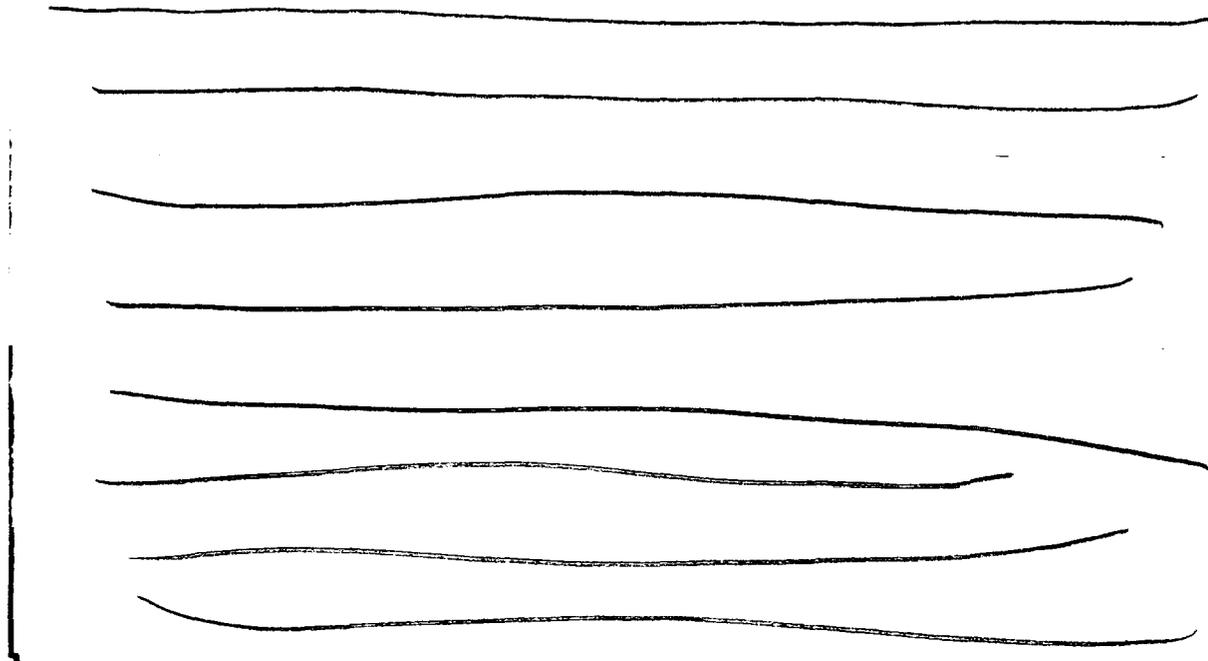


1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Figure 6: Simulation of the effect of a 50 µg/kg loading dose of argatroban followed by a 2 µg/kg/minute infusion for 4 hours. Pharmacodynamic steady state is reached immediately with a loading dose.



XI. Formulation

The market formulation is shown in Table 11. The product will be available in 250 mg/2.5 ml ampules for dilution in an appropriate diluent.

Table 11: Market formulation of agatroban.

Ingredient	Amount per vial
Argatroban	_____
D-Sorbitol	_____
Dehydrated Alcohol	_____
Water for Injection, USP	_____

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XIII. Labeling Comments (to be sent to Sponsor)

1) The text under **Pharmacokinetics** should be replaced with the following:

Pharmacokinetics

Distribution

Argatroban is 54% bound to human serum proteins, with binding to albumin and α_1 -acid glycoprotein being 20% and 34%, respectively.

Metabolism

The main route of argatroban metabolism is hydroxylation and aromatization of the 3-methyl-tetrahydroquinoline ring in the liver. The formation of each of the four known metabolites is catalyzed *in vitro* by the human liver microsomal cytochrome P450 enzymes CYP3A4/5. The metabolite (M1) exerts 3 to 5-fold weaker anticoagulant effects than argatroban. The other metabolites (M2-4) are found only in low quantities in the urine and have not been detected in plasma or feces.

Total body clearance is approximately 5.1 mL/min/kg (0.31 L/hr/kg) for infusion doses up to 40 μ g/kg/min. The half-life of argatroban ranges between 39 and 51 minutes.

There is no interconversion of the 21-(R):21-(S) diastereoisomers. The plasma ratio of these diastereoisomers is unchanged by metabolism or hepatic impairment, remaining constant at 65:35 ($\pm 2\%$).

Excretion

Argatroban is excreted primarily in the urine and feces. In a study in which 14 C-argatroban (5 μ g/kg/min) was infused for 4 hours into healthy subjects, approximately of the radioactivity appeared in the urine within 12 hours of the start of infusion. Little or no additional urinary radioactivity was subsequently detected. Approximately 65% of the radioactivity was recovered in the feces within 6 days of the start of infusion with little or no radioactivity subsequently detected. Average percent recovery of unchanged drug, relative to total dose, was 16% in the urine and 14% in the feces.

Pharmacokinetic/ Pharmacodynamic Relationship: When is administered by continuous infusion, anticoagulant effects and plasma concentrations of argatroban follow similar, predictable temporal response profiles, with low intersubject variability. Immediately upon initiation of infusion, anticoagulant effects are produced and plasma argatroban concentrations begin to rise. Steady state levels of both drug and anticoagulant effect are typically attained within 1-3 hours (0.5-1.0 hour if a loading bolus is administered) and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state argatroban plasma concentrations increase proportionally with dose (for infusion doses up to 40 μ g/kg/min in healthy subjects) and are well correlated with steady-state anticoagulant effects. For infusion doses up to 40 μ g/kg/min and for

bolus doses up to 350 $\mu\text{g}/\text{kg}$, _____ increases in dose-dependent fashion, the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the prothrombin time (PT) and International Normalized Ratio (INR), and the thrombin time (TT). Representative steady-state plasma argatroban concentrations and anticoagulant effects are shown below for NOVASTAN[®] infusion doses of 10 $\mu\text{g}/\text{kg}/\text{min}$.

(See Figure 1)

Special Populations

Renal Impairment

Hepatic Impairment

Hepatic impairment is associated with decreased clearance and increased elimination half-life of argatroban (to 1.9 ml/kg/minute and 181 minutes, respectively, for patients with a Child-Pugh score >6) _____

Age, Gender

There are no clinically significant effects of age or gender on the pharmacokinetics or pahrmacodynamics (apTT) of argtroban.

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Clearance and Half-life values of Agatrobab in Selected Populations. Mean ± SD (range)

Population	Clearance (ml/kg/minute)	Half-Life (Minutes)
Normal Volunteers (n=16)	6.5±1.5	60±15
Patients with unstable angina (n=43)	4.6±1.6	57±46
Patients undergoing PTCA (n=6)	2.8±1.1	107±60
Patients with hepatic impairment (n=5)	1.9±1.2	181±131

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2) In the PRECAUTIONS section under Drug Interactions, the section titled *Drugs metabolized by Cytochrome P450 3A4* should be re-located to the top of that section. Also, for each drug interaction study, the doses of each drug in the study should be clearly stated.

/S/

2/24/98

Michael J. Fossler, Pharm. D., Ph. D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/

2/24/98

K. Gary Barnette, Ph.D.
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RD initialed by Lydia Kaus, Ph.D., Team Leader, LCK 12/7/97
FT signed by Mei-Ling Chen, Ph.D., Division Director
Version: Final

/S/ 2/25/98

Required Office Level briefing held 12/15/97. Present: Sizer, Kaus, Huang, El-Tahtawy, Johnson, Cronenberger, M. Chen, Miller, Barnette, Fossler

CC: NDA 20-883 (orig., 1 copy), HFD-180(Sizer, DuBeau), HFD-850(Lesko), HFD-870(M. Chen 13B-17, Fossler 14B-18, Barnette 17B-30), Central Document Room(Barbara Murphy)
Recommendation Code: AE

Appendix:

Study Summaries

Proposed Package Insert

Study #: ARG-101

Title of Study: Comparison of the anticoagulant effect of four infusion doses of heparin vs. argatroban in normal human volunteers

Objectives: To evaluate and compare the safety of four ascending-dose continuous IV infusions of argatroban and heparin, with and without initial bolus loading doses, in normal healthy volunteers.

To evaluate and compare the relationship between doses and changes to the coagulation parameters (time course, magnitude, dose-response) following IV infusions of argatroban and heparin, with or without an initial bolus, in normal healthy volunteers. The coagulation parameters used as primary indices of anticoagulant efficacy were the activated clotting time (ACT) and activated partial thromboplastin time (aPTT).

Study Design: This was a randomized, double-blind, parallel-group, dose-escalation trial. The following four treatment groups were used:

- (1) IV infusion of argatroban at four escalating dose levels without a bolus loading dose,
- (2) IV infusion of heparin at four escalating dose levels without a bolus loading dose,
- (3) IV infusion of argatroban at four escalating dose levels with a bolus loading dose, and
- (4) IV infusion of heparin at four escalating dose levels with a bolus loading dose.

Subjects (planned and analyzed): Thirty-seven normal healthy subjects were enrolled in this study (36 completers). Subjects were randomized to the four treatment groups (9 subjects/group).

Test product, dose, duration, and mode of administration, batch number: The test product was argatroban, batch number 3601 manufactured by _____ administered as a 4 hour infusion at the rate of 1.25, 2.5, 5.0 or 10.0 µg/kg/min on 4 consecutive days. The bolus dose was 250 µg/kg of argatroban given over 1 minute.

Reference product, dose, duration, and mode of administration, batch number: The reference product was heparin, batch number 013042 manufactured by _____ administered as a 4 hour infusion at the rates of 0.15, 0.20, 0.25 or 0.30 IU/kg/min on 4 consecutive days. The bolus dose was 125 IU/kg heparin given over 1 minute.

Assay Validation: The assay used to assess plasma argatroban concentrations is an _____

The validation of the assay is included in table 1.

Results:

Pharmacokinetics: The plasma concentrations of the two isomers of argatroban (21-(R) and 21-(S)) were assessed at 240 minutes after initiation of treatment (see Table 2, below).

Table 2. Mean Argatroban Concentrations (ng/ml) after 240 Minutes of Infusion

Infusion Dose (µg/kg/min)	Bolus + Infusion		Infusion	
	21-(R)-argatroban	21-(S)-argatroban	21-(R)-argatroban	21-(S)-argatroban
1.25	169.7 ± 34.48	79.53 ± 12.79	176.3 ± 60.85	87.28 ± 35.74
2.5	349.5 ± 54.99	175.5 ± 29.58	360.4 ± 87.22	175.6 ± 46.19
5.0	639.6 ± 87.23	311.7 ± 40.42	693.4 ± 190.54	328.4 ± 102.47
10.0	1315 ± 122.97	647.5 ± 80.93	1365 ± 295.58	668.2 ± 150.58

Efficacy: The primary efficacy parameters assessed in this study were the activated clotted time (ACT) and the activated partial thromboplastin time (aPTT). These data comparing argatroban infusion doses of 1.25, 2.5, 5.0 and 10.0 µg/kg/min, with and without a 250 µg/kg IV bolus dose are included in Tables 3 and 4 and in Figures 1-6. An additional comparison between the aforementioned argatroban doses and heparin infusion doses of 0.15, 0.20, 0.25 and 0.30 IU/kg/min, with and without a 125 IU/kg IV bolus dose was made and these data are also included in Tables 3 and 4.

Table 3. Median ACT Values

Argatroban					
Dose (Bolus/Infusion)	Peak Value (s)	T _{Peak} (m)	Steady State (s)	Time to Steady State (m)	Pharmacodynamic T _{1/2} (m)
0 µg/kg/1.25 µg/kg/min	165 (142-184)	180 (90-240)	154 (141-183)	196 (79-227)	29 (15-49)
250 µg/kg/1.25 µg/kg/min	252 (222-297)	5 (5-5)	142 (128-168)	93 (78-101)	32 (6-49)
0 µg/kg/2.5 µg/kg/min	188 (163-214)	180 (90-240)	177 (160-199)	69 (35-151)	36 (10-74)
250 µg/kg/2.5 µg/kg/min	256 (228-290)	5 (5-20)	173 (155-203)	74 (66-86)	19 (6-87)
0 µg/kg/5.0 µg/kg/min	225 (187-264)	120 (90-240)	218 (178-253)	64 (44-108)	40 (17-74)
250 µg/kg/5.0 µg/kg/min	259 (221-304)	5 (5-5)	219 (188-254)	51 (41-63)	40 (22-63)
0 µg/kg/10.0 µg/kg/min	280 (223-317)	120 (60-240)	268 (210-304)	51 (32-89)	36 (24-72)
250 µg/kg/10.0 µg/kg/min	269 (245-313)	60 (5-240)	262 (231-305)	29 (15-33)	34 (25-67)
Heparin					
Dose (Bolus/Infusion)	Peak Value (s)	T _{Peak} (m)	Steady State (s)	Time to Steady State (m)	Pharmacodynamic T _{1/2} (m)
0 IU/kg/0.15 IU/kg/min	124 (118-133)	180 (0-240)	122 (109-135)	214 (37-238)	--
125 IU/kg/0.15 IU/kg/min	242 (185-325)	5 (5-30)	--	--	58 (32-279)
0 IU/kg/0.20 IU/kg/min	126 (123-135)	180 (90-240)	124 (117-131)	164 (146-182)	--
125 IU/kg/0.20 IU/kg/min	238 (196-323)	5 (5-5)	--	--	81 (42-224)
0 IU/kg/0.25 IU/kg/min	135 (123-146)	120 (20-240)	138 (124-144)	157 (91-231)	--
125 IU/kg/0.25 IU/kg/min	241 (189-354)	5 (5-10)	--	--	75 (56-189)
0 IU/kg/0.30 IU/kg/min	139 (133-151)	240 (120-240)	137 (136-138)	229 (223-235)	--
125 IU/kg/0.30 IU/kg/min	254 (198-331)	5 (5-20)	--	--	117 (63-191)

Table 4. aPTT

Argatroban					
Dose (Bolus/Infusion)	Peak Value (s)	T _{Peak} (m)	Steady State (s)	Time to Steady State (m)	Pharmacodynamic T _{1/2} (m)
0 µg/kg/1.25 µg/kg/min	55 (44-74)	180 (120-240)	53 (46-72)	148 (89-199)	22 (<1-74)
250 µg/kg/1.25 µg/kg/min	88 (68-120)	5 (5-5)	43 (42-48)	107 (104-128)	18 (11-75)
0 µg/kg/2.5 µg/kg/min	64 (53-150)	180 (30-180)	57 (48-77)	78 (49-124)	41 (17-161)
250 µg/kg/2.5 µg/kg/min	98 (69-112)	5 (5-5)	61 (44-65)	93 (84-125)	24 (18-46)
0 µg/kg/5.0 µg/kg/min	75 (61-106)	240 (120-240)	67 (55-95)	57 (54-140)	28 (19-75)
250 µg/kg/5.0 µg/kg/min	92 (80-107)	5 (5-30)	76 (58-80)	68 (42-107)	38 (25-80)
0 µg/kg/10.0 µg/kg/min	102 (77-128)	180 (20-240)	86 (68-115)	50 (3-65)	25 (19-112)
250 µg/kg/10.0 µg/kg/min	100 (82-108)	5 (5-240)	83 (75-93)	58 (42-80)	40 (15-69)
Heparin					
Dose (Bolus/Infusion)	Peak Value (s)	T _{Peak} (m)	Steady State (s)	Time to Steady State (m)	Pharmacodynamic T _{1/2} (m)
0 IU/kg/0.15 IU/kg/min	47 (37-69)	180 (180-240)	40 (35-45)	179 (121-236)	23 (15-31)
125 IU/kg/0.15 IU/kg/min	>150(all>150)	-	-	-	94 (41-120)
0 IU/kg/0.20 IU/kg/min	68 (46-133)	180 (60-240)	62 (62-62)	212 (212-212)	26 (13-38)
125 IU/kg/0.20 IU/kg/min	>150(all>150)	-	-	-	101 (44-122)
0 IU/kg/0.25 IU/kg/min	91 (62->150)	180 (180-240)	-	-	35 (25-41)
125 IU/kg/0.25 IU/kg/min	>150(all>150)	-	-	-	122 (68-147)
0 IU/kg/0.30 IU/kg/min	124 (79->150)	240 (180-240)	-	-	43 (27-73)
125 IU/kg/0.30 IU/kg/min	>150(all>150)	-	-	-	134 (94-155)

Figure 1.

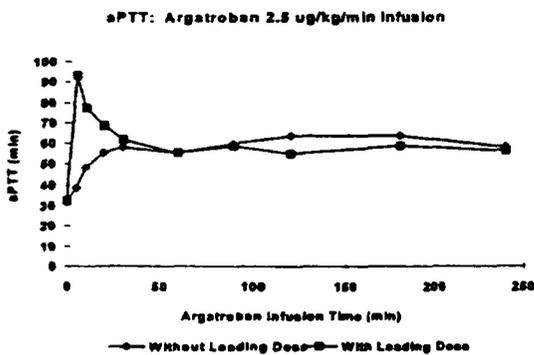
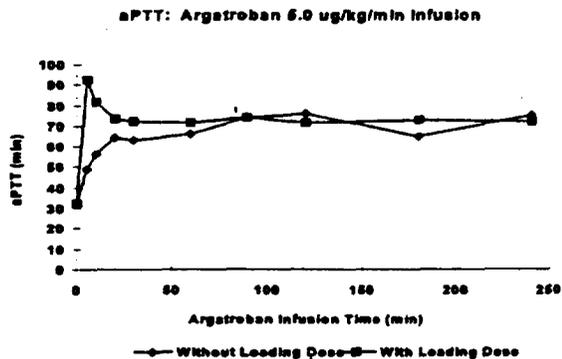


Figure 2.



ACT: Argatroban 5.0 ug/kg/min Infusion

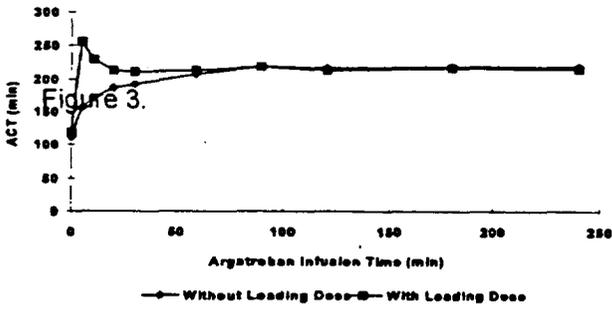


Figure 4.

ACT: Argatroban 2.5 ug/kg/min Infusion

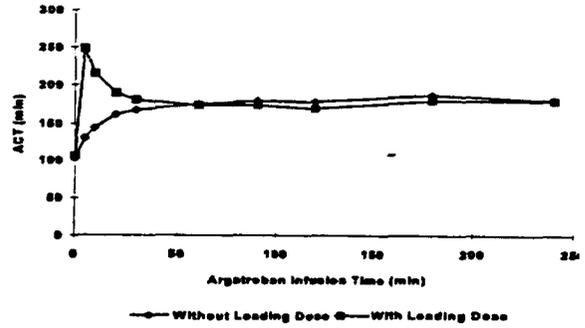


Figure 5.

aPTT: Argatroban 10.0 ug/kg/min Infusion

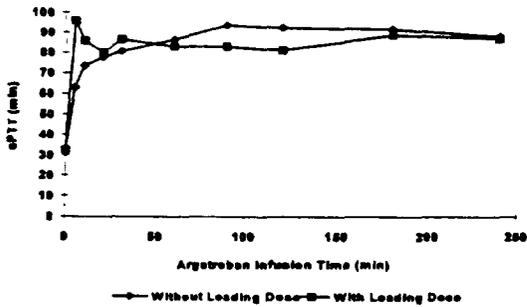
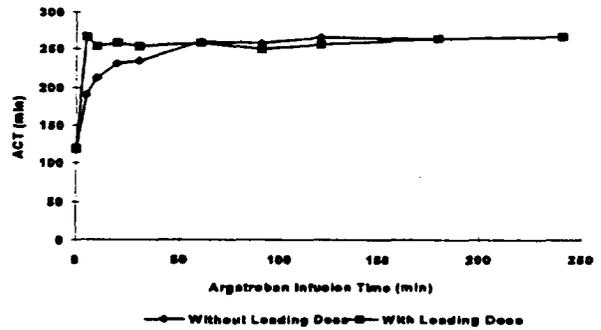


Figure 6.

ACT: Argatroban 10.0 ug/kg/min Infusion



Dose-Response Relationship: A linear dose response model that was used to estimate the relationship between the efficacy parameters (ACT and aPTT) and the dose of argatroban or heparin. Table 5 includes the mean slope and mean intercept of this analysis.

Table 5.

Drug	Treatment	Intercept	Slope	R ²
ACT				
Argatroban	Infusion	3.61	0.62	0.55
	Bolus + Infusion	3.52	0.65	0.76
Heparin	Infusion	2.20	-0.40	0.01
	Bolus + Infusion	5.25	0.85	0.21

aPTT				
Argatroban	Infusion	2.72	0.57	0.60
	Bolus + Infusion	2.42	0.71	0.72
Heparin	Infusion	7.53	2.55	0.71
	Bolus + Infusion	—	—	—

Sponsor's Conclusions:

1. Both argatroban and heparin were well tolerated up to the highest dose delivered. There were no serious adverse events reported and no clinically significant changes in the safety parameters observed.
2. The anticoagulation response to argatroban was rapid (median time to peak between 3-4 hours by infusion alone and <1 hour by infusion + bolus loading dose. Upon discontinuation of infusion, PD levels returned quickly to pre-infusion levels.
3. The relationship between argatroban dose and anticoagulation response followed a classic proportional model, and a linear relationship existed between argatroban dose and the plasma concentration of argatroban at 240 minutes after initiation of infusion.
4. Heparin infusion alone had a minimal effect on ACT responses and had an unstable effect when a bolus loading dose was added and the aPTT response was correlated with heparin doses.

Reviewer Comments:

1. I concur with the sponsor's conclusions.
2. With the addition of a bolus loading dose of argatroban the steady state levels of ACT and aPTT are achieved in <1 hour, while the peak levels of ACT and aPTT were not achieved until 3-4 hours after initiation of the infusion without the bolus loading dose.
3. There was no significant difference in the adverse event profiles between argatroban infusion with and without a bolus loading dose.

**APPEARS THIS WAY
ON ORIGINAL**

Study #: ARG-102

Title of Study: Comparison of the Anticoagulation Effect of Four Infusion Doses of Argatroban Over Four Hours in Normal Human Volunteers

Objectives: To evaluate and compare, 1) the safety of four ascending-dose continuous intravenous infusions of argatroban, with an initial bolus loading dose and, 2) the relationship between doses and changes to the coagulation parameters (time course, magnitude, dose-response) following IV infusions of argatroban.

Study Design: This was an open-label, dose-escalation trial.

Subjects: Nine healthy male volunteers, between the ages of 18 and 65 years.

Formulation, batch number and doses: Argatroban (batch# 24010694) was formulated into 500 ml isotonic solutions for injection with D-sorbitol in water for injection, USP by the University of Iowa, Iowa City; Iowa. The argatroban doses to be tested were a 250 µg/kg bolus dose followed by 15, 20, 30 or 40 µg/kg/min infusions for 4 hours.

Assay Validation: The assay used to assess plasma argatroban concentrations is an _____
The validation of the assay is included in Table 1.

Results:

Pharmacokinetics: The plasma concentrations of the two isomers of argatroban (21-(R) and 21-(S)) were assessed at 240 minutes after initiation of treatment (see Table 2, below).

Table 2. Mean Argatroban Concentrations (ng/ml) after 240 Minutes of Infusion

Argatroban Dose	21-(R)-argatroban	21-(S)-argatroban
250 ug/kg bolus + 15 µg/kg/min infusion	2383 ± 941.93	1176.21 ± 448.92
250 ug/kg bolus + 20 µg/kg/min infusion	2620.42 ± 328.53	1362.06 ± 211.87
250 ug/kg bolus + 30 µg/kg/min infusion	3774.54 ± 452.49	2000.56 ± 226.99
250 ug/kg bolus + 40 µg/kg/min infusion	4882.99 ± 475.44	2549.37 ± 342.31

Pharmacodynamics: ACT and aPTT assessments were made at 0, 10, 20, 30, 60, 90, 120, and 240 minutes after initiation of an argatroban infusion. The argatroban infusion was discontinued at 240 minutes and the pharmacodynamic measures at 270, 300, 360, and 480 minutes.

Table 3. ACT Parameters

Dose (µg/kg/min)	15	20	30	40
N	9	8	8	7
Peak Effect (sec)	320 (278-426)	342 (294-372)	398 (352-452)	463 (400-521)
Time to Peak (min)	90 (20-245)	120 (30-241)	105 (90-242)	90 (60-241)
Steady State Effect Level (sec)	292 (27-317)	316 (282-347)	393 (343-421)	447 (381-501)
Time to Steady State (min)	30 (21-43)	29 (20-41)	38 (35-56)	56 (46-108)
T½ (min)	35 (19-42)	37 (29-43)	34 (29-45)	33 (18-36)

Table 4. aPTT Parameters

Argatroban Dose (µg/kg/min)	15	20	30	40
N	9	8	8	7
Peak Effect (sec)	95 (83-120)	108 (88-120)	118 (104-128)	131 (120-149)
Time to Peak (min)	120 (30-238)	60 (20-237)	214 (30-241)	240 (30-241)
Steady State Effect Level (sec)	89 (79-107)	98 (79-109)	105 (90-118)	122 (103-143)
Time to Steady State (min)	13 (2-39)	29 (2-45)	38 (21-66)	36 (2-74)
T½ (min)	24 (14-56)	26 (9-41)	33 (17-36)	29 (22-38)

Sponsor's Conclusions:

1. Argatroban was well tolerated over the dosing range used herein (15-40 µg/kg/min). There were no serious adverse events reported, although two subjects were withdrawn from the study (one due to a rash and one due to ACT values exceeding a safety limit of 400 seconds).
2. Argatroban exhibited desirable anticoagulation effects suitable for invasive cardiac procedures, as measured by ACT and aPTT.
3. Plasma argatroban concentrations increased proportionally with argatroban dose infused over the range of 15 to 40 µg/kg/min.
4. A correlation existed between plasma argatroban concentrations (PK) and the anticoagulation effects (PD).

Reviewer Comments:

1. The proposed infusion dose of argatroban is 2 - 10.0 µg/kg/min. Therefore, the doses used herein, 15 - 40 µg/kg/min, are not within the proposed therapeutic range.
2. No significant adverse events were reported with argatroban doses from 15 to 40 µg/kg/min. Therefore, these data provide substantive safety information.
3. I concur with the sponsor's conclusions.

Study # ARG-103

Title: Pharmacokinetics and Anticoagulant Effect of an Infusion Dose of Argatroban in Humans with Impaired Renal Function

Objective: To evaluate the safety and PK/PD of a single dose of argatroban in subjects with no ($Cl_{cr} > 80$), mild ($Cl_{cr}=50-80$), moderate ($Cl_{cr}=30-49$) or severely ($Cl_{cr} < 29$) impaired renal function.

Design: Parallel design with $n=6$ per group. Each subject was given a four hr infusion of argatroban ($5 \mu\text{g/kg/min}$). Plasma samples were drawn to evaluate argatroban pharmacokinetics. Blood samples were drawn to evaluate the ACT and the aPTT.

Results: See table below.

Argatroban Pharmacokinetics: Mean \pm SD

Parameter	Renal Function Group			
	Normal	Mild	Moderate	Severe
CL (ml/min/kg)	4.6 \pm 1.5	3.3 \pm 0.6	3.4 \pm 0.8	3.4 \pm 1.0
Vdss (ml/kg)	156 \pm 13.3	155 \pm 14.7	164 \pm 24.9	200 \pm 53.9
$t_{1/2}$ (min)	47 \pm 22	52 \pm 14	50 \pm 13	64 \pm 35

Argatroban Pharmacodynamics: Median (min, max)

Parameter	Renal Function Group			
	Normal	Mild	Moderate	Severe
Peak aPTT (sec)	61 (54, 76)	66 (56, 77)	65 (51, 79)	62 (52, 86)
aPTT _{ss} (sec)	55 (47, 59)	60 (54, 70)	69 (65, 74)	53 (45, 85)
$t_{1/2}$ aPTT (min)	42 (7, 134)	54 (17, 125)	43 (26, 67)	30 (22, 88)

Sponsor's Conclusion:

1) No difference in the PK/PD of argatroban in subjects with widely differing renal function.

Reviewer's Comments:

1) Although n 's are small, agree that there is little difference between the groups.

Study #: ARG-107

Title of Study: Mass Balance Study of Argatroban (Novastan®) Injection in Healthy Volunteers Following Administration of the ¹⁴C-Labeled Compound

Objectives: The objective of this study was to characterize the mass balance, metabolic profile and pharmacokinetics of argatroban (Novastan®) in healthy volunteers after administration of a 4-hour continuous intravenous infusion of the ¹⁴C-labeled compound.

Study Design: This was an open-label, one period, pharmacokinetic and metabolism study.

Subjects: Six (6) subjects were enrolled and completed the study (four males and two surgically sterile females). These subjects were 18 to 45 years of age, the males weighing at least 60 kg and the females, 45 kg, and were within 15% of their ideal body weights. All subjects enrolled in this study were judged by the investigator to be normal, healthy volunteers.

Product, Dose, Duration, Mode of Administration, and Batch Number: The test product was 5 µg/kg/min of ¹⁴C-argatroban over a 4 hour infusion, Lot No. CFQ 9003.

Blood, Urine and Feces Collection: Blood samples were collected for determine argatroban, the primary argatroban metabolite (M-1) and plasma and blood radioactivity at 0 (pre-dose), 0.25, 0.5, 1, 2, 3, 4, 4.033, 4.167, 4.33, 4.5, 4.75, 5, 5.5, 6, 6.5, 7, 7.5, 8, 10, 12, 24, and 48 hours after initiation of treatment. Urine was collected over the following intervals, 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120 and 120-144 hours after initiation of treatment. Complete fecal collections were carried out for 6 days (144 hours) after initiation of treatment.

Analytical Methodology: The plasma argatroban concentrations were determined by an LC/MS/MS method by ~~_____~~. The validation of the assay including quality control data are included in Table 1.

Results:

Pharmacokinetics: The pharmacokinetic parameter estimates for plasma argatroban, plasma ¹⁴C, blood ¹⁴C, and plasma estimated argatroban metabolite(s) are summarized in Tables 2 and 3.

Table 2. Mean (SD) Pharmacokinetic Parameters

Parameter	Argatroban	Plasma ¹⁴ C	Blood ¹⁴ C	Estimated Argatroban Metabolite(s)
C _{max} (ng/mL*, g equiv/g**, or ng equiv/mL****)	1063 (279.5)*	1.459 (0.3706)**	0.8627 (0.2032)**	559.2 (128.8)***
T _{max} (hr)	4.04 (0.0164)	4.03 (0.00678)	4.03 (0.00678)	3.87 (0.428)
AUC(0-t) (ng·hr/mL*, g equiv·hr/g**, or ng equiv·hr/mL****)	3526 (1013)*	5.201 (1.419)**	3.225 (0.8991)**	2135 (645.4)***
AUC(0-inf) (ng·hr/mL*, g equiv·hr/g**, or ng equiv·hr/mL****)	3541 (1014)*	5.261 (1.430)**	3.280 (0.9028)**	2215 (656.1)***
AUC(0-t)/ AUC(0-inf)	0.9957 (0.001443)	0.9884 (0.005237)	0.9826 (0.004621)	0.9617 (0.02005)
T _{1/2el} (hr)	1.032 (0.1522)	1.660 (0.2170)	2.219 (0.2761)	2.115 (0.4742)
K _{el} (1/hr)	0.6846 (0.1046)	0.4240 (0.06057)	0.3163 (0.03841)	0.3429 (0.08274)

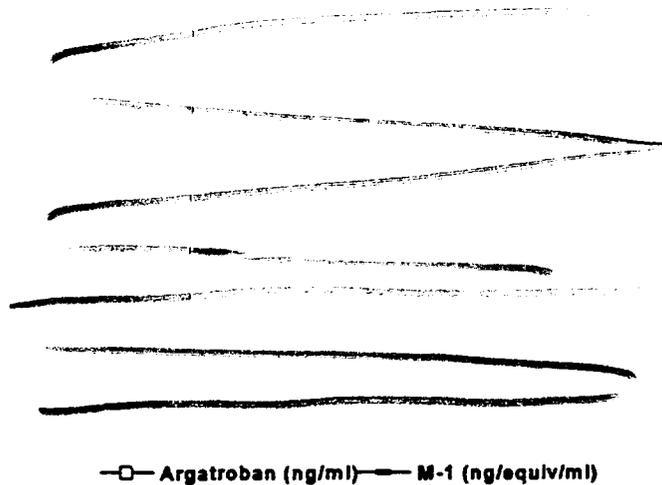
Table 3. Mean (SD) Urine and Feces Excretion Data

Parameter	Urine Argatroban	Feces Argatroban	Urine ¹⁴ C	Feces ¹⁴ C	Urine Estimated Metabolite(s)	Feces Estimated Metabolite (s)
Cumulative Amount Excreted (mg*, mg equiv**)	13.79 (4.368)*	11.78 (6.353)*	19.97 (5.832)**	60.91 (13.49)**	6.180	49.13
Cumulative Percent Excreted (%)	16.42 (5.200)	14.02 (7.563)	21.80 (5.828)	65.42 (7.105)**	7.357	58.49

* Mean cumulative percent excreted values for urine and feces argatroban and estimated metabolite(s) were based upon an average target amount infused of 84 mg (0.005 mg/kg/min x 240 min x 70 kg). Urine and feces estimated metabolite(s) values were determined by difference between the respective ¹⁴C and argatroban values.

The plasma concentration versus time profiles of argatroban and the primary metabolite, M-1, are include in Figure 1.

Figure 1.



Safety: During the trial there was a total of six treatment-emergent adverse events reported by three subjects. Five of the adverse events were considered "mild" in severity and one was considered "moderate". No serious adverse events were reported during the study.

The only adverse event with more than one occurrence was "pain" reported by one subject. None of the adverse events were considered drug-related by the Investigator.

No clinically significant trends in vital signs, physical examinations, or clinical laboratory tests were observed regarding subject safety.

Sponsor's Conclusions:

1. The mean plasma concentration profile of argatroban following continuous intravenous infusion for 4 hours appeared to be consistent with compounds that exhibit multicompartmental pharmacokinetic characteristics.
2. The T_{1/2} of argatroban was shorter than that of the total radioactivity in plasma and blood, indicating that the mean apparent elimination of the combined metabolites was slower than that of the parent compound.
3. The ratio of plasma to whole blood concentrations of radioactivity presented no evidence of distribution of either argatroban, or its metabolites, into red blood cells.
4. The majority of the administered dose of radiation, 65.4 %, was recovered in the feces, while 21.8 % was recovered in the urine. The urinary excretion of the administered dose of radiation was nearly complete within 24 hours with approximately 16 % of the total drug dose recovered in the urine as unchanged drug. Fecal elimination of the administered dose of radiation was nearly complete within 168 hours with approximately 14 % of the total drug dose recovered in the feces as unchanged drug.
5. The mass balance characteristics of argatroban were well characterized and consistent with compounds that undergo extensive hepatic metabolism and biliary secretion.

Reviewer Comments:

1. I concur with the sponsor's conclusions.
2. The protocol indicates that the primary argatroban metabolite (M-1) would be assayed by a specific method. However, no methodology or validation of this method is presented for review. Additionally, in the study results the sponsor does not refer to M-1 specifically, rather to estimated argatroban metabolite(s), casting further doubt on, of what exactly these estimates are and how these estimates were made.
3. A full metabolic profile of argatroban was not assessed in Study ARG-107.

APPEARS THIS WAY
ON ORIGINAL

Study # ARG-951

Title: Study of the new formulation of argatroban alcoholic solution in healthy volunteers.

Objective: 1) To study the effects of different infusion rates and doses of argatroban on coagulation parameters. 2) To study the effects on safety, 3) To determine the stereospecific pharmacokinetics of argatroban.

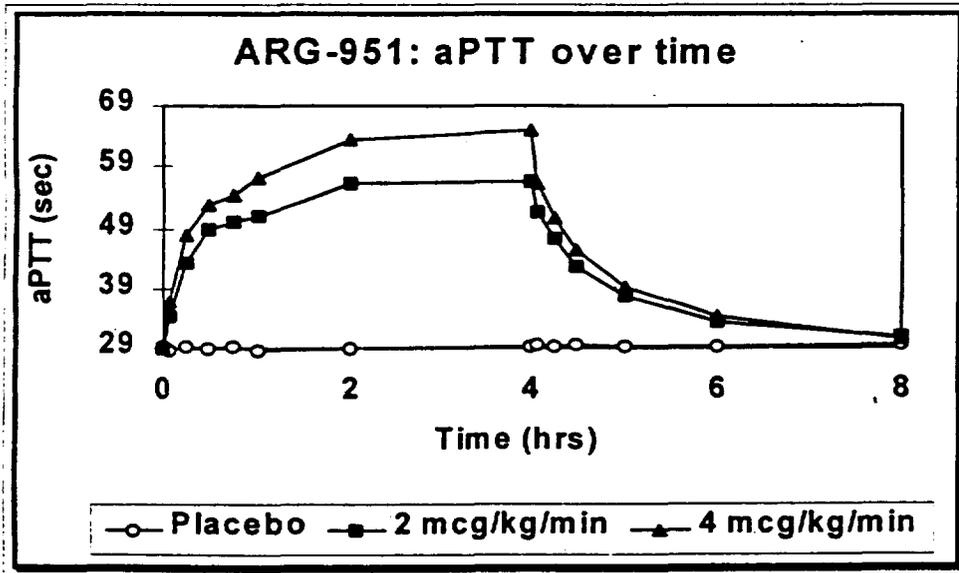
Study Design: Randomized, double-blind crossover single-dose study in 9 normal volunteers.

Results: See Below

Pharmacokinetics of argatroban

Dose	Stereoisomer	AUC(0-inf) (ng*hr/ml)	Cmax (ng/ml)	CL (L/hr/kg)	t½ (hr)
2 µg/kg/min x 4 hours	R	1246±247	313±59.6	0.26±0.06	0.91±0.28
	S	720±131	183±32.4	0.24±0.05	0.64±0.09
4 µg/kg/min x 4 hours	R	2466±675	657±154	0.27±0.06	1.2±0.31
	S	1398±341	378±79	0.25±0.05	0.76±0.27

Plot of pharmacodynamics of argatroban



Conclusions:

- 1) The ratio of the isomers did not change over time, indicating no preferential metabolism.
- 2) Formulation was well-tolerated and showed dose-proportionality in both PK and PD.

Study # : ARG-105

Title: An open-label evaluation of the pharmacokinetics and pharmacodynamics of a 4 hr infusion of Novastan in elderly and young male and female volunteers.

Objectives:

- To evaluate and compare the PK/PD of argatroban in male and female elderly and young volunteers.
- To evaluate the effect of a bolus dose of argatroban followed by a infusion.

Design: Open-label, single-dose study in 40 elderly or young/ male or female volunteers. Each volunteer received a 125 µg/kg bolus of argatroban followed by a 2.5 µg/kg/min infusion.

Results:

	Young (18-45)		Elderly (65-80)	
	Men (n=10)	Women (n=10)	Men (n=10)	Women (n=10)
CL (ml/kg/min)	4.7±1.0	5.4±0.8	3.8±0.9	4.7±1.0
Vdss (ml/kg)	175±39	175±37	174±21	195±33
Css (ng/ml)	541±139	473±85	657±165	511±110
t½ (min)	46±10	39±10	51±10	49±7.6
†Peak aPTT (sec)	73 (61, 80)	57 (52, 75)	63 (50, 84)	61 (52, 84)
†t½ aPTT (min)	44 (37, 56)	44 (21, 73)	53 (26, 78)	51 (26, 63)

Conclusions:

No clinically significant effect of gender or age on the pharmacokinetics and pharmacodynamics of argatroban.

APPEARS THIS WAY
ON ORIGINAL

Study #: B0147g

Title: A Phase 1 Study of argatroban in patients with unstable angina

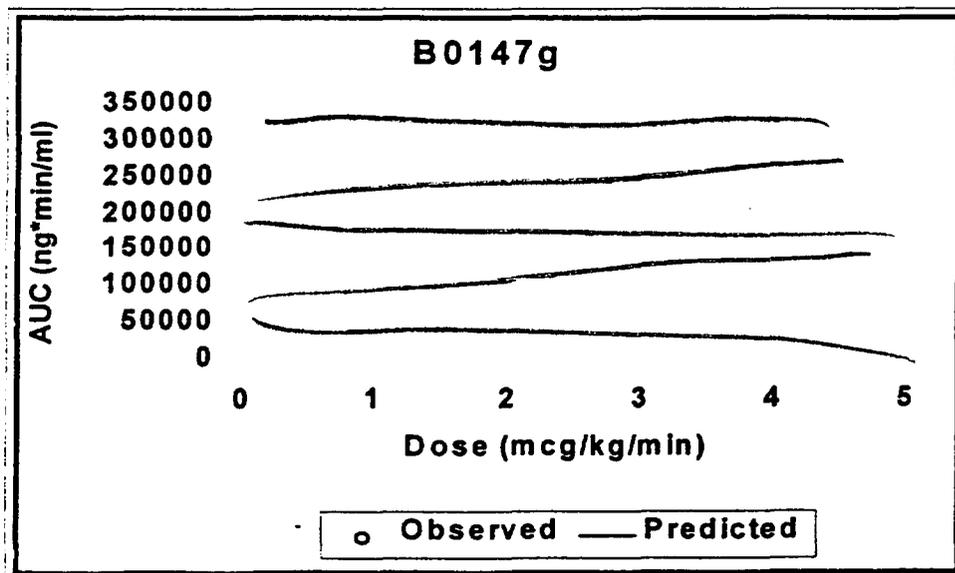
Objective: To determine the safety and pharmacokinetics of argatroban in patients with unstable angina

Study Design: Parallel dose-escalation trial, n=4 per dose.

Results: Mean±SD

Dose (mg/kg/min)	C _{ss} (ng/ml)	CL (ml/min/kg)	V _{ss} (ml/kg)
0.5	94±28	5.6±1.4	187±57
1.0	189±29	5.4±0.7	221±61
1.5	296±146	5.8±2.1	237±69
2.0	535±166	4.0±1.0	150±62
2.5	937±427	3.1±1.3	151±8
3.0	780±394	4.5±1.7	153±7
3.5	910±75	3.9±0.3	215±107
4.0	1336±398	3.3±1.3	138±30
4.5	894±183	5.2±1.0	196±23
5.0	1402±730	4.2±1.9	169±26

AUC vs. Dose



Conclusions:

- 1) Safe and effective in patients with unstable angina.
- 2) Dose-dependent prolongation of anticoagulation can be produced.

Reviewer Comments:

- 1) No assay validation data, but results do agree with other studies.
- 2) Genentech study.
- 3) PK not altered compared with normal volunteers.

Study #: B0272g

Title: A Phase 1 Study in Patients undergoing percutaneous transluminal coronary angioplasty

Objective: To determine the safety and pharmacokinetics of argatroban in patients undergoing PTCA.

Study Design: Randomized single-dose parallel study in 12 patients undergoing PTCA. Each subject was given either a 15 µg/kg/min bolus followed by a 2 µg/kg/min infusion for 4 hrs or heparin (10,000 U bolus followed by 100 U/hr).

Results: Mean±SD (n=6)

Css (ng/ml)	CL (ml/min/kg)	Vss (ml/kg)
775±288	2.8±1.13	215±54

Conclusions:

- 1) Clearance of argatroban slightly lower in this population as compared with normal population.
- 2) No dosage adjustment necessary, since the drug will be titrated.

Reviewer Conclusions:

- 1) Small study, so can not draw any definitive conclusions.
- 2) ~~Small~~ study, no validation.

Study #: ARG-106

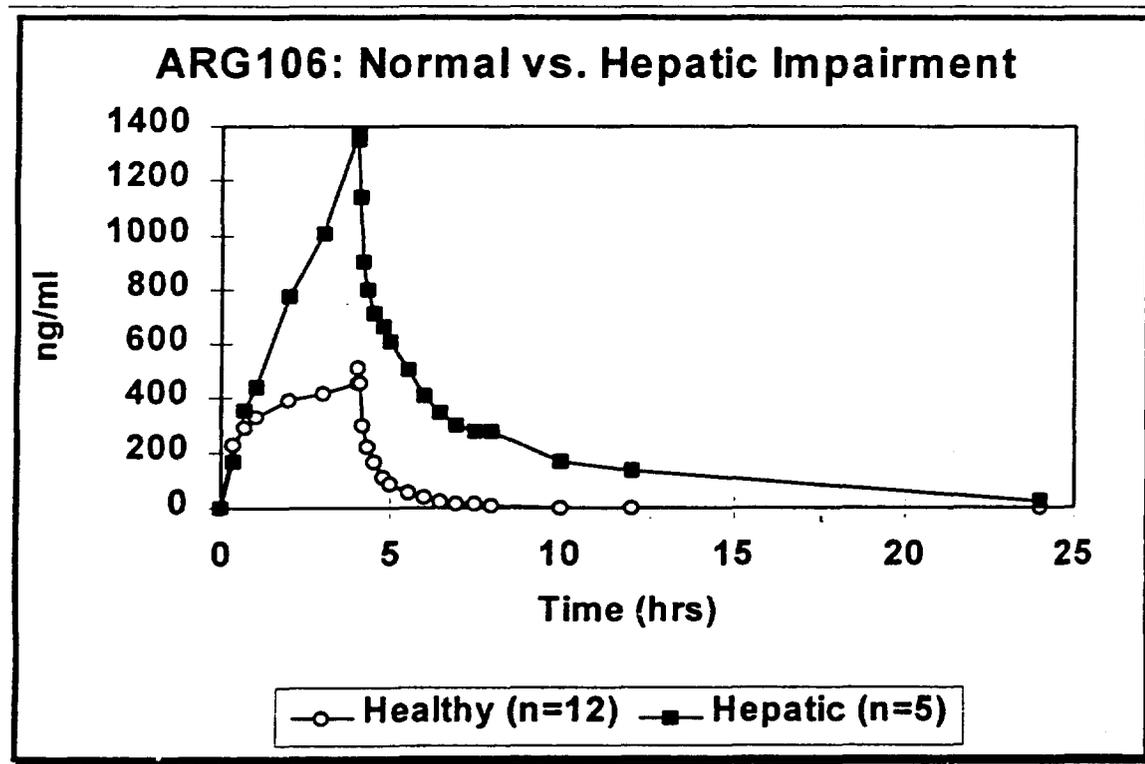
Title: Pharmacokinetic/Pharmacodynamic study of argatroban injection in healthy volunteers and patients with hepatic disease

Objective: To assess the pharmacokinetics and pharmacodynamics of argatroban in healthy volunteers and in patients with hepatic disease.

Design: Single-dose, parallel group study in healthy volunteers (n=12) and patients with hepatic disease (n=5)

Results:

	Healthy (N=12)	Hepatic Disease (n=5)
AUC(0-inf.) (ng*hr/ml)	1768±389	4956±2378
Cmax (ng/ml)	578±231	1073±283
t½ (hours)	1.03±0.23	3.02±2.2
CL (L/hr/kg)	0.36±0.08	0.115±0.07



Conclusions: Mean hepatic clearance of argatroban in hepatic subjects was only 26% of that in healthy volunteers.

Reviewer Comments

- 1) Although only 5 hepatic patients studied, the large effect seen makes this a reasonable study.
- 2) Initial dosing of patients with hepatic disease is 1/4 that of normal volunteers, which is reasonable.

Report No.: ARG-108

Title of Study: Bioequivalence of Two NOVASTAN® (Brand of Argatroban) Injections in Healthy Volunteers

Investigator: James C. Kisicki, M.D.

Study Center: _____

Publication (Reference): Not applicable

Studied period:
(date of first enrollment)
11-October-1996
(date of last completed)

14-October-1996 **Phase of development:** 1

Objectives: The primary objective of this study was to assess the bioequivalence of two preparations of NOVASTAN® (brand of argatroban) Injection (100 mg/mL) following administration by 4-hour, constant-rate intravenous infusion in healthy volunteers. Plasma drug concentrations were determined for determination of pharmacokinetic parameters.

A secondary objective was to assess the effects of argatroban on coagulation when administered by constant-rate intravenous infusion (pharmacodynamic assessment), and to assess safety and tolerability.

Methodology: Blood samples used to determine coagulation and argatroban concentration results were obtained immediately prior to, at scheduled intervals during, and at scheduled intervals following the infusion of argatroban. Argatroban concentrations were determined for assessment of bioequivalence between the test and reference formulations of argatroban. A coagulation parameter was also determined for assessment of the effect of argatroban on coagulation when administered by constant-rate intravenous infusion.

Safety parameters including serum chemistry, urinalysis, and hematology clinical laboratory results, physical examination results, electrocardiogram results, recording of adverse events and vital sign measurements were assessed before, during and after the administration of study compounds.

Number of Subjects (planned and analyzed): Eighteen (18) subjects were enrolled in this study and included in all safety and pharmacodynamic analyses. Seventeen (17) subjects completed all study events and were included in all pharmacokinetic analyses. The remaining subject was removed from the study by

the Investigator due to adverse events after dosing in the first period.

Diagnosis and main criteria for inclusion: All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers. Enrolled subjects met inclusion and exclusion criteria reflective of the fact that they were normal, healthy volunteers.

Test product, dose, duration, and mode of administration, batch number: The test product was argatroban manufactured by _____ batch number M245PF, administered as a four hour infusion at the rate of 2.5 µg/kg/min.

Reference product, dose, duration, and mode of administration, batch number: The reference product was argatroban manufactured by The University of Iowa, batch number 17710795 administered as a four hour infusion at the rate of 2.5 µg/kg/min.

Criteria for Evaluation:

Efficacy: For Argatroban plasma concentrations obtained after treatments A (test formulation) and B (reference formulation), the following summarization was conducted: Individual subject and average concentrations were listed for each sampling time. Summary statistics at each time point were also calculated. Individual subject and average concentrations versus time were plotted in both linear and semi-log scale. Individual subject and average pharmacokinetic parameters were listed and summary statistics were calculated.

The pharmacodynamic parameter (aPTT) was assessed via summary statistics and visual inspection of plots.

Safety: Individual subject safety was assessed via comparison of predose and poststudy results for electrocardiograms, vital signs, clinical laboratory (hematology, serum chemistry, urinalysis), aPTT measurements, physical examinations, and adverse event assessments.

The safety of the test treatment versus the reference was assessed via comparison of the following adverse event information: frequency of occurrence, number of subjects experiencing, severity, and relationship to compound administered. Additionally, a comparison of abnormal and clinically significant coagulation parameter results, and a comparison of vital sign measurements recorded during administration was conducted.

Statistical methods:

Efficacy: Statistical analyses of the single-dose pharmacokinetic parameters were carried out to assess the bioequivalence of the argatroban manufactured at _____ and The University of Iowa. Statistical analyses of the individual plasma concentrations at each sampling time and the pharmacokinetic parameters: C_{max}, AUC(0-t), AUC(0-inf), T_{1/2} and K_{el} were performed in the context of an analysis of variance (ANOVA) model, using the General Linear Model (GLM) procedure of SAS® (Version 6.09). C_{max}, AUC(0-t) and AUC(0-inf) data were log-transformed, a priori, for ANOVA. The model included sequence, subject within sequence, period and treatment. A test for sequence effects was conducted using the subject within sequence error mean square from the ANOVA as the error term. The remaining factors were tested using the residual error (Mean Square Error) from the ANOVA. The bioequivalence assessment of the argatroban manufactured at _____ (Treatment A) relative to that manufactured at The University of Iowa (Treatment B) was made on the basis of the two one-sided t-tests procedure. The argatroban prepared at The University of Iowa was considered the reference in the bioequivalence assessment and 90% confidence limits around the mean difference (test-reference) for each parameter, expressed as a percentage relative to the reference, was calculated using the untransformed and log-transformed data.

Safety: Descriptive statistics including the mean, minimum, maximum, standard deviation and sample size were calculated at appropriate timepoints. Categorical data was summarized by frequency at appropriate timepoints. When appropriate, this summarization was conducted by drug administered (test and reference formulations of argatroban).

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

The pharmacokinetic parameters and comparisons between treatments are summarized in the following table for both formulations of argatroban. The pharmacokinetic and statistical analyses demonstrated that the two formulations of argatroban were bioequivalent for all relevant pharmacokinetic parameters.

Arithmetic Mean (SD) Pharmacokinetic Parameters for Argatroban Following Administration of Each Formulation

Parameter (Sanofi Winthrop) (The University of Iowa)	Treatment A	Treatment B	90% Confidence Interval
C _{max} (ng/mL)	440 (127)	450 (111)	90.7 - 105.8
T _{max} (hr)	3.7 (0.69)	2.9 (1.2)	112.7 - 143.5
AUC(0-t) (ng*hr/mL)	1630 (450)	1640 (401)	95.1 - 104.8
AUC(0-inf) (ng*hr/mL)	1650 (483)	1650 (404)	94.2 - 104.9
T _{1/2} (hr)	0.979 (0.251)	1.10 (0.426)	63.9 - 107.3
Kel (hr ⁻¹)	0.750 (0.180)	0.706 (0.233)	92.4 - 127.5

SAFETY RESULTS:

This trial assessed the safety and tolerability of two formulations of argatroban administered by constant-rate infusion in healthy volunteers. No clinically significant trends in vital signs, physical examinations, ECGs, or clinical laboratory tests were observed in regard to subject safety.

There was a total of 31 treatment emergent adverse events reported by eight subjects during the trial. Nausea and vomiting, dizziness, and headache were the most frequently reported events during the trial. Twenty-six of the adverse events were experienced following the test treatment. However, Subject 5, in the test treatment group, reported 14 of these events. This subject was removed from the study by the Investigator, and received the test treatment only.

All of the events were considered either moderate or mild in intensity. No serious adverse events were reported during the study. The Investigator considered all of the adverse events either "unlikely" to be related or "unrelated" to the study medication.

CONCLUSION:

The two formulations of argatroban were found to be bioequivalent since the 90% confidence interval for the ratio of product means for C_{max}, AUC(0-t), and AUC(0-inf) were within the range of 80 - 120%.

Thirty-one (31) adverse events were reported by eight subjects during the trial, which mainly included nausea and vomiting, dizziness and headache. The test treatment reported a greater number of adverse events than the reference treatment, predominantly due to Subject 5. This subject was removed from the trial by the Investigator after experiencing 14 adverse events following the test treatment in Period 1. The Investigator considered all of the adverse events either "unlikely" to be related or "unrelated" to the study medication.

No clinically significant trends in vital signs, physical examinations, ECGs, or routine clinical laboratory tests were observed in regard to subject safety. Regarding coagulation test results, the administration of argatroban (both treatments) increased the aPTT values to the point where many results were considered clinically significant by the Investigator. Otherwise, the two treatments appeared to be well tolerated.

Study #: ARG-109

Title of Study: Comparative, Randomized, Three-Way Crossover Drug-Drug Interaction Study of NOVASTAN® (Brand of Argatroban) Concentrate and Coumadin® (Crystalline Warfarin Sodium, USP) in Healthy Volunteers

Objectives: The primary objective of this study was to assess the drug-drug interaction between NOVASTAN® (brand of argatroban) concentrate and _____ in healthy volunteers by measurement of drug concentrations and drug effects on coagulation.

A secondary objective was to assess the safety and tolerability of argatroban when administered by itself and with warfarin.

Study Design: This was a single center, open-label, randomized, three-period, crossover study. The following three dosing regimens were administered to each of the subjects during one to the three treatment periods.

Regimen A: Single oral 7.5 mg dose of warfarin sodium administered with 240 ml of water. The time of dosing for the first subject was approximately 11 A.M.

Regimen B: 1.25 µg/kg/min argatroban dose, for continuous IV infusion for 100 hours. The time of initiation of infusion for the first subject was approximately 7 A.M. Four hours following the beginning of the argatroban infusion, a single oral 7.5 mg dose of warfarin sodium was administered with 240 ml of water.

Regimen C: 1.25 µg/kg/min argatroban dose, for continuous IV infusion for 100 hours. The time of initiation of infusion for the first subject was approximately 7 A.M.

Subjects: Twelve normal healthy volunteers (7 males, 5 females) were enrolled in and completed this study.

Test product, dose, duration, and batch number: The test product was argatroban, batch number 25311095, administered as a 100 hour infusion at the rate of 1.25 µg/kg/min.

Reference product, dose, duration, and batch number: The reference product was warfarin, batch number EKC136A, administered as a single oral 7.5 mg dose with 240 mL water.

Blood Sampling: The blood samples for each dosing regimen will be collected at the following times;

Regimen A: 4 (just prior to dosing), 4.5, 5, 5.5, 6, 7, 8, 12, 16, 28, 52, 76 and 100 hours post dosing for analysis of S- and R- warfarin.

Regimen B: 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 12, 28, 52, 76, 100.067, 100.167, 100.33, 100.5, 100.75, 101, 102 and 104 hours post dosing for analysis of argatroban and 0 (pre-dose) 0, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, 28, 52, 76 and 100 hours post dosing for analysis of warfarin.

Regimen C: 1, 2, 3, 4, 5, 6, 8, 12, 16, 28, 52, 76, 100, 100.067, 100.167, 100.33, 100.5, 100.75, 101, 102 and 104 hours post dosing.

Analytical Methodology: The plasma argatroban concentrations were determined by an LC/MS/MS method

by _____ The validation of the assay including quality control data are included in Table 1.



Statistical methods: A drug interaction of warfarin on the pharmacokinetics of argatroban was assessed using general linear model analyses to investigate differences in CL and Kel for argatroban between Regimens B and C. A drug interaction of argatroban on the pharmacokinetics of R- and S-warfarin was assessed using general linear model analyses to investigate differences in C_{max}, AUC(0-t), and AUC(0-inf) for R- and S-warfarin between Regimens A and B. A significant interaction was declared if the pharmacokinetic parameter following administration of both drugs differed by more than 25% from the value when the drug was administered alone.

The pharmacodynamic parameters aPTT, CaTT, PT, and PT/INR were assessed via data listings and calculation of summary statistics including the mean, minimum, maximum, standard deviation and sample size. Mean values were plotted as a function of time for each parameter to allow visual comparisons.

Results:

Pharmacokinetics:

The pharmacokinetic parameters and comparisons between Regimens are summarized in the following tables for argatroban, R-warfarin and S-warfarin.

Examination of the mean pharmacodynamic parameter values and plots for aPTT, CaTT, PT, and PT/INR did not provide evidence of a drug interaction of warfarin on argatroban.

Table 2. Mean±SD Pharmacokinetic Parameters for Argatroban With (Regimen B) and Without (Regimen C) Coadministered Warfarin Sodium.

Parameter	Regimen B	Regimen C ¹	Percent Difference ²
C _{max} (ng/mL)	262 ± 53.9	266 ± 55.0	-1.35
T _{max} (hr)	27 ± 32	15 ± 28	81.1
AUC(0-t) (ng*hr/mL)	22,000 ± 5,090	20,800 ± 4,100	5.99
AUC(0-inf) (ng*hr/mL)	22,000 ± 5,080	20,800 ± 4,100	5.99

$T_{1/2}$ (hr)	0.677 ± 0.126	0.743 ± 0.201	-8.91
Kel (hr ⁻¹)	1.05 ± 0.171	0.993 ± 0.249	5.98
C _{ss} avg (ng/mL)	222 ± 51.9	207 ± 45.6	7.54
CL (mL/min/kg)	5.88 ± 1.20	6.30 ± 1.23	-6.65

¹Subject 6, Regimen C, 6 and 8 hour concentrations excluded from analysis

²Percent Difference of Least Square Mean values expressed as percentage of Regimen C

Table 3. Mean (SD) Pharmacokinetic Parameters for R-Warfarin With (Regimen B) and Without (Regimen A) Coadministered Argatroban

Parameter	Regimen A	Regimen B	Percent Difference ¹
C _{max} (ng/mL)	491 ± 116	461 ± 68.5	-6.16
T _{max} (hr)	0.85 ± 0.44	1.0 ± 0.54	18.2
AUC(0-t) (ng*hr/mL)	14,900 ± 3,400	15,800 ± 3,400	5.65
AUC(0-inf) (ng*hr/mL)	19,300 ± 5,730	21,000 ± 6,280	8.94
T _{1/2} (hr)	43.2 ± 11.4	47.1 ± 15.5	9.11
Kel (hr ⁻¹)	0.0171 ± 0.00462	0.0158 ± 0.00403	-7.35

¹Percent Difference of Least Square Mean values expressed as percentage of Regimen A

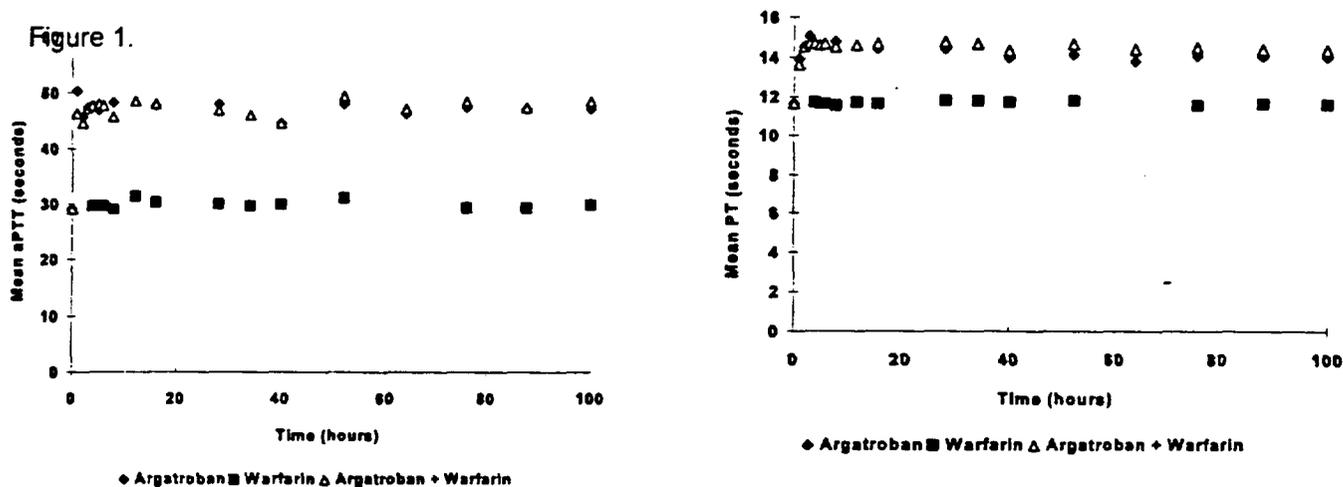
Table 4. Mean (SD) Pharmacokinetic Parameters for S-Warfarin With (Regimen B) and Without (Regimen A) Coadministered Argatroban

Parameter	Regimen A	Regimen B	Percent Difference ¹
C _{max} (ng/mL)	502 ± 122	471 ± 70.0	-6.19
T _{max} (hr)	0.85 ± 0.44	1.0 ± 0.54	18.2
AUC(0-t) (ng*hr/mL)	10,600 ± 3,440	11,300 ± 3,050	7.28
AUC(0-inf) (ng*hr/mL)	12,700 ± 5,260	13,800 ± 5,560	9.30
T _{1/2} (hr)	36.1 ± 10.6	37.9 ± 12.1	4.95
Kel (hr ⁻¹)	0.0204 ± 0.00481	0.0195 ± 0.00403	-4.71

¹Percent Difference of Least Square Mean values expressed as percentage of Regimen A

APPEARS THIS WAY
ON ORIGINAL

Pharmacodynamics: An assessment of pharmacodynamic interaction was made. The parameters estimated and compared were aPTT, calcium-thrombin time (CaTT), and prothrombin time (PT). It should be noted that no differences in aPTT, PT and CaTT values between argatroban alone versus argatroban + warfarin were observed. However, there does appear to be a difference in these values between warfarin alone and argatroban, either with or without warfarin. The aPTT and PT measurements are illustrated in Figure 1.



Sponsor's Conclusions:

1. There was no evidence that a single dose of warfarin altered the pharmacokinetic parameters of continuously infused argatroban. Additionally, there was no evidence of a time dependent difference in the concentrations of argatroban when administered with or without a single dose of warfarin. There was no evidence that the administration of a single dose of warfarin altered the pharmacodynamic profile of a continuous argatroban infusion.
2. There was no evidence of a significant effect of argatroban on the pharmacokinetic parameters of R-warfarin or S-warfarin following the administration of a single dose of warfarin. The effect of argatroban on the pharmacodynamics of warfarin could not be assessed in a study in which a single dose of warfarin was given. To assess the effect of argatroban on the pharmacodynamics of R- and S-warfarin would require multiple dosing of warfarin.
3. Of the 42 adverse events reported, 11 were considered "possibly" related to the study medication and included "leg cramps", "redness or itching of eyes", and "bleeding gums". Although the warfarin/argatroban treatment group reported over twice as many adverse events (24, compared to eight in the warfarin treatment group and ten in the argatroban treatment group) many of the events reported were isolated incidences and were considered unrelated to the study drug.
4. No clinically significant trends in vital signs, physical examinations, ECGs, or routine clinical laboratory tests were observed in regard to subject safety. Regarding coagulation test results, the administration of argatroban, either alone or in combination with warfarin, increased the aPTT and CaTT values to the point where many results were considered clinically significant by the Investigator. Otherwise, the coadministration of warfarin and argatroban appeared to be well tolerated.

Reviewer's Comments:

1. A pharmacokinetic interaction between argatroban and a single oral dose of warfarin does not appear to exist.
2. Since the warfarin dose used herein is single 7.5 mg dose, a pharmacodynamic interaction between

argatroban and warfarin is not likely to be assessable.

APPEARS THIS WAY ON ORIGINAL

Study #: ARG-110

Title of Study: A Pharmacodynamic Evaluation of the Transition From Intravenous Anticoagulation with NOVASTAN® (Brand of Argatroban) to Oral Anticoagulation with Coumadin® (Crystalline Warfarin Sodium, USP) in Healthy Volunteers

Objectives: The primary objective of this pharmacodynamic study was to evaluate the temporal relationships of various clinical laboratory measures including INR and factor X during the transition from intravenous anticoagulation with NOVASTAN® (brand of argatroban) to oral anticoagulation with Coumadin® (crystalline warfarin sodium USP) in healthy volunteers by measurement of drug effects on coagulation. A secondary objective was to confirm the safety and tolerability of argatroban with and without warfarin.

Study Design: This was a single center, open-label, randomized, pharmacodynamic study. Subjects were randomized to the following treatment regimens;

- Treatment A: IV infusion of 1.0 µg/kg/min argatroban from 0-23, 28-47, 52-71, 76-95, 100-119 and 124-143 hours and a single oral dose of 5.0 mg of warfarin at 4 hours and 2.5 mg of warfarin at 28, 52, 76, 100 and 124 hours.
- Treatment B: IV infusion of 1.0 µg/kg/min argatroban from 0-23, 28-47, 52-71, 76-95, 100-119 and 124-143 hours and a single oral dose of 5.0 mg of warfarin at 4, 28, 52, 76, 100 and 124 hours.
- Treatment C: IV infusion of 2.0 µg/kg/min argatroban from 0-23, 28-47, 52-71, 76-95, 100-119 and 124-143 hours and a single oral dose of 5.0 mg of warfarin at 4 hours and 2.5 mg of warfarin at 28, 52, 76, 100 and 124 hours.
- Treatment D: IV infusion of 2.0 µg/kg/min argatroban from 0-23, 28-47, 52-71, 76-95, 100-119 and 124-143 hours and a single oral dose of 5.0 mg of warfarin at 4, 28, 52, 76, 100 and 124 hours.

Subjects: Twelve (12) normal, healthy volunteers were enrolled in and completed the study.

Products, Doses, Durations, and Batch Numbers: The test product was NOVASTAN® (argatroban) concentrate, Lot No. M020PJ, Expiration date not provided, 2.5 mL per vial 100 mg/mL, administered as a constant-rate intravenous infusion at the rate of 1.0 or 2.0 mcg/kg/min (depending upon randomization) from 0-23, 28-47, 52-71, 76-95, 100-119 and 124-143 hours. The reference product was warfarin, batch number EKJ342A, administered as one or two 2.5 mg tablets (depending on randomization) for six doses. The first dose was given four hours after the start of the first infusion of argatroban and the other five administrations were given just prior to the start of the other infusions.

Blood Sampling: Blood was collected for determination of plasma argatroban concentrations at 0 (pre-dose), 23, 27, 28, 47, 51, 52, 71, 75, 76, 95, 99, 100, 119, 123, 124, 143, 147 and 148 hours post dose.

Analytical Methodology: The plasma argatroban concentrations were determined by an LC/MS/MS method by ~~_____~~. The validation of the assay including quality control data are included in Table 1.

Results:

Pharmacokinetics: The plasma argatroban concentrations after a 4 hour infusion of argatroban at doses of 1.0 µg/kg/min and 2.0 µg/kg/min with warfarin doses of 2.5 and 5.0 mg are included in Table 2.

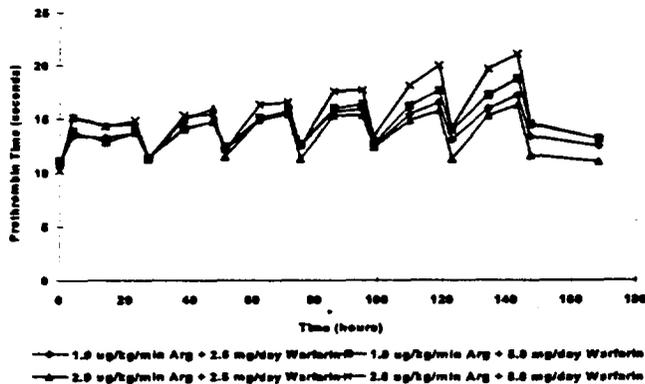
Table 2.

Argatroban Dose (µg/kg/min)	Warfarin Dose (mg)	Argatroban Concentration (ng/ml)
1.0	2.5	232.75 ± 29.76
1.0	5.0	208.46 ± 47.28
2.0	2.5	462.41 ± 65.94
2.0	5.0	385.76 ± 78.34

Pharmacodynamics:

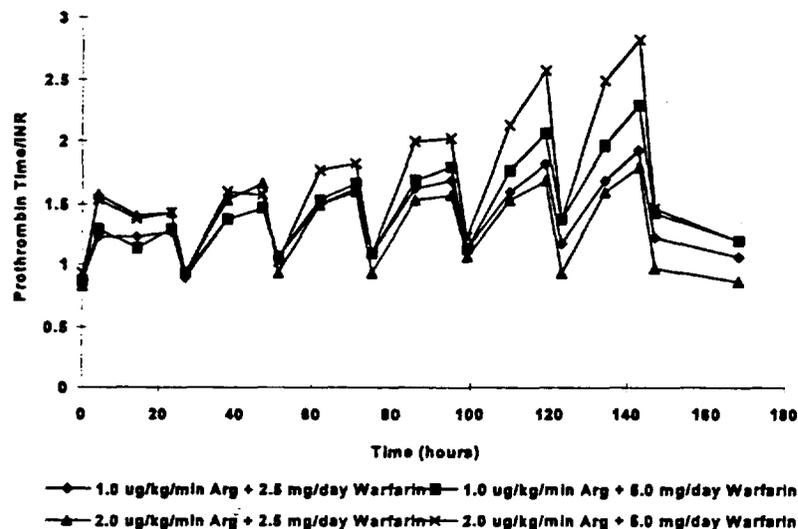
The mean prothrombin time versus time profiles for each of the dosing regimen are included in Figure 1.

Figure 1.



Similarly, the mean prothrombin time/international normalized ratio (INR) versus time profiles for each dosing regimen are included in Figure 2.

Figure 2.



Plots of observed INR values versus chromogenic factor X in the presence of argatroban suggested a negative, curvilinear relationship, although the variability in the data precluded firm conclusions. Plots of only the mean data demonstrated the mean chromogenic factor X tends to decrease with increasing INR, perhaps in an apparent linear relationship. The results were similar for the relationship between INR values and chromogenic factor X in the absence of argatroban, consistent with previous reports describing this relationship. The mean chromogenic factor X level may be negatively, linearly related to INR, at least up to INR 1.8.

The relationship between chromogenic factor X in the presence of argatroban and INR in the absence of argatroban was also examined. The results suggest argatroban does not affect chromogenic factor X measured *ex vivo*, consistent with the lack of argatroban interference in *in vitro* chromogenic factor X assays. Confirming this suggestion, there was no noticeable trend in chromogenic factor X values with and without argatroban present.

aPTT and CaTT were sensitive to argatroban, but not warfarin, returning to baseline 4-5 hours after discontinuation of the argatroban infusion. The prolongation of the CaTT was greater at the higher argatroban infusion rate (2 vs. 1 g/kg/min). The prothrombin time and INR appeared sensitive to both argatroban and warfarin therapy, with trough values slowly increasing during the course of the study.

The primary purpose for measuring the other coagulation factors was to show that warfarin, even during concurrent argatroban therapy, was affecting them in a predictable manner, consistent with the known, time-dependent, suppressive effects of warfarin on vitamin K-dependent coagulation factors. It appears that this did occur.

There was no effect of treatment on fibrinogen concentration, consistent with fibrinogen not being a vitamin K-dependent factor. Subjects receiving 5.0 mg per day warfarin tended to have greater suppression of factor activity over time than those receiving the lower warfarin dose. When baseline factor levels were normalized to 100%, mean levels of all vitamin K-dependent factors had decreased in treatment group D (5.0 mg/day warfarin, 2 g/kg/min argatroban) at 148 hours to 61% of normal.

There was a linear relationship ($r^2 = 0.85$ and 0.83 , respectively) between the INR and P&P in the absence of argatroban. Also, there was a good correlation ($r^2 = 0.83$) between the INR calculated from the P&P of patients on combined therapy and the INR in the absence of argatroban, but only after the data from three subjects considered outliers were excluded.

Sponsor's Conclusions:

1. The relationship between INR values of warfarinized plasma with and without argatroban is linear (for INR values in absence of argatroban up to 1.8) with a slope greater than 1. This linear relationship may allow for prediction of the contribution of warfarin alone to the INR based on the INR measured in the presence of both warfarin and argatroban.
2. The relationships (in warfarinized plasma) between chromogenic factor X in the presence or absence of argatroban versus INR in the absence of argatroban are similar, with chromogenic factor X decreasing with increasing INR. Because argatroban does not affect the chromogenic factor assay, this assay may be useful for monitoring warfarin therapy during concurrent argatroban treatment.
3. Activated PTT and Ca-thrombin time were sensitive to argatroban, but not warfarin, and could be useful for monitoring argatroban dosage during the transition from argatroban to warfarin anticoagulation.
4. Chromogenic factor X, factors II, VII, IX, and X, protein C, and protein S decreased over several days of concurrent warfarin and argatroban therapy in a predictable manner, consistent with the known effects of warfarin on these vitamin K-dependent coagulation factors.

Reviewer's Comments:

1. I concur with the sponsor's conclusions.
2. Complete pharmacokinetic profiles for argatroban or warfarin were not generated from Study ARG-110.

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Study #: ARG-112

Title of Study: Comparative, Randomized, Three-Way Crossover Drug-Drug Interaction Study of NOVASTAN® (Brand of Argatroban) Concentrate and Heparin in Healthy Volunteers

Objectives: The primary objective of this study was to assess the drug-drug interaction between NOVASTAN® (brand of argatroban) concentrate and heparin in healthy volunteers by measurement of drug concentrations and drug effects on coagulation.

A secondary objective was to assess the safety and tolerability of argatroban when administered by itself and with heparin.

Study Design: This was a single center, open-label, randomized, three-period, crossover study. The following dosing regimens were used.

Regimen A: Constant rate infusion of heparin sodium, 0.15 IU/kg/min, for 8 hours.

Regimen B: Constant rate infusions of argatroban, 1.25 µg/kg/min for 10 hours, and heparin sodium, 0.15 IU/kg/min, for 8 hours. The heparin infusion was initiated 2 hours after the argatroban infusion was initiated in each patient.

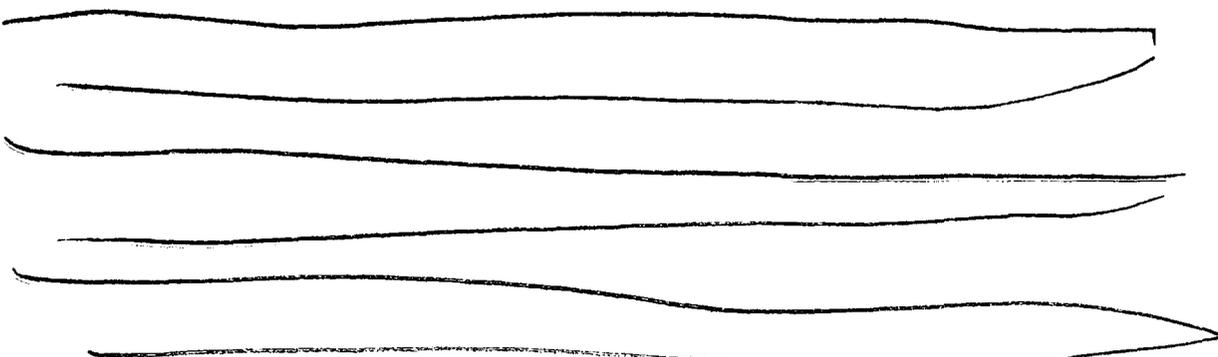
Regimen C: Constant rate infusion of argatroban, 1.25 µg/kg/min for 10 hours.

Subjects: Twelve (12) normal healthy volunteers were enrolled in this study and included in all safety analyses. Eleven subjects completed all study events and were included in all efficacy analyses. The remaining subject decided he did not want to participate in the study shortly after his initial infusion began and was dropped from the study.

Products, dose, duration, and batch number: The test product was argatroban, batch number 25311095, administered as a 10 hour infusion at the rate of 1.25 µg/kg/min. The potentially interacting product was heparin, batch number 16 218 FJ, administered as a 8 hour infusion at the rate of 0.15 IU/kg/min.

Blood Sampling: Blood samples were collected for pharmacokinetic assessments at 0 (pre-dose) and 1, 2, 3, 4, 5, 6, 7, 8, 8.067, 8.167, 8.33, 8.5, 8.75, 9, 9.5, 10, 10.5, 11, 12, 13, 14 and 15 hours after initiation of the heparin infusion (Regimen A) or argatroban infusion (Regimens B and C).

Analytical Methodology: Plasma argatroban concentrations were estimated by an LC/MS/MS method by  The validation of the method, including quality control samples is outlined in Table 1.



No methodology or validation thereof for the assay used to estimate plasma heparin levels were included for

Study ARG-112.

Results:

Pharmacokinetics:

The pharmacokinetic parameters and comparisons between Regimens are summarized in the following tables for argatroban and heparin.

Examination of the mean pharmacodynamic parameter values and plots for aPTT and CaTT for each Regimen indicated that there was a drug interaction in terms of both aPTT and CaTT when argatroban and heparin were coadministered.

Table 2. Mean (SD) Pharmacokinetic Parameters for Argatroban Following NOVASTAN® 1.25 g/kg/min and/or Heparin Sodium 0.15 IU/kg/min

Parameter	Regimen B Argatroban/Heparin	Regimen C Argatroban	Percent Difference ¹
C _{max} (ng/mL)	255 (93.4)	252 (84.0)	-0.07
T _{max} (hr)	5.5 (1.6)	6.0 (2.8)	-6.87
AUC(0-t) (ng*hr/mL)	1960 (675)	2020 (593)	-3.00
AUC(0-inf) (ng*hr/mL)	1970 (677)	2040 (628)	-1.70
T1/2 (hr)	0.900 (0.374)	1.02 (0.563)	-10.06
Kel (hr ⁻¹)	0.839 (0.193)	0.824 (0.327)	-0.12
C _{ssavg} (ng/mL)	201 (59.8)	194 (44.8)	2.13
CL (mL/min/kg)	6.72 (1.88)	6.76 (1.50)	0.32

¹ Percent Difference of Least Square Mean values expressed as percentage of Regimen C

Table 3. Mean (SD) Pharmacokinetic Parameters for Heparin Following Heparin Sodium 0.15 IU/kg/min and/or NOVASTAN® 1.25 g/kg/min

Parameter	Regimen A Heparin	Regimen B Heparin/Argatroban	Percent Difference ¹
C _{max} (mU/mL)	68.8 (25.6)	66.8 (17.1)	-2.98
T _{max} (hr)	5.9 (1.5)	7.1 (0.95)	19.84
AUC(0-t) (mU*hr/mL)	488 (217)	378 (136)	-22.52
AUC(0-inf) (mU*hr/mL)	553 (407)	440 (212)	-3.12
T1/2 (hr)	2.49 (3.96)	1.96 (2.81)	-18.59
Kel (hr ⁻¹)	2.28 (2.85)	1.23 (1.48)	-36.96
C _{ssavg} (mU/mL)	58.8 (25.9)	55.3 (17.0)	-5.85
CL (mU/min/kg)	6.39 (12.8)	3.00 (1.10)	-54.19

¹ Percent Difference of Least Square Mean values expressed as percentage of Regimen A

Pharmacodynamics: The pharmacodynamic parameters, (E_{max} and T_{max}) for aPTT, are included in Table 4.

Table 4.

	Parameter	Heparin Alone	Argatroban + Heparin	Argatroban Alone
aPTT	E _{max} (seconds)	12.1 ± 5.41	51.3 ± 10.5	21.0 ± 5.18
	T _{max} (hours)	5.5 ± 2.5	4.5 ± 2.0	2.2 ± 2.3

CaTT	E _{max} (seconds)	0.200 ± 0.190	25.4 ± 9.89	15.61 ± 6.05**
	T _{max} (hours)	6.1 ± 2.9	6.0 ± 2.2	1.43 ± 2.14**

** The CaTT E_{max} and T_{max} parameters occurred at time = 0 in 8 out of 15 assessments.

Sponsor's Conclusions:

1. There was no evidence that a continuous infusion of heparin significantly altered the pharmacokinetic parameters of continuously infused argatroban. There was also no evidence that a continuous infusion of argatroban significantly altered the pharmacokinetics of continuously infused heparin.
2. There was a drug interaction in terms of both aPTT and CaTT when argatroban and heparin were coadministered. Simultaneous administration of argatroban and heparin appeared to have a synergistic effect on both aPTT and CaTT. The CaTT was sensitive to argatroban but not heparin alone, making the assay of interest for monitoring argatroban but not heparin therapy.
3. No clinically significant trends in vital signs, physical examinations, ECGs, or routine clinical laboratory tests were observed in regard to subject safety. Three adverse events were reported during the trial, all considered "unlikely" related to the study drug. Regarding coagulation test results, the administration of argatroban, either alone or in combination with heparin, increased the aPTT values to the point where many results were considered clinically significant by the Investigator. Otherwise, the coadministration of heparin and argatroban appeared to be well tolerated.

Reviewer Comments:

1. I concur with the sponsor's conclusions.

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Study #: ARG-113

Title of Study: Investigation of the Steady-State Pharmacokinetic Interaction Between NOVASTAN® (Brand of Argatroban) and Acetaminophen in Healthy Subjects.

Objectives: The primary objective of this study was to assess the drug-drug interaction between NOVASTAN® (brand of argatroban) and acetaminophen in healthy subjects by measurement of plasma drug concentrations.

A secondary objective was to assess the safety and tolerability of argatroban when administered by itself and with acetaminophen.

Study Design: This was a single center, open-label, randomized, multiple-dose crossover study. The following dosing regimens are included;

Treatment A: Acetaminophen (APAP) 1000 mg orally at 0, 6, 12, 18, and 24 hours.

Treatment B: Constant rate infusion of argatroban, 1.5 µg/kg/min from 12 to 30 hours.

Treatment C: Acetaminophen 1000 mg orally at 0, 6, 12, 18, and 24 hours; plus administration of constant rate infusion of argatroban, 1.5 µg/kg/min from 12 to 30 hours. The time of initiation of the argatroban infusion coincided with the oral dose of APAP at 12 hours.

Subjects: Twelve (12) normal, healthy volunteers were enrolled in this study and included in all safety analyses. Eleven subjects completed all study events and were included in all efficacy analyses. The remaining subject was dropped from the study due to abnormal laboratory results at Period 3 check-in.

Products, doses, durations, and batch numbers: The test product was Novastan®, lot number M020PJ, administered as a 18 hour infusion at the rate of 1.5 µg/kg/min. The coadministered product was Tylenol® Extra Strength, lot number SPA775, administered as a multiple oral dose of 2 x 500 mg caplets at 0, 6, 12, 18, and 24 hours.

Blood Sampling: Bloods will be collected for analysis of plasma acetaminophen levels at 0, 6, 12, 18, 24, 24.5, 25, 25.5, 26, 27, 28 and 30 hours during Treatments A and C. Collections will be made at 12, 15, 18, 21, 24, 27 and 30 hours for assessments of plasma argatroban levels during Treatments B and C.

Analytical Methodology: Plasma argatroban concentrations were estimated by an LC/MS/MS method by ~~_____~~ The validation of the method, including quality control samples is outlined in Table 1.

~~_____~~
~~_____~~
~~_____~~
~~_____~~
~~_____~~

Plasma acetaminophen concentrations were estimated by an ~~_____~~ method with UV detection at 248 nm by

The validation of the method, including quality control samples in outlined in Table 2.

Table 2.

Sensitivity (LLQ)					
Linearity					
Quality Control	Target Concentration ($\mu\text{g/ml}$)	0.3 (n=6)	3.0 (n=6)	22.5 (n=6)	
	Interday	Precision (% CV)	3.57	2.98	21.67
		Accuracy (% recovery)	93.33	99.33	96.31

Results:

Pharmacokinetics:

The pharmacokinetic parameters and comparisons between treatments are summarized in the following tables for argatroban and acetaminophen.

Table 3. Mean (SD) Pharmacokinetic Parameters for Argatroban Following NOVASTAN® 1.5 g/kg/min IV Infusion from 12 to 30 Hours Alone and With 2 x 500 mg Acetaminophen Caplets at 0, 6, 12, 18, and 24 Hours

Parameter	Argatroban	Argatroban/Acetaminophen	Percent Difference ¹
C _{ss} avg (ng/mL)	261.0 (71.94)	248.3 (62.15)	-5.04
AUC(12-30) (ng*hr/mL)	4269 (1056)	4141 (954.3)	-3.50
Cl (mL/min/kg)	6.153 (1.674)	6.374 (1.497)	4.08

¹ Percent Difference of Least Square Mean values expressed as percentage of Treatment B

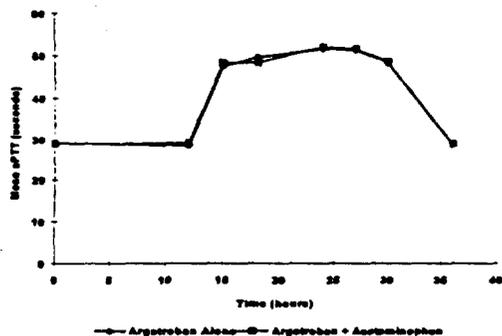
Table 4. Mean (SD) Pharmacokinetic Parameters for Acetaminophen Following 2 x 500 mg Acetaminophen Caplets at 0, 6, 12, 18, and 24 Hours Alone and With NOVASTAN® 1.5 g/kg/min IV Infusion from 12 to 30 Hours

Parameter	Acetaminophen	Argatroban/Acetaminophen	Percent Difference ¹
Trough C(6) (g/mL)	2.94 (0.910)	2.93 (0.943)	-0.93
Trough C(12) (g/mL)	4.08 (1.42)	3.90 (1.29)	-5.09
Trough C(18) (g/mL)	4.46 (1.50)	4.39 (1.54)	-3.15
Trough C(24) (g/mL)	4.61 (1.42)	4.69 (1.38)	1.42
C _{max} (g/mL)	17.4 (2.89)	17.4 (5.26)	-0.16
T _{max} (hr)	0.82 (0.34)	1.00 (0.50)	24.54
C _{min} (g/mL)	4.35 (1.49)	4.45 (1.54)	1.77
AUC (g*hr/mL)	56.8 (10.8)	56.0 (13.5)	-1.53

¹Percent Difference of Least Square Mean values expressed as percentage of Treatment A

Pharmacodynamics: The aPTT measurements after a 1.5 $\mu\text{g/kg/min}$ argatroban infusion with and without repeated 1000 mg acetaminophen doses are depicted in Figure 1.

Figure 1.



Sponsor's Conclusions:

1. There was no evidence that multiple-dose oral administration of acetaminophen every six hours for five doses significantly altered the pharmacokinetic parameters of continuously infused argatroban. There was also no evidence that a continuous infusion of argatroban significantly altered the pharmacokinetics of acetaminophen following multiple-dose oral administration every six hours for five doses.
2. There was no evidence of a drug interaction in terms of aPTT when argatroban and acetaminophen were coadministered.
3. No clinically significant trends in vital signs, physical examinations, ECGs, or routine clinical laboratory test were observed in regard to subject safety. Only one adverse event was reported during the trial, a headache which occurred prior to treatment and was considered "unrelated" to the study medication. Regarding coagulation test results, the administration of argatroban, either alone or in combination with acetaminophen, increased the aPTT values to the point where many results were considered clinically significant by the Investigator. Otherwise, the coadministration of acetaminophen and argatroban appeared to be well tolerated.

Reviewer Comments:

1. I concur with the sponsor's conclusions.

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Plasma lidocaine concentrations were estimated by an LC/MS/MS method by _____ in _____ The validation of the method, including quality control samples is outlined in Table 2.

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Table 2.

Sensitivity (LLQ)	_____				
Linearity	_____				
Quality Control	Target Concentration (ng/ml)	15.00 (n=14)	80.00 (n=14)	375.00 (n=14)	
	Interday	Precision (% CV)	6.88	3.57	7.27
		Accuracy (% recovery)	106.67	105.12	97.92

Results:

Pharmacokinetics:

The pharmacokinetic parameters and comparisons between treatments are summarized in the following tables for argatroban and lidocaine.

Table 3. Mean (SD) Pharmacokinetic Parameters for Argatroban Following NOVASTAN® 1.5 g/kg/min IV Infusion for 16 Hours Alone and With 1.5 mg/kg Lidocaine IV Infusion Over 10 Minutes and 2 mg/kg/hr Lidocaine IV Infusion to 16 Hours

Parameter	Argatroban	Argatroban/Lidocaine	Percent Difference ¹
AUC(tau) (ng*hr/mL)	4785 (1014)	3965 (800.8)	-17.14
Cssavg (ng/mL)	344.4 (82.90)	274.9 (52.76)	-20.19
Cl (mL/min/kg)	4.686 (1.590)	5.698 (1.414)	21.61

¹Percent Difference of Least Square Mean values expressed as percentage of Treatment B

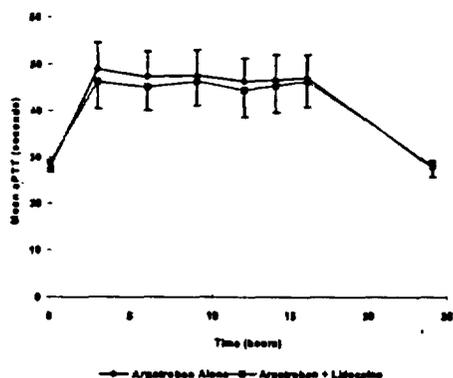
Table 4. Mean (SD) Pharmacokinetic Parameters for Lidocaine Following 1.5 mg/kg Lidocaine IV Infusion Over 10 Minutes and 2 mg/kg/hr Lidocaine IV Infusion to 16 Hours Alone and With NOVASTAN® 1.5 g/kg/min IV Infusion for 16 Hours

Parameter	Lidocaine	Argatroban/Lidocaine	Percent Difference ¹
AUC(tau) (ng*hr/mL)	30077 (4823)	32080 (6103)	6.66
Cssavg (ng/mL)	2545 (444)	2692 (596)	5.79
Cl (mL/min/kg)	13.45 (2.188)	12.93 (2.748)	-3.83

¹Percent Difference of Least Square Mean values expressed as percentage of Treatment A

Pharmacodynamics: The mean (± SD) aPTT measurements versus time after 1.5 µg/kg/min argatroban infusion with and without a 1.5 mg/kg lidocaine bolus followed by a 2.0 mg/kg/hr lidocaine infusion and depicted in Figure 1.

Figure 1.



Sponsor's Conclusions:

1. There was insufficient evidence that a continuous infusion of lidocaine significantly (>25% change in a pharmacokinetic parameter) altered the pharmacokinetics of continuously infused argatroban. A 22% increase in argatroban CI when coadministered with lidocaine was observed, leading to a 20% reduction in argatroban steady-state concentrations. There was also insufficient evidence that a continuous infusion of argatroban significantly altered the pharmacokinetics of continuously infused lidocaine.
2. The coadministration of argatroban and lidocaine consistently resulted in slightly lower aPTT values than did argatroban alone, possibly suggesting a pharmacodynamic interaction between argatroban and lidocaine. This pharmacodynamic response is probably due to the 20% lower average steady-state argatroban concentrations attained when coadministered with lidocaine.
3. No clinically significant trends in vital signs, physical examinations, ECGs, or routine clinical laboratory tests were observed in regard to subject safety. Five mild adverse events were reported during the trial, three of which were considered "possibly" related to the study drug and two of which were considered "unlikely" related to the study drug. As expected, the administration of argatroban, either alone or in combination with lidocaine, increased the aPTT values to the point where many results were considered clinically significant by the Investigator. Otherwise, the coadministration of lidocaine and argatroban appeared to be well tolerated.

Reviewer Comments:

1. The metabolism of lidocaine and argatroban are both at least partly catalyzed by cytochrome P-450 3A4 and a competitive inhibition interaction between these compounds is possible. It should be noted that lidocaine has not been shown to be an enzyme inducer. Therefore, the observed increase in argatroban clearance can not be readily explained by known historical information.
2. I concur with the sponsor's conclusions.