B. Limited Food Study

Within-Study Validation

		Conc., ng/mL	CV, %	%Diff.
Std. Curve;	n=23	2.00	7.9	- 1.0
	n=23	4.00	4.9	- 2.2
	n=23	35.06	3.8	5.5
	n=23	100.07	2.8	-3.3
	n=23	350.64	1.9	0.6
	n=23	500.34	2.0	0.2
	n=23	600.41	2.4	-0.4
	n=23	700.48	3.6	1.9
	n=23	840.58	1.8	-0.3
	n=23	1051.12	2.5	-1.0
QC Samples;	n=53	5.01	6.1	-4.1
	n=51	300.36	2.7	-1.3
	n=52	800.97	2.6	2.2

1. Blood/Plasma Drug Concentration

The average plasma concentration data, test/reference ratios, and plasma profiles are given in Tables 11-12 and Attachment-7. T/R (food) ratios during 1-24 hours are 0.8-1.4, and food did not appear to change the drug plasma concentration.

2. Pharmacokinetic Parameters

- Average pharmacokinetic parameters and test/reference (food) ratios are given in Tables 13-14.
- The ratios of average test/reference (food) for AUCs and C_{max} are within 0.8-1 2 as required (Tables 14, 15).
- ANOVA analysis showed no significant sequence or period effects on AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, $LAUC_{0-inf}$, C_{max} and LC_{max}.
- Individual PK parameters are given in Attachments 8-10.
- Food appeared to show increased C_{max}, T_{max}, and AUCs values.
- None of the subjects had C_{max} at the first non-zero time point.

- Plasma concentration-time profiles were checked. $AUC_{0-\infty}$ were obtained correctly for all subjects.

C. Adverse Reaction: No significant differences between test and reference were observed (See the table below).

	No. Of Subjects			
Sign/Symptom	**Test (A)** Fast	**Test (B)** Fed	**Reference (C)** Fed	**Drug Related**
Nausea	3	0	0	Possible/Probable
Tired	1	0	0	Possible/Probable
Loss of Appetite	1	0	0	Possible/Probable
Stomach Pain	1	0	0	Possible/Probable
Headache	0	0	1	Possible/Probable

Conclusion: The non-fasting *in vivo* study is acceptable.

VI. FORMULATION

Table 16 shows the composition of 250 mg ticlopidine hydrochloride tablets manufactured by Invamed.

TABLE 11. MEAN PLASMA TICLOPIDINE HYDROCHLORIDE LEVELS FOR TEST AND REFERENCE PRODUCTS (N=22)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3
TIME HR					
0	0.00	0.00	0.00	0.00	0.00
0.5	26.67	76.16	8.04	22.98	18.92
1	253.93	407.30	184.79	255.06	206.57
1.33	353.91	398.85	389.21	426.67	367.97
1.67	399.78	296.88	438.06	358.39	461.38
2	390.51	230.61	451.91	273.51	465.22
2.33	361.75	163.42	430.40	204.19	398.72
2.67	339.03	136.31	391.51	211.78	312.24
3	315.03	163.22	343.97	195.62	248.34
3.5	272.63	195.04	276.51	171.72	185.52
4	209.35	174.91	217.29	156.04	132.66
6	71.64	61.15	74.45	46.07	53.27
8	39.86	26.53	43.59	24.31	34.97
12	21.64	9.99	25.08	11.55	19.54
16	15.64	7.90	17.97	8.26	14.04
24	11.09	4.54	11.76	4.77	9.37
36	7.39	3.38	8.33	3.33	5.91
48	4.69	1.77	5.54	2.02	4.25
72	2.55	1.61	3.05	1.85	1.99

1=TEST FED 2=REFERENCE FED, 3=TEST FASTING

TABLE 12. RATIO OF TEST/REFERENCE MEAN PLASMA Ticlopidine HYDROCHLORIDE LEVELS (N=22)
(UNIT: PLASMA LEVEL=NG/ML TIME=HRS)

	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR				
0	0.00	.	.	.
0.5	22.09	3.32	1.41	0.42
1	132.03	1.37	1.23	0.89
1.33	178.76	0.91	0.96	1.06
1.67	211.40	0.91	0.87	0.95
2	207.89	0.86	0.84	0.97
2.33	164.62	0.84	0.91	1.08
2.67	147.37	0.87	1.09	1.25
3	135.73	0.92	1.27	1.39
3.5	115.75	0.99	1.47	1.49
4	83.96	0.96	1.58	1.64
6	37.18	0.96	1.34	1.40
8	20.71	0.91	1.14	1.25
12	8.69	0.86	1.11	1.28
16	5.78	0.87	1.11	1.28
24	3.38	0.94	1.18	1.26
36	2.31	0.89	1.25	1.41
48	1.79	0.85	1.11	1.31
72	1.79	0.84	1.28	1.53

1=TEST FED 2=REFERENCE FED, 3=TEST FASTING

TABLE 13. TEST MEAN/REFERENCE MEAN (n=22; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	MEAN1	SD1	MEAN2	SD2	MEAN3
PARAMETER					
AUCI	2015.14	894.35	2170.98	948.35	1752.46
AUCT	2013.45	893.92	2169.08	947.81	1750.67
CMAX	637.22	359.45	664.37	335.15	523.24
KE	2.16	0.79	2.11	0.72	1.82
LAUCI	1830.18	0.46	1976.37	0.45	1628.56
LAUCT	1828.56	0.46	1974.50	0.45	1626.61
LCMAX	552.09	0.55	582.42	0.54	488.98
THALF	0.37	0.15	0.36	0.11	0.40
TMAX	2.16	0.79	2.11	0.72	1.82

1=TEST FED 2=REFERENCE FED 3=TEST FASTING (CONTINUED)

TABLE 14. TEST MEAN/REFERENCE MEAN RATIOS (n=22; ANTILOG CONVERSION)
(UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR)

	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER				
AUCI	720.26	0.93	1.15	1.24
AUCT	720.32	0.93	1.15	1.24
CMAX	201.46	0.96	1.22	1.27
KE	0.37	1.02	1.19	1.16
LAUCI	0.39	0.93	1.12	1.21
LAUCT	0.39	0.93	1.12	1.21
LCMAX	0.37	0.95	1.13	1.19
THALF	0.08	1.02	0.93	0.91
TMAX	0.37	1.02	1.19	1.16

TABLE 15. LSMEANS AND RATIOS (N=22)

	LSM1	LSM2	LSM3	RLSM12	RLSM13
PARAMETER					
AUCI	2044.59	2213.04	1781.92	0.92	1.15
AUCT	2042.90	2211.12	1780.11	0.92	1.15
CMAX	640.19	673.27	526.20	0.95	1.22
LAUCI	1853.99	2011.45	1649.74	0.92	1.12
LAUCT	1852.34	2009.57	1647.77	0.92	1.12
LCMAX	556.46	590.52	492.85	0.94	1.13

1=TEST FED 2=REFERENCE FED 3=TEST FASTING

[NOT FOR RELEASE UNDER F.O.I.]

Table 16. Composition of Invamed's Ticlopidine Hydrochloride Tablets

INGREDIENT	MG/TABLET
Ticlopidine Hydrochloride	250.0
Corn Starch,	
Hydroxypropyl Cellulose,	
Hydrogenated Vegetable Oil,	
Total Tablet Weight	**306.0**

*This component does not appear in significant quantity in the finished product.

VII. *IN VITRO* RESULTS (DISSOLUTION)

There is no USP method available. The firm has used water as dissolution medium (Table 17). The product passes the dissolution specification of r.

TABLE 17. *In Vitro* Dissolution Testing

A. Conditions

Method, Apparatus II (Paddle) **RPM: 50** **No. of Units: 12**
Medium: DI Water **Volume:** 900 mL
Reference Drug: Ticlid[R] **Manufacturer:** Syntex (Roche)
Assay Methodology:

B. Results

Sampling Time	Reference Product			Test Product		
(Minutes)	Mean % Dissol.	Range	CV	Mean % Dissol.	Range	CV
	Lot #07633A		Strength 250 mg	Lot # D970509		
5	64.6		16.4	69.1	)	25.9
10	92.9		3.1	98.5	1	1.8
15	97.6	1	2.9	100.1	2	1.1
30	99.9	3	2.3	100.3	2	1.3
45	101.3	5	1.8	100.5	3	1.5

VIII. DEFICIENCY

None

IX. RECOMMENDATION

1. The *in vivo* bioequivalence study conducted under fasting conditions by Invamed on its ticlopidine hydrochloride tablets, 250 mg strength, Lot #D970509, comparing it to Roche's 250 mg strength Ticlid[R] tablets, 250 mg strength, Lot #07633A, has been found acceptable by the Division of Bioequivalence.

2. The *in vivo* bioequivalence study conducted under non-fasting conditions by Invamed on its ticlopidine hydrochloride tablets, 250 mg strength, Lot #D970509, comparing it to

Roche's Ticlid[R] tablets, 250 mg strength, Lot #07633A, has been found acceptable by the Division of Bioequivalence.

3. The dissolution testing conducted by Invamed, on its ticlopidine hydrochloride 250 mg, Lot #D970509 is acceptable.

   The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37 °C using USP 23 Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

4. From the bioequivalence point of view, the firm has met the *in vivo* bioavailability and *in vitro* dissolution testing requirements for its ticlopidine hydrochloride 250 mg tablets, and the application is acceptable.

The firm should be informed of the recommendations.

/S/

S. P. Shrivastava, Ph.D.
Division of Bioequivalence
Review Branch II

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FT INITIALED SNerurkar /S/ 5/1/1998

Concur: /S/ Date: 5/4/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Attachments-10

SPS/sps/4-27-98/75318SD.198

Attachment-1

July 31, 1997

TABLE 1
RANDOMIZATION SCHEME
Project: 962265

A = Invamed 1 x 250 mg ticlopidine HCl tablet
B = Roche (Ticlid®) 1 x 250 mg ticlopidine HCl tablet

Subject ID	Study Period 1	2
1	B	A
2	A	B
3	B	A
4	B	A
5	A	B
6	A	B
7	A	B
8	B	A
9	A	B
10	B	A
11	A	B
12	A	B
13	A	B
14	B	A
15	B	A
16	B	A
17	B	A
18	A	B
19	A	B
20	B	A
21	A	B
22	B	A
23	B	A
24	A	B
25	B	A
26	A	B
27	B	A
28	A	B
29	B	A
30	A	B
31	A	B
32	A	B
33	B	A
34	B	A
35	A	B
36	A	B
37	A	B
38	B	A
39	A	B
40	B	A
41	A	B
42	B	A
43	B	A
44	B	A
45	A	B
46	B	A
47	A	B
48	B	A

Authentication: (S) Date: 31 JUL 97
Philippe Colucci, B.Sc.
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Pharmacokinetics Department

Approval: (S) Date: 31 July 1997
David Goblot, B.Sc.
Senior Project Manager,
Pharmacokinetics Department

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Attachment-2

22/Oct/1997

TABLE 1
RANDOMIZATION SCHEME
Project: 962266

A = Invamed 1 x 250 mg ticlopidine HCl tablet under fasting conditions.
B = Invamed 1 x 250 mg ticlopidine HCl tablet under fed conditions.
C = Roche (Ticlid®) 1 x 250 mg ticlopidine HCl tablet under fed conditions.

Subject ID	Study Period 1	2	3
1	A	B	C
2	C	B	A
3	B	A	C
4	A	C	B
5	C	B	A
6	A	C	B
7	A	C	B
8	C	B	A
9	B	A	C
10	A	B	C
11	C	A	B
12	A	C	B
13	A	B	C
14	B	A	C
15	C	A	B
16	A	B	C
17	B	C	A
18	B	C	A
19	C	A	B
20	B	C	A
21	C	A	B
22	C	B	A
23	B	C	A
24	B	A	C

Authentication: /S/ Date: 22/OCT/97
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Approval: /S/ Date: 22/Oct/97
Catherine Chin, B.Sc.
Project Manager,
Pharmacokinetics Department

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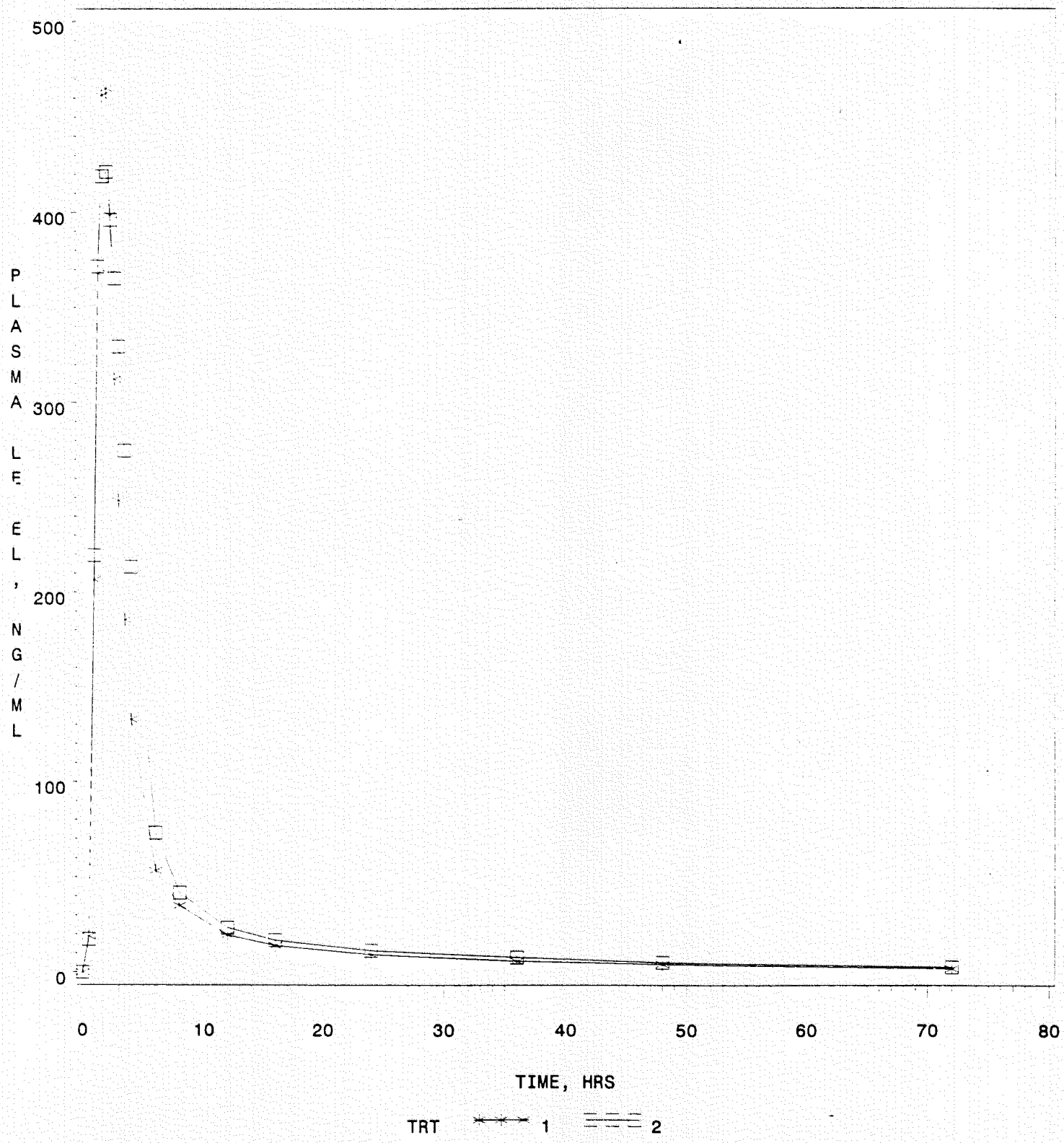
Attachment-3

FIG P-1. PLASMA TICLOPIDINE LEVELS (N=44)

TICLOPIDINE TABLETS, 250 MG, ANDA #75-318
UNDER FASTING CONDITIONS
DOSE=1 X 250 MG

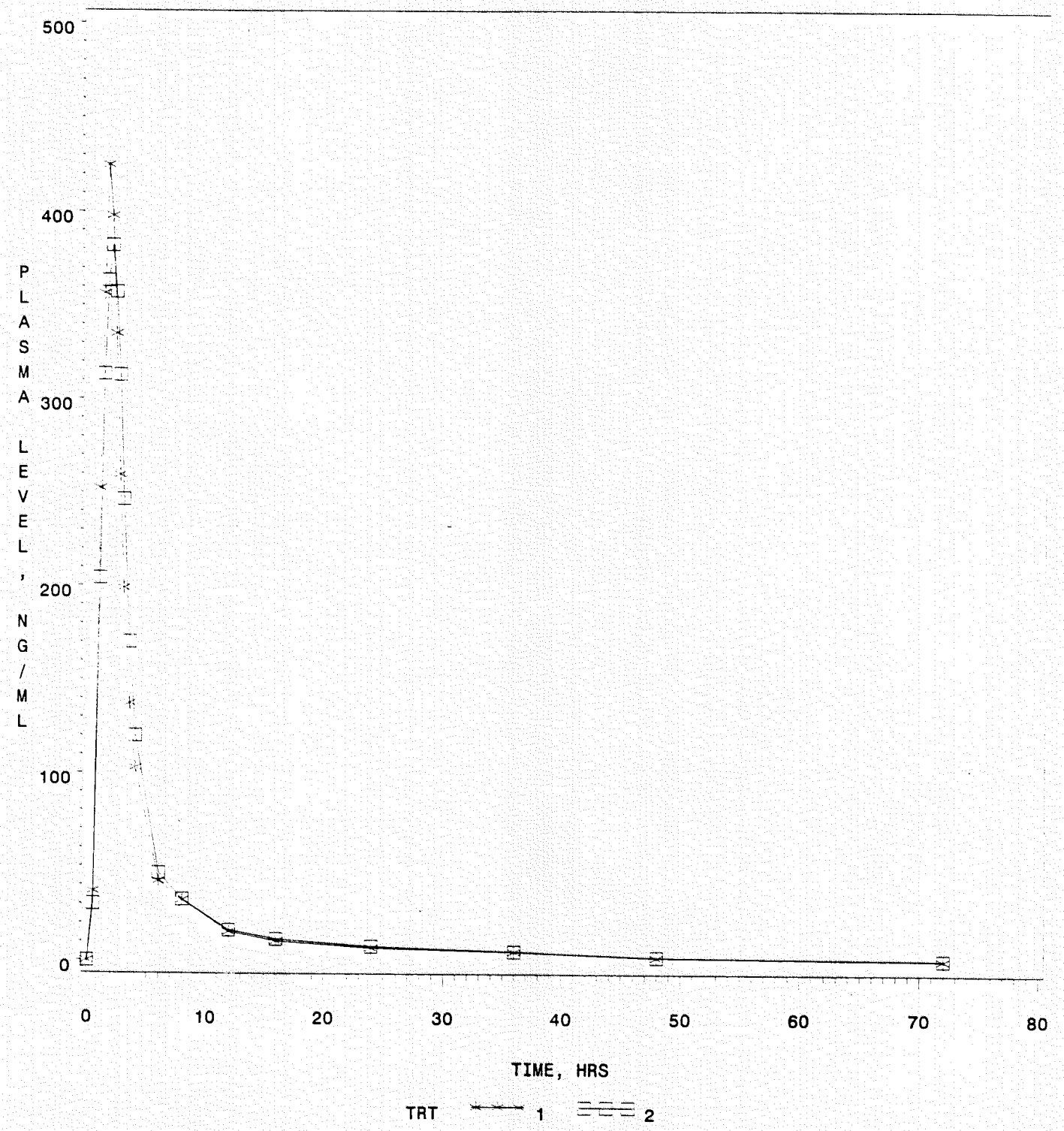


1=TEST(INVAMED) 2=REF(ROCHE)

Attachment - 4

FIG P-2. PLASMA TICLOPIDINE LEVELS (N=43)

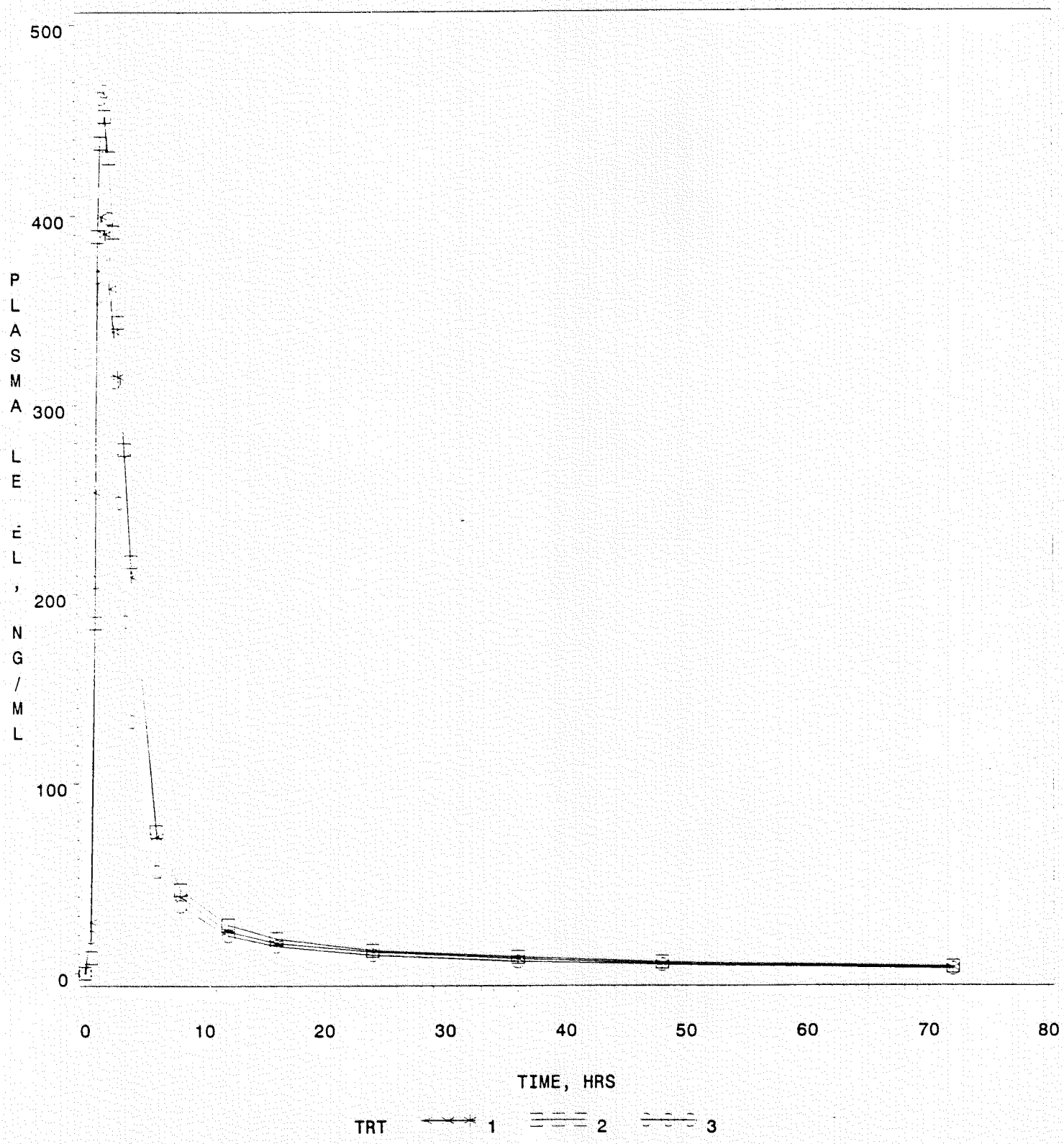
TICLOPIDINE TABLETS, 250 MG, ANDA #75-318
UNDER FASTING CONDITIONS
DOSE=1 X 250 MG



Attachment - 7

FIG P-3. PLASMA TICLOPIDINE LEVELS (N=22)

TICLOPIDINE TABLETS, 250 MG, ANDA #75-318
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 250 MG



1=TEST(INVAMED-FOOD) 2=REF(ROCHE-FOOD) 3=TEST(INVAMED-FAST)

28-Oct-1997 13:40

Table D3
Project Number :962265
Ticlopidine in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Invamed (A)

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC/AUCinf (%)	Cmax (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
25										
26										
27										
28										
29										
30										
31										
32										
33										
34										
35										
36										
37										
38										
39										
40										
41										
42										
44										
46										
Arithmeti					490.394	1.745	0.05455	16.263		
± SD		931.67	920.33	4.551	289.7878	0.4807	0.034829	6.8835		
CV%		64.9	60.0	4.8	59.1	27.6	63.8	42.3		
n		44	39	39	44	44	39	39		

AUCinf, kel, and half-life not estimable for some subjects

DEFAULT

PhAST PTAB 2.3-000

Attachment- 5(b)

000140

Table D4
Project Number :962265
Ticlopidine in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Roche (B)

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC/AUCinf (%)	Cmax (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
25										
26										
27										
28										
29										
30										
31										
32										
33										
34										
35										
36										
37										
38										
39										
40										
41										
42										
44										
46										
Arithmetic Mean		1481.8	1640.1	94.75	487.934	2.047	0.05257	15.793		
± SD		1019.68	1056.08	2.330	286.5646	1.0634	0.027634	5.5739		
CV%		68.8	64.4	2.5	58.7	52.0	52.6	35.3		
n		44	40	40	44	44	40	40		

AUCinf, kel, and half-life not estimable for some subjects

Attachment - 6(b)

Table D4
Project Number :962265
Ticlopidine in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Roche (B)

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC/AUCinf (%)	Cmax (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
20										
21										
22										
23										
24										

AUCinf, kel, and half-life not estimable for some subjects

000141

Attachment 6(a)

Table D3
Project Number :962265
Ticlopidine in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Invamed (A)

Subject ID	Period	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	AUC/AUCinf (%)	Cmax (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)	kel Start (h)	kel Stop (h)
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
20										
21										
22										
23										
24										

AUCinf, kel, and half-life not estimable for some subjects

000139

Attachment - 5(a)

Table D4
Project Number :962266
Ticlopidine in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Invamed (fast) (A)

Subject ID	Period	AUC 0-t	AUCinf	AUC/AUCinf	Cmax	tmax	kel	Half-life	kel Start	kel Stop
1										
2										
3										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
21										
22										
23										
24										
Arithmetic Mean		1750.8	1845.0	94.72	523.242	1.818	0.03687	19.81		
± SD		720.01	751.98	2.292	201.4589	0.3676	0.008271	4.836		
CV%		41.1	40.8	2.4	38.5	20.2	22.4	24.4		
n		22	21	21	22	22	21	21		

Aucinf, kel and half-life was not estimable for some subjects.

Attachment F-8

Table D5
Project Number :962266
Ticlopidine in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Invamed (fed) (B)

Subject ID	Period	AUC 0-t	AUCinf	AUC/AUCinf	Cmax	tmax	kel	Half-life	kel Start	kel Stop
1										
2										
3										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
21										
22										
23										
24										
Arithmetic Mean		2011.2	2111.0	94.91	637.224	2.159	0.03407	21.80		
± SD		894.97	916.14	1.467	359.4523	0.7863	0.009050	5.070		
CV%		44.5	43.4	1.5	56.4	36.4	26.6	23.5		
n		22	22	22	22	22	22	22		

Attachment - 9

Table D6
Project Number :962266
Ticlopidine in Plasma
Pharmacokinetic Parameters by Formulation
Formulation: Roche (fed) (C)

Subject ID	Period	AUC 0-t	AUCinf	AUC/AUCinf	Cmax	tmax	kel	Half-life	kel Start	kel Stop
1										
2										
3										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
19										
21										
22										
23										
24										
Arithmetic Mean		2167.9	2382.9	94.75	664.366	2.113	0.03397	21.56		
± SD		951.25	976.72	1.801	335.1515	0.7231	0.009262	4.675		
CV%		43.9	41.0	1.9	50.4	34.2	27.3	21.7		
n		22	20	20	22	22	20	20		

Aucinf, kel and half-life was not estimable for some subjects.

Attachment - 10