 mEq/h compared to 0.80 mEq/h for the BAO_{LPO}. Both values were not too dissimilar to those seen with i.v. PL: $BAO_{FI.V.}$ = 1.11 mEq/h.

vi) $\underline{BAO_{LI.V.} \text{ vs } BAO_{FI.V.}}$

- As shown below, these comparisons gave inconsistent statistical results. In all three study populations, the p-values were significant on the t-test but not significant when using the sign test. The signed-rank test was significant in the ITT population (0.03) but borderline in the M-ITT (p=0.085) and the VFE (p=0.066) populations.

TEST	ITT	M-ITT	VFE
t	0.02	0.05	0.04
sign	N.S.	N.S.	N.S.
Signed-rank	0.03	N.S. [0.09]	N.S. [0.07]

- The mean $BAO_{FI.V.}$ was 0.99 mEq/h compared to 0.53 mEq/h for the $BAO_{LI.V.}$. Both values were lower than the 4.14 mEq/h seen on last day i.v. PL (4.14 mEq/h).

2) **Results With 20 mg PANTO**

i) $\underline{MAO_{LI.V.} \text{ vs } MAO_{LPO}}$ **(Table 10)**

- In the ITT analysis group, all three sub-analyses (t-test=0.029; sign test=0.022; and signed-rank test=0.005) established the equivalence of the 20 mg I.V. PANTO formulation and the 20 mg oral PANTO formulation. However, for the M-ITT and VFE analysis populations, only the signed-rank test was consistently significant (M-ITT=0.014; VFE=0.03) while the sign and the signed-rank test were borderline. Nonetheless, all of these p-values were <0.1. All in all, these findings support the conclusion that the two dose formulations of 20 mg PANTO were equivalent.

- For 20 mg I.V. PANTO, the mean MAO_{LPO} was 14.5 mEq/h, $MAO_{LI.V.}$ was 11.1 mEq/h. Both were much lower than the last day I.V. MAO with PL (30.5 mEq/h).

TABLE 10

Study 3001K1-309-US

PRIMARY EFFICACY ENDPOINT: Comparison of the Mean MAO following the last dose of I.V. PANTO with that after the last oral dose of PANTO [$MAO_{I.V.}$ -12•MAO_{LPO} for the 20 mg PANTO Treatment Groups

Study Population Analyzed →	ITT			M-ITT			VFE		
	I.V. PANTO		I.V. PL	I.V. PANTO		I.V. PL	I.V. PANTO		I.V. PL
Last Day Oral MAO_{PO}		14.50±15.51 (0.3-69.6) [n=33]			14.85±15.58 (0.9-69.6) [n=29]			13.54±14.14 (0.9-69.6) [n=28]	
Last Day I.V. $MAO_{I.V.}$	11.05±10.22 (0.2-46.2) [n=25]		30.50±12.80 (13.3-50.6) [n=8]	11.75±10.55 (1.0-46.2) [n=22]		30.91±13.77 (13.3-50.6) [n=7]	10.10±7.39 (1.0-34.7) [n=21]		30.91±13.77 (13.3-50.6) [n=7]
STATISTICS [p-values for testing $MAO_{I.V.}$ inferior to MAO_{LPO} by 20% or more]									
Stat. Test →	t Test	Sign Test	Signed-Rank Test	t Test	Study Test	Signed-Rank Test	t Test	Study Test	Signed-Rank Test
p-value	0.028980	0.02164	0.005304	N.S. [0.053502]	N.S. [0.06690]	0.013548	N.S. [0.073984]	N.S. [0.09462]	0.025532

Reviewer's Table
The p-values for the ITT, M-ITT and VFE study populations were taken from sponsor's vol. 3.1, Section C, p. 015.

ii) $MAO_{FI.V.}$ vs MAO_{LPO} (Table 11)

- These comparisons yielded inconsistent results. Although the t-test showed equivalence in the three analysis populations [ITT=0.02, M-ITT=0.03 and VFE=0.03], only the signed-rank test confirmed these results in the ITT analysis [p=0.04]. All other comparisons were N.S. It is concluded that, in general, equivalence between acid output after one day I.V. dosing and after oral therapy was not demonstrated with consistent statistical significance for the 20 mg dose level.

- For the 20 mg I.V. PANTO, the mean $MAO_{FI.V.}$ was 12.8 mEq/h; MAO_{LPO} was 14.5 mEq/h. Both were lower than the 21.7 mEq/h value seen with PL on the first day.

iii) $MAO_{LI.V.}$ vs $MAO_{FI.V.}$ (Table 12)

- The difference is acid output between the $MAO_{LI.V.}$ and $MAO_{FI.V.}$ was not significant for the 20 mg PANTO groups.

- For the 20 mg I.V. PANTO dose level, the mean $MAO_{LI.V.}$ was 11.1 mEq/h; as previously mentioned, the mean $MAO_{LI.V.}$ was 12.8 mEq/h. Both values much lower than the I.V. PL $MAO_{LI.V.}$ of 30.5 mEq/h.

iv) $BAO_{LI.V.}$ vs BAO_{LPO} (Table 13)

- Except for results in the ITT analysis, where only the signed-rank test showed statistically significant p-value (0.02), all other comparisons resulted in N.S. p-values, although some were borderline. It is concluded that, based on these results, equivalence was not established between the last day I.V. and the oral formulations of PANTO (20 mg).

- The mean $BAO_{LI.V.}$ was 1.3 mEq/h compared to 3.3 mEq/h for the BAO_{LPO}. The mean $BAO_{LI.V.}$ for i.v. placebo was 3.24 mEq/h.

TABLE 11

Study 3001K1-309-US

SECONDARY EFFICACY ENDPOINT: Comparison of the Mean MAO following the First Dose of I.V. PANTO With That After the Last Oral Dose of PANTO $[MAO_{F1.V.} - 1.2 \bullet MAO_{LPO}]$ for the 20 mg PANTO Treatment Groups

Study Population Analyzed →	ITT			M-ITT			VFE		
	I.V. PANTO		I.V. PL	I.V. PANTO		I.V. PL	I.V. PANTO		I.V. PL
Last Day Oral MAO_{PO}		14.50±15.51 (0.3-69.6) [n=33]			14.85±15.58 (0.9-69.6) [n=29]			13.54±14.14 (0.9-69.6) [n=28]	
First Day I.V. $MAO_{F1.V}$	12.83±13.41 (1.0-60.4) [n=24]		21.66±11.86 (6.1-36.4) [n=7]	13.30±13.84 (2.1-60.4) [n=21]		22.82±12.55 (6.1-36.4) [n=6]	10.94±8.89 (2.1-43.9) [n=20]		22.82±12.55 (6.1-36.4) [n=6]
STATISTICS [p-values for testing $MAO_{F1.V.}$ inferior to MAO_{LPO} by 20% or more]									
Stat. Test →	**t Test**	**Sign Test**	**Signed-Rank Test**	**t Test**	**Sign Test**	**Signed-Rank Test**	**t Test**	**Sign Test**	**Signed-Rank Test**
p-value	0.01568	N.S.	0.04319	0.02984	N.S.	N.S. [0.07682]	0.03166	N.S.	N.S. [0.09467]

Reviewer's Table.
The p-values for the ITT, M-ITT and VFE study populations were taken from sponsor's vol. 3.1, Section C, p. 014.

TABLE 12
Study 3001K1-309-US

SECONDARY EFFICACY ENDPOINT: Comparison of the Mean MAO following the Last Dose of I.V. PANTO With That After the First Dose of I.V. PANTO [$MAO_{LI.V.}$ – $MAO_{FI.V.}$] for the 20 mg PANTO Treatment Groups

Study Population Analyzed →	ITT		M-ITT		VFE	
	I.V. PANTO	I.V. PL	I.V. PANTO	I.V. PL	I.V. PANTO	I.V. PL
First Day IV $MAO_{FI.V.}$	12.83±13.41 (1.0-60.4) [n=24]	21.66±11.86 (6.1-36.4) [n=7]	13.30±13.84 (2.1-60.4) [n=21]	22.82±12.55 (6.1-36.4) [n=6]	10.94±8.89 (2.1-43.9) [n=20]	22.82±12.55 (6.1-36.4) [n=6]
Last Day IV $MAO_{LI.V.}$	11.05±10.22 (0.2-46.2) [n=25]	30.50±12.80 (13.3-50.6) [n=8]	11.75±10.55 (1.0-46.2) [n=22]	30.91±13.77 (13.3-50.6) [n=7]	10.10±7.39 (1.0-34.7) [n=21]	30.91±13.77 (13.3-50.6) [n=7]

STATISTICS [p-values for testing $MAO_{LI.V.}$ inferior to $MAO_{FI.V.}$ by 20% or more]

Stat. Test →	t Test	Sign Test	Signed-Rank Test	t Test	Sign Test	Signed-Rank Test	t Test	Sign Test	Signed-Rank Test
p-value	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

Reviewer's Table.
The p-values for the ITT, M-ITT and VFE study populations were taken from sponsor's vol. 3.1, Section 3, p. 16.

TABLE 13
Study 3001K1-309-US

SECONDARY EFFICACY ENDPOINT: Comparison of Mean BAO following the last dose of I.V. PANTO With That After the Last Oral Dose of PANTO [$BAO_{LI.V.} - 1.2 \bullet BAO_{LPO}$] for the 20 mg PANTO Treatment Groups

Study Population Analyzed →	**ITT**			**M-ITT**			**VFE**		
	I.V. PANTO		**I.V. PL**	**I.V. PANTO**		**I.V. PL**	**I.V. PANTO**		**I.V. PL**
Last Day Oral BAO_{PO}		3.25±7.56 (0.0-41.8) [n=33]			3.23±7.92 (0.0-41.8) [n=29]			1.86±2.82 (0.0-10.3) [n=28]	
Last Day I.V. $BAO_{LI.V.}$	1.31±1.72 (0.0-5.9) [n=25]		3.24±1.86 (1.3-6.7) [n=8]	1.28±1.79 (0.0-5.9) [n=22]		3.26±2.01 (1.3-6.7) [n=7]	1.21±1.80 (0.0-5.9) [n=21]		3.26±2.01 (1.3-6.7) [n=7]
STATISTICS [p-values for testing $BAO_{LI.V.}$ inferior to BAO_{LPO} by 20% or more]									
Stat. Test →	***t* Test**	***Sign* Test**	***Signed-Rank* Test**	***t* Test**	***Sign* Test**	***Signed-Rank* Test**	***t* Test**	***Sign* Test**	***Signed-Rank* Test**
p-value	N.S. [0.055732]	N.S. [0.06690]	0.015611	N.S. [0.082780]	N.S.	N.S. [0.053188]	N.S. [0.074756]	N.S.	N.S. [0.092541]

Reviewer's Table.
The p-values for the ITT, M-ITT and VFE study populations were taken from sponsor's vol. 3.1, Section C, p. 015.

v) $BAO_{FI.V.}$ vs BAO_{LPO}

- In general, for the 20 mg PANTO dose, equivalence between BAO after one day or i.v. dosing and after oral therapy was not consistently demonstrated. Statistically significant p-values were shown only with the signed-rank test for the ITT and M-ITT analysis and with the t-test in the BFE population. All other comparisons were N.S.

- The mean $BAO_{FI.V.}$ was 1.6 mEq/h compared to 3.25 mEq/h for the BAO_{LPO} and 2.4 mEq/h for the $BAO_{FI.V.}$ seen with the i.v. PL.

vi) $BAO_{LI.V.}$ vs $BAO_{FI.V.}$

- As shown below, except for a p-value of 0.03 (ITT, t-test) none of the other analyses supported equivalence because the p-values were N.S.

	STUDY POPULATION		
Test	**ITT**	**M-ITT**	**VFE**
t	N.S.	0.03	N.S. [0.053]
sign	N.S.	N.S. [0.07]	N.S. [0.09]
signed-rank	N.S.	N.S.	N.S.

3) I.V. Dose Groups vs PL

Results of these evaluations are summarized below.

Acid Output mEq/h By Treatment Group

	PANTO (mg)		Pooled
	40	**20**	**PL**
Mean $MAO_{LI.V.}$	6.6 [n-23]	8.1 [n=20]	30.4[d] [n=13]
Mean $MAO_{FI.V.}$	8.5	9.0	15.1[d]
Mean $BAO_{LI.V.}$	0.5	1.0	3.8[b]
Mean $BAO_{FI.V.}$	1.0	1.0	1.7[c]

a, b, and c) Each was statistically significantly higher than each of the 40 and 20 mg PANTO groups.

The sponsor notes that a preliminary analysis showed no significant differences in acid output between the two PL groups so their results were pooled. Also, due to high acid output rates at the end of oral therapy (>5.5 mEq/h BAO, >20.3 mEq/h MAO), some patients were excluded from the previously defined analysis subsets in order to better balance this covariate among the I.V. treatment groups (details were provided in sponsor's Section 6.7.1.2). All excluded patients received 20 mg PO PANTO during the oral phase. A summary of the exclusions from each analysis subset by treatment group was provided in sponsor's Supportive Table 13.

d) No statistically significant difference between PL and each of the treatment groups.

- For all of the treatment groups acid output rate on i.v. therapy increased as a function of the initial output rate on oral therapy.

- There was a statistically significant effect due to treatment on $MAO_{LI.V.}$, $BAO_{LI.V.}$ and $BAO_{FI.V.}$ but not on $MAO_{FI.V.}$.

4) Comparison Between Oral PANTO Dose Groups

- MAO_{PO} was significantly lower in the 40 mg PANTO group than in the 20 mg PANTO group (6.5 mEq/h in the 40 mg vs 14.5 mEq/h in the 20 mg PANTO group, p=0.02, Wilcoxon test). This conclusion was consistently reached under all analysis subsets.

- BAO_{PO} did not differ significantly between the two dose groups (0.8 in the 40 mg group vs. 3.3 in the 20 mg group, p=0.15).

5) Difference in Acid Output Following Switch From Oral to I.V. PANTO

Table 14 depicts the mean change in acid output - calculated as the difference from the last day oral BAO or MAO determination – following switchover to one and seven days on I.V. PANTO.

A scatter plot of the individual changes in MAO following seven days of I.V. therapy ($MAO_{LI.V.} - MAO_{LPO}$) for the 40 mg and PL I.V. PANTO treatment groups are illustrated in Figure 1.

- For patients who were stabilized on 20 mg PO PANTO, changes in BAO and MAO were significantly increased in the PL group after both one day and seven days compared to patients who were switched to the I.V. formulation of pantoprazole the drug.

- For patients that were stabilized on 40 mg PO PANTO, the change in BAO was significantly different from the 40 mg I.V. group only after 7 days of I.V. therapy (3.64 vs –0.35 mEq/h).

- For patients who were stabilized on 40 mg PO PANTO, the increase in $MAO_{FI.V.}$ and $MAO_{LI.V.}$ was significantly greater in the PL group than with I.V. PANTO.

- For patients who received I.V. PL, MAO rose 8.53 mEq/h after one day and nearly 23.5 mEq/h after 7 days.

- Whereas, for patients who received 40 mg I.V. PANTO MAO rose 1.80 mEq/h one day after switching from oral therapy, while after 7 days of I.V. PANTO, it decreased 0.11 mEq/h compared to the end of oral dosing.

6) Summary of Antacid Usage

These data were presented in sponsor's Table 9.4.4A and supportive Table 14. From the frequency Table of the proportion of days of oral or I.V. study treatment in which antacids were taken, the following is concluded.

- There was no difference in antacid use between the oral and I.V. phases for either patients who received 20 mg PANTO or those who received 40 mg PANTO.
- In both groups the same number of patients used antacids more frequently during the oral phase (difference in proportions <0) as those who used antacids more frequently during the I.V. phase (difference in proportions >0).
- For those patients who were switched to PL during the I.V. phase, the differences in proportions were not statistically significantly different from 0, although the trend indicated greater antacid use than during oral PANTO treatment. In fact only one PL patient used antacids less frequently than during the oral phase, while 7 used antacids more frequently.
- Antacid use did not differ significantly between the two oral dose groups of PANTO [p=0.48, Wilcoxon test].
- Use of antacids during the I.V. phase was significantly lower in the 40 mg PANTO group than in the PL group [p=0.003, ANOVA using arcsine transformation on proportions].
- Under the ITT analysis antacid use was also significantly lower in the 20 mg PANTO group than in the PL group (p=0.02). However, significance was not obtained under either of the other two analyses [M-ITT: p=0.34; VFE: p=0.18].
- There was no significant difference in antacid use between the two PANTO groups [p=0.35].

TABLE 14
Study 3001K1-309-US

Change in Acid Output During I.V. Treatment[a]
Intent-To-Treat Analysis Patients

Measurement Type	Treatment Phase	PANTO: 20 mg		PANTO: 40 mg	
		I.V. PANTO	I.V. PL	I.V. PANTO	I.V. PL
BAO	BAO_{FIV}	-2.37±7.43	0.70±2.49	0.10±0.81	0.61±0.71
	BAO_{LIV}	-2.50±8.20	1.74±3.41	-0.35±0.94	3.64±4.42
MAO	MAO_{FIV}	-2.58±9.68	8.77±7.39	1.80±5.56	8.53±5.67
	MAO_{LIV}	-3.99±14.78	17.70±17.05	-0.11±2.34	23.417±8.96

a) Calculated as the difference from the last day oral acid output (BAO_{LPO} or MAO_{LPO} determination.

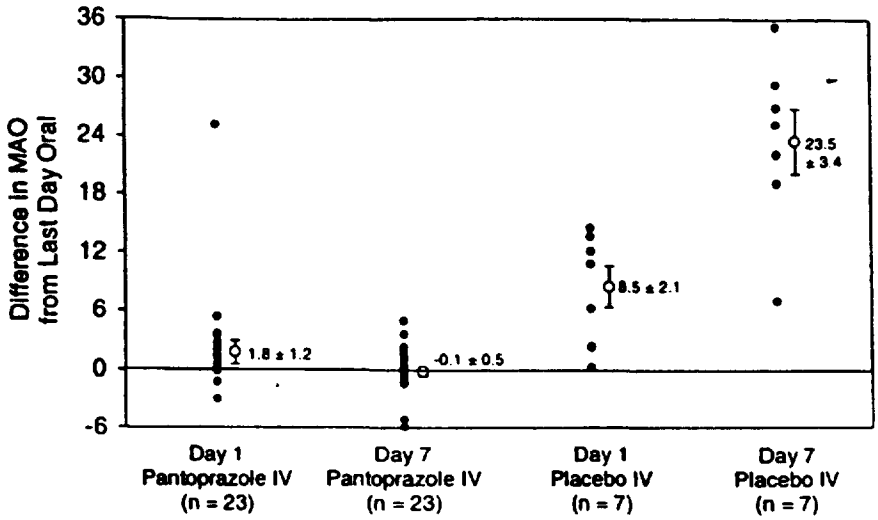

Fig. 1. - Difference in MAO between oral and intravenous PANTO: 40 mg I.V. PANTO vs PL groups.
Numerical values are mean ± SEM.
This Fig. corresponds to sponsor's Fig. 9.4.3.6A. As in all calculations, the AO (mEq) per 15 min. was determined as volume (ml) x 0.001 x concentration (mEq/L). Then MAO was determined as the sum of 15-min. rates.

g. Results of Safety Evaluations

1) Extent of exposure

Cumulative duration of exposure (i.e. the number of patients that took the drug for at least the time interval defined) can be summarized as follows:

PANTOPRAZOLE: Cumulative Duration of Exposure, n (%)

Total Daily Dose	DAYS							
	<1	≥1	≥2	≥3	≥4	≥5	≥6	≥7
Any dose	50 (100)	50 (100)	48 (96)	47 (94)	47 (94)	47 (94)	47 (94)	47 (94)
20 mg	26 (100)	26 (100)	25 (96)	24 (92)	24 (92)	24 (92)	24 (92)	24 (92)
40 mg	24 (100)	24 (100)	23 (96)	23 (96)	23 (96)	23 (96)	23 (96)	23 (96)
From sponsor's Table 10.1A, with minor modifications.								

2) Deaths, other serious AEs, discontinuations, and other clinically important AEs

- No deaths or SAEs were reported in the trial.
- The following 2 patients D/C from the study for reasons related to safety [taken from narrative provided in sponsor's supportive Table 18].

Pt. 309A5-0005

This 42-y old F reported a possible hypersensitivity reaction after receiving her 3rd dose of I.V. PANTO 20 mg ca. 1 h after completion of the infusion. She reported tightness in the chest, itching, nausea, hot flashes, and uncontrollable shaking of the arm in which the I.V. solution was infused. This Rx was not witnessed by any medical personnel and the symptoms resolved within 1/2 h. The patient was D/C from the trial and had no recurrence of this AR or related symptoms. In further questioning, she reported a similar occurrence while receiving a different PPI in the past.

Pt. 309A5-0002

This 35-y old F had elevated WBC count before starting the I.V. phase of the study. Before the day 12 gastric analysis and second I.V. administration of I.V. PANTO, 40 mg, she experienced flue symptoms (vomiting, headache, and achiness). A fever was not apparent upon a vital sign assessment. She was D/C on study Day 12 and W/D consent on study on Day 14. The condition resolved after 3 days.

3) Treatment emergent AEs (TEAEs)

- 63/65 patients had at least one TEAE, without consideration of the investigator's opinion regarding relationship to treatment. A summary of AEs by selective body systems is given in Table 15.

TABLE 15
Study 3001K1-309-US

Number (%) of patients Reporting TEAE by Treatment
(Selective Systems)

BODY SYSTEM	PANTO 20 mg PO [n=34]	PANTO 20 mg I.V. [n=26]	PANTO 40 mg PO [n=31]	PANTO 40 mg I.V. [n=24]	PL I.V. Combined [n=15]
Any AE (1 or more)	31 (91%)	20 (77%)	22 (71%)	21 (99%)	15 (100%)
Body as a Whole	17 (50%)	13 (50%)	17 (55%)	15 (63%)	6 (40%)
Headache	8 (24%)	9 (35%)	14 (45%)	7 (29%)	6 (40%)
Cardiovascular	3 (9%)	3 (12%)	0	1 (4%)	1 (7%)
Digestive	20 (59%)	11 (42%)	15 (48%)	12 (50%)	13 (87%)
Constipation	2 (6%)	0	1 (3%)	1 (4%)	2 (13%)
Diarrhea	1 (3%)	1 (4%)	2 (6%)	3 (13%)	3 (20%)
Dyspepsia	10 (29%)	7 (27%)	11 (35%)	6 (25%)	9 (60%)
Nausea	2 (6%)	4 (15%)	2 (6%)	4 (17%)	3 (20%)
Nervous	3 (9%)	3 (12%)	1 (3%)	2 (8%)	2 (13%)
Skin & Appendages	1 (3%)	3 (12%)	0	2 (8%)	0
Special senses	5 (15%)	3 (12%)	1 (3%)	2 (8%)	1 (7%)

This Table was extracted from sponsor's Table 10.2.2.A. Shown are results from selective body systems.

- Headache and dyspepsia were the most common TEAEs for all treatments, including PL.
- For pts. taking PANTO, headaches were judged to be mild to moderate in all but 6 of the cases.
- 1 pt. receiving the I.V. formulation of PANTO experienced severe headaches.
- Dyspepsia was judged to be mild to moderate in severity in all but 8 cases; no pts. receiving I.V. PANTO reported severe dyspepsia.
- Several numerical differences are noted in Table 15. However, the only statistically significant differences between I.V. PANTO and PL were for any digestive symptom. In this comparison. PL had the higher rate compared to either 20 mg I.V. PANTO (87% vs 42%, p=0.008) or 40 mg I.V. PANTO

(87% vs 50%, p=0.037). Also, the incidence of dyspepsia was significantly less than PL for 20 mg (60% vs 27%, p=0.05) and 40 mg I.V. PANTO (60% vs 25%, p=0.044).

- There was a higher proportion of patients with any TEAE in the 20 mg PO PANTO group than the 40 mg PO PANTO group (91% vs 71%, p=0.054).

- The higher incidence of headache in the 40 mg vs the 20 mg PO PANTO approached statistical significance (45% vs 24%, p=0.074). It is worth noting that three of the four PANTO treatment groups were actually lower than PL.

- There were no statistically significant differences between 20 mg and 40 mg I.V. PANTO for any system or symptom (p=0.22).

4) Changes in laboratory parameters

Review of these data allow the conclusions that intravenously administered PANTO is safe. Changes in laboratory parameters were infrequent, non-serious and although there were some with statistically significant mean differences between on-therapy and the baseline measurements, none were clinically significant.

5) Changes in vital signs, others

The number of patients in each treatment group with changes in vital signs and/or body weight of potential clinical importance and patient identification were provided by treatment group in sponsor's Table 10.5.1.1A while their Table 10.5.1.1B listed the potentially clinically important changes in vital signs by the drug formulation the patient was on when the change was noted. The reviewer agrees with the clinical monitor that none of the 13 patients that were identified as having potentially clinically important changes in VS had changes of actual clinical significance. An increase in systolic readings between baseline and day eight of the I.V. treatment phase was statistically significant in both the 40 mg I.V. PANTO (p=0.007) and I.V. PL (p=0.02) groups. The larger increase occurred in the PL group (13.3 mm Hg vs 8.1 mm Hg). Similarly, a decrease in diastolic readings from baseline to Day 6 was statistically significant in the 40 mg I.V. PANTO group (p=0.03). The mean decrease was 5 mm Hg.

- There were no statistically significant changes from baseline in EKGs in patients taking PANTO.

- In this small series of patients monitored for short periods of time (all in all, <1 month) there was no evidence of ophthalmic or optic nerve complications and no changes that were attributable to the use of PANTO.

11. Sponsor's Conclusions

"Results of this study indicate that the 40 mg oral and 40 mg I.V. pantoprazole dose formulations are equivalent in the suppression of both basal and maximal gastric acid secretion in GERD patients. I.V. pantoprazole therapy effectively suppresses the increase in acid secretion that occurs upon withdrawal of oral pantoprazole therapy. Relief of GERD symptoms while on the I.V. formulation of pantoprazole is equivalent that of oral pantoprazole. GERD patients who have been stabilized on 40 mg oral pantoprazole can be

safely switched to 40 mg I.V. pantoprazole for one week and they will maintain their level of acid suppression."

12. Reviewer's Additional Comments

Study under Protocol 3001K1-309-US (GMR-32141) was one of the two critical trials in NDA 20-999. Results of these studies were submitted by the sponsor in support of the approval of 40 mg of PROTONIX® (pantoprazole=PANTO) intravenous (I.V.) for the short-term (up to 7 days) gastric acid suppression in gastro-esophageal reflux disease (GERD) patients who are unable to take orally administered PANTO.

For the GERD indication (NDA 20-987; Hugo E. Gallo-Torres, M.D., Ph.D.; MOR of April 9, 1999) the recommended adult oral dose of PANTO is 40 mg once-a-day for the treatment (up to 8 weeks) of erosive esophagitis (EE) and associated symptoms. The scientific rationale behind the use of PANTO in the treatment of EE is the ability of this proton pump inhibitor (PPI) to inhibit both basal and stimulated gastric acid secretion, irrespective of the stimulus. With these considerations in mind, study –309-US tested the hypothesis that 40 mg PANTO I.V. formulation is an effective suppressant of gastric acid production induced by I.V. administered pentagastrin (PG) at maximally stimulating doses and that this I.V. formulation of 40 mg of the drug is equipotent to 40 mg of PANTO administered in an oral formulation. The trial's main objective was to compare the basal gastric acid output (BAO) and the maximum pentagastrin-stimulated acid output (MAO) response in GERD patients with a history of EE who were switched from oral to I.V. PANTO dose formulations. The trial consisted of 4 arms, since comparison was also made with two additional arms: repeated I.V. administration of 20 mg PANTO and intravenously administered placebo (PL).

It is worth clarifying that, as acknowledged during a pre-NDA meeting with the sponsor, inhibition of gastric acid secretion is an acceptable endpoint for this type of study [Maria R. Walsh, Memorandum of Meeting Minutes, April 29, 1997]. The PD endpoint, gastric acid secretion, can be assessed either by pH measurements (stomach, esophagus) or measurement of acid output. Of these two main approaches, gastric AO (MAO and BAO) is more precise than the pH measurement. Reasons for this statement include that the latter may vary depending upon the localization of the pH probe. Also, recording of gastric pH may not necessarily be representative of esophageal pH; it is the latter pH that may be more related to GERD than gastric pH. In addition, at the aforementioned meeting, Dr. Walsh (CURE), a recognized world expert in this field, explained that AO measurement is more precise than the pH measurement because the pH tends to remain at the same level until gastric acid production is abolished.

This two-period, randomized, double-blind, placebo-controlled study was well designed and apparently well executed. Each patient participated for ca. 42 days. This overall experimental period included a 3-week prestudy screening period, a 10 to 14 day PO treatment period of PANTO (20 or 40 mg once daily, PO), and a 7-day I.V. treatment period of PANTO (20 or 40 mg Q.D.) or PL. The gastric acid stimulant (PG) was administered on three occasions, identified as gastric acid measurement days (after the last PO dose, after the first I.V. dose and after the last I.V. dose). The number of patients planned in the protocol was 48. Of the 65 that were enrolled, 62 completed the study. The primary efficacy variable was MAO following the last dose of I.V. PANTO compared with that after the last dose of oral PANTO. This comparison, identified throughout this review as $\mathbf{MAO_{LI.V.}}$ **vs** $\mathbf{MAO_{LPO}}$ is of primary clinical interest because AO following the last I.V. dose represents the "stabilized" PD performance of the I.V. formulation and it is appropriate for comparison to the effect obtained with the final oral dose of the drug. Comparison was also made between the first I.V. dose

mean and the last oral dose mean. This comparison, identified throughout this review as $MAO_{FI.V.}$ vs AO_{LPO} was a secondary endpoint of efficacy because data following the first I.V. dose represents a composite of the effects of the first I.V. dose and any residual effects of orally administered PANTO. In addition, these data would be more relevant if the sponsor were to request *de novo* (for the first time) use of I.V. drug but this is not the case.

Statistically, to demonstrate equivalence in MAO between the I.V. and oral formulations of PANTO, it was necessary to show that $MAO_{LI.V.}$ was no more than 20% higher than MAO_{LPO}. The null hypothesis was that $MAO_{LI.V.} - 1.2 \times MAO_{LPO} \geq 0$; the alternative was that this difference was <0. For each patient, the equivalence difference $MAO_{LI.V.} - 1.2 \times MAO_{LPO}$ was calculated; a one-sided signed rank test was then applied to check the null hypothesis that the I.V. and oral formulations were **not** equivalent.

In study –309-US, for 40 mg PANTO, the mean $MAO_{LI.V.}$ was 6.62 mEq/h, whereas the mean MAO_{LPO} was 6.49 mEq/h. These results established equivalence for this dose of PANTO with both formulations. This equivalence of the $MAO_{LI.V.}$ and the MAO_{LPO} was established for this dose of PANTO in all three statistical analysis populations by rejecting the hypothesis that they differed by more than 20%. This was also shown regardless of the statistical test used, whether t-test, sign test or signed-rank test. With the latter, the p-values for testing $MAO_{LI.V.}$ inferior to MAO_{LPO} by 20% or more were 0.004 in the ITT population, 0.009 in the M-ITT population and 0.006 in the VFE population.

For the 40 mg PANTO treatment dose, results using BAO as the PD parameter of efficacy were similar to those using MAO. The mean $BAO_{LI.V.}$ was 0.53 mEq/h, whereas the mean BAO_{LPO} was 0.80 mEq/h. These results established bioequivalence for this dose of PANTO with both formulations. This equivalence of the $AO_{LI.V.}$ and the BAO_{LPO} was established for this dose of PANTO in all three statistical analysis populations by rejecting the hypothesis that they differed by more than 20%. This was also shown regardless of the statistical test used, whether t-test, sign test, or signed-rank test. With the latter, the p-values for testing $BAO_{LI.V.}$ inferior to BAO_{LPO} by 20% or more were 0.027 in the ITT population, 0.009 in the M-ITT population and 0.024 in the VFE population.

From the results of the study, the 40 mg PANTO I.V. is preferred to the 20 mg I.V. dose, because, for the latter, using MAO as the PD parameter of valuation, equivalence was established by all three tests only for the ITT population but in only one (signed-rank test) of the three tests in the M-ITT and VFE population. Furthermore, the p-values for testing $BAO_{LI.V.}$ inferior to BAO_{LPO} by 20% or more were all N.S. for all three statistical tests in all three study populations except ITT. In summary, whether using MAO or BAO as the PD parameter of comparison, the 20 mg PANTO I.V. is not consistently equivalent to the 40 mg PANTO PO. It is however, worth mentioning that for the 20 mg PANTO treatment dose the mean $MAO_{LI.V.}$ in all three populations was numerically lower (ITT=11.05, M-ITT=11.75 and VFE=10.10 mEq/h) than the respective mean MAO_{LPO} (ITT=14.50, M-ITT=14.85 and VFE=13.54 mEq/h).

Whether using MAO or BAO as the PD parameter of comparison, in study –309-US, equivalence on inhibition of AO in the first day of I.V. PANTO to the last day of oral PANTO was not established. The mean difference $MAO_{FI.V.} - MAO_{LPO}$ was 1.80 mEq/h for the 40 mg I.V. PANTO and –2.58 mEq/h for the 20 mg I.V. PANTO; equivalence of $MAO_{FI.V.}$ vs MAO_{LPO} or $BAO_{FI.V.}$ vs BAO_{LPO} was not established for either dose of intravenous PANTO.

Other analyses showed that each dose of I.V. PANTO treatment was accompanied by significant lower acid ecretion (wither MAO vs BAO) than the I.V. placebo group. In the latter, both MAO and BAO increased substantially after stopping oral PANTO therapy. For example, in the ITT population with the 40 mg PANTO dose, MAO_{LPO} was 6.49 mEq/h, $MAO_{LI.V.}$ was 6.62 mEq/h and this was substantially lower than the $MAO_{LI.V.}$ seen with I.V. placebo (29.19 mEq/h). The values seen with the 20 mg PANTO dose were 14.50, 11.05 and 30.50 mEq/h, respectively. In addition, with I.V. placebo, the corresponding values for the 40 and 20 mg groups were 29.19 and 21.66 mEq/h.

As expected, both MAO and BAO increased substantially after stopping oral PANTO therapy. Although the use of antacids was significantly lower in the 40 mg I.V. PANTO group than in the PL group, the use of antacids was unchanged after switchover from oral to I.V. PANTO therapy.

In study –309-US, 40 (and 20) mg doses of intravenously administered PANTO were safe and well tolerated. There were no deaths reported. Three patients were withdrawn from the trial; two of these were due to AEs most likely related to the procedure. The rate of occurrence of treatment-emergent AEs was similar among all the four treatment groups; there was no correlation observed between drug dose and treatment-emergent AEs. Not unexpectedly, headache and dyspepsia were the most commonly reported adverse experiences for all treatment groups, including placebo.

XI. STUDY 3001K1-100-US

"A dose-range study of inhibition of pentagastrin induced bastric-acid secretion by single doses of ntravenous pantoprazole, intravenous famotidine and oral pantoprazole; Final Report"

Date of Report: 29 May 1998

Principal Investigator: Joseph Pisegna, M.D.
CURE/West LA VA Medical Center
Los angeles, CA

Results of this study have been published in Abstract form.[13]

1. Objective

- The primary objective of this trial was to assess the magnitude and time course of inhibition, by various doses of i.v. PANTO, of pentagastrin (PG)-stimulated gastric acid secretion in healthy subjects, as a model for patients with ZES.

- The secondary objectives were to compare these variables with those mediated by oral PANTO, I.V. famotidine, and placebo, and to determine the pharmacodynamic dose response of PANTO I.V. over a sixfold dose range (20, 40, 60, and 120 mg).

[13] [J. Pisegna et al. Inhibition of pentagastrin-induced gastric acid secretion by intravenous pantoprazole: a dose ranging study (Abstr.). Gastroenterology (Suppl.) p. A-274 (1998)]

2. Study Population

This consisted of essentially healthy men and women. The inclusion criteria and the reasons for exclusion were adequate for this type of study. Included were volunteer subjects that were to be healthy, of either sex (non-pregnant, non-lacting females), 18 to 45 y of age, with body weights within 15% of the ideal for sex, height, and frame as specified by the 1983 Metropolitan Height and Weight Tables.[14] Subjects were to have a) no significant abnormal cardiovascular, endocrine gastrointestinal, hematologic, hepatic, neurologic, psychiatric, renal, or respiratory findings at the prestudy screening evaluation, as determined by the investigator; b) a high probability for compliance and completion of the study and c) clinical laboratory values within the normal limits of the investigator's laboratory and normal results for a 12-lead electrocardiogram (EKG), unless the investigator documented that the deviations were not clinically significant. In addition, in order to participate in the trial, subjects were to sign and date an IRB-approved IC form in the presence of a witness before study entry. Women of childbearing potential[15] were to use a medically acceptable method of birth control.

3. Study Design[16]

From the review of the evidence, this was an open-label, single site, single-dose, placebo- and comparator-controlled, rising dose trial conducted in apparently healthy men and women.

4. Study Periods

a. Pre-study Screening

Each subject was to undergo a complete clinical evaluation 2 to 14 days before test medication administration consisting of the following:

- Medical history including ethnic origin
- P.E. including height (cm), weight (kg), and frame size (small, medium, large)
- Sitting vital signs (oral temperature, BP, pulse rate, and respiratory rate)
- Standard 12-lead EKG
- Routine laboratory evaluation
- Blood chemistry
- Routing urinalysis: protein, glucose, ketones, nitrites, blood or Hb, and leukocyte esterase
- Serology for *H. pylori* antibody
- Urine drug screen for drugs of potential abuse (eg, marijuana, cocaine, opiates, amphetamines, and barbiturates)
- Pregnancy test (serum β-HCG) for female subjects only: prestudy and on day −1

---

[14] (Protocol Attachment 2). The determination of body frame size was to be made using protocol Attachment 3.

[15] (A woman of childbearing potential was defined as a woman who was biologically capable of becoming pregnant.).

[16] Under the original protocol (submitted to the FDA on 10 December 1996), rising doses of PANTO lyophile were administered to subjects in Group 1. Amendment 1 (submitted on 19 may 1997) granted the sponsor the option to review preliminary data in order to discontinue enrollment for a dose group and to reassign remaining subjects to another dose group. Under Amendment II submitted on 23 June 1997) Groups 2, 3, and 4 were added, to which were administered. respectively. PANTO tablet, famotidine I.V. and placebo I.V.

- Stool for occult blood (3 specimens)
- Serology for hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV) antibody, and human immunodeficiency virus (HIB).[17]

b. Pre-study Period

Subjects were to be admitted to the study unit on day –1. They were given a brief physical evaluation, including a 12-lead EKG and vital signs, and provided samples for a urine drug screen, laboratory evaluation, and serum pregnancy test for women. After an evening meal, subjects were required to fast for at least 6 h before NG tube insertion and to eat no leafy green vegatables for at least 12 h. On the morning of day 1, the NG tube was inserted approximately 1 h before pentagastrin was administered.

c. Study Period

During this period subjects underwent complete physical, vital sign and laboratory evaluation, pentagastrin administration, administration of the I.V. test medication; they were given I.V. fluids (maintenance plus gastric volume loss). Gastric Acid Contents and gastric pH (optional) were measured at the times specified in Table 16.

[17] HIV status was not recorded on the CRF.

TABLE 16
Study 3001K1-100-US

Sample Measurement Flow Chart

I. For I.V. Study Drugs (Groups 1, 3, and 4)

Day	PG Stabilization								1																				
Hour	-1	-.75	-.5	-.25	0	.25	.5	.75	1	1.25	1.5	1.75	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5
Min		-.45	-30	-15		15	30	45		15	30	45		30		30		30		30		30		30		30		30
Gastric Acid Secretion Measurement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
pH (optional)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(Continued)

Day	1																		2										
Hour	10	10.5	11	11.5	12	12.5	13	13.5	14	14.5	15	15.5	16	16.5	17	17.5	18	18.5	19	19.5	20	20.5	21	21.5	22	22.5	23	23.5	24
Min		30		30		30		30		30		30		30		30		30		39		39		39		39		30	
Gastric Acid Secretion Measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
pH (optional)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

II. For Oral Pantoprazole (Group 2)

Day	1																												
Hour	-1	-.75	-.5	-.25	0	.25	.5	.75	1	1.25	1.5	1.75	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5
Gastric Acid Secretion Measurement													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
pH (optional)													X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

(Continued)

Day	1																												
Hour	10	10.5	1	11.5	12	12.5	13	13.5	14	14.5	15	15.5	16	16.5	17	17.5	18	18.5	19	19.5	20	20.5	21	21.5	22	22.5	23	23.5	24
Gastric Acid Secretion Measurement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
pH (optional)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

This Table is a composite from sponsor's Tables 6.1 C and 6.1 D, with minor modifications.

d. Post Study Period

At the end of the trial, a complete clinical evaluation was to be performed. This was to include a complete P.E., vital signs, an EKG, and a laboratory evaluation as described above. All clinical and laboratory evaluations after drug administration that deviated significantly from baseline or from the normal reference range, and that were considered to be clinically significant, were to be followed until the results returned to normal. If this did not occur within 2 weeks or within a reasonable period, the etiology was to be identified, if possible, and W-AR notified.

5. Clinical Supplies, Methods of Assignment to Treatment Groups/Dosage Schedules/Concomitant Therapy

Summarized below is the information on the identity of the investigational products.

Protocol No. 3001K1-100-US

Drug Information

Drug and Dosage	Dosage Form	Batch No.	Formulation No.	Manufacturer
PANTO lyophile	40 mg/vial	9620679	0930662J	Byk Gulden
PANTO tablet, enteric-coated	40 mg	9620674	923001302303AA	Byk Gulden
PANTO tablet, enteric-coated	40 mg	W22341A	053001300AC	Byk Gulden
Famotidine (PEPCID Injection Premixed)	50-mL iso-osmotic solution	2199e	929874	Trade package (Merck)
Pentagastrin	2 mL/ampule, 0.25 mg/mL	Lot No. L042	9184910A	Trade package (Wyeth-Ayerst) NDC 0046-3290-10

Subjects were assigned to treatment groups according to the method described below.

- The first 8 eligible subjects in group 1 were assigned to receive 40 mg PANTO I.V.
- Additional subjects in Group 1 were randomly assigned to the 20 mg, 80 mg, and 120 mg dose groups according to the randomization table shown in the protocol.
- After Group 1 completed, additional subjects were enrolled sequentially in Groups 2 through 4 under Amendment II.
- There was to be no oral fluid or food intake permitted during the entire study period. However, maintenance I.V. fluids were to be started prior to initiation of the PG infusion and fluid volume lost from gastric aspiration was to be replaced continuously over the 25 h (24 h for Group 2) of the PG infusion.[18]
- On the morning of day 1, subjects had an NG tube (ca. 14 French) placed. This tube was to be passed into the dependent portion of the stomach, and its position ascertained by an accepted method such as the phenol red or the water recovery method. If the investigator suspected an incorrect placement of the tube (ie, a subject developed gastrointestinal

[18] Maintenance fluids were to be begun before initiation of the PG infusion at a rate of 100 ml/h to prevent dehydration. Dextrose 5% and 0.45% NaCl with 20 mEq/L KCl solution were infused in conjunction with the PG.

discomfort or there was a rapid change in volume of aspirated gastric fluid) during the course of the study, the subject could receive up to two radiological (x-ray/fluoroscopy) evaluations to determine proper placement of the NG tube.[19]

- Gastric secretions were to be continuously aspirated with low, continuous suction throughout the study period such that all gastric juice was removed, and the contents of the gastric aspirate samples were to be analyzed in an ongoing manner for total acid content by titration to pH 7.0 (and an optional pH to be determined by the site).

- In the case of subjects receiving I.V. test medication or PL, the secretions were to be collected in 15-min fractions for the first hour of the PG infusion. After I.V. test medication was administered, one hour after the beginning of the PG infusion, gastric aspirate fractions were to be collected every 15 min for 2 h, and then every 30 min until the end of the study period.

- In the case of subjects receiving PANTO tablet, the PG infusion was to begin at the time that test medication was administered. For the first 2 h after that, the NG tube was to be clamped (ie, no secretions aspirated) in order to permit the oral medication to pass through the stomach.

- 2 h after administration of PANTO tablet, the NG tube was to be unclamped and gastric secretions continuously aspirated throughout the study period as described above. The secretions were to be collected in 30-min fractions throughout the remainder of the study period.

- All test medications were administered as single doses, and the actual time of administration recorded on the CRF.

- Concomitant medications were not to be permitted (except non-oral hormonal contraception or hormone replacement therapy used by female subjects) during the study. However, if needed, any concomitant medication required for treatment was to be recorded on the CRF and the W-AR monitor notified. In addition, the name of the drug, dose, date, and time of administration was to be recorded during the confinement period; the consumption of any alcohol- or xanthine-containing products (ie, coffee, tea, choclate) was prohibited for 48 h before and during the study period.

6. Summary of Mode of Administration of Test Medication

a. Test Medication

Pantoprazole lyophile: 40 mg/vial, manufactured by Byk Gulden, batch number 9620679, dissolved in 0.9% sodium chloride; final volume infused intravenously was 90 mL, at a rate of 6 ml/min over 15 minutes; dose varied according to dose group (20, 40, 80, or 120 mg).

Pentagastrin (PG): 0.25 mg/mL, manufactured by Wyeth-Ayerst, lot number 1042, administered at 1 μg/Kg/h at a rate of 10 mL/h. Pentagastrin and study drugs were infused in opposite arms.

b. Reference Therapy

Famotidine (FAM): PEPCID Injection Premixed, 50 mL iso-osmotic solution at 0.4 mg/mL (20 mg total), manufactured by Merck, batch number 2199c; 20 mg (50 mL) infused over 15 min.

---

[19] This measure was to be applied only in the event that it was not possible for the investigator to demonstrate with acceptable certainty the position of the NG tube.

Placebo I.V.: 80 mL 0.9% sodium chloride, infused over 15 min.

Oral pantoprazole: 40 mg enteric-coated tablet, manufactured by Byk Gulden, 2 different batches used 9620674 and W22341A.

7. Bioanalytical Methodology

Assays for pH and acid content were performed in the laboratory of the investigator. Clinical chemistry analyses were performed by SK Labs. for pre-study samples. Analysis of the samples collected during the trial was performed[redacted]. The rate of acid output was calculated by W-AR from the acid concentrations and volumes recorded in the CRF.

8. PK, PD and Statistical Analyses

- Because this was an exploratory dose ranging study in apparently normal subjects to assist in dose choice for definitive trials in ZES patients and to determine the dose response range, sample size determination was made on practical, not statistical, considerations.

- A formal analysis of PK parameters was not presented, as PANTO concentrations were not measured as part of the trial. Instead, a computer model of the PD/PK characteristics of intravenously administered PANTO was generated and presented.

9. Safety Assessment Methods

These were all adequate. They were based on reports of study events and results of routine physical examinations, EKGs, and laboratory determinations.

- The criteria for determining potentially important clinical changes[20] in vital signs were as follows.

Variable	Criteria
Pulse rate	Increase of ≥15 beats/min and rate ≥120 beats/min or Decrease of ≥15 beats/min and rate ≤50 beats/min
Systolic blood pressure	Increase of ≥20 mm Hg and pressure ≥180 mm Hg or Decrease of ≥20 mm Hg and pressure ≤90 mm Hg
Diastolic blood pressure	Increase of ≥15 mm Hg and pressure ≥105 mm Hg or Decrease of ≥15 mm Hg and pressure ≤50 mm Hg

- The W-AR criteria for determining potentially clinically important changes in EKG results were as follows.

[20] Baseline values were calculated as the mean of all values before the first dose, including those from prestudy screening, day –1, and day 1 before actual dose administration.

Variable	Criteria
PR interval	Increase of ≥ 10% from baseline to value > 240 ms
QRS interval	Increase of ≥ 120 ms
QTc interval	Increase of ≥ 10% from baseline to value > 460 ms
Rhythm	Change from normal to abnormal
Overall interpretation	Change from normal to abnormal

10. Results

a. Subject Disposition (Table 17)

- Of a total of 39 apparently healthy subjects enrolled, 33 completed the trial. All of the subjects were included in the safety analysis.

TABLE 17
Study 3001K1-100-US

Subject Disposition

I. ALL SUBJECTS			
Group	**Drug and Dose**	**Enrolled**	**Completed**
1	I.V. PANTO – 20, 40, 80 or 120 mg	27	24
2	Oral PANTO – 40 mg	4	2
3	I.V. FAM – 20 mg	4	4
4	PL	4	3
Total	**All groups**	**39**	**33**

II. DISPOSITION OF SUBJECTS WHO RECEIVED PANTO I.V.		
Dose (mg)	**Enrolled**	**Completed**
20	6	4
40	8	8
80	8	8
120	5	4

This Table is a composite of sponsor's Tables 7.1A and 7.1B, with major modifications.

b. Premature Withdrawals

- A total of 6 subjects W/D from the trial prematurely, all because of AEs, with the following distribution:

Group	n
1 (PANTO I.V.)	3
2 (PANTO ORAL)	2
4 (PL)	1
	6

AEs in these 6 subjects are discussed in detail under Results of Safety Evaluations

c. Protocol Violations

No significant protocol violations were reported in this study.

d. Demographic and Baseline Characteristics

- The number of subjects per group (Table 17) was too small so that comparisons of the proportion of patients falling under the various demographic factors resulted in apparent gross imbalances and was not very useful. Nonetheless, some generalizations[21] seem possible. All the participating subjects were apparently healthy, had no significant coexisting medical conditions and were between 21 and 45 y of age (mean = 31.4 y); 69% were F, 31% M; 59% were White, 31% Black, the rest Hispanic or Asian; the mean weight was 79.4 Kg..

e. Concomitant and Other Drug Therapy

- Subject 10015-0024 in the 80 mg PANTO I.V. group, received a dose (2 drops) of phenylephrine hydrochloride (Neo-Synephrine) at the time of PG administration on day 1 (study hour –1); 1 subject in the PL group received Nicorette for ca. 3 months. This medication was D/C 6 days before test medication was administered.

- In all instances where omeprazole, H_2-receptor antagonists, or antacids were given, as either concomitant medications or at or just after the time of discharge, they were given to relieve symptoms related to gastric acid secretion.

- 2 subjects received medications for the relief of these symptoms shortly before discontinuation: 10015-0023, who received 40 mg of FAM I.V. at study hour 14, 3 hours before discontinuing, and 10015-0029, who received Mylanta and Tylenol at study hour 18, one-half hour before discontinuing.

- 8 additional subjects received oral omeprazole and/or famotidine at the time of discharge or just after discharge: 10015-0007, -0014, -0018, -0033, -0034, -0036, -0037, and –0039 (subject 10015-0007 also received Mylanta).

[21] These are based on information presented by the sponsor in their Table 7.2A.

f. Results of Pharmacodynamic Evaluations

The variables measured or calculated were:

- onset of response (time until AO decreased to **under 10 mEq/h**)
- duration of response (time AO was **maintained at under 10 mEq/h**)
- magnitude of response (expressed as **relative decrease in AO at various time points**, as compared with the derived value for initial PG response (defined below)
  - cumulative AO over time and
  - gastric pH over time.

1) Pentagastrin[22] Stimulation as Model for ZES (Table 18)

This Table presents the response to PG before administration of study drugs for all groups except Group 2 (PANTO tablet).

- The overall mean PSAO for all four I.V. PANTO groups (n=27) was 16.7±11 (SD) mEq/h (range=1.2 to 58.4 mEq/h).

TABLE 18
Study 3001K1-100-US

Pentagastrin Response (PSA)), Hour –1 to Hour 0

PG-Stimulated Acid Output (AO) (mEq/h)	PANTO I.V. (mg) 20 [n=6]	40 [n=8]	80 [n=8]	120 [n=5]	All I.V. Doses [n=27]	FAM I.V. (mg) 20 [n=4]	PL [n=4]
Mean[a] ±SD	18.8 ± 8.8	22.3 ± 13.0	18.8 ± 17.4	6.9 ± 4.8	16.7 ± 11.0	29.1 ± 15.4	35.2 ± 9.3
Range	3.1 – 29.8	9.9 – 50.2	1.2 – 58.4	1.4 – 12.2	1.2 – 58.2	11.8 – 27.7	25.7 – 45.4

a) This Table corresponds to sponsor's Table 8.2.1A. with major modifications.

- These values were calculated by summing values from the four 15-min. fractions of gastric aspirate taken during the hour between hour –1, when PG administration was begun, and hour 0, when study drug was administered.
- For PL-treated subjects, mean (±SD) **hourly AO** from hours 1 through 24 was 34.2±3.0 mEq/h (with a range of 31.0 to 38.2 mEq/h).

[22] PG was administered I.V., at 1 μg/Kg/h, starting 1 h before infusion of the study drug and continued for 25 h, except for Group 2, in which I.V. administration of PG was begun at the same time as oral PANTO administration and continued for 24 h.

- A comparison of this value with the mean PSAO level of the PL group during hour –1 to hour 0 (35.2±9.3 (range 25.7 to 45.4 mEq/h) indicates that there was no decrease in response to PG over the 24 h of PG administration in the PL group.

2) Onset, Duration of PD Response and Cumulative Acid Output

Calculated rates of AO[23] for each subject, organized by dose group, were listed in sponsor's supportive Table 3 and DPR R6-1GAW, which listed gastric aspiration volume, acid concentration, calculated rate of AO, and gastric pH for each subject, was reproduced in sponsor's supportive Table 4.

Onset time was defined as the time at which AO levels fell below 10 mEq/h and the average rate over the next hour remained below 10 mEq/h.

Duration was defined as the time from onset until the time when AO levels rose above 10 mEq/h and the average rate over the next hour remained above 10 mEq/h.

If AO levels then dropped below 10 mEq/h for another period of time, another duration was calculated and the longest duration and its corresponding time of onset were reported.

Illustration of the Algorithm Used to Calculate Onset and Duration

This concept is illustrated in Fig. 1. Detailed explanation of the arrows in Figure 2 is given in the legend to this Figure. This example corresponds to the example given in the sponsor's Fig. 8.2.2A.

In the Clinical Report, it is noted that data from all but 1 subject were included in the calculation of the means of onset and duration: for **subject 10015-0007** in the 40 mg PANTO I.V. group, calculation of onset by the above algorithm yielded an unreliable value, and the data were therefore excluded. Data for the 5 subjects who withdrew trial (10015-0014, -0018, -0023, -0028, and –0029) were not included in the calculation of means for cumulative AO.

Results of the mean time to onset of response, the duration of response, and the cumulative AO are given in Table 19. This serves as a summary measure of the variables referred to above as well as of the **magnitude of the response**. Individual data were listed in sponsor's Supportive Table 1.

[23] Gastric aspirates were collected in 15-min fractions from hour –1 through the end of hour 2 and in 30-min fractions from hour 3 through the end of hour 24.

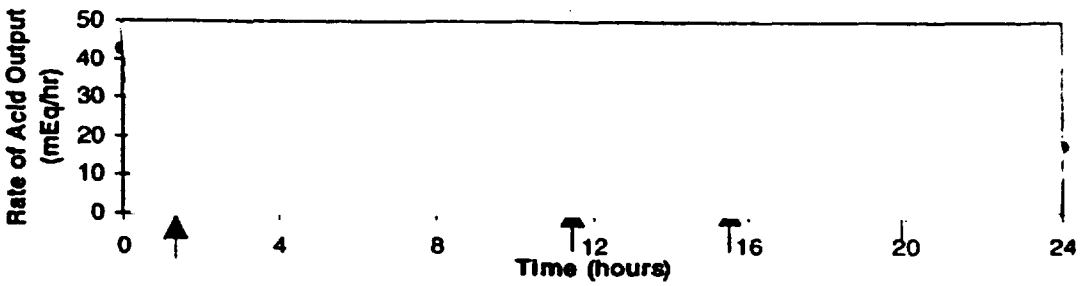

***Fig. 2.** – Example of Calculation of Onset and Duration. Data from Subject 10015-0010.*

In this example,

- ***The first time AO falls below 10 mEq/h and the average rqte over the next hour remains below 10 mEq/h is at 1.5 h.***
- ***The time point at which AO exceeds 10 mEq/h and the average rate of AO over the next hour remains above 10 mEq/h is at 10 h.***
- ***The above represents a duration of 8.5 h (1.5 h to 10 h).***
- ***Similarly, onsets are calculated at 11.5 h for a durqtion of 1 h, at 15.5 h for a duration of 3.5 h, and at 20 h for a duration of 1.5 h.***
- ***The longest calculated duration is 8.5 h with an onset of 1.5 h, and these are the values used in the calculation of the means for these variables.***
- ***If a subject's AO never fell below 10 mEq/h, the onset was set as missing and duration was set as 0, so as not to bias the means.***

TABLE 19
Study 3001K1-100-US

Results of Pharmacodynamic Evaluations: Onset, Duration of Response and Cumulative Acid Output (0-24h)

Variable	PANTO I.V. (mg)				PANTO Oral (mg)	FAM I.V. (mg)	PL
	20	40	80	120	40	20	
ONSET (h)							
n	5[a]	7[b]	8	5	4	4	
Mean ± SD	2.8 ± 3,3	1.6 ± 1.4	0.8 ± 0.3	0.4 ± 0.2	10.3 ± 4.5	0.5 ± 0.2	
Range							
DURATION (h)							
n	6	7[b]	8	5	4	4	
Mean ± SD	8.4 ± 8.0	15.9 ± 7.6	21.2 ± 1.9	20.8 ± 3.9	5.0 ± 2.9	6.5 ± 2.1	
Range							
CUMULATIVE AO (mEq)							
n[c]	4	8	8	4	2	4	3
Mean ± SD	355 ± 282	181 ± 96	80 ± 39	64 ± 8	294 ± 23	437 ± 143	829 ± 86
Range							

This Table corresponds to sponsor's Table 8.2.2A, with major modifications.

a) The values for subject 10015-0016 never fell below 10 mEq/h for an extended period of time, so no onset was calculable.

b) By the sponsor's onset and duration criteria, the values for subject 10015-0007 were considered unreliable and were not included in those means.

c) Subjects who withdrew from the study were not included in the calculation of cumulative AO means.

From the information depicted in Table 19, the following is concluded.

- Acid suppression activity in PANTO-treated subjects was observed within 15 to 30 min. post dose.
- Reduction of AO to <10 mEq/h occurred within 1 h post-dose with doses.of 80 and 120 mg of PANTO I.V. and with 20 mg of FAM I.V..
- The time of onset with the PANTO 40-mg tablet was **markedly longer.**
- 40 mg of PANTO I.V. suppressed AO for ca. 16 h but the duration was very variable among individual subjects in this dose group. The variability of both onset and duration time was also markedly less with the 80- and 120-mg doses than with the 20 and 40 mg doses.
- The duration of action of both 80 and 120 mg of PANTO I.V. was ca. 21 h. This was markedly longer than that of 20 mg of PANTO I.V., the 40-mg PANTO tablet or 20 mg of FAM I.V.

Information on mean cumulative AO with increasing dose levels of PANTO I.V. is depicted in Fig. 3. It is clear from this Figure that AO remained constant for the PL group over the entire 25-h PG administration. It is also clear that all PANTO I.V. doses drastically reduced cumulative AO, compared with PL, in a dose-dependent manner.

Consistent with the data shown in Table 19 for mean onset and duration of response, the cumulative AO among the various PANTO I.V. groups was markedly lower in the 80 mg and 120 mg groups than in the 20 and 40 mg groups. Also, there was a moderate numerical but not statistically significant difference in cumulative AO between the 80 and 120 mg groups.

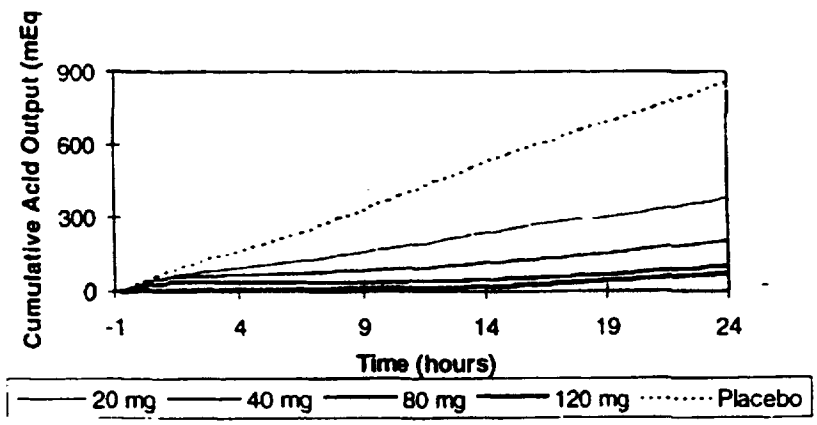

Fig. 3 – Mean Cumulative AO: PANTO I.V.
The sponsor reporduced Fig. 2 as their Supportive Fig. 1. Their supportive Fig. 2 (not reproduced in this review) presented the mean cumulative AO for the 20 mg I.V. FAM, 80 mg I.V. PANTO and PL treatment groups.

3) Magnitude of Response (Table 20)

This Table depicts the mean hourly AO rate for each dose group for both the entire 24-h study period (upper panel) and for sequential 6-h periods within the study. The following is worth noting.

- PANTO 40 mg I.V. (and 80 and 120 mg) is more effective than PANTO 40 mg oral, FAM 20 mg I.V. and certainly PL in decreasing AO during the entire 24-h period.
- There were notable differences between PANTO 40 mg I.V. (more effective) and PANTO 40 mg oral at periods 0-6 h, 6-12, but less difference at 12-18 h and 18-24 study periods.
- The effect of FAM 40 mg I.V. was, as expected, of short duration (at the 0-6 h period FAM 20 mg I.V. was more effective than PANTO 40 or 20 mg I.V., although less effective than PANTO 80 or 120 mg I.V).
- At all time periods and as expected, PL treatment was associated with the highest hourly rate of AO than any comparator at any dose.

TABLE 20
Study 3001K1-100-US

HOURLY RATE OF ACID OUTPUT (mEq/h)

	PANTO I.V. (mg)				PANTO Oral (mg)	FAM I.V. (mg)	
Variable	20	40	80	120	40	20	PL
AO/h OVER STUDY							
n	6	8	8	5	4	4	4
Mean ± SD	11.9 ± 10.3	7.6 ± 4.0	3.3 ± 1.6	2.4 ± 0.7	13.6 ± 4.8	18.2 ± 5.6	34.2 ± 3.0
Range							
0 – 6 h							
n	6	8	8	5	4	4	4
Mean ± SD	11.7 ± 10.5	8.1 ± 5.4	2.4 ± 1.5	1.3 ± 0.8	16.6 ± 4.7	4.4 ± 2.5	34.1 ± 8.7
Range							
6 – 12 h							
n	5	8	8	5	4	4	4
Mean ± SD	13.6 ± 13.3	4.8 ± 4.0	1.2 ± 0.6	0.7 ± 0.2	13.4 ± 7.2	17.7 ± 5.1	35.8 ± 8.7
Range							
12 – 18 h							
n	4	8	8	4	3	4	3
Mean ± SD	15.1 ± 13.7	7.3 ± 4.1	3.7 ± 1.9	3.7 ± 0.7	9.6 ± 4.4	25.8 ± 9.3	34.8 ± 2.2
Range							
18 – 24 H							
n	4	8	8	4	2	4	3
Mean ± SD	14.2 ± 8.6	10.1 ± 3.7	6.1 ± 3.2	5.2 ± 0.4	11.5 ± 2.9	25.0 ± 10.4	33.1 ± 9.6
Range							

This Table corresponds to sponsor's Table 8.2.3.A. with major modifications.
The rate of AO for each individual over the entire study was calculated by dividing his or her cumulative AO from time 0 to the end of the PG stimulation period by the total time that the subject received PG.

Each 6-h rate of AO was calculated as the cumulative AO over the 6-h period divided by 6 hours.

Data for individual subjects' percent inhibition of AO for these time intervals were listed in sponsor's supportive Table 1

Table 21 depicts the mean percent inhibition of AO at various times after administration of test medication as compared with an average maximal PSAO during the initial 2h of PG infusion. Once again, the two highest dose levels of PANTO I.V. (80 and 120 mg) were more effective than the two lowest doses (40, but especially 20 mg I.V.). The effect of FAM 20 mg I.V. was short-lived.

TABLE 21
Study 3001K1-100-US

Percent Inhibition of Acid Output[a]
PANTO I.V. vs FAM I.V.

	% INHIBITION AT SPECIFIED HOURS			
	4	8	12	24
20 mg PANTO I.V.				
Mean ± SD	83 ± 21	67 ± 30	54 ± 44	45 ± 43
Range				
40 mg PANTO I.V.				
Mean ± SD	90 ± 11	89 ± 12	81 ± 13	52 ± 36
Range				
80 mg PANTO I.V.				
Mean ± SD	99 ± 1	94 ± 7	90 ± 7	63 ± 18
Range				
120 mg PANTO I.V.				
Mean ± SD	100 ± 1	95 ± 6	83 ± 7	0 ± 60
Range				
20 mg FAM I.V.				
Mean ± SD	94 ± 5	64 ± 27	2 ± 34	5 ± 60
Range				

This Table corresponds to sponsor's Table 8.2.3B, with major modifications.
a) This parameter was calculated as:
[1 – (average rate of AO over time period)/average maximum PSAO h – 1 to h 1]•(100%).

The average maximum AO (PSAO) for each subject was calculated by the sponsor by taking the maximum PSAO during the period [hour – 0.75 to hour 1] and averaging it with the PSAO during the preceding and following 15-min. collection periods. This method is based on historical convention. According to the sponsor, the calculated values were presented for completeness and comparison, but no formal conclusions should be inferred.

The mean rate of AO for each PANTO I.V. dose group over time is displayed in Fig. 4[24]. It is clear from this Figure that AO for the PL group remained well differentiated from all PANTO I.V. doses over the entire 25-h PG administration and in a dose dependent fashion. For the first 16h the two highest doses of the drug (80 and 120 mg) appear to be more effective than the lower doses (especially the
20 mg dose).

[24] The data shown in this Figure are also reflected in Table 19 and in Figure 3.

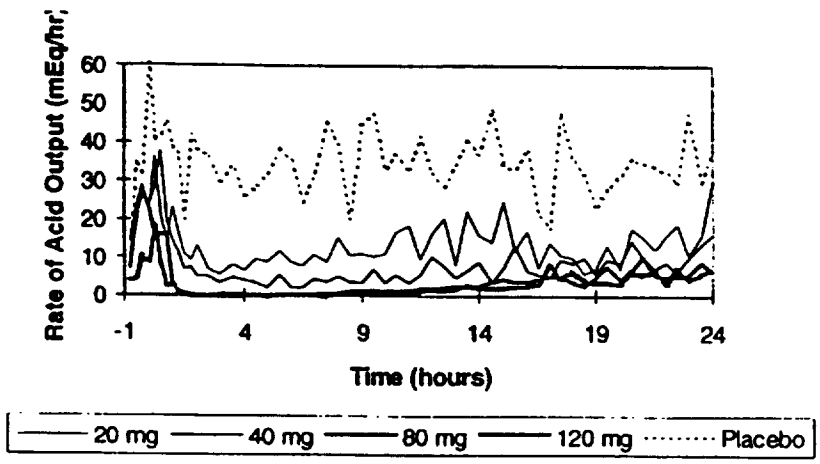

Fig. 4. *- Study 3001K1-100-US: Mean Rate of Acid Output*

g. PK/PD Modeling

The sponsor stated that a formal analysis per se of PK parameters was not possible for this trial. However, a computer model of the PD/PK characteristics of intravenously administered PANTO was generated and was included in the Clinical Report. The PK/PD model developed described the profile of PG-stimulated gastric acid secretion after a 15-min. I.V. infusion of 20, 40, 80 or 120 mg of PANTO or PL in apparently healthy subjects.

- Because PANTO concentrations were not measured during this study, PK data from Byk Gulden study FHP003 were used to build the pharmacokinetic model.[25] In that study, serum concentrations of PANTO were measured after a 15-min. I.V. infusion of 10, 20, 40, or 80 mg of PANTO. The function Q_1/V_c describing the PANTO concentration-time profile was fitted simultaneously to the mean data (minus the 10 mg group) by using a two-compartment first-order elimination I.V. infusion model.

- The modeled PANTO concentration data, including a stimulated 120 mg dose group, served as the drug input to the following irreversible effect PD model. This model was fit simultaneously for all dose levels (20, 40, 80 and 120 mg):

[25] [W. Wurst. Influence of repeated i.v. administration of B8610-23/SK&F96022-Z on the elimination of diazepam in healthy volunteers. Byk Gulden Report 34/90-K2 (W-A GMR 30074) (1991)]

$$\frac{dR}{dt} = -k \bullet C \bullet R + k_{prod} - k_{red} \bullet R \qquad \text{with} \qquad k_{prod} = k_{red} \bullet R_o$$

where R is the rate of AO
Ro is the baseline rate of gastric acid output, obtained from the rate of acid output for the PL treatment group averaged over the 0 h to 24 h range
k is the first-order rate constant for reduction of acid secretion due to PANTO
C is the serum concentration of PANTO
k_{prod} is the zero-order rate constand for production of acid with PG administration
k_{red} is the first-order rate constand for endogenous reduction of gastric acid secretion.

- The results of the model fitting for the PK data are presented graphically in Fig. 5. The mean ± SE parameter estimates for several PK parameters calculated from the two-compartment first order elimination i.v. infusion model were:
-

PK Parameter	Mean ± SE Parameter Estimate
Rate Constant from the central to the peripheral compartment [k_{12}]	0.4 ± 0.09 h^{-1}
Rate constant from the peripheral to the central compartment [k_{21}]	0.91 ± 0.09 h^{-1}
Elimination rate constant from the central compartment [k_{10}]	1.12 ± 0.06 h^{-1}
Volume of distribution for the central compartment [V_c]	6.9 ± 0.5 L

- The results of the model fitting for the PD data are presented in Fig. 6. Analysis of PD parameters in this Figure, resulted in the following mean ± SE parameter estimates.

PD Parameter	Mean ± SE Parameter Estimate
Baseline rate of gastric AO, obtained from the rate of AO for the PL treatment group averaged over the 0h to 24h range [R_o]	35 ± 1.6 mEq/h
First-order rate constant for endogenous reduction of gastric acid secretion [k_{red}]	0.007 ± 0.001 h^{-1}
First-order rate constant for reduction of acid secretion due to PANTO [k]	0.555 ± 0.019 h^{-1}
Zero-order rate constant for production of acid with PG administration [k_{prod}]	**0.22 mEq/h**

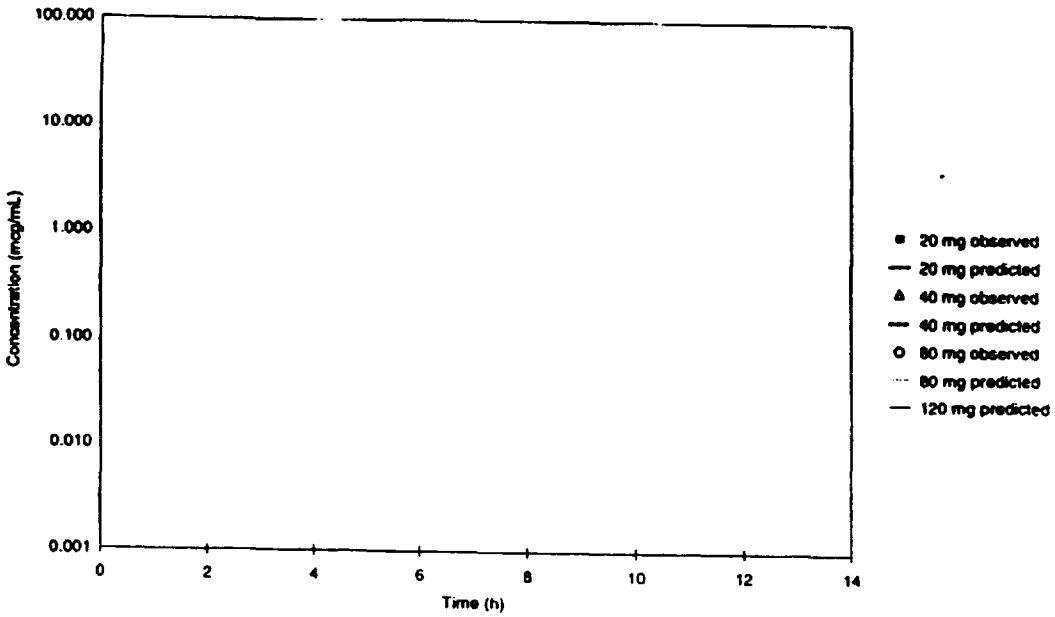

Fig. 5. – Study 3001K1-100-US: PK Profile of I.V. PANTO
The concentrations predicted for the 120 mg dose are based on the assumption that the dose proportionality is linear.

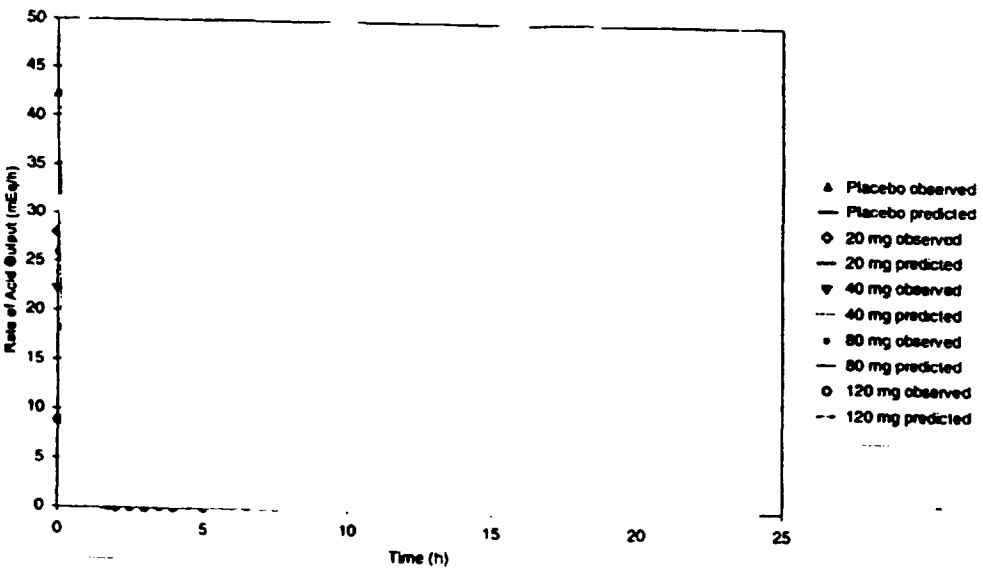

Fig 6. – Study 3001Kd1-100-US: PD Profile of I.V. Panto

Note the variable data for PL, the improvement over 20 mg when 40 mg of PANTO was given and the superimposable maximal AO reductions with the 80- and the 120-mg doses.

- From the mean ± SE parameter estimates, a k_{prod} (see above) value of 0.22 mEq/h is to be contrasted to the data for PL. Although quite variable, the latter demonstrated that a constant 1 μg/Kg/h PG infusion resulted in an approximate 35 mEq/h baseline gastric AO.

- There was a clear dose response for the reduction in AO between 20 and 120 mg of PANTO.

- A 20-mg I.V. dose of PANTO reduced AO by two-thirds to ca. **10 mEq/h**.

- There was more improvement when 40 mg of the drug was given as AO had dropped to **less than 5 mEq/h** by 2.5 h.

- As previously noted, both the 80- and the 120-mg doses showed maximal AO reductions that were virtually superimposable when modeled.

- The sponsor also noted that it is known that initial serum concentrations (C_{max}) of PANTO I.V. correlate with the magnitude of initial suppression of AO. Since PANTO binds irreversibly to the proton pump, and increases in AO over time are parallel across dose groups as a result of synthesis of new pumps, the initial magnitude of suppression of AO predicts the **relative duration of suppression of AO**.

h. Results of Safety Evaluations

- All subjects [n=39] received single doses of either PANTO I.V. (20, 40, 80 or 120 mg), PANTO tablets (40 mg), FAM I.V. (20 mg), or PL I.V.

- Exposure to PG was constant in proportion to body weight, 1 μg/Kg/h; length of exposure to this secretagogue depended on the dose and whether the subject completed the trial. All subjects who received I.V. drugs or PL and completed the study were exposed to PG for 25 h, whereas those who received PANTO tablets (Group 2) who completed the study were exposed to PG for 24 h (sponsor's Table 9.1A, not reproduced in this review).

- No deaths or SAEs were reported in the trial.

- AEs leading to discontinuation occurred in 6 subjects. As summarized in Table 22, reasons for D/C included dyspepsia [mostly mild] and gastrointestinal hemorrhage [also mild] due to the NG tube.

TABLE 22
Study 3001K1-100-US

Adverse Events Leading to Discontinuation

PANTO 20 mg I.V.	PANTO 120 mg I.V.	PANTO Tablet 40 mg	PLACEBO I.V.
10015-0014: **Dyspepsia** 28y-old F who developed epigastric distress beginning 7.5h after receiving test med. One h later, reddish brown NG secretions were seen. The PG infusion was terminated at h 10 due to continued reddish brown NG aspirates. W/D from the trial at h 11 due to "gastritis" and complications due to NG tube trauma. 10015-0018: **Dyspepsia** 47y-old M complained of nausea, dyspepsia and gastric reflux-like symptoms beginning 9h after receiving test med. Symptoms worsened over the next several hours; he also experienced cold sweating. PG was D/C at study hour 15 and the symptoms resolved. At study hour 17 the NG tube was removed and the subject received 40 mg PEPCID® I.V. Further exaluations were normal. He was discharged on the morning of Day 2.	10015-0023: **Vasodilation; nausea, local reaction to NG procedure.** 24y-old F developed these symptoms 11h after receiving test med. Symptoms continued for the next several hours. At study hour 14, the PG infusion was D/C due to the subject's discomfort (throat irritation and nausea). She received PEPCID® I.V. 40 mg. Symptoms resolved; the NG tube remained in place until study hour 17.	10015-0028: **Dyspepsia** 38y-old M developed nausea, a tolerable sinus headache apparently related to the NG tube, and intermittent regurgitation of acid into the upper esophagus and throat 15h after receiving test med. The frequency of heartburn and frontal headache increased and the NG was terminated at study hour 16 and removed 15 min. later. He developed diarrhea at study hour 20, after ingesting water and milk. A stool sample was (-) for Hb. His symptoms resolved 4h later. 10015-0029: **Abdominal pain, dyspepsia; g.i. hemorrhage[a]; nausea** 26y-old M developed mild upper abdominal discomfort 14h after receiving test med. The symptoms which progressively worsened to heartburn, frontal headaches and nausea, persisted and at study hour 17 PG infusion W/D due to minor gastric bleeding. At study hour 18, he received Mylanta 30 ml and Tylenol 650 mg to relieve symptoms. The subject reported a significant improvement in symptoms after the NG tube removal at study hour 18.5, with only mild epigastric discomfort.	10015-0036: **Abdominal pain, dyspepsia, gastrointestinal hemorrhage** 46y-old M, developed abdominal discomfort and g.i. bleeding ca. 9h after receiving I.V. PL. The PG infusion was D/C at study hour 11.5 due to the presence of blood clots in the NG aspirate. PEPCID® I.V. 20 mg was administered at study hour 12 and again at study hour 14. The next morning the subject was asymptomatic. At this time, a CBC and Hct were normal.

a) Evidenced by a small amount of "coffee ground" material observed in the NG aspirate.

- As summarized in Table 23, 16 of the 39 subjects who entered the trial reported a total of 34 AEs, mostly mild. The most frequently reported AEs were due to the treatment methodology, mostly the NG and/or consistent with the pharmacodynamic profile of pentagastrin. Not surprisingly the largest absolute number of AEs and the highest proportion of AEs per subject were reported by the groups receiving oral PANTO and those given PL I.V. All AEs resolved without clinical sequelae. Some of the participating subjects were administered nonstudy drugs concomitantly to releive symptomatic discomfort associated with stimulation of gastric acid secretion.

- There were no clinically important changes in laboratory results.

- Regarding clinically important changes in vital signs, subject 10015-0019 (PANTO I.V. 20 mg) was automatically flagged as having a slightly low sitting diastolic BP of 50 mmHg. This event, which was recorded one hour after administration of the drug, was judged by the medical monitor to have no clinical importance.

- No clinically important changes in EKG[26] parameters were reported.

11 Sponsor's Conclusion

This PG stimulation model in healthy subjects is valid for investigating the pharmacodynamic effects of pantoprazole I.V. in hypersecretory disease. Pantoprazole I.V. has a rapid onset of activity, and 80 and 120 mg afford nearly complete suppression of gastric acid output for up to 24 h. Given these findings, and the fact that the 80 mg dose has a mean duration of activity of 21 h, 80 mg every 12 h was recommended for further investigation in patients with Zolinger-Ellison syndrome.

[26] 12-lead EKGs were performed during prestudy screening, on day −1, and at the final evaluation. The variables assessed were HR, rhythm, PR interval, QRS interval, and QT_c. Any change from previous EKGs was noted; the criteria for flagging potentially clinically important changes in EKGs were listed in sponsor's Table 6.7.4A.

TABLE 23
Study 3001K1-100-US

Adverse Events by Body System: Number of Subjects With Events

	PANTO I.V. (mg)				PANTO ORAL (mg)	FAM I.V. (mg)	PL	Total (%)
	20 [n=6]	40 [n=8]	80 [n=8]	120 [n=5]	40 [n=4]	20 [n=4]	[n=4]	[n=a39]
Subjects with any AE	2	1	0	2	4	3	4	16
Total number of AEs	2	1	0	4	13	5	9	34
Body as a whole								
Abdominal pain	0	0	0	0	1	0	1	2 (5)
Headache	0	0	0	0	3	0	0	3 (8)
Cardiovascular system								
Vasodilation	0	0	0	1	0	0	0	1 (3)
Digestive system								
Diarrhea	0	0	0	0	1	0	0	1 (3)
Dyspepsia	2	0	0	0	2	1	3	8 (21)
GI hemorrhage	0	1	0	0	1	2	3	7 (18)
Nausea	0	0	0	1	2	0	0	3 (8)
Respiratory system								
Pharyngitis	0	0	0	0	0	0	2	2 (5)
Rhinitis	0	0	0	0	1	0	0	1 (3)
Skin and appendages								
Application site reaction	0	0	0	0	1	0	0	1 (3)
Urogenital system								
Hematuria	0	0	0	0	0	1	0	1 (3)
Terms not classifiable								
Injection site reaction	0	0	0	1	0	0	0	1 (3)
Miscellaneous study event								
Local reaction to procedure	0	0	0	1	1	1	0	3 (8)

This Table corresponds to sponsor's Table 9.2.1A, with some modifications.