CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40301

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40-301 SPONSOR: Taro Pharmaceuticals USA, Inc.

DRUG & DOSAGE FORM: Warfarin Sodium Tablets

STRENGTH(S): 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg

TYPE OF STUDY: Three single dose fasting studies

STUDY SITE:(

STUDY SUMMARY: Bioequivalence between the test and reference products was determined on the basis of pharmacokinetic and dissolution data of warfarin tablets. The firm has conducted single-dose fasting studies on 2, 5, and 10 mg tablets, and dissolution testing on 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg strengths of test and reference products. The results of the studies indicate that Taro's 2, 5 and 10 mg tablets are bioequivalent to the reference product, Coumadin® 2, 5 and 10 mg tablets. The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{inf}$, and LC_{max} are in the acceptable range of 80-125 for single-dose studies.

DISSOLUTION:

The test products, 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg tablets meet the agency's dissolution specifications (USP Method). The amount of drug dissolved from the test product was NLT % in 30 minutes. Waivers for bioequivalence studies for 1, 2.5, 3, 4, 6, and 7.5 mg warfarin tablets are granted.

PRIMARY REVIEWER: S.P.Shrivastava, Ph.D. BRANCH: II

INITIAL: S.P.S DATE 10/30/98

BRANCH CHIEF: S. G. Nerurkar, Ph.D. BRANCH: II

INITIAL: DATE 11/2/1998

DIRECTOR

DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: DATE 11/2/98

DIRECTOR

OFFICE OF GENERIC DRUGS: Douglas L. Sporn

INITIAL: DATE

BIOEQUIVALENCY COMMENTS

ANDA: 40-301 APPLICANT: Taro Pharmaceutical, Inc.

DRUG PRODUCT: Warfarin Sodium Tablets 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of water, at 37 °C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 40-301
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Secretary - Bio Drug File
HFD-655/ SShrivastava

Printed in final on 7/9/98

Endorsements: (Final with Dates)
HFD-650/ SShrivastava 10/30/98
HFD-655/ SNerurkar 11/2/98
HFD-617/ L. Sanchez
HFD-650/ D. Conner 11/2/98

BIOEQUIVALENCY - ACCEPTABLE

1. **FASTING STUDY** (STF) Strengths: 2 mg
Clinical:
Analytical
Outcome: AC

2. **FASTING STUDY** (STF) Strengths: 5 mg
Clinical:
Analytical
Outcome: AC

3. **FASTING STUDY** (STF) Strengths: 10 mg
Clinical:
Analytical
Outcome: AC

4. **DISSOLUTION ~~DATA~~ (DIS)** 1, ~~2~~, 2.5, 3, 4, ~~5~~, 6, 7.5 and ~~10~~ mg
WAIVER (DIW Outcome: **AC**

Outcome Decisions:
AC - Acceptable

WINBIO COMMENTS:

Attachment - 1

TABLE 2

RANDOMIZATION SCHEME

A. Test: Single oral 4 mg (2x2 mg) dose of Taro Pharmaceuticals Industries Limited 2 mg warfarin sodium tablets.

B. Reference: Single oral 4 mg (2x2 mg) dose of DuPont Pharma USA (Coumadin®) 2 mg warfarin sodium tablets.

Subject No.	Study Period	
	1	2
1	A	B
2	B	A
3	A	B
4	B	A
5	A	B
6	B	A
7	B	A
8	A	B
9	B	A
10	B	A
11	A	B
12	A	B
13	B	A
14	A	B
15	B	A
16	A	B
17	A	B
18	A	B
19	B	A
20	B	A
21	A	B
22	B	A
23	B	A
24	A	B
25	A	B
26	B	A
27	A	B
28	B	A
29	B	A
30	A	B
31	A	B
32	B	A
33	B	A
34	A	B
35	B	A
36	A	B

Attachment - 2

CLINICAL REPORT

STUDY No.: (ANA) 97-129

RANDOMIZATION SCHEME

A. Test: Taro Pharmaceuticals Ind. LTD. Israel warfarin sodium 5 mg tablet USP
B. Reference: DuPont Pharma, USA warfarin sodium 5 mg tablet USP (Coumadin®)

Subject No.	Group*
01	3
02	4
03	2
04	4
05	2
06	3
07	2
08	2
09	1
10	1
11	3
12	3
13	1
14	2
15	4
16	4
17	3
18	2
19	4
20	1
21	1
22	4
23	3
24	1

RANDOMIZATION SCHEDULE

	Group I	Group II	Group III	Group IV
Period 1	Test 1	Reference 1	Test 2	Reference 2
Period 2	Reference 2	Test 1	Reference 1	Test 2
Period 3	Test 2	Reference 2	Test 1	Reference 1
Period 4	Reference 1	Test 2	Reference 2	Test 1

NOTE: Group I (seen in Randomization Schedule) = Group 1 (seen in Randomization Scheme)
In the same manner: II=2, III=3 and IV=4.

Attachment-3

TABLE 2

RANDOMIZATION SCHEME

A. Test: Single oral 10 mg dose of Taro Pharmaceuticals Industries Limited 10 mg warfarin sodium tablets.

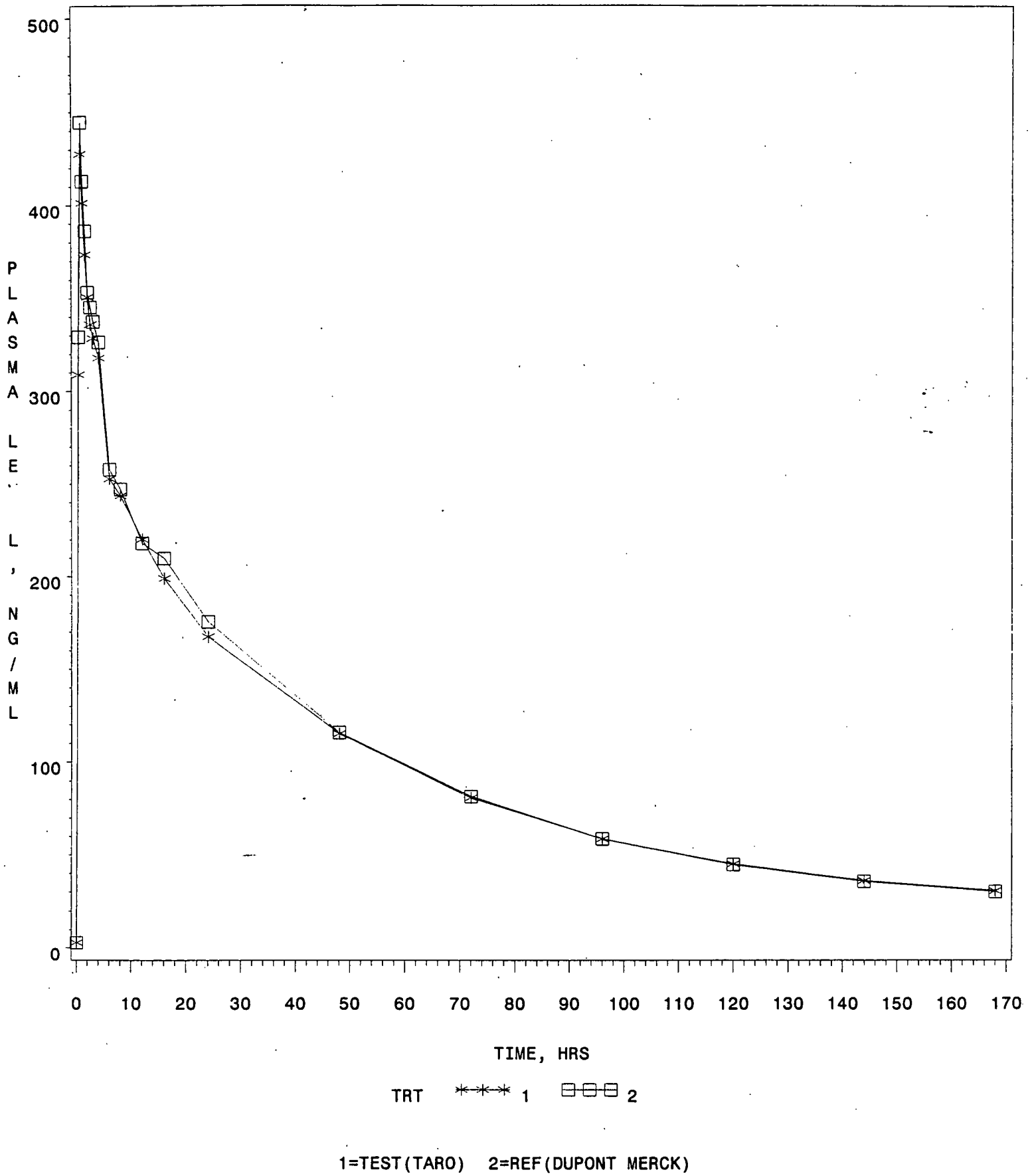
B. Reference: Single oral 10 mg dose of DuPont Pharma (Coumadin®) 10 mg warfarin sodium tablets.

Subject No.	Study Period	
	1	2
1	A	B
2	B	A
3	A	B
4	B	A
5	B	A
6	A	B
7	B	A
8	A	B
9	A	B
10	B	A
11	B	A
12	A	B
13	A	B
14	B	A
15	B	A
16	A	B
17	A	B
18	A	B
19	B	A
20	B	A
21	A	B
22	A	B
23	B	A
24	B	A
25	A	B
26	B	A
27	A	B
28	B	A
29	B	A
30	A	B
31	B	A
32	A	B
33	B	A
34	A	B
35	A	B
36	B	A

FIG P-1. PLASMA WARFARIN LEVELS (N=35)

WARFARIN TABLETS 2 MG, ANDA #40-301
UNDER FASTING CONDITIONS
DOSE=2 X 2 MG

Attachment 4

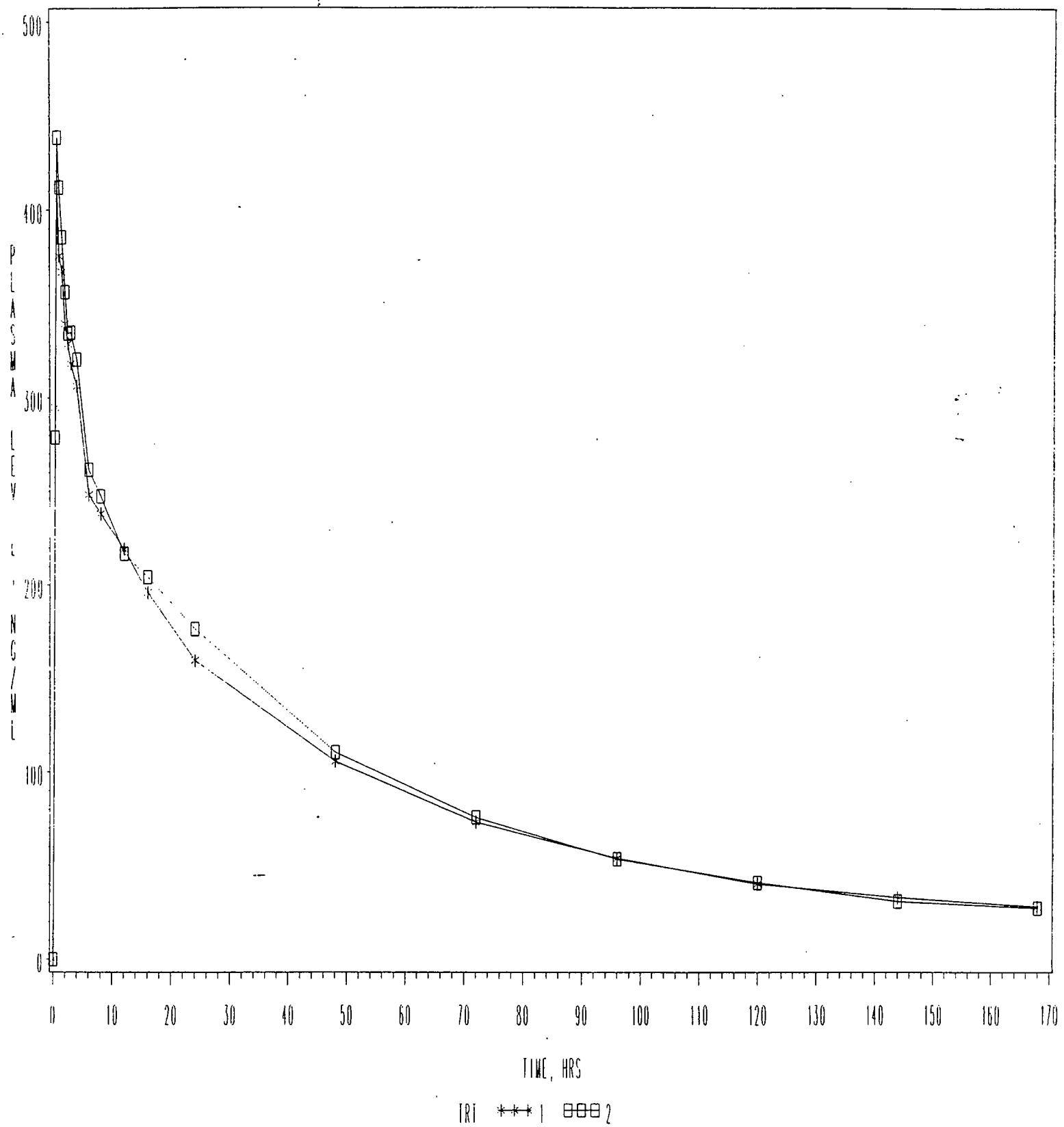


1=TEST(TARO) 2=REF(DUPONT MERCK)

FIG P-1a. PLASMA WARFARIN LEVELS (N=12)

WARFARIN TABLETS 2 MG, ANDA #40-301
UNDER FASTING CONDITIONS
DOSE=2 X 2 MG

Attachment - 5



1=TEST(TARO) 2=REF(DUPONT MERCK)

Attachment-6

2 mg Single Dose

TABLE D2
Project GP711
BIOAVAILABILITY PARAMETERS - WARFARIN
Observed Results

---------- Treatment=A:TARO ----------

Subject	PERIOD	AUC0-t (ng-hr/mL)	AUCinf (ng-hr/mL)	Cmax (ng/mL)	Tmax (hrs)	KEL (1/hrs)	Halflife (hours)
1	1						
2	2						
3	1						
4	2						
5	1						
6	2						
7	2						
8	1						
9	2						
10	2						
11	1						
12	1						
13	2						
14	1						
15	2						
16	1						
17	1						
18	1						
19	2						
20*	2						
21	1						
22	2						
23*	2						
24	1						
25	1						
26	2						
27	1						
28	2						
29	2						
30	1						
31	1						
32	2						
34	1						
35	2						
36	1						
MEAN		16080.2	19207.5	461.8	0.81	0.0105	68.03
STD		3416.8	4708.7	77.2	0.48	0.0016	12.87
CV		21.2	24.5	16.7	60.04	15.542	18.91

* No meaningful value of Kel, and therefore no AUCinf or Halflife, could be calculated for this subject, for this treatment.

Exclude Subj # 2, 8, 15, 17, 21, 25
(11) 26, 28, 29, 35, 36

PLEASE IDENTI
FY THE STUDY

Attachment -7

2 mg. Single Dose

TABLE D2 (CONT'D)
Project GP711
BIOAVAILABILITY PARAMETERS - WARFARIN
Observed Results

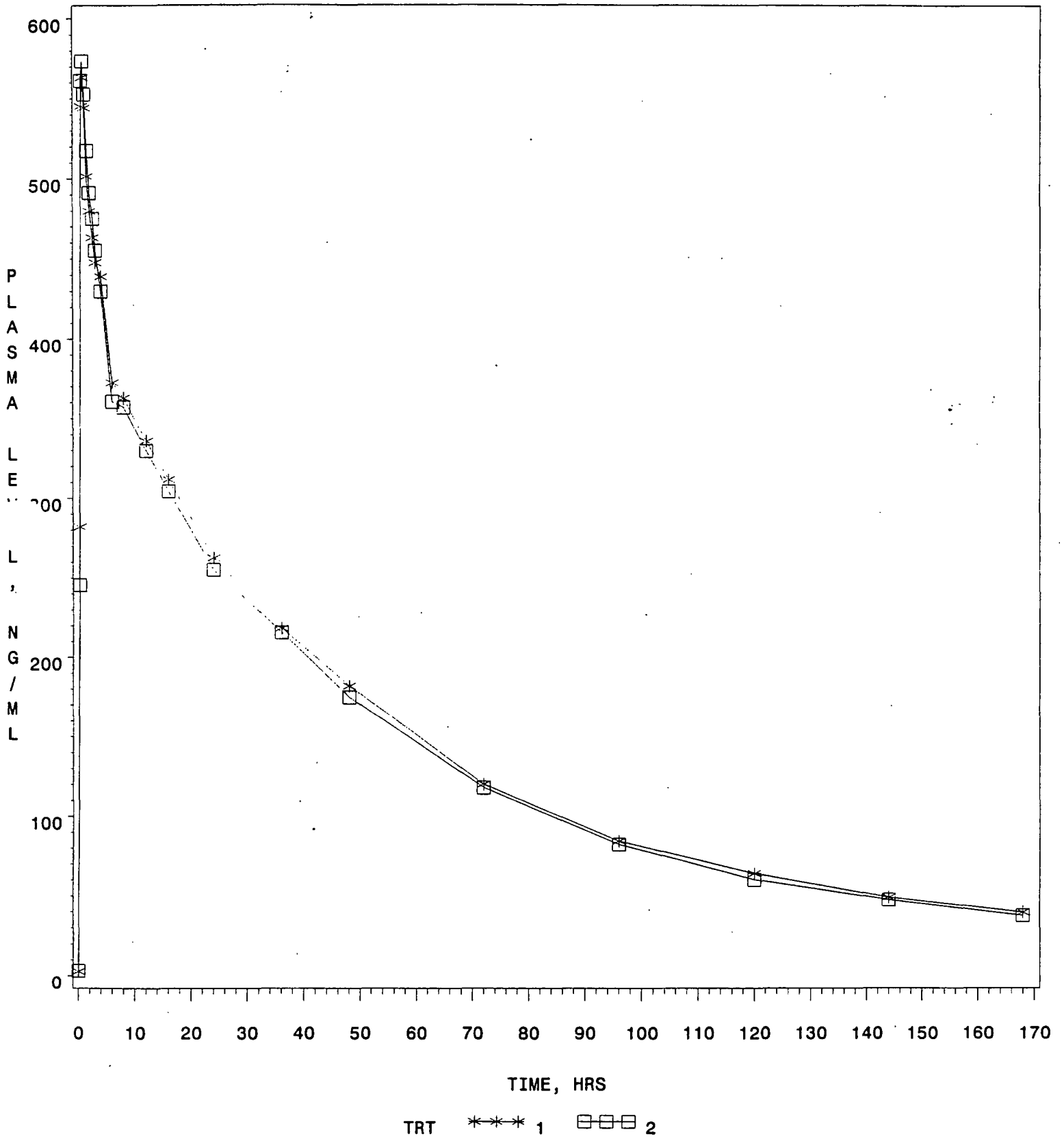
Treatment=B:DuPONT

Subject	PERIOD	AUC0-t (ng·hr/mL)	AUCinf (ng·hr/mL)	Cmax (ng/mL)	Tmax (hrs)	KEL (1/hrs)	Halflife (hours)
1	2						
2	1						
3	2						
4	1						
5	2						
6	1						
7	1						
8	2						
9	1						
10	1						
11	2						
12	2						
13	1						
14	2						
15	1						
16	2						
17	2						
18	2						
19	1						
20	1						
21	2						
22	1						
23	1						
24	2						
25	2						
26	1						
27	2						
28	1						
29	1						
30	2						
31	2						
32	1						
34	2						
35	1						
36	2						
MEAN		16350.8	19308.2	488.2	0.80	0.0106	66.68
STD		3750.1	4597.2	86.2	0.57	0.0017	10.31
CV		22.9	23.8	17.7	72.05	15.767	15.46

FIG P-2. PLASMA WARFARIN SODIUM LEVELS (N=23)

WARFARIN SODIUM TABLETS 5 MG, ANDA #40-301
UNDER FASTING CONDITIONS
DOSE=1 X 5 MG

Attachment - 8

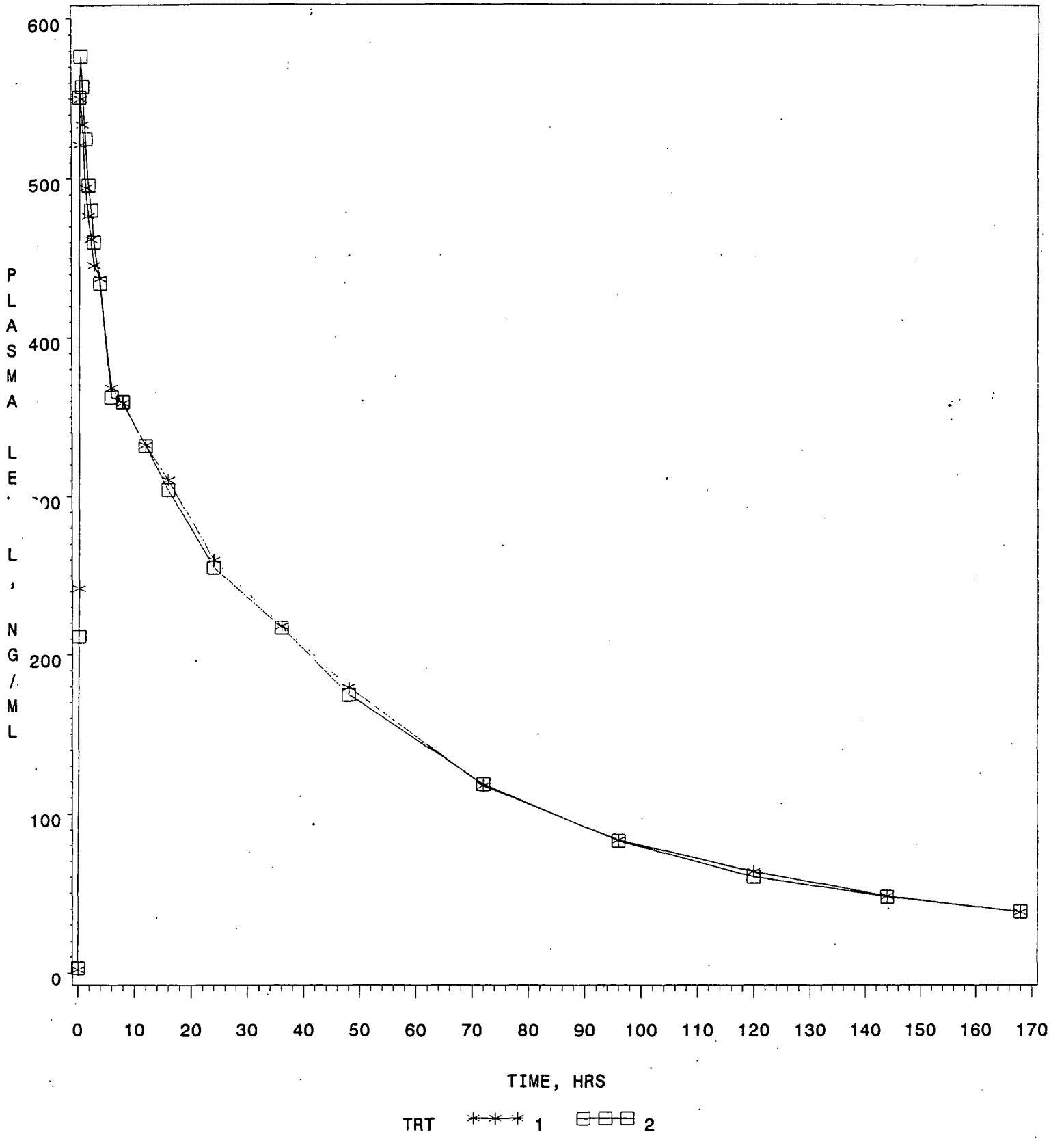


1=TEST(TARO) 2=REF(DUPONT MERCK)

FIG P – 2a. PLASMA WARFARIN SODIUM LEVELS (N = 19)

WARFARIN SODIUM TABLETS 5 MG, ANDA #40-301
UNDER FASTING CONDITIONS
DOSE=1 X 5 MG

Attachment - 9

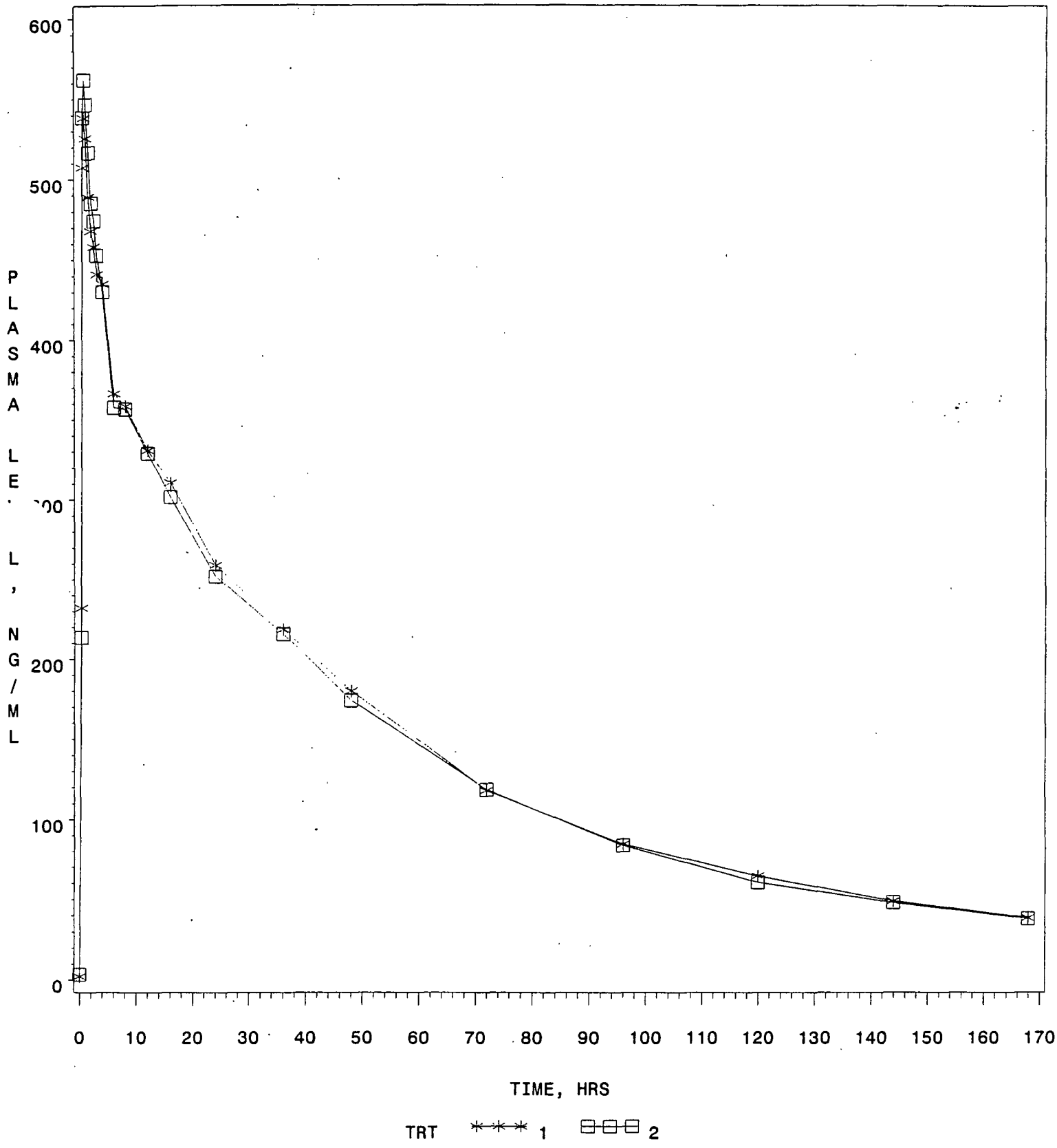


1=TEST(TARO) 2=REF(DUPONT MERCK)

FIG P-2b. PLASMA WARFARIN SODIUM LEVELS (N=17)

WARFARIN SODIUM TABLETS 5 MG, ANDA #40-301
UNDER FASTING CONDITIONS
DOSE=1 X 5 MG

Attachment-10



1=TEST(TARO) 2=REF(DUPONT MERCK)

STATISTICAL REPORT

STUDY No.: 97-129

Period 1 vs Period 2

Attachment - II

TABLE 3

Pharmacokinetic Parameters of Test Formulation: Warfarin (Taro)

Subject	Seq.	Period	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$AUC_{t/inf}$ (%)	K_{el} (h^{-1})	TLIN (h)	LQCT (h)	$T_{½ el}$ (h)
01	AB	1									
02	BA	2									
03	BA	2									
04	BA	2									
06	AB	1									
07	BA	2									
08	BA	2									
09	AB	1									
10	AB	1									
11	AB	1									
12	AB	1									
13	AB	1									
14	BA	2									
15	BA	2									
16	BA	2									
17	AB	1									
18	BA	2									
19	BA	2									
20	AB	1									
21	AB	1									
22	BA	2									
23	AB	1									
24	AB	1									
MEAN			617.04	0.83	23689.78	27300.70	87.23	0.0113	95.0	167	64.81
SD (±)			100.22	0.47	5480.31	6880.79	4.32	0.0024	5.0	5	20.22
CV (%)			16.24	56.24	23.13	25.20	4.95	20.97	5.3	3	31.21
Range (min.)											
Range (max.)											

Exclude Subj. # 7, 8, 14, 19, 23, 24

(6)

Period 1 vs Period 2

Attachment-12

TABLE 4

Pharmacokinetic Parameters of Reference Formulation: Warfarin (DuPont)

Subject	Seq.	Period	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$AUC_{t/inf}$ (%)	K_{el} (h^{-1})	TLIN (h)	LQCT (h)	$T_{½ el}$ (h)
01	AB	2									
02	BA	1									
03	BA	1									
04	BA	1									
06	AB	2									
07	BA	1									
08	BA	1									
09	AB	2									
10	AB	2									
11	AB	2									
12	AB	2									
13	AB	2									
14	BA	1									
15	BA	1									
16	BA	1									
17	AB	2									
18	BA	1									
19	BA	1									
20	AB	2									
21	AB	2									
22	BA	1									
23	AB	2									
24	AB	2									
MEAN			612.50	0.83	22569.18	25911.17	87.37	0.0110	96.0	168	65.26
SD (±)			122.23	0.33	3912.57	4875.66	3.43	0.0020	0.0	0	15.03
CV (%)			19.96	40.36	17.34	18.82	3.93	17.93	0.0	0	23.04
Range (min.)											
Range (max.)											

Period 3 vs Period 4

Attachment - 13

TABLE 3

Pharmacokinetic Parameters of Test Formulation: Warfarin (Taro)

Subject	Seq.	Period	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$AUC_{\%inf}$ (%)	K_{el} (h^{-1})	TLIN (h)	LQCT (h)	$T_{1/2\,el}$ (h)
01	AB	3									
02	BA	4									
03	BA	4									
04	BA	4									
06	AB	3									
07	BA	4									
08	BA	4									
09	AB	3									
10	AB	3									
11	AB	3									
12	AB	3									
13	AB	3									
14	BA	4									
15	BA	4									
16	BA	4									
17	AB	3									
18	BA	4									
19	BA	4									
20	AB	3									
21	AB	3									
22	BA	4									
23	AB	3									
24	AB	3									
MEAN			617.01	1.06	24104.52	28200.44	85.96	0.0103	96.0	168	69.65
SD (±)			138.78	1.01	4769.82	6276.87	3.87	0.0019	0.0	0	15.13
CV (%)			22.49	95.28	19.79	22.26	4.50	18.06	0.0	0	21.72
Range (min.)											
Range (max.)											

0.3 HR? TMAX THERE IS NO SUCH TIME PT.

Period 3 vs Period 4

Attachment - 14

TABLE 4

Pharmacokinetic Parameters of Reference Formulation: Warfarin (DuPont)

Subject	Seq.	Period	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$AUC_{\%inf}$ (%)	K_{el} (h^{-1})	TLIN (h)	LQCT (h)	$T_{½ el}$ (h)
01	AB	4									
02	BA	3									
03	BA	3									
04	BA	3									
06	AB	4									
07	BA	3									
08	BA	3									
09	AB	4									
10	AB	4									
11	AB	4									
12	AB	4									
13	AB	4									
14	BA	3									
15	BA	3									
16	BA	3									
17	AB	4									
18	BA	3									
19	BA	3									
20	AB	4									
21	AB	4									
22	BA	3									
23	AB	4									
24	AB	4									
MEAN			662.58	0.70	23990.58	28051.57	86.03	0.0108	92.9	165	67.14
SD (±)			138.16	0.47	5384.73	6864.51	3.85	0.0022	8.3	8	14.66
CV (%)			20.85	67.52	22.45	24.47	4.47	20.64	8.9	5	21.84
Range (min.)											
Range (max.)											

Printed by Surendra Shrivastava

Attachment - 15

Electronic Mail Message

itivity: COMPANY CONFIDENTIAL

Date: 19-Aug-1998 02:55pm
From: Surendra Shrivastava
SHRIVASTAVAS
Dept: HFD-655 MPN2 130
Tel No: 301-827-5847 FAX 301-594-0181

TO: Yi Tsong (TSONG)

CC: Shriniwas Nerurkar (NERURKAR)
CC: Dale Conner (CONNERD)
CC: Rabindra Patnaik (PATNAIK)
CC: Lizzie Sanchez (SANCHEZL)
Subject: ANDA 40-301 Consult: Warfarin Sodium 5 mg Tablets

Hello Yi:

Concerning the above consult, I am the primary reviewer for this submission. The biostudy on 5 mg tablets is a four-way crossover replicate design study. Therefore, we need your statistical evaluation. This submission has two other biostudies (2 mg and 10 mg tablets; two-way crossover design), which I have already finished, and I am waiting for a response from your office. So, at this stage, I would like to know if any reviewer has looked at the above study, and if it could be expedited in any way. Thank you very much for an early response.

Surendra

Printed by Surendra Shrivastava

Attachment-16

Electronic Mail Message

itivity: COMPANY CONFIDENTIAL

Date: 25-Aug-1998 01:43pm
From: Donald Schuirmann
SCHUIRMANN
Dept: HFD-705 PKLN 15B45
Tel No: 301-827-3211 FAX 301-480-2825

TO: Surendra Shrivastava (SHRIVASTAVAS)

CC: Shriniwas Nerurkar (NERURKAR)
CC: Lizzie Sanchez (SANCHEZL)
CC: Yi Tsong (TSONG)
Subject: info on ANDA 40-301

Surendra,

Regarding the statistical review of ANDA 40-301, Taro Pharmaceuticals Warfarin Sodium tablets, I have some questions:

1. Warfarin, I believe, is generally regarded as a Narrow Therapeutic Index drug. Are the equivalence limits for this study still %?

2. There are 11 instances, involving 5 subjects, where the time zero blood concentration is non-zero. These are

   subject 4, periods 3 and 4
   subject 7, periods 2, 3, and 4
   subject 8, period 3
   subject 20, periods 3 and 4
   subject 21, periods 2, 3, and 4

   is there any special way that you would like me to treat these observations/subjects?

3. There appear to be 4 instances where Cmax is observed at the first blood-sampling time (0.25 hrs) after time zero. These cases are

   subject 7, period 4
   subject 9, period 3
   subject 14, period 3
   subject 19, period 3

   Is there any special way you would like me to handle these cases?

Don Schuirmann

Printed by Surendra Shrivastava

Electronic Mail Message

Attachment - 1;

itivity: COMPANY CONFIDENTIAL

Date: 26-Aug-1998 04:07pm
From: Surendra Shrivastava
SHRIVASTAVAS
Dept: HFD-655 MPN2 130
Tel No: 301-827-5847 FAX 301-594-0181

TO: Donald Schuirmann (SCHUIRMANN)

CC: Shriniwas Nerurkar (NERURKAR)
CC: Rabindra Patnaik (PATNAIK)
CC: Dale Conner (CONNERD)
Subject: Re: info on ANDA 40-301

Hello Don:

Thank you for you response.

Answers to your questions are as follows:

1. Yes, the 90% CI limits are still %.

2. We would like analyses on: (a) All 23 subjects; (b) 18 Subjects, after excluding Subjects #4, 7, 8, 20 and 21, where zero time point shows non-zero drug concentration; (c) 19 Subjects, excluding Subjects #7, 9, 14, and 19, who show Cmax at first non-zero time point; (d) 15 Subjects, after excluding Subjects #4, 7, 8, 20, 21, 9, 14, and 19; and (e) We also want to see analyses with and without Residuals in the r el, in each case.

I have a question too. How are you going to treat Subjects #23 and 24, who were sort of add-ons, and were treated in periods 2-5? In the past, we have treated them as separate group (too small number for a group), or excluded them. I will let you decide.

Thank you.

Surendra

>Surendra,
>
>Regarding the statistical review of ANDA 40-301, Taro
>Pharmaceuticals Warfarin Sodium tablets, I have some questions:
>
> 1. Warfarin, I believe, is generally regarded as a Narrow
> Therapeutic Index drug. Are the equivalence limits for this
> study still %?
>
> 2. There are 11 instances, involving 5 subjects, where the time
> zero blood concentration is non-zero. These are
>
> subject 4, periods 3 and 4
> subject 7, periods 2, 3, and 4
> subject 8, period 3

> subject 20, periods 3 and 4
> subject 21, periods 2, 3, and 4
>
> is there any special way that you would like me to treat these observations/subjects?

> 3. There appear to be 4 instances where Cmax is observed at the first blood-sampling time (0.25 hrs) after time zero. These cases are
>
> subject 7, period 4
> subject 9, period 3
> subject 14, period 3
> subject 19, period 3
>
> Is there any special way you would like me to handle these cases?
>
>
>
> Don Schuirmann

Printed by Surendra Shrivastava

Electronic Mail Message

Attachment - 18

itivity: COMPANY CONFIDENTIAL

Date: 15-Oct-1998 11:45am
From: Donald Schuirmann
SCHUIRMANN
Dept: HFD-705 PKLN 15B45
Tel No: 301-827-3211 FAX 301-480-2825

TO: Surendra Shrivastava (SHRIVASTAVAS)

CC: Shriniwas Nerurkar (NERURKAR)
CC: Rabindra Patnaik (PATNAIK)
CC: Dale Conner (CONNERD)
CC: Stella Machado (MACHADOS)
Subject: ANDA 40-301 Taro's Warfarin Sodium tablets

Dr. Shrivastava,

Here is my preliminary e-mail review of ANDA 40-301, Warfarin Sodium Tablets USP, Taro Pharmaceuticals USA, Inc.:

Material reviewed: one orange-colored volume of ANDA 40-301, volume 6 of 14. Data for my analyses were provided on diskette in data files sent to me by the Office of Generic Drugs.

The issues in the review involve the sponsor's two-treatment, two-sequence, four-period replicated-crossover BE study (study no. 97-129, Three PK parameters (AUCt, AUCinf, and Cmax) were analyzed.

PK parameters were statistically analyzed after log-transformation. These log-transformed parameters are designated as LAUCT=ln(AUCt), LAUCINF=ln(AUCinf), and LCMAX=ln(Cmax).

23 subjects (out of 24 subjects enrolled) completed the BE study.

The two treatments studied were:

treatment T - Taro 5 mg tablet, manufactured in Israel
(Lot No. 780049, Expiry date: N/A)
dose = 1 tablet

treatment R - DuPont Pharma, USA 5 mg USP crystalline
(Coumadin) tablet, marketed in the USA.
(Lot No. ELB048A, Expiry Date: 01-00)
dose = 1 tablet

The study was conducted in two groups of subjects. The experimental design and subject numbers for those subjects who completed the study are as follows:

		period 1	2	3	4
p 1	sequence 1	T	R	T	R
	sequence 2	R	T	R	T

period 1	2	3	4

group 2 sequence 1 T R T R

subject numbers:
up 1, sequence 1: 1 6 9 10 11 12 13 17 20 21
up 1, sequence 2: 2 3 4 5 7 8 14 15 16 18 19 22
group 2, sequence 1: 23 24

Periods 2, 3, and 4 of group 1 occurred at the same time as periods 1, 2, and 3, respectively, of group 2. There was a two week washout period between periods. Both subjects in group 2 received the treatments in the same sequence.

At the request of Dr. Shrivastava, statistical analyses were carried out for the following subsets of subjects:

all subjects (23 subjects, 92 observations)

subset 1: excluding subject nos. 4, 7, 8, 20, and 21, who had non-zero concentrations in some zero time blood samples
(18 subjects, 72 observations)

subset 2: excluding subject nos. 7, 9, 14, and 19, who had Cmax occurring at the first non-zero sampling time (0.25 hours)
(19 subjects, 76 observations)

subset 3: excluding subject nos. 4, 7, 8, 9, 14, 19, 20, and 21, the subjects who were excluded in subset 1 and/or subset 2
(15 subjects, 60 observations)

In addition, I carried out analyses for one other subset of subjects:

subset 4: excluding subject 7, period 4
subject 9, period 3
subject 14, period 3
subject 19, period 3

only excluding the specific observations where Cmax occurred at the first non-zero sampling time. For these four observations, AUC's as well as Cmax were excluded.
(23 subjects, 88 observations)

STATISTICAL MODELS

Statistical analyses were carried out using SAS PROC MIXED. For analyses without carryover effects, the SAS statements used initially were:

```
PROC MIXED MAXITER=500;
CLASSES GRP SEQ SUBJ PER TRT;
MODEL <y> = GRP SEQ GRP*SEQ PER PER*GRP TRT;
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.10;
```

where <y> is the particular response (LAUCT, LCMAX, LAUCINF) being analyzed. These SAS statements allow for possible subject-by-treatment interaction and also allow the within-subject iances of T and R to differ. This analysis provides an imated variance-covariance matrix for the subject-specific treatment means. If this estimated variance-covariance matrix was not positive definite (which means that the between-subject correlation between the subject-specific means for T and R was estimated to be 1.0), the SAS statements were modified to the following:

```
PROC MIXED MAXITER=500;
CLASSES GRP SEQ SUBJ PER TRT;
MODEL <y> = GRP SEQ GRP*SEQ PER PER*GRP TRT;
RANDOM SUBJ(GRP*SEQ);
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.10;
```

In fact, the estimated variance-covariance matrix was not positive definite in all cases except three: LAUCT and LAUCINF for the all subjects analysis, and LAUCT for the subset 4 analysis.

For analyses with carryover effects in the model, an additional factor was included in the CLASSES and MODEL statements to reflect the carryover effects.

ANALYSES WITHOUT CARRYOVER EFFECTS

ave carried out analyses of the sponsor's replicated-crossover BE study for all of the indicated subsets of subjects. The resulting 90% confidence intervals (in percentages) for the ratio of test product geometric mean response over reference product geometric mean response are:

	LAUCT	LCMAX	LAUCINF
all subjects	99.59 , 106.19	93.04 , 102.09	99.77 , 107.22
subset 1	99.08 , 103.18	91.24 , 101.38	98.99 , 104.78
subset 2	99.91 , 104.58	90.78 , 99.68	99.17 , 104.73
subset 3	99.97 , 104.62	89.44 , 99.72	98.96 , 105.00
subset 4	99.71 , 105.89	92.77 , 102.02	99.96 , 106.13

For each of the specified subsets of subjects, the 90% confidence intervals fall within the usual limits of % for LAUCT, LAUCINF, and LCMAX.

ANALYSES WITH CARRYOVER EFFECTS

Dr. Shrivastava has requested that analyses be done examining the possibility of unequal carryover effects in this bioequivalence study. This is a legitimate concern given the that there was evidence of direct carryover of the drug stance from one study period to the next in several cases (i.e. non-zero Cmin values).

If a treatment administered in a crossover study has an effect on the response to a treatment administered at a later period of the

study, this is called a carryover effect. In bioequivalence studies, we have generally assumed that we only need to worry about first-order carryover effects - i.e. effects that a treatment has on the response to a treatment administered in the t period. In the design for the bioequivalence study under A 40-301, treatment T is always preceded by treatment R and treatment R is always preceded by treatment T. We therefore only have to worry about two possible carryover effects: the effect that administration of T has on the response to R administered in the next period, and the effect that administration of R has on the response to T administered in the next period. If these two possible carryover effects are not equal, then the estimate of the difference between the average response to T and the average response to R that we would obtain with no carryover effects in the model will be biased. The p-values for the test of this bias are as follows:

	p-values for bias		
	LAUCT	LCMAX	LAUCINF
all subjects	0.2837	0.2335	0.2958
subset 1	0.5674	0.7103	0.4728
subset 2	0.3387	0.5890	0.4294
subset 3	0.4066	0.9958	0.4630
subset 4	0.3325	0.2287	0.3339

In the analysis of bioequivalence studies where the possibility of unequal carryover needs to be considered, it has been the practice to test for bias due to carryover effects and to drop carryover effects from the statistical model if the p-value for such bias is greater than 0.10. If the p-value for bias is less than or equal to 0.10, carryover effects are retained in the statistical model used to make the final inference. In the above table, the p-value for bias is greater than 0.10 in all cases. Nevertheless, at the request of Dr. Shrivastava I have calculated the 90% confidence intervals resulting from analyses using a statistical model that includes carryover effects. These 90% confidence intervals are:

	LAUCT	LCMAX	LAUCINF
all subjects	100.14 , 112.25	93.86 , 116.50	100.20 , 114.80
subset 1	97.82 , 107.65	87.05 , 111.74	97.76 , 111.80
subset 2	99.62 , 110.94	87.98 , 109.76	98.26 , 111.71
subset 3	99.30 , 110.53	83.00 , 107.53	97.73 , 112.39
subset 4	99.71 , 112.50	93.70 , 116.59	99.65 , 114.53

As may be seen, even with carryover effects included in the statistical model the resulting 90% confidence intervals fall within the limits of % in all cases.

Summary

1. With or without carryover effects included in the statistical model, the 90% confidence intervals for the ratio of the average response for treatment T over the average response for treatment R fall within the usual bioequivalence limits of % for all three PK parameters (AUCt, Cmax, and AUCinf), for all of the examined subsets of subjects.

2. Potential bias due to carryover effects was not statistically significant in any case ($p > 0.10$ in all cases).

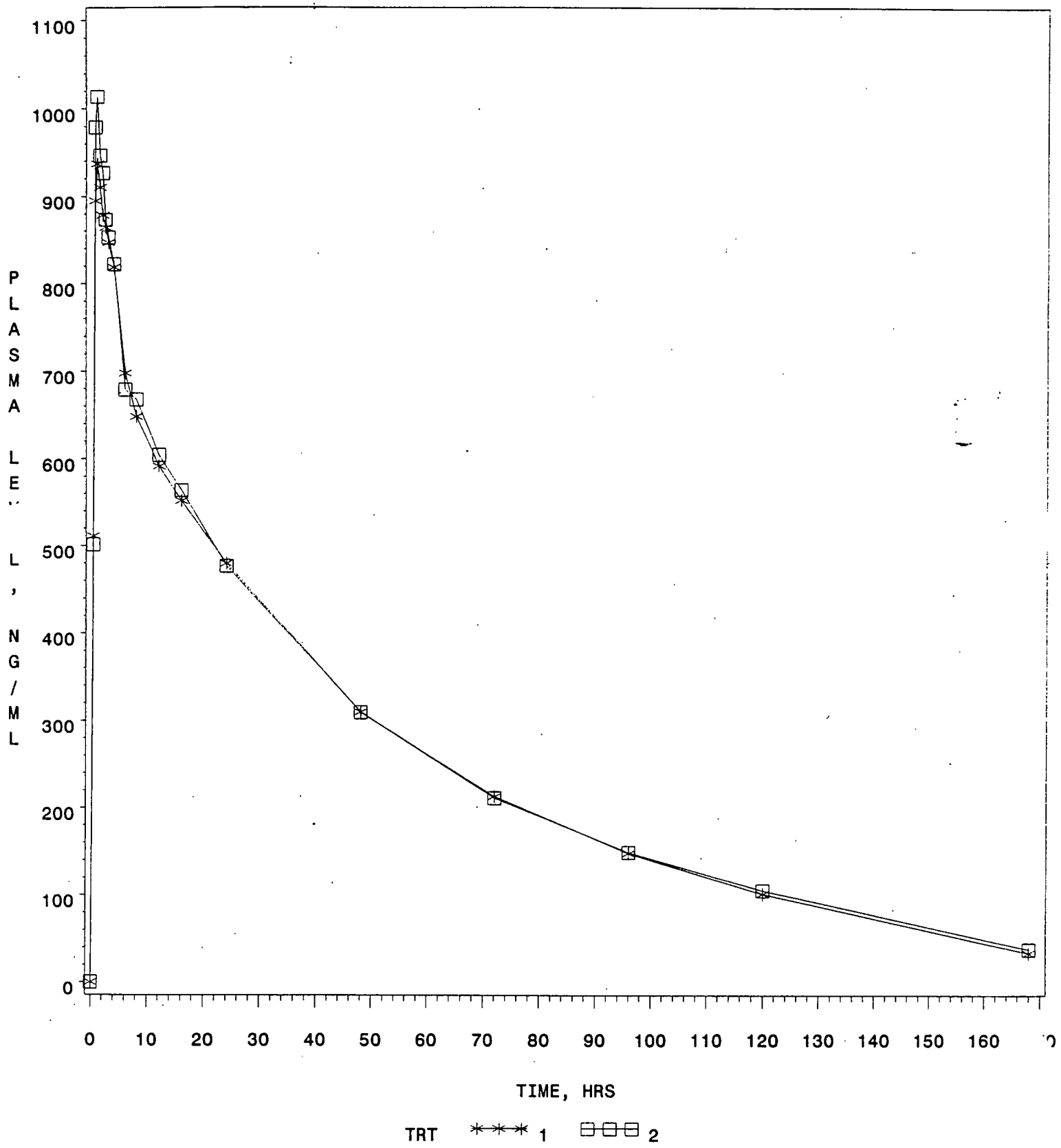
ase let me know if you require any further information.
erwise, the formal paper review will be issued with
essentially the same information as this message.

Donald J. Schuirmann

FIG P-3. PLASMA WARFARIN SODIUM LEVELS (N=34)

Attachment -19

WARFARIN SODIUM TABLETS 10 MG, ANDA #40-301
UNDER FASTING CONDITIONS
DOSE=1 X 10 MG

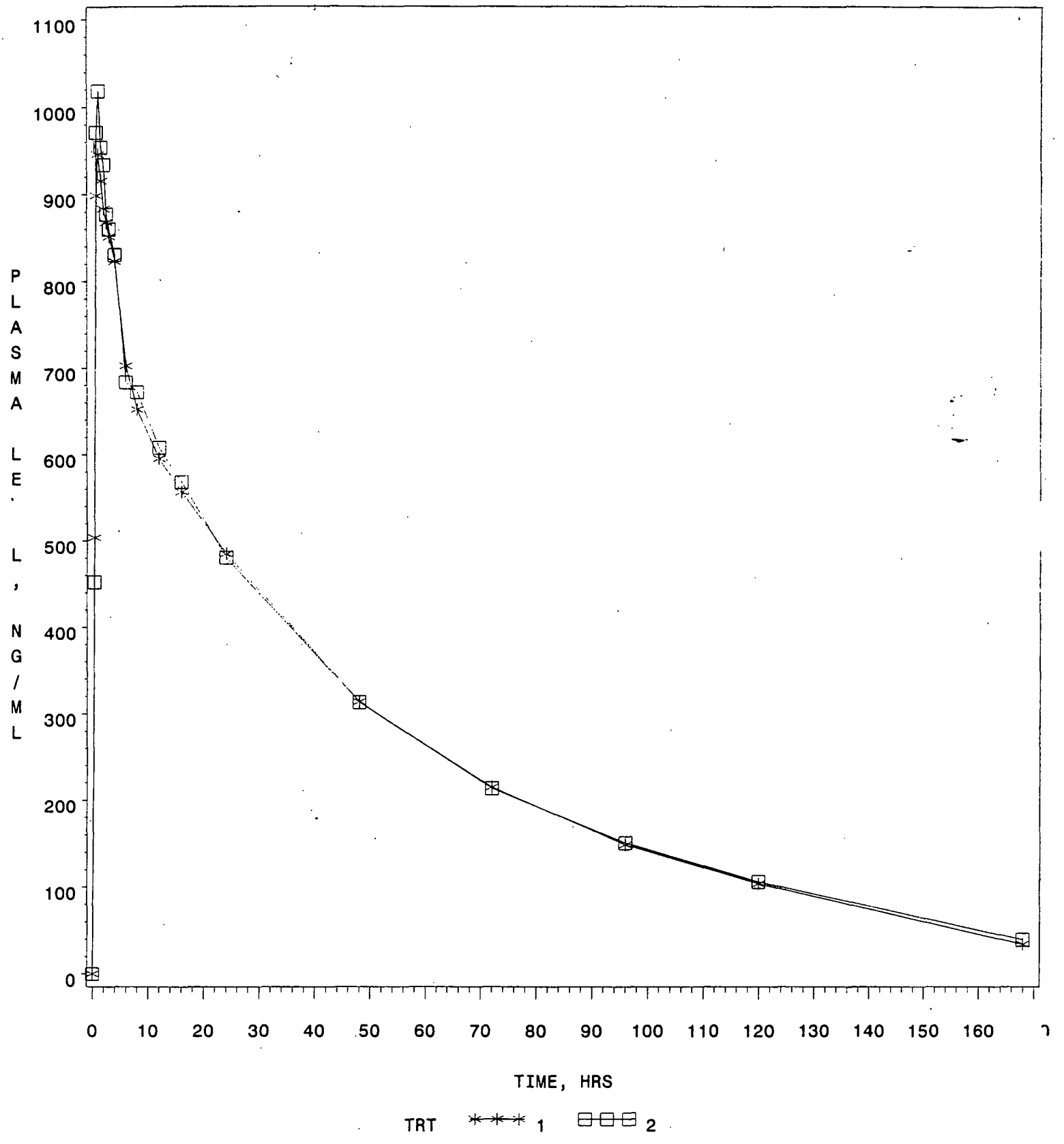


1=TEST(TARO) 2=REF(DUPONT MERCK)

FIG P-3a. PLASMA WARFARIN SODIUM LEVELS (N=31)

WARFARIN SODIUM TABLETS 10 MG, ANDA #40-301
UNDER FASTING CONDITIONS
DOSE=1 X 10 MG

Attachment-2c



1=TEST(TARO) 2=REF(DUPONT MERCK)

Attachment - 21

TABLE D2
Project GP576
BIOAVAILABILITY PARAMETERS - WARFARIN
Observed Results

---------- Treatment=A:TARO ----------

Subject	PERIOD	AUC0-t (ng-hr/mL)	AUCinf (ng-hr/mL)	Cmax (ng/mL)	Tmax (hrs)	KEL (1/hrs)	Halflife (hours)
1	1						
2	2						
3	1						
4	2						
5	2						
6	1						
7	2						
8	1						
9	1						
10	2						
11	2						
12	1						
13	1						
14	2						
15	2						
16	1						
17	1						
18	1						
19	2						
20	2						
21	1						
22	1						
23	2						
24	2						
25	1						
27	1						
28	2						
29	2						
30	1						
31	2						
32*	1						
33	2						
34	1						
35	1						
MEAN		40151.0	45739.5	1067.0	1.22	0.0160	45.37
STD		9204.0	11149.7	193.0	0.83	0.0034	10.94
CV		22.9	24.4	18.1	68.57	21.378	24.11

*No meaningful value of Kel, and therefore no Halflife or AUCinf, could be calculated for this subject, for this treatment.

Exclude Subj 20 27 29

(3)

Attachment - 22

TABLE D2 (cont'd)
Project GP576
BIOAVAILABILITY PARAMETERS - WARFARIN
Observed Results

---------- Treatment=B:DuPONT ----------

Subject	PERIOD	AUC0-t (ng-hr/mL)	AUCinf (ng-hr/mL)	Cmax (ng/mL)	Tmax (hrs)	KEL (1/hrs)	Halflife (hours)
1	2						
2	1						
3	2						
4	1						
5	1						
6	2						
7	1						
8	2						
9	2						
10	1						
11	1						
12	2						
13	2						
14	1						
15	1						
16	2						
17	2						
18	2						
19	1						
20	1						
21	2						
22	2						
23	1						
24	1						
25	2						
27	2						
28	1						
29	1						
30	2						
31	1						
32	2						
33	1						
34	2						
35	2						
MEAN		40736.3	46341.0	1141.2	1.08	0.0151	47.81
STD		9044.2	10500.4	204.3	0.65	0.0030	9.80
CV		22.2	22.7	17.9	60.36	19.672	20.49

CLINICAL PROCEDURES

The clinical procedures followed in this study may be found in the protocol dated September 25, 1997. This report provides details of the clinical portion of the study with emphasis on those aspects that may be relevant to the rate and extent of absorption of a test and a reference warfarin sodium 5 mg tablet under fasting conditions. The clinical portion of this study was conducted at

Subjects arrived at the clinical research facility between 17:45 and 21:30 on the night before dosing in each of the four study periods (See Memo to File). Urine drug screen tests were done for Subject No. 13 before Period 4 and for Subject No. 24 before Periods 3 and 4. Results for these urine drug screens were negative (See Memo to File). In all periods, following a supervised fast of 10 hours, all subjects were dosed according to the Randomization Scheme and Schedule (See Table C6).

Drug administration was between 07:00 and 07:42 for each of the study periods of 97-129, and between 07:44 and 07:46 for 97-129 (M). Subjects received a single oral dose of 1 X 5 mg warfarin sodium tablet with 240 ml of fresh water under fasting conditions. Study period dates for subjects are shown below.

	Subject Nos. 1-22	Subject Nos. 23-24
Period 1	September 27, 1997	October 11, 1997
Period 2	October 11, 1997	October 25, 1997
Period 3	October 25, 1997	November 8, 1997
Period 4	November 8, 1997	November 22, 1997

The dosing schedule was identical in all periods of the study, with subjects receiving dosage each over 2-minutes intervals. No deviations occurred from this drug administration schedule.

Water was permitted *ad libitum* 2 hours before dosing and again 2 hours after dosing.

During drug administration in all study periods, the Medical Co-Investigator was present up to four hours after dosing of the last subject and was on call until the end of the study. Subjects were monitored by medically qualified designates for any adverse events or discomfort. Subjects engaged in normal activity for the first 4 hours post-dose and were forbidden to rest completely or lie down during this time.

A controlled lunch was served at 4 hours post-dose, a standardized meal at approximately 9 hours post-dose and a snack approximately 12 hours post-dose.

RANDOMIZATION SCHEME

A. Test: Taro Pharmaceuticals Ind. LTD. Israel warfarin sodium 5 mg tablet USP
B. Reference: DuPont Pharma, USA warfarin sodium 5 mg tablet USP (Coumadin®)

Subject No.	Group*
01	3
02	4
03	2
04	4
05	2
06	3
07	2
08	2
09	1
10	1
11	3
12	3
13	1
14	2
15	4
16	4
17	3
18	2
19	4
20	1
21	1
22	4
23	3
24	1

RANDOMIZATION SCHEDULE

	Group I	Group II	Group III	Group IV
Period 1	Test 1	Reference 1	Test 2	Reference 2
Period 2	Reference 2	Test 1	Reference 1	Test 2
Period 3	Test 2	Reference 2	Test 1	Reference 1
Period 4	Reference 1	Test 2	Reference 2	Test 1

NOTE: Group I (seen in Randomization Schedule) = Group 1 (seen in Randomization Scheme)
In the same manner: II=2, III=3 and IV=4.

IV. OBJECTIVE

The objective of this study is to compare the rate and extent of absorption of a test and a reference Warfarin sodium tablet (test Warfarin sodium tablet by Taro Pharmaceutical U.S.A. Inc. , U.S.A., versus a reference Warfarin sodium tablet, Coumadin® by DuPont Pharma, U.S.A.) administered as 1 X 5mg tablet in healthy adult male subjects following a single oral dose using a four-way fasting replicate study design. To facilitate comparison of bioequivalence, the plasma concentration of Warfarin sodium at each sampling point will be measured and the following parameters will be calculated and compared for each treatment:

a) Area under the plasma concentration/time curve (AUC) for Warfarin sodium extrapolated to infinity where possible.
b) Peak plasma drug concentration (Cmax).
c) Observed time at which Cmax occurred (Tmax).
d) Terminal elimination rate constants K_{el} and the apparent half-live $T_{1/2\ el}$ for Warfarin sodium. It is not intended to compare these parameters for treatment effects. It is then intended to compare Tmax, Cmax and AUC to treatment effects.

V. STUDY POPULATION

A. Subject Numbers

24 healthy subjects will enter the study. Drop-outs will not be replaced. All subjects completing the study will have their blood samples analyzed. If any of the exclusion criteria are applicable to a potential subject, they will not be included in the study.

VI. INCLUSION CRITERIA

a. Non-institutionalized subjects consisting of students and members of the community at large. Note: Recruitment is most often done using newspaper advertisement.

b. Subjects will be aged between 18 and 45 years.

c. Subjects will be Caucasians males.

d. Subjects selected will be non-smokers.

XI. MATERIALS AND PROCEDURE

A. Drug Products

On each of these four studies periods, subjects will take either the test or the reference medication, allocated in accordance with a randomization schedule. The randomization code will be provided by to the sponsor upon request. The randomization code is not available to either the statistical or analytical divisions of until the clinical phase of the study has been completed.

Test Product 1 and 2: Warfarin sodium 5mg tablet (by Taro Pharmaceutical USA Inc. U.S.A.)

Reference Product 1 and 2: Warfarin sodium 5mg tablet (Coumadin® by DuPont Pharma, U.S.A.)

The products used must conform with compendial and/or corporate quality control standards and appropriate dissolution tests, if applicable. Warfarin sodium will be stored and dispensed at room temperature in a light-resistant container as defined in the USP.

Randomization Schedule:

	Group I	Group II	Group III	Group IV
Period 1	Test 1	Reference 1	Test 2	Reference 2
Period 2	Reference 2	Test 1	Reference 1	Test 2
Period 3	Test 2	Reference 2	Test 1	Reference 1
Period 4	Reference 1	Test 2	Reference 2	Test 1

B. Procedure

a. Study design

(1) Design: replicate design, open-label, fasting, single dose, 4 treatments

(2) Interval between periods: at least 14 days

(3) Number of subjects: 24 healthy adult males.

(4) Confinement: subjects will be confined to the clinical research facility from 18:00 the night before dosing and up to 36 hours after

OBJECTIVE

The objective of this study was to determine if warfarin sodium 5 mg tablets manufactured by Taro Pharmaceutical Ind. LTD. and DuPont Pharma U.S.A's Coumadin® were bioequivalent under fasting conditions.

STUDY TITLE

Replicate Design Four-Way Single Dose Fasting Study of Warfarin Sodium 5 mg Tablet in Normal Healthy Male Subjects.

STUDY DESIGN

Design: Single center, replicate design, open-label, fasting, single dose, 4-treatments study in fasting volunteers.

Study site and sponsor: The study was conducted at _ for Taro Pharmaceuticals (USA), Five Skyline Drive, Hawthorne, NY, U.S.A.

Treatments: A. Test 1 and Test 2:: Taro 5 mg tablets, manufactured in Israel. (Lot No. 780049, Expiry date: N/A)

B: Reference 1 and Reference 2 : DuPont Pharma, USA 5 mg USP crystalline (Coumadin®) tablets, marketed in the USA. (Lot No. ELB048A, Expiry Date: 01-00)

Randomization: Each subject received two doses of the test and reference products. The sequence (groups I-IV) were randomly selected for each subject as follow:

	Group I	Group II	Group III	Group IV
Period 1	Test 1	Reference 1	Test 2	Reference 2
Period 2	Reference 2	Test 1	Reference 1	Test 2
Period 3	Test 2	Reference 2	Test 1	Reference 1
Period 4	Reference 1	Test 2	Reference 2	Test 1

Dose: Treatment: 1 tablet of warfarin sodium 5 mg administered with 240 ml of water. Total dose per period was 5 mg of warfarin sodium.

Number of subjects: A total of 24 male volunteers were enrolled and 23 completed the study (See Clinical and Statistical Reports).

RESULTS AND DISCUSSION

Time Deviations

The following tables present time deviations exceeding the previously described acceptance criteria (n = 5 in Period I, n = 5 in Period II, n = 7 in Period III and n = 7 in Period IV).

STUDY PERIOD I

Subject	Sampling Time (hours)	Scheduled Time (hh:mm)	Actual Time (hh:mm)	Deviation (%)	Corrected Sampling Time (hours)
02	0.500	07:32	07:35	10.0	0.550
04	0.750	07:51	07:59	17.8	0.883
07	0.500	07:42	07:47	16.7	0.583
09	0.500	07:46	07:49	10.0	0.550
21	0.500	08:10	08:13	10.0	0.550

STUDY PERIOD II

Subject	Sampling Time (hours)	Scheduled Time (hh:mm)	Actual Time (hh:mm)	Deviation (%)	Corrected Sampling Time (hours)
04	0.250	07:21	07:26	33.3	0.333
04	0.750	07:51	07:56	11.1	0.833
09	0.250	07:31	07:33	13.3	0.283
11	0.250	07:35	07:37	13.3	0.283
14	3.00	10:26	10:52	14.4	3.43

STUDY PERIOD III

Subject	Sampling Time (hours)	Scheduled Time (hh:mm)	Actual Time (hh:mm)	Deviation (%)	Corrected Sampling Time (hours)
07	0.250	07:27	07:30	20.0	0.300
11	0.750	08:05	08:10	11.1	0.833
11	1.50	08:50	08:59	10.0	1.65
11	2.00	09:20	09:35	12.5	2.25
13	0.250	07:39	07:41	13.3	0.283
14	0.250	07:41	07:47	40.0	0.350
17	0.250	07:47	07:55	53.3	0.383

STUDY PERIOD IV

Subject	Sampling Time (hours)	Scheduled Time (hh:mm)	Actual Time (hh:mm)	Deviation (%)	Corrected Sampling Time (hours)
04	0.500	07:36	07:42	20.0	0.600
07	0.250	07:27	07:30	20.0	0.300
09	0.250	07:31	07:34	20.0	0.300
11	0.250	07:35	07:39	26.7	0.317
11	1.00	08:20	08:30	16.7	1.17
12	0.250	07:37	07:39	13.3	0.283
13	0.250	07:39	07:41	13.3	0.283

I. Period 1 and Period 2: first dose of each product (n=23):

Plots of mean warfarin plasma concentrations versus time for the test (Taro) and reference (Dupont) product during period 1 and 2 are displayed in Figures 1a and 1b of the summary report for linear and ln linear scales, respectively. A summary of the statistical analysis comparing pharmacokinetic parameters for test and reference during period 1 and period 2 is provided in Table 1 of the summary report. As shown, there were no statistical differences detected by ANOVA for any of the pharmacokinetic parameters. Moreover, the the 90 and 95% confidence intervals (CI) for ln transformed ratio of AUC_{0-t}, $AUC_{0-inf.}$, and C_{max} were all within the eptable limits (80-125%) supporting bioequivalence of Taro vs Dupont warfarin sodium 5 mg. .ie mean plasma concentrations at each sampling time point is summarized in Table 2 of the Summary Report.

The individual plasma concentrations and individual pharmacokinetic parameters during period 1 and 2 can be found in Tables 1-4 of Annex I. The complete stastistical analysis for each pharmacokinetic parameters can be found in Tables 5-29 of Annex I. The individual plasma concentrations versus time profiles are provided in Figures 01a-23a of Annex I. Figure 24a shows the mean plasma-concentrations versus time profile to be identical to figure 1 of the Summary Report. Finally, the profile of plasma concentrations and statistical analysis at each sampling timepoint can be found in Annex I (see Tables 1a-22a and Tables 1b-22b, respectively).

Thus, under single dose fasting conditions, warfarin sodium 5 mg Taro and Dupont formulations are judged bioequivalent when comparing first dose of test and reference products during period 1 and 2.

II. Period 3 and Period 4: second dose of each product (n=23):

The second analysis was conducted using data from the repeated dosing sequence for each subject (i.e. period 3 and 4; n=23). Plots of mean warfarin plasma concentrations versus time for the test (Taro) and reference (Dupont), during period 3 and 4, are displayed in Figures 2a and 2b the summary report for linear and ln linear scales, respectively. A summary of the statistical .lysis comparing pharmacokinetic parameters for test and reference during period 3 and period + is provided in Table 3 of the summary report. As shown, there were no statistical differences

detected by ANOVA for any of the pharmacokinetic parameters except C_{max} (test<reference; p=0.0171) and T_{max} (test>reference; p=0.0464). However, the 90 and 95% confidence intervals (CI) for ln transformed ratio of AUC_{0-t}, AUC_{0-inf}, and C_{max} were all within the acceptable limits (80-125%) supporting bioequivalence of Taro vs Dupont warfarin sodium 5 mg. The mean plasma concentrations at each sampling time point are summarized in Table 4 of the Summary Report.

The individual plasma concentrations and individual pharmacokinetic parameters during period 3 and 4 can be found in Tables 1-4 of Annex II. The complete stastistical analysis for each pharmacokinetic parameters can be found in Tables 5-29 of Annex II, whereas the individual plasma concentrations versus time profiles are provided in Figures 01a-23a of Annex II. Figure 24a shows the mean plasma-concentrations versus time profile to be identical to figure 2 of the Summary Report. Finally, the profile of plasma concentrations and statistical analysis at each sampling timepoint can be found in Annex II (see Tables 1a-22a and Tables 1b-22b, respectively).

Thus, under single dose fasting conditions, warfarin sodium 5 mg Taro and Dupont formulations are judged bioequivalent when comparing the alternate dosing sequence of test and reference products during period 3 and 4.

III. Pooled analysis (Average Period 1 and 3 vs Period 2 and 4)

The third analysis was conducted using the average plasma concentrations of the two repeated dosing sequences of each product (i.e. average of tests 1 and 2 vs average of references 1 and 2 plasma concentrations; n=23). Plots of mean warfarin plasma concentrations versus time for the test and reference averaged are displayed in Figures 3a and 3b of the summary report for linear and ln linear scales, respectively. A summary of the statistical analysis comparing pharmacokinetic parameters for pooled test and reference is provided in Table 5 of the summary report. As shown, there were no statistical differences detected by ANOVA for any of the pharmacokinetic parameters. In addition, the 90 and 95% confidence intervals (CI) for ln transformed ratio of AUC_{0-t}, AUC_{0-inf}, and C_{max} were all within the acceptable limits (80-125%) supporting bioequivalence of Taro vs Dupont warfarin sodium 5 mg. The mean plasma concentrations at each sampling time point are summarized in Table 6 of the Summary Report.

The individual plasma concentrations and individual pharmacokinetic parameters during period 3 and 4 can be found in Tables 1-4 of Annex III. The complete stastistical analysis for each pharmacokinetic parameters can be found in Tables 5-29 of Annex III, whereas the individual plasma concentrations versus time profiles are provided in Figures 01a-23a of Annex III. Figure 24a shows the mean plasma-concentrations versus time profile being identical to figure 3 of the Summary Report. Finally, the profile of plasma concentrations and statistical analysis at each sampling timepoint can be found in Annex III (see Tables 1a-22a and Tables 1b-22b, respectively).

Thus, under single dose fasting conditions, warfarin sodium 5 mg Taro and Dupont formulations are judged bioequivalent when comparing pooled data (Average Period 1 and 3 vs Period 2 and 4).

IV. Repeated Cross-Over Design Analysis (all four periods considered):

Because there are no established statistical methods or criteria for testing individual bioequivalence, no attempts were made to conduct such analyses at this time. Instead, we choose to test bioequivalence using data from all four periods individually by ANOVA using a previously published method as stated in the Methodology section.

A summary of this statistical analysis comparing pharmacokinetic parameters for the test and reference products is provided in Table 7. As shown, there was no statistical differences between ln transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}, and the 90% and 95% CI were all within the acceptable limits (80-125%) supporting bioequivalence of Taro vs Dupont warfarin sodium 5 mg. Bar graphs representing the following pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-inf.}$ and C_{max}, are provided in Figures 4a-4c. As shown, these bar graphs show similar variability betweeen and within formulation.

Note that since this analysis used data from each period for all subjects (n=23), the raw data for this analysis can be found in Annex I and II. Statistical analysis by ANOVA for ln transformed parameters (AUC_{0-t}, $AUC_{0-inf.}$, and C_{max}) are provided in Tables 1-3 of Annex IV.

CONCLUSION

Based on the results of this study, it is concluded that Taro warfarin sodium 5 mg immediate release tablets are bioequivalent to the DuPont (Coumadin®, Reference product) warfarin sodium mg immediate release tablets under fasted single dose conditions.

Warfarin Sodium Tablets
1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg
ANDA #40-301
Reviewer: S. P. Shrivastava

Taro Pharmaceuticals USA, Inc.
Howthorne, NY
Submission Date:
March 2, 1998

REVIEW OF THREE BIOEQUIVALENCE STUDIES, NINE DISSOLUTION TESTING DATA AND WAIVER REQUESTS

I. OBJECTIVE

The firm has submitted three bioequivalence studies under fasting conditions. The objective of these studies was to compare the plasma levels of warfarin from single oral doses of 2, 5, and 10 mg tablets of test warfarin sodium tablets to plasma levels from the reference warfarin sodium tablets (Coumadin^R, DuPont-Merck), 2, 5, and 10 mg, respectively. The firm has also requested waivers of *in vivo* bioequivalence testing requirements for its 1, 2.5, 3, 4, 6 and 7.5 mg strengths. To support the requests, firm has submitted comparative dissolution profiles for its warfarin sodium 1, 2.5, 3, 4, 6 and 7.5 mg tablets versus Coumadin^R 1, 2.5, 3, 4, 6 and 7.5 mg Tablets, respectively. The formulations for all 9 strengths of the drug products warfarin sodium tablets were also submitted.

II. INTRODUCTION

Warfarin Sodium is an anticoagulant drug. The drug acts by inhibiting the synthesis of vitamin K dependent coagulation factors. The resultant in vivo effect is a sequential depression of Factors VII, IX, X, and II activities. The degree of depression depends on the administered dose. It is indicated for the prophylaxis and/or treatment of venous thrombosis.

Warfarin is a racemic mixture of S and L enantiomers. The S- enantiomer is 3-5 times more potent than the R-enantiomer. The oral absorption of warfarin sodium is complete. Maximum plasma concentrations occur in 1 to 9 hours. It is approximately 97% bound to plasma albumin. An anticoagulation effect generally occurs within 24 hours. However, peak anticoagulant effect may be delayed 72 to 96 hours and its duration of action may persist for 4 to 5 days. The half-life of warfarin sodium is about 2.5 days and it is metabolized in the liver to inactive metabolites.

The dosage of the drug is dependent on the response of the patient. Dosage should be controlled by determination of one stage prothrombin time. Most patients are satisfactorily maintained at 2-10 mg/day.

The listed reference drug of warfarin sodium is Coumadin^R tablets, 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg, manufactured by DuPont Merck Pharmaceutical Co..

III. PROTOCOLS

A. #GP-711:	**SINGLE-DOSE FASTING, TWO-WAY CROSSOVER STUDY: DOSE 2 X 2 MG**
Study Site:	
Principal Investigators:	
Analytical Site:	
Sponsor:	Taro Pharmaceuticals, USA, Inc.
Study Design:	Single-dose, two-way crossover bioequivalence study, under fasting conditions.
Dosing Dates	October 4, 1997 - October 25, 1997
Analysis Dates	November 10, 1997 - December 10, 1997.
Storage Period	67 Days
Subjects:	Thirty-six (36) normal, adult healthy males were enrolled, and 35 subjects completed the study. Subject #33 was withdrawn due to viremia.
Subjects Eligibility:	Thirty-six (36) healthy male subjects (ages 18-45 years), within $\pm$15% of their IBW were enrolled for the study. Each subject received a complete physical examination, laboratory tests of hematology, clinical chemistry and urinalysis. Only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study.
Restrictions:	The subjects were instructed to take no prescribed medications for at least 14 days prior to the initial dosing and throughout the study. No medications were permitted during the confinement except those administered. Subjects were also instructed to abstain from any over-the-counter medications within 14 days of period I and products containing alcohol or caffeine (xanthine) for 24 hours prior to dosing and throughout the study.
Dose and Treatment: A.	Test product: Single oral 2 x 2 mg warfarin sodium tablet manufactured by Taro Pharmaceutical Inc., Lot #780100, lot size

tablets, potency 97.6%, content uniformity 96.9%, following an overnight fast.

B. Reference product: 2 x 2 mg Coumadin[R] tablet manufactured by Dupont Merck, Lot #ELD242A, Exp. 02/00, potency 99.5%, content uniformity 98.2%, following an overnight fast.

Randomization Scheme: See Attachment-1

Food and Fluid Intake: Subjects were required to fast at least 10 hours prior to and 4 hours after drug administration. Water was prohibited from two hours pre-dose until four hour post-dose except for water (240 mL) administered with the dose. Four hours after the dose, water was permitted *ad lib* for the remainder of the study period. Standard meals were served during the study.

Washout period: Fourteen days between dosing periods.

Blood Samples: Blood samples (2x7 mL/1x7 mL each) were collected in Vacutainers containing EDTA at 0 hour pre-dose, and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144 and 168 hours post-dose. These samples will also be used for coagulation and safety tests at 24, 48 and 168 hours post-dose.

Safety Monitoring: Prior to dosing, subjects will be examined for bruises and contusions. Subjects will be monitored throughout the study by a physician on site.

B 97-129: SINGLE-DOSE FASTING, REPLICATE DESIGN, FOUR-WAY CROSSOVER STUDY: DOSE 1 x 5 MG

Study Site:

Principal Investigators:

Analytical Site:

Sponsor: Taro Pharmaceuticals, USA, Inc.

Study Design: Single-dose fasting, replicated four-way crossover design, under fasting conditions. The study was two treatment, two sequence (TRTR and RTRT combinations), and five period study. First dose for Subjects 23 and 24 started two weeks later (i.e. Per 2).

Therefore, ANOVA was run with or without subjects 23 and 24.

Dose Dates: September 27, 1997 - November 22, 1997.

Analysis Dates: December 1, 1997 - January 7, 1998

Storage Period: 37 Days

Subjects: Twenty-four (24) normal, adult healthy males were enrolled, and 23 subjects completed the study. Subject #5 dropped out due to personal reasons.

Subjects Eligibility: Twenty-four (24) healthy male subjects (ages 18-45 years), within ±15% of their IBW were enrolled for the study. Each subject received a complete physical examination, laboratory tests of hematology, clinical chemistry and urinalysis. Only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study.

Restrictions: The subjects were instructed to take no prescribed medications for at least 14 days prior to the initial dosing and throughout the study. No medications were permitted during the confinement except those administered. Subjects were also instructed to abstain from any over-the-counter medications within 14 days of period I and products containing alcohol or caffeine (xanthine) for 24 hours prior to dosing and throughout the study.

Dose and Treatment: A. Test product 1 and 2: Single oral 1 x 5 mg warfarin sodium tablet manufactured by Taro Pharmaceutical Inc., Lot #780049, lot size tablets, potency 96.4%, content uniformity 101.2%, following an overnight fast.

B. Reference product 1 and 2: 1 x 5 mg Coumadin® tablet manufactured by Dupont Merck, Lot #ELB048A, Exp. 01/00, potency 97.0%, content uniformity 97.5%, following an overnight fast. T1 and T2, and R1 and R2 represent one test and one reference products, i.e. two-treatment BE study. N24 Subjects will be treated in 4 sequences as follows:

Grp1	T1	R2	T2	R1
Grp2	R1	T1	R2	T2
Grp3	T2	R1	T1	R2
Grp4	R2	T2	R1	T1

Randomization Scheme:	See Attachment-2. The firm's treatment designations are confusing. See Attachment-18 for clear understanding of the study design.
Food and Fluid Intake:	Subjects were required to fast at least 10 hours prior to and 4 hours after drug administration. Water was prohibited from two hours pre-dose until four hour post-dose except for water (240 mL) administered with the dose. Four hours after the dose, water was permitted *ad lib* for the remainder of the study period. Standard meals were served during the study.
Washout Period:	Fourteen days between dosing periods.
Blood Samples:	Blood samples (1x7 mL each) were collected in Vacutainers containing EDTA at 0 hour pre-dose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144 and 168 hours post-dose. These samples will also be used for coagulation and safety tests at 24, 48 and 168 hours post-dose.
Safety Monitoring:	Subjects will be monitored throughout the study by a physician on site. Coagulation test (PT) will be performed in each period.

C. #GP-576: **SINGLE-DOSE FASTING, TWO-WAY CROSSOVER STUDY: DOSE 1 X 10 MG**

Study Site:	( )
Principal Investigators:	( )
Analytical Site:	( )
Sponsor:	Taro Pharmaceuticals, USA, Inc.
Study Design:	Single-dose, two-way crossover bioequivalence study, under fasting conditions.
Dosing Dates	July 16, 1997 - August 6, 1997
Analysis Dates	August 14, 1997 to August 27, 1997.
Storage Period	42 Days
Subjects:	Thirty-five (35) normal, adult healthy male subjects were enrolled, and 34 completed the study. Subject #26 was withdrawn because

he did not show up for period 2 dosing.

Subjects Eligibility: Thirty-five (35) healthy male subjects (ages 18-45 years), within ±15% of their IBW were enrolled for the study, and 34 completed the study. Subject #26 dropped due to personal reasons. Each subject received a complete physical examination, laboratory tests of hematology, clinical chemistry and urinalysis. Only medically healthy subjects with clinically normal laboratory profiles were enrolled in the study.

Randomization Scheme: See Attachment-3

Restrictions: The subjects were instructed not to take any prescription medicines for at least 14 days prior to the initial dosing and throughout the study. No medications were permitted during the confinement except those administered. Subjects were also instructed to abstain from any over-the-counter medications within 14 days of period I and products containing alcohol or caffeine (xanthine) for 24 hours prior to dosing and throughout the study.

Dose and Treatment: A. Test product: Single oral 1 x 10 mg warfarin sodium tablet manufactured by Taro Pharmaceutical Inc., Lot #780060, lot size _____ tablets, potency 98.5%, content uniformity 98.7%, following an overnight fast.

B. Reference product: 1 x 10 mg Coumadin® tablet manufactured by Dupont Merck, Lot #ELB085B, Exp. 01/00, potency 97.7%, content uniformity 98.6%, following an overnight fast.

Other lots used in dissolution for waivers:

	TARO	DUPONT
Strength	Batch #	Batch #
1 mg	780075	ELJ391A
2.5	780095	ELB061A
3	780096	EKL399G
4	780086	JL333A
6	780097	EKL400G
7.5	780098	EJE158A

Food and Fluid Intake: Subjects were required to fast at least 10 hours prior to and 4 hours

after drug administration. Water was prohibited from two hours pre-dose until four hour post-dose except for water (240 mL) administered with the dose. Four hours after the dose, water was permitted *ad lib* for the remainder of the study period. Standard meals were served during the study.

Washout Period: Fourteen days between dosing periods.

Blood Samples: Blood samples (2x7 mL/1x7 mL each) were collected in vacutainers containing EDTA at 0 hour pre-dose, and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 120, 144 and 168 hours post-dose. These samples will also be used for coagulation and safety tests at 24, 48 and 168 hours post-dose.

Safety Monitoring: Prior to dosing, subjects will be examined for bruises and contusions. Subjects will be monitored throughtout the study by a physician on site.

IV. PRE-STUDY VALIDATION OF ASSAY METHOD FOR PLASMA SAMPLES

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Assay
Method

Storage Test	Conc. ng/mL	Storage Period	Temperature	% Diff.
(Autosampler)	30	67.4 Hours	Room	2.8
(n=3)	1500			2.6
	3500			3.2
Four Freeze-Thaw	30	4 Cycles	Room/-22 °C	-1.4
Cycles (n=3)	1500			-0.2
	3500			0.9
Bench-Top	30	4 Hours	Room	2.0
(n=3)	1500			3.4
	3500			4.0
Long-Term Stab.	125	61 Days	-25 °C	-6.5
(n=3)	1600			-3.8
	3500			-3.5

V. RESULTS

A. Single-Dose Fasting Study - 2 x 2 mg Dose

1. Within-Study Validation

		Conc., ng/mL	CV, %	%Diff.
Std. Curve;	n=19	10	8.9	3.9
	n=21	20	8.0	-2.0
	n=22	50	6.2	1.8
	n=21	100	5.9	-4.5
	n=20	200	3.9	-0.4
	n=22	400	2.3	2.2
	n=22	500	3.2	-1.0
QC Samples;	n=44	30	10.5	-3.1
	n=24	150	4.0	1.9
	n=20	175	3.3	-2.2
	n=43	350	4.7	-2.1

2. **Blood/Plasma Drug Concentration:** SAS GLM Procedure was used to analyze PK parameters for 35 (all) or 12 (excluding Subjects #2, 8, 15, 17, 21, 25, 26, 28, 29, 32, 35, 36 with C_{max} at first non-zero time-point, and Subjects # 1, 5, 7, 10, 11, 13, 14, 23, 27, 30 and 31 for nonzero drug concentrations at predose sampling time point) subjects. The mean plasma concentration data are given in Tables 5 and 8, and graphic profiles are shown in Attachments 4-5.

3. **Pharmacokinetic Parameters**: Mean PK parameters and statistical analyses are given in Tables 6-7 and 9-10. Individual data are shown in Attachments 6-7.

- The 90% CI for LAUCs are within 80-125% as required (Tables 7, 10).
- ANOVA analysis showed no significant sequence effects on C_{max}, LC_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, and $LAUC_{0-inf}$. However, there was a significant period and treatment effects on AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, and $LAUC_{0-inf}$.
- Individual Test/Reference ratios for AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and T_{half} averaged between 0.92 and 1.11.
- The ratios of AUC_{0-t}/AUC_{0-inf} averaged 0.85.
- Plasma concentration-time profiles were checked for subjects. $AUC_{0-\infty}$ was obtained correctly for all subjects.

4. **Adverse Reaction**: Some differences between test and reference products were observed (See the table below).

	No. Of Subjects		
Sign/Symptom	**Test**	**Reference**	**Drug Related**
Abdominal Pain/Cramps	3	1	Probable/Possible
Bruise	3	0	Probable/Possible
Diarrhea	2	1	Probable/Possible
Dizziness	2	1	Probable/Possible
Ecchymosis	6	1	Probable/Possible
Fainting	1	0	Unknown
Headache	7	4	Probable/Possible
Nausea	0	2	Probable/Possible
Nose Bleeding	2	1	Probable/Possible
Pain in Legs	0	1	Probable/Possible
Red Patches on Arm	0	1	Probable/Possible
Hematoma on Elbow	0	2	Probable/Possible

Swelling of Arm	0	1	Probable/Possible
Swollen Lymph nodes	1	0	Probable/Possible
Tiredness	2	2	Probable/Possible
Weakness	2	0	Unknown
Total	**30**	**18**	

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

TABLE 5. MEAN PLASMA WARFARIN LEVELS FOR TEST AND REFERENCE PRODUCTS (N=35)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	2.89	6.12	2.80	5.25	1.03
0.33	308.98	144.87	329.23	159.03	0.94
0.67	427.78	88.82	444.64	94.63	0.96
1	401.40	63.21	413.06	70.31	0.97
1.5	373.52	48.53	386.24	61.41	0.97
2	350.91	53.20	353.42	50.73	0.99
2.5	336.05	45.71	345.30	59.48	0.97
3	328.59	42.25	337.58	49.51	0.97
4	318.05	44.99	326.53	54.36	0.97
6	252.82	38.84	257.97	39.05	0.98
8	243.75	35.18	247.16	45.62	0.99
12	220.29	37.08	218.08	41.62	1.01
16	198.93	32.76	209.83	35.57	0.95
24	167.37	32.26	175.43	38.46	0.95
48	115.10	32.46	115.64	35.02	1.00
72	80.88	23.22	81.64	25.54	0.99
96	58.61	16.82	58.64	20.39	1.00
120	45.05	15.88	44.75	13.70	1.01
144	36.04	11.55	35.69	11.82	1.01
168	30.62	10.66	30.18	9.60	1.01

UNIT: PLASMA LEVEL=NG/ML TIME=HRS; MEAN1=TEST MEAN2=REFERENCE

TABLE 6. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	19207.49	4708.72	19308.17	4597.20	0.99
AUCT	16080.22	3416.79	16350.78	3750.15	0.98
CMAX	461.80	77.19	488.18	86.19	0.95
KE	0.01	0.00	0.01	0.00	0.99
LAUCI	18719.87	0.23	18808.17	0.23	1.00
LAUCT	15778.59	0.19	15963.54	0.22	0.99
LCMAX	455.86	0.16	481.12	0.17	0.95
THALF	68.03	12.87	66.68	10.31	1.02
TMAX	0.81	0.48	0.80	0.57	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 7. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	19156.50	19275.39	0.99	97.05	101.72
AUCT	16095.86	16320.15	0.99	96.57	100.68
CMAX	461.30	487.42	0.95	90.22	99.06
LAUCI	18657.77	18771.80	0.99	97.29	101.54
LAUCT	15791.49	15930.99	0.99	97.15	101.14
LCMAX	455.39	480.44	0.95	90.62	99.14

TABLE 8. MEAN PLASMA WARFARIN LEVELS FOR TEST AND REFERENCE PRODUCTS (N=12)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	294.93	98.18	278.88	109.31	1.06
0.67	414.75	82.11	438.72	79.90	0.95
1	375.49	51.70	412.10	45.26	0.91
1.5	367.08	38.73	385.59	47.28	0.95
2	339.63	44.06	356.54	36.71	0.95
2.5	328.92	28.84	334.39	56.20	0.98
3	318.22	27.84	334.96	26.01	0.95
4	306.09	33.32	320.55	33.60	0.95
6	248.23	33.74	261.55	24.99	0.95
8	237.92	30.31	247.43	25.02	0.96
12	219.20	33.31	216.81	22.27	1.01
16	195.87	23.45	204.24	16.64	0.96
24	159.53	16.87	176.28	25.02	0.90
48	105.68	11.95	110.48	22.10	0.96
72	73.24	11.47	75.77	19.73	0.97
96	53.76	9.93	53.33	16.48	1.01
120	40.06	6.12	40.73	11.30	0.98
144	32.78	5.99	30.76	6.87	1.07
168	27.76	5.77	27.09	7.17	1.02

UNIT: PLASMA LEVEL=NG/ML .TIME=HRS; MEAN1=TEST MEAN2=REFERENCE

TABLE 9. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	18122.70	2357.67	18194.63	2782.11	1.00
AUCT	15089.11	1426.53	15654.38	2291.66	0.96
CMAX	433.30	47.12	462.10	62.09	0.94
KE	0.01	0.00	0.01	0.00	0.92
LAUCI	17979.72	0.13	18006.78	0.15	1.00
LAUCT	15025.11	0.10	15514.37	0.14	0.97
LCMAX	431.15	0.10	458.13	0.14	0.94
THALF	70.91	16.56	64.01	11.04	1.11
TMAX	0.91	0.37	0.95	0.55	0.96

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

TABLE 10. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	17819.34	18194.62	0.98	92.82	103.05
AUCT	15089.11	15654.38	0.96	90.99	101.79
CMAX	433.30	462.10	0.94	89.16	98.38
LAUCI	17623.49	18006.78	0.98	93.41	102.54
LAUCT	15025.11	15514.37	0.97	92.14	101.79
LCMAX	431.15	458.13	0.94	89.57	98.88

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

B. 97-129: **Single-dose fasting, replicate design, four-way crossover study: dose 1 x 5 mg**

1. **Within-Study Validation**

		Conc., ng/mL	CV, %	%Diff.
Std. Curve;	n=28	20.3	2.8	2.6
	n=29	40.6	6.0	- 3.8
	n=29	152	3.4	-1.4
	n=28	305	3.0	1.4
	n=27	610	5.5	-0.1
	n=29	914	2.9	2.4
	n=28	1220	3.4	1.3
	n=29	1520	3.2	0.1
QC Samples;	n=56	60.1	7.8	0.4
	n=57	501	5.6	1.2
	n=58	1000	4.8	0.9

2. **Blood/Plasma Drug Concentration:** PK parameters were analyzed by SAS GLM procedure using 23 (all), 19 (excluding Subject # 7, 9, 14, 19 with C_{max} at first non-zero time-point), and 17 subjects (excluding Subject # 7, 9, 14, 19 with C_{max} at first non-zero time-point, and Subjects #23 and 24 who were treated in period 5). The mean plasma concentration data are given in Tables 11, 14 and 17, and graphic profiles are shown in Attachments 8-10.

3. **Pharmacokinetic Parameters**: Statistical analyses of PK parameters for warfarin were analyzed by the following model for SAS Proc GLM procedures:

   The mean square associated with TRT*SUB(SEQ) interaction was the basis for the error term used in the calculation of 90% CI. This was confirmed by the statistician in the Biometrics. This model was also used in Sano's repeated dose study on nitroglycerin, 0.4 mg/hour trans-dermal drug delivery system (see Review, ANDA by Moo Park, 8/27/96).

   Mean PK parameters and statistical analysis are given in Tables 12-13, 15-16 and 18-19. Individual data are shown in Attachments 11-14.

- The 90% CI for LAUCs are within 80-125% as required (Tables 13, 16, and 19).

- ANOVA analysis showed significant period and sequence effects on AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, and $LAUC_{0-inf}$. However, the differences were less than 10%.

- Individual Test/Reference ratios for AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and T_{half} averaged between 0.95 and 1.39.

- The ratios of AUC_{0-t}/AUC_{0-inf} averaged 0.87.

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

- ANOVA analysis showed no significant treatment or sequence effects on AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, there was a significant period effect on AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, , $LAUC_{0-inf}$ and LC_{max}. The LS means for Period 2 were approx. 17% higher than for Period 1.

- Individual Test/Reference ratios for AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and T_{half} averaged between 1.06 and 1.10.

- The ratios of AUC_{0-t}/AUC_{0-inf} averaged 94%.

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

4. **Statistical Consult:** Since the division has a policy, that all replicated design studies be sent for statistical consult, this study was also sent for consult (Attachments 15-17). The study was reviewed by Don Schuirmann, and his report is attached (Attachment 18). Data were analyzed in five different ways, with and without carryover effects as follows:

    1. All subjects

    2. Excluding Subjects 4, 7, 8, 20, and 21, who had non-zero drug concentrations in some zero time blood samples.

    3. Excluding Subjects # 7, 9, 14, and 19, who had Cmax occurring at the first non-zero sampling time point.

    4. Excluding Subjects 4, 7, 8, 9, 14, 19, 20 and 21, the subjects who were excluded in 2 and 3 above.

    5. Excluding Specific Observations: Subject 7, period 4; Subject 9, period 3; subject 14, period 3; and Subject 19, period 3.

The 90% CI for PK parameters for the five different sets of data, with and without carryover effects, were:

	LAUC0-t	LAUC0-inf	LCmax
Analysis without Carryover Effects			
1.	99.6-106.2	99.8-107.2	93.0-102.1
2.	99.1-103.2	99.0-104.8	91.2-101.4
3.	99.9-104.6	99.2-104.7	90.8-99.7
4.	100.0-104.6	99.0-105.0	89.4-99.7
5.	99.7-105.9	100.0-106.1	92.8-102.0
Analysis with Carryover Effects			
1.	100.1-112.3	100.2-114.8	93.9-116.5
2.	97.8-107.7	97.8-111.8	87.1-111.7
3.	99.6-110.9	98.3-111.7	88.0-109.8
4.	99.3-110.5	97.7-112.4	83.0-107.5
5.	99.7-112.5	99.7-114.5	93.7-116.6

As evident from the data, even with carryover effects included in the statistical model, the resulting 90% CIs fall within the 80-125% in all cases.

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

	No. Of Subjects		
Sign/Symptom	**Test**	**Reference**	**Drug Related**
Abdominal Gas	1	0	Probable/Possible
Acne	1	0	Probable/Possible
Bruise	2	3	Probable/Possible
Diarrhea	1	2	Probable/Possible
Dizziness	1	0	Probable/Possible
Elevated AST	1	0	Probable/Possible
Headache	3	1	Probable/Possible
Heartburn	0	1	Probable/Possible
RBC/WBC in Urine	3	3	Probable/Possible
Pain in Wrist	0	1	Probable/Possible
Rash and Itching	1	0	Probable/Possible
Red Patches on fingers	1	1	Probable/Possible
Vomiting	2	0	Probable/Possible
Total	**17**	**12**	

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

TABLE 11. MEAN PLASMA WARFARIN SODIUM LEVELS FOR TEST AND REFERENCE PRODUCTS (N=23)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	2.82	8.25	3.26	8.59	0.86
0.25	282.06	208.00	245.63	192.87	1.15
0.5	545.22	175.60	561.26	192.34	0.97
0.75	563.28	125.51	573.51	120.34	0.98
1	544.24	102.02	552.84	87.87	0.98
1.5	501.66	77.01	517.65	86.52	0.97
2	479.89	81.96	491.32	79.76	0.98
2.5	463.38	78.37	475.10	73.66	0.98
3	447.89	71.37	455.32	75.23	0.98
4	439.22	63.46	430.20	72.44	1.02
6	372.49	66.47	360.58	58.50	1.03
8	362.74	59.03	357.14	59.96	1.02
12	336.00	58.65	329.72	67.12	1.02
16	311.68	52.32	304.37	55.45	1.02
24	262.67	49.33	255.14	49.90	1.03
36	218.18	40.47	215.57	43.68	1.01
48	181.77	44.84	174.62	39.18	1.04
72	119.96	33.50	117.88	29.85	1.02
96	84.38	27.75	82.39	23.70	1.02
120	63.92	21.82	60.10	17.12	1.06
144	48.99	17.12	47.52	14.31	1.03
168	39.52	14.83	37.53	13.63	1.05

UNIT: PLASMA LEVEL=NG/ML TIME=HRS; MEAN1=TEST MEAN2=REFERENCE

TABLE 12. ARITHMETIC MEANS AND RATIOS (N=23)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	27750.57	6528.04	26981.37	5985.81	1.03
AUCT	23897.15	5084.29	23279.88	4709.12	1.03
CMAX	617.02	119.69	637.54	131.44	0.97
KE	0.01	0.00	0.01	0.00	0.99
LAUCI	27056.66	0.22	26364.35	0.22	1.03
LAUCT	23403.95	0.20	22838.22	0.20	1.02
LCMAX	605.61	0.20	624.63	0.20	0.97
THALF	67.23	17.83	66.20	14.71	1.02
TMAX	0.94	0.78	0.76	0.41	1.23

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 13. LSMEANS AND 90% CONFIDENCE INTERVALS (N=23)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	27835.99	26962.09	1.03	100.27	106.22
AUCT	23968.64	23272.56	1.03	100.49	105.49
CMAX	617.09	637.81	0.97	92.24	101.27
LAUCI	27133.72	26339.94	1.03	100.38	105.72
LAUCT	23469.30	22826.75	1.03	100.62	105.06
LCMAX	605.70	624.77	0.97	92.54	101.57

TABLE 14. MEAN PLASMA WARFARIN SODIUM LEVELS FOR TEST AND REFERENCE PRODUCTS (N=19)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	1.96	6.83	3.19	8.37	0.62
0.25	242.01	172.44	211.51	139.25	1.14
0.5	521.28	180.34	550.97	195.87	0.95
0.75	549.70	132.26	576.49	125.24	0.95
1	533.73	105.00	557.65	89.48	0.96
1.5	494.41	79.12	524.96	89.37	0.94
2	476.54	84.88	495.75	82.10	0.96
2.5	462.03	83.67	480.19	75.32	0.96
3	445.68	75.80	460.19	78.07	0.97
4	437.48	67.32	434.39	70.70	1.01
6	368.21	67.63	362.34	60.00	1.02
8	358.61	58.59	359.35	63.12	1.00
12	331.98	60.67	331.68	71.38	1.00
16	310.29	54.80	304.05	57.85	1.02
24	259.84	50.53	255.02	53.91	1.02
36	217.73	41.61	216.77	45.30	1.00
48	179.31	43.78	174.70	41.07	1.03
72	117.49	28.91	118.40	31.14	0.99
96	83.44	23.69	82.95	25.03	1.01
120	63.44	19.18	60.16	17.85	1.05
144	48.04	14.76	47.60	14.65	1.01
168	38.01	13.17	38.23	14.27	0.99

UNIT: PLASMA LEVEL=NG/ML TIME=HRS; MEAN1=TEST MEAN2=REF

TABLE 15. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	27160.57	6178.07	27112.88	6310.90	1.00
AUCT	23602.14	4885.91	23381.68	5036.82	1.01
CMAX	600.50	121.74	632.88	129.23	0.95
KE	0.01	0.00	0.01	0.00	1.04
LAUCI	26517.18	0.22	26433.02	0.23	1.00
LAUCT	23133.06	0.20	22880.88	0.21	1.01
LCMAX	588.86	0.20	620.54	0.20	0.95
THALF	63.77	13.71	66.77	14.39	0.96
TMAX	1.04	0.83	0.77	0.40	1.34

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 16. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	27409.97	27059.53	1.01	97.91	104.68
AUCT	23834.27	23380.09	1.02	99.09	104.79
CMAX	597.71	631.89	0.95	89.92	99.26
LAUCI	26742.67	26354.66	1.01	98.59	104.44
LAUCT	23346.25	22856.49	1.02	99.67	104.68
LCMAX	586.27	619.06	0.95	90.28	99.35

TABLE 17. MEAN PLASMA WARFARIN SODIUM LEVELS FOR TEST AND REFERENCE PRODUCTS (N=17)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	2.19	7.19	3.56	8.79	0.62
0.25	232.16	171.64	213.57	146.70	1.09
0.5	507.55	185.91	538.55	202.68	0.94
0.75	538.39	134.24	562.08	124.11	0.96
1	525.60	107.82	546.69	87.89	0.96
1.5	489.05	81.48	516.75	90.47	0.95
2	468.03	84.55	485.13	79.66	0.96
2.5	458.26	87.60	474.25	77.50	0.97
3	441.14	77.79	452.90	78.65	0.97
4	435.33	70.54	430.45	73.62	1.01
6	366.40	70.78	357.81	61.85	1.02
8	358.57	61.32	356.72	65.65	1.01
12	330.85	63.78	328.97	74.91	1.01
16	310.50	57.88	301.66	60.38	1.03
24	259.06	52.84	251.98	55.82	1.03
36	218.47	43.63	215.60	47.46	1.01
48	180.05	46.11	174.08	42.73	1.03
72	118.00	29.98	118.44	32.61	1.00
96	84.61	24.73	83.77	25.94	1.01
120	64.53	19.85	60.63	18.58	1.06
144	49.08	15.10	48.22	15.20	1.02
168	38.80	13.64	38.28	15.02	1.01

UNIT: PLASMA LEVEL=NG/ML TIME=HRS; MEAN1=TEST MEAN2=REF

TABLE 18. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	27343.26	6477.59	26984.54	6631.49	1.01
AUCT	23679.79	5131.08	23292.38	5280.44	1.02
CMAX	593.89	126.20	623.53	132.81	0.95
KE	0.01	0.00	0.01	0.00	1.02
LAUCI	26636.44	0.23	26240.52	0.24	1.02
LAUCT	23163.54	0.21	22746.35	0.22	1.02
LCMAX	581.53	0.21	610.69	0.21	0.95
THALF	64.31	13.95	65.40	11.29	0.98
TMAX	1.09	0.86	0.78	0.42	1.39

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 19. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	27434.72	26969.93	1.02	98.01	105.43
AUCT	23770.05	23296.69	1.02	98.93	105.14
CMAX	593.12	623.65	0.95	89.99	100.22
LAUCI	26721.83	26219.44	1.02	98.77	105.16
LAUCT	23248.57	22743.92	1.02	99.57	104.93
LCMAX	580.89	610.64	0.95	90.29	100.22

C. #GP-576: **Single-dose fasting, two-way crossover study: dose 1 x 10 mg**

1. **Within-Study Validation**

		Conc., ng/mL	CV, %	%Diff.
Std. Curve;	n=12	50	6.8	11.0
	n=17	100	6.8	-2.9
	n=17	400	2.2	3.0
	n=16	1500	1.3	-7.2
	n=17	2500	1.6	-5.7
	n=17	4000	1.8	3.4
	n=17	5000	1.4	2.2
QC Samples;	n=34	125	10.2	-0.1
	n=34	1600	2.4	-1.5
	n=34	3500	2.1	1.3

2. **Blood/Plasma Drug Concentration:** PK parameters were analyzed by SAS GLM procedure using 34 (all) and 31 (excluding Subject # 20, 27, 29 with C_{max} at first non-zero time-point) subjects. The mean plasma concentration data are given in Tables 20 and 23, and graphic profiles are shown in Attachments 19-20.

3. **Pharmacokinetic Parameters**: Mean PK parameters and statistical analysis are given in Tables 21-22 and 24-25. Individual data are shown in Attachments 21-22.

- The 90% CI for LAUCs are within 80-125% as required (Tables 22, 25).
- ANOVA analysis showed no significant treatment or sequence effects on AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max}. However, there was a significant period effect on AUC_{0-t}, $AUC_{0-\infty}$, $LAUC_{0-t}$, , $LAUC_{0-inf}$ and LC_{max}. The differences were less than 10%.
- Individual Test/Reference ratios for AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and T_{half} averaged between 0.94 and 1.12.
- The ratios of AUC_{0-t}/AUC_{0-inf} averaged 0.88.
- Plasma concentration-time profiles were checked for subjects. $AUC_{0-\infty}$ was obtained correctly for all subjects.

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

Sign/Symptom	No. Of Subjects Test	Reference	Drug Related
Bruise	5	3	Probable/Possible
Tiredness	0	1	Probable/Possible
Headache	1	2	Probable/Possible
Nose Bleeding	0	1	Probable/Possible
Total	**6**	**7**	

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

APPEARS THIS WAY
ON ORIGINAL

TABLE 20. MEAN PLASMA WARFARIN SODIUM LEVELS FOR TEST AND REFERENCE PRODUCTS (N=34)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	511.29	354.61	501.51	384.19	1.02
0.67	895.07	330.43	978.96	293.41	0.91
1	936.83	232.96	1013.69	212.89	0.92
1.5	910.39	186.40	946.59	166.12	0.96
2	878.45	156.00	926.61	151.95	0.95
2.5	864.20	149.30	873.12	138.16	0.99
3	846.96	139.15	852.90	158.79	0.99
4	818.89	127.26	822.20	140.70	1.00
6	697.83	111.94	678.84	97.70	1.03
8	648.11	102.85	667.43	118.84	0.97
12	591.71	103.73	604.34	101.86	0.98
16	551.78	97.46	564.03	93.72	0.98
24	479.58	86.59	476.36	88.91	1.01
48	309.51	63.49	309.17	66.73	1.00
72	213.04	56.94	211.08	56.41	1.01
96	148.09	47.34	149.10	41.63	0.99
120	101.37	43.33	105.31	33.42	0.96
168	33.86	44.17	38.14	41.38	0.89

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR; MEAN1=TEST MEAN2=REF

TABLE 21. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	45739.46	11149.75	46340.98	10500.37	0.99
AUCT	40151.05	9204.00	40736.33	9044.22	0.99
CMAX	1066.95	192.98	1141.23	204.25	0.93
KE	0.02	0.00	0.02	0.00	1.06
LAUCI	44462.19	0.24	45199.96	0.23	0.98
LAUCT	39146.41	0.23	39776.22	0.22	0.98
LCMAX	1051.02	0.17	1122.40	0.19	0.94
THALF	45.37	10.94	47.81	9.80	0.95
TMAX	1.22	0.83	1.08	0.65	1.12

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 22. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	45746.76	46207.37	0.99	96.30	101.71
AUCT	40208.75	40609.81	0.99	96.35	101.68
CMAX	1068.79	1138.99	0.94	88.42	99.26
LAUCI	44482.37	45052.89	0.99	96.09	101.45
LAUCT	39188.54	39645.35	0.99	96.30	101.46
LCMAX	1052.95	1120.00	0.94	88.97	99.34

TABLE 23. MEAN PLASMA WARFARIN SODIUM LEVELS FOR TEST AND REFERENCE PRODUCTS (N=31)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.33	503.89	341.15	452.33	333.34	1.11
0.67	898.90	342.84	971.26	304.61	0.93
1	946.05	239.19	1018.55	221.19	0.93
1.5	915.68	192.35	954.20	171.64	0.96
2	883.82	161.32	934.05	156.76	0.95
2.5	867.94	153.96	877.01	142.97	0.99
3	851.26	144.20	859.88	163.54	0.99
4	823.07	131.55	830.50	144.26	0.99
6	702.70	114.60	683.49	100.22	1.03
8	652.22	104.64	672.27	122.99	0.97
12	595.69	105.30	608.02	104.09	0.98
16	556.69	98.54	568.13	93.43	0.98
24	484.88	84.88	480.35	88.58	1.01
48	313.46	60.27	312.91	65.64	1.00
72	215.02	55.65	213.73	55.91	1.01
96	148.80	47.16	150.73	40.70	0.99
120	103.77	41.25	105.93	33.61	0.98
168	34.43	44.55	39.54	41.82	0.87

UNIT: PLASMA LEVEL=NG/ML TIME=HRS; MEAN1=TEST MEAN2=REF

TABLE 24. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	46145.03	11043.53	46759.67	10454.84	0.99
AUCT	40582.13	9044.12	41162.62	9011.69	0.99
CMAX	1072.59	193.25	1134.39	203.44	0.95
KE	0.02	0.00	0.02	0.00	1.07
LAUCI	44942.56	0.23	45665.50	0.22	0.98
LAUCT	39654.12	0.22	40237.81	0.22	0.99
LCMAX	1056.85	0.17	1115.66	0.19	0.95
THALF	45.27	10.90	47.92	9.97	0.94
TMAX	1.18	0.79	1.15	0.65	1.03

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 25. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	46237.84	46576.24	0.99	96.37	102.18
AUCT	40720.19	40975.54	0.99	96.55	102.21
CMAX	1074.85	1131.38	0.95	89.91	100.10
LAUCI	45044.79	45466.80	0.99	96.23	102.00
LAUCT	39779.80	40050.27	0.99	96.63	102.09
LCMAX	1059.18	1112.26	0.95	90.50	100.21

VI. FORMULATION: (NOT FOR RELEASE UNDER F.O.I.)

TABLE 26. Composition of Test Product Formulations (mg/tablet)

Ingredients	1 mg	2 mg
Warfarin Sodium Crystalline Clathrate*, USP		
Anhydrous Lactose, NF		
Pregelatinized (corn) Starch, NF		
Magnecium Stearate, NF		
D&C Red No. 6 - Lake		
FD&C Red No. 40 - Lake		
FD&C Blue No. 2 - Lake		
Total Dry Wt.	216.00	217.50

* 1.09 Mg Warfarin sodium crystalline clathrate = 1 mg Warfarin sodium

TABLE 27 . Composition of Test Product Formulations (mg/tablet)

Ingredients	2.5 mg	3 mg	4 mg	5 mg
Warfarin Sodium Crystalline Clathrate*, USP				
Anhydrous Lactose, NF				
Pregelatinized (corn) Starch, NF				
Magnecium Stearate, NF				
D&C Yellow No. 10 - Lake				
FD&C Blue No. 2 - Lake				
FD&C Red No. 40 - Lake				
Color D&C Red No. 6 - Lake				
Total Dry Wt.	217.93	218.53	219.26	220.48

* 1.09 Mg Warfarin sodium crystalline clathrate = 1 mg Warfarin sodium

VI. FORMULATION (CONT'D): (NOT FOR RELEASE UNDER F.O.I.)

TABLE 28 . Composition of Test Product Formulations (mg/tablet)

Ingredients	6 mg	7.5 mg	10 mg
Warfarin Sodium Crystalline Clathrate*, USP			
Anhydrous Lactose, NF			
Pregelatinized (corn) Starch, NF			
Magnecium Stearate, NF			
D&C Yellow No. 10 - Lake			
FD&C Blue No. 2 - Lake			
Total Dry Wt.	221.81	222.96	225.70

* 1.09 Mg Warfarin sodium crystalline clathrate = 1 mg Warfarin sodium

VII. IN VITRO **RESULTS (DISSOLUTION):** All strengths meet the dissolution specification (Q) of NLT ( )% in 30 minutes.

Table 29. *In Vitro* Dissolution Testing

Conditions

Method, Apparatus II (Paddle): RPM: 50 **No. of Units: 12**
Medium: Deionized Water at 37 °C
Volume: 900 mL
Reference Drug: Coumadin[R] **Manufacturer:** DuPont
Assay Methodology: USP Method

Sampling Time	Reference Product			Test Product		
(Minutes)	Mean % Dissol	Range	CV	Mean % Dissol	Range	CV
	Lot # ELJ391A		**1 mg Strength**	**Lot # 780075**		
10	100		4.4	79		1.8
20	102		1.5	93		1.7
30	102		1.7	94		1.2
	Lot # ELD242A		**2 mg Strength**	**Lot #780100**		
10	75		22.1	55		7.1
20	98		2.0	99		3.6
30	99		1.7	99		3.3
	Lot # ELB061A		**2.5 mg Strength**	**Lot # 780095**		
10	100		1.3	74		14.3
20	99		1.5	97		3.1
30	99		1.7	99		3.4
	Lot #EKL399G		**3 mg Strength**	**Lot # 780096**		
10	80		17.9	62		1.2
20	101		1.1	94		5.3
30	101		1.0	98		4.1

	Lot # JL333A	**4 mg Strength**	**Lot # 780086**	
10	62	11.9	64	11.5
20	101	1.6	99	3.9
30	102	1.6	101	2.9
	Lot # ELB048A	**5 mg Strength**	**Lot #780049**	
10	75	18.7	69	5.0
20	98	1.3	97	2.4
30	98	1.2	97	2.4
	Lot # EkL400G	**6 mg Strength**	**Lot # 780097**	
10	59	7.6	62	10.0
20	99	2.1	99	2.8
30	100	1.8	100	2.9
	Lot #EJE158A	**7.5 mg Strength**	**Lot # 780098**	
10	58	8.9	70	13.9
20	101	1.6	100	2.1
30	102	1.6	101	2.7
	Lot #ELB085B	**10 mg Strength**	**Lot # 780060**	
10	64	6.0	71	5.4
20	98	1.4	99	1.5
30	98	1.2	99	1.5

VIII. DEFICIENCIES

None

IX. RECOMMENDATIONS

1. The single-dose fasting bioequivalence studies conducted by Taro Pharmaceutical Inc., on its Warfarin Sodium 2 mg (Lot #780100), 5 mg (Lot #780049) and 10 mg (Lot

#780060) tablets, comparing them to Coumadin® 2 mg (Lot # ELD242A), 5 mg (Lot # ELB248A), and 10 mg (Lot # ELB085B) tablets, respectively, manufactured by Dupont Merck, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Taro's warfarin sodium 2 mg, 5 mg and 10 mg tablets are bioequivalent, respectively, to Dupont's Coumadin®, 2 mg, 5 mg and 10 mg tablets.

2. The dissolution tests conducted by Taro Pharmaceutical's., on its warfarin sodium 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg and 10 mg tablets, Lots # 780075, 780100, 780095, 780096, 780086, 780049, 780097, 780098, and 780060, respectively, are acceptable. The formulations for 1, 2.5, 3, 4, 6, and 7.5 mg strengths are proportionally similar to 2, 5 and 10 mg strengths of the test products, which underwent acceptable bioequivalence testing. Waivers of *in vivo* bioequivalence study requirements for the 1, 2.5, 3, 4, 6, and 7.5 mg, tablets of the test products are granted. The Division of Bioequivalence deems warfarin sodium tablets, 1, 2.5, 3, 4, 6, and 7.5 mg, tablets manufactured by Taro Pharmaceutical to be bioequivalent to Coumadin® tablets, 1, 2.5, 3, 4, 6, and 7.5 mg tablets, respectively, manufactured by Dupont Merck.

3. 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 II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than ( )% of the labeled amount of the drug in dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations.

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S. P. Shrivastava, Ph.D.
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