

Concomitant Medication Use

Concomitant medication usage was similar to Study ARG-911.

Entry Category

Below is a table of the entry category for the patients enrolled in Study ARG-915. These results are similar to those seen in Study ARG-911.

Argatroban-treated Patients for ARG-915 (Intention-to-Treat Analysis)

Subcategory	Number of Patients
HIT	125
New diagnosis	(103/125 = 82.4%)
Previous diagnosis (HIT OR HITTS) in absence of current thrombocytopenia	(22/125 = 17.6%)
HITTS (new diagnosis)	139

Reviewer's table

Efficacy Analysis

Listed below are the efficacy results for Study ARG-915. Patients are counted once by the most severe endpoint. The historical control used for comparison is that used for Study ARG-911. Statistically significant results in favor of argatroban are seen for the HIT patients and a trend toward statistically significant results is seen for the HITTS patients. For both argatroban-treatment a statistically significant benefit is demonstrated for the new thrombosis endpoint.

Primary Efficacy Results (ITT) for Study ARG-915

Parameter	HIT / Historical control	HIT/ argatroban-treated	P-value	HITTS/ Historical control	HITTS/ argatroban-treated	P-value
Total number	147	125		46	139	
Reached composite endpoint	57 (38.8%)	32 (25.6%)	0.021 ^a	26 (56.5%)	57 (41.0%)	0.067 ^a
Death (all causes)	32 (21.8%)	21 (16.8%)	0.357 ^b	13 (28.3%)	35 (25.2%)	0.700 ^b
Amputation (all causes)	3 (2%)	6 (4.8%)	0.309 ^b	4 (8.7%)	16 (11.5%)	0.786 ^b
New thrombosis	22 (15%)	5 (4.0%)	0.004 ^b	9 (19.6%)	6 (4.3%)	0.003 ^b

^aChi-squared test

^bFisher's exact

Reviewer's table

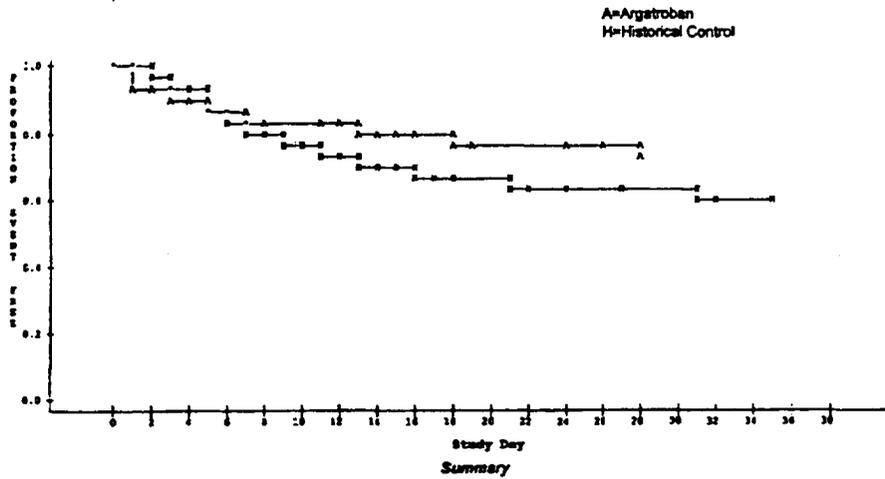
Repeat Patients

Only three of the repeat patients reached an endpoint (death). Patient 020-106 died in multisystem organ failure on low dose argatroban. Patient 007-101 died after development of a series of complications (pancreatitis, vaginal and upper GI bleeding, and dehydration). No patient developed thrombosis. Two patients (123-001 and 145-003) underwent amputations after the thirty-day follow-up period.

The graphs below are the Kaplan-Meier Time-to-Event analyses. Statistically significant differences are observed for both the HIT and HITTs arms.

HIT arm of the study

ARG-915 HIT Arm: Time to First Event for the Composite Efficacy Endpoint



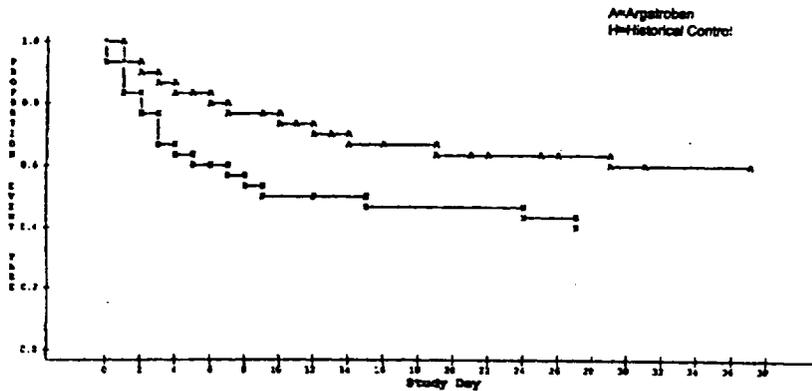
TRT	Total	No. Events	Median Time (Days)	Uncensored range(Days)	Log Rank Chi Sq. 1df	p-value	Hazard Ratio	95% CI
ARG	125	17		0 - 28	2.21	0.14	0.24	0.07-0.83
HC	147	37		1 - 35				

Sponsor's graph volume 28.32

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HITTs arm

ARG-915, HITTs Arm: Time to First Event for the Composite Efficacy Endpoint



TRT	Total	No. Events	Median Time (Days)	Uncensored range(Days)	Log Rank Chi Sq. 1df	p-value	Hazard Ratio	95% CI
ARG	139	5		0 - 37	2.21	0.14	0.24	0.07-0.83
HC	46	28	12	0 - 27				

Sponsor's graph volume 28.32

The sponsor did not perform additional analyses.

Secondary Efficacy Results

The secondary efficacy results included:

- 1) resolution of thrombocytopenia
- 2) anticoagulant effect as evidenced by aPTT > 1.5X the patient's baseline aPTT

Resolution of thrombocytopenia

Below is a table with the platelet count from day 0 to 3. The results are similar to those seen in Study ARG-911.

Table 9 Change in Platelet Count Following Argatroban Administration Days 0-3: HIT and HITTS Patients

Parameter	HIT Patients		HITTS Patients	
	Historical Control	Argatroban	Historical Control	Argatroban
Baseline Platelet Count ^a	(N = 129) 124.79 ± 80.72	(N = 123) 99.21 ± 67.84	(N = 39) 103.16 ± 81.43	(N = 137) 85.02 ± 76.20
Platelet Count Change ^b	(N = 97) -32.61 ± 93.80	(N = 85) +42.32 ± 55.72	(N = 33) -13.40 ± 107.73	(N = 109) +47.83 ± 82.32

^a Units are 1000's/ μ L.

^b Change between study days 0 and 3.

Sponsor's table volume 28.32

Anticoagulation

The table below shows the mean initial aPTT obtained after start of the infusion.

Table 10 Initial aPTT Assessment and Timepoints

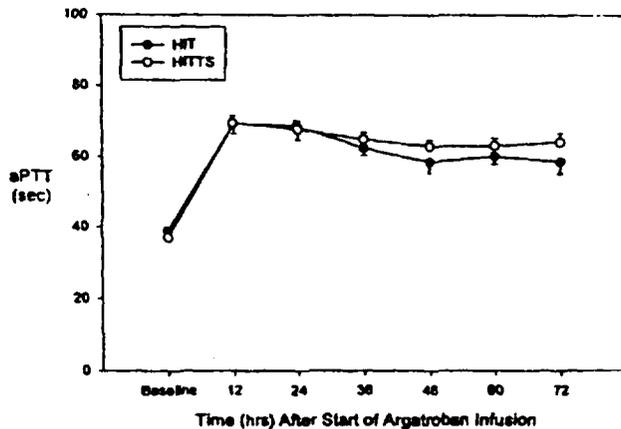
Parameter	HIT	HITTS
	Number of patients	122
Mean Initial aPTT (sec)	58.3	65.6
Mean time to Initial aPTT (hrs)	4.50	3.08

Reference Documentation Appendix 16.1.9 (P. 10) (V. 10) (E. 10)

Sponsor's table volume 28.32

The graph below shows that adequate anticoagulation was achieved for 50% of patients between 3-5 hours after start of infusion.

FIGURE 5
Time Course of aPTT Levels Following
Argatroban Administration



Sponsor's table volume 28.32

Conclusion

Study ARG-915 is a supportive study for this submission. Similar efficacy results were seen in this trial as in Study ARG-911 in the ITT population suggesting that the drug is active as an anticoagulant and significantly reduces the combined risk of the new thrombosis, amputation and death for this patient population. The efficacy results seen in the HITTS population are trending towards a statistically significant reduction in the categorical analysis and are statistically significant in the Kaplan-Meier analysis. Statistically significant results are seen for the endpoint of new thrombosis.

Study ARG-310

Protocol Summary:

Title:

An Open-label, single-treatment, multicenter, in-patient trial of argatroban in patients with a history of HIT or HITTS who require percutaneous coronary intervention procedures

Inclusion criteria were similar to those for Study ARG-911 and Study ARG-915. The only additional inclusion criteria were:

- 1) male or non-pregnant female patients older than 18 years of age
- 2) documented coronary artery disease requiring elective, urgent, or emergent PTCA, atherectomy, or stent implantation with an FDA-approved device

Exclusion criteria were:

- 1) any condition that contraindicated or endangered the patient if they participated in the study
- 2) thrombolytic therapy within 24 hours prior to dosing or heparin within 6 hours prior to dosing
- 3) laboratory evidence of hepatic dysfunction (AST and/or ALT three times the upper limit of normal) at baseline
- 4) documented coagulation disorder (other than HIT or HITTS) or bleeding disorder
- 5) any previous history of hemorrhagic stroke or documented evidence of a thrombotic stroke within 7 days prior to enrollment unrelated to HITTS
- 6) active, uncontrolled peptic ulcer disease, uncontrolled GI bleeding within 6 weeks prior to study

- 7) uncontrolled hypertension
- 8) oral anticoagulant therapy within 72 hours prior to the initiation of the study infusion
- 9) females known or suspected to be pregnant
- 10) lactating females
- 11) concomitant use of GPIIb/IIIa inhibitor
- 12) participation in other clinical investigational trials with the exception of Study ARG-911
- 13) known uncontrolled cirrhosis or hepatitis
- 14) history of sensitivity to aspirin or argatroban
- 15) concomitant use of cimetidine

Thirty (30) patients were entered in this study. Patients could be withdrawn from the study for the following reasons:

- 1) Withdrawn from assessment
 - a) clinically significant bleeding unresponsive to the usual clinical interventions
 - b) requirement for CABG
- 2) Withdrawal from study
 - a) Significant adverse reaction or sensitivity
 - b) Intercurrent illness which may, in the judgement of the investigator, significantly affect assessments of clinical status
 - c) Protocol violation
 - d) Patient non-compliance or request to withdraw
 - e) Inability to implant stent (although they may have continued to receive the medication on a compassionate basis)

Patients withdrawn early were to be included in the intent-to-treat analysis. New patients could be entered to replace early withdrawals. The study allowed repeat patients. Five patients designated as "repeat patients" were re-entered with different patient number.

Treatments

All patients received one tablet of oral aspirin 2 to 24 hours prior to intervention. After placement of arterial and venous sheaths, patients received a bolus of 350 μ g/kg argatroban over 3 to 5 minutes. The bolus was followed by an initial infusion of 25 μ g/kg/min. If the ACT obtained 5 to 10 minutes after the bolus was less than 300 seconds, another 150 μ g/kg was administered and the infusion rate increased to 30 μ g/kg/min. If the ACT obtained was greater than 450 seconds, the infusion rate was decreased to 15 μ g/kg/min. Once the ACT was between 300 and 450 seconds, the infusion was maintained at that dose. The maximum initial infusion rate was 40 μ g/kg/min.

The protocol permitted additional boluses of argatroban in case of dissection, abrupt vessel closure, or thrombus formation during the procedure. A patient was considered a treatment failure if, after a second bolus dose of argatroban was given, there was still evidence of thrombus or the investigator deemed the level of anticoagulation inadequate to proceed. There was a provision for those patients requiring argatroban after the procedure to receive it but at a lower rate for up to 7 days.

Prior and Concomitant medication

Conventional medical therapy for patients with coronary artery disease was permitted. Transfusions were permitted during study treatment only if patients had a hematocrit less than 26% with a documented source of blood loss, or less than 30% with significant hemodynamic deterioration or ischemia.

Primary Efficacy Endpoints

The primary efficacy variables were:

- 1) investigator's assessment of the adequacy of anticoagulation attained with argatroban during the procedure
- 2) the investigator's assessment of the attainment of a satisfactory outcome

Other efficacy variables were:

- 1) proportion of patients with acute procedural success (absence of death, emergent CABG, or Q-wave myocardial infarction)
- 2) change in percent stenosis in the primary target lesion after angioplasty from the percent stenosis in the primary lesion prior to angioplasty

Safety Endpoints

The primary safety endpoints were:

- 1) the incidence of major bleeding (overt bleeding that was associated with a fall in hemoglobin level — 5g/dL; led to a transfusion of — 2 units or more; was retroperitoneal; occurred in a major prosthetic joint; or was intracranial)
- 2) need for red blood cell transfusions
- 3) intracerebral bleeding
- 4) change of hematocrit from baseline
- 5) adverse drug experiences
- 6) incidence of major bleeding compared to historical controls derived from the EPILOG trial (heparin + ASA + GPIIb/IIIa inhibitor)

Results

Investigator Determined Adequacy of Anticoagulation

From the NDA submission, *The investigators determined that anticoagulation was achieved in 30 (100%) of the 30 patients. One patient whose ACT ranged between 252 and 282 seconds (below 300-450 seconds planned for the trial) was judged by the investigator to have a satisfactory ACT. This patient had a satisfactory procedural outcome.*

Investigator Assessment of Procedural Outcome

The investigator determined that 28 out of 30 (93%) patients had a satisfactory procedural outcome. Patient 006-001 became acutely hypotensive with ventricular tachycardia during the procedure. Although this patient had a good angiographic result, it was felt the hypotension and ventricular tachycardia were due to coronary artery embolus to the right ventricular branch. Patient 015-001 failed to have the target lesion in the circumflex artery revascularized. During the procedure, a previously stented left anterior descending (LAD) artery became occluded at the origin therefore the procedure on the circumflex artery was abandoned and the LAD was reopened and stented.

There were 12 adverse procedural events reported for 12 patients: 6 episodes of chest pain, 2 myocardial infarction (MI), 1 abrupt closure, 1 episode of ischemia, 1 impending closure, and 1 repeat PTCA.

Protocol Violations

The majority of protocol violations were either due to ECGs and/or vital signs not being taken at protocol-specified intervals or laboratory evaluations not being performed at protocol specified intervals.

Safety

The mean duration of exposure to argatroban was 0.7 ± 0.23 days. Most patients were on argatroban for 2 hours or less during the procedure. There were 12 patients who were on the drug post-procedure. Seven patients received the drug for less than one day post-procedure. Three patients received the drug for 2-3 days and 2 patients for 3-5 days post-procedure.

Overall 24 (80%) out of 30 patients, including repeat patients, reported 77 adverse events. The most frequent adverse events reported were back pain, chest pain, abdominal pain, nausea, hypotension, hematoma, headache, and anemia. Serious adverse events were MI, upper gastrointestinal bleed, retroperitoneal hemorrhage, chest pain, coronary thrombosis, cardiac arrest, pulmonary edema, and a vascular disorder (perforation of the proximal circumflex artery).

Most Frequent Adverse Events for ARG-310

Event	Number of Events	Number of Patients	Percent of Patients
Body as a Whole			
Back Pain	8	7	23.3
Chest Pain	11	7	23.3
Gastrointestinal System			
Abdominal Pain	4	3	10
Nausea	4	4	13.3
Cardiovascular system			
Hypotension	5	5	16.7
Platelet, Bleeding, and Clotting Disorders			
Hematoma	2	2	6.7
Central and Peripheral Nervous System			
Headache	3	2	6.7
Red Cell Blood Disorders			
Anemia	3	2	6.7

Reviewer's table

There were multiple confounding issues in these patients each of which could have contributed to the events.

There were 25 bleeding events for 15 patients during the study; two of these events were considered major bleeds.

The actual incidence of minor bleeds beginning after the argatroban infusion was 40% (19 events in 12 out of 30 patients). The commonly reported bleeding events were groin/access site bleeding (9 patients), gastrointestinal bleeding (4 patients), hematocrit drop only (3 patients), genitourinary (2 patients), hemopytysis (1 patient), and other (3 patients). The two major bleeds involved a gastrointestinal bleed and a retroperitoneal bleed.

Incidence of Transfusions

During the study 7 patients received 11 transfusions.

Laboratory Changes

One patient with a complicated medical history had an abnormal platelet count. The argatroban infusion was stopped with the platelet count of 14,000/cmm. The table below gives the time course of platelet counts for Patient 015-001.

Platelet count

Date/Time	Platelet Count
Baseline (1/15/97 7:37 am)	242 x 10 ³ /mm ³
1/16/97 1:14 am	14 x 10 ³ /mm ³
1/16/97 5:38 am***	160 x 10 ³ /mm ³

Reviewer's table

*** This platelet count was obtained after transfusion of 2 units of platelets. A case report form could not be located to determine whether the platelet count was erroneous or whether other clinical information was available.

Statistical analysis demonstrated that the hemoglobin (hgb), hematocrit (hct), and red blood cells (RBCs) all significantly decreased from baseline to post-treatment. There were statistically significant increases in white blood cell counts (WBCs) and serum creatinine. There were statistically significant decreases in basophils and serum potassium. Below is the table of median changes noted from baseline to post-treatment.

Median Laboratory Changes

Laboratory Parameter	Median change
Hemoglobin	Decrease 1.05 g/dL
Hematocrit	Decrease 2.75%
RBCs	Decrease 0.39 x 10 ⁶ /mm ³
WBCs	Increase 0.6 x 10 ³ /mm ³
Basophils	Decrease 0.15%
Serum Creatinine	Increase 0.11 mg/dL
Serum potassium	Decrease 0.15 mg/dL

Reviewer's table

Four patients and one repeat patient had laboratory changes that were considered adverse events. Patient 003-005 had an increased non-protein nitrogen (serum creatinine 1.8g/dL) and anemia. The same patient entered the study again as a repeat patient and did not experience the same changes in laboratory parameters. Patient 003-006 reportedly had mild hypokalemia (4.1 g/dL) post-treatment. However the patient initially had a high potassium level. Patient 012-002 had mild hyperkalemia (5.5 g/dL). Patient 003-105 actually had a higher hemoglobin post-treatment. Patient 023-001 experienced a drop in hemoglobin from 12.3 baseline to 10.8 g/dL post-treatment. The precise causes of these abnormalities are difficult to identify given the complex clinical status of the patients.

Post-treatment EKG did not demonstrate a specific pattern of changes from baseline.

Overall Safety Assessment

General comments

The safety assessment was confounded by the fact the comparison was made with historical controls. The data for the historical controls were collected retrospectively and may not have been as accurate as those collected prospectively for the argatroban treated patients. Underreporting of adverse events most likely occurred in the historical controls.

Study ARG-911

Extent of Drug Exposure

The table below shows the average daily dose and duration for patients in the HIT arm of Study ARG-911. Two patients are not included in this table because the average daily dose could not

be determined. The majority of patients in the HIT arm were dosed at greater than 1.0-2.0 µg/kg/min and for 4 days or more. The largest group of patients received a dose between 0.5 – 3.0 µg/kg/min (81%). The results above are consistent with the sponsor's intended use of argatroban in clinical practice.

Table 34 Number and Percentage of HIT Patients Receiving Argatroban According to Average Dose and Duration of Therapy

Duration of Exposure (Days) ^a	Average Dose (µg/kg/min) ^b							Total (Any Dose) N %
	0.1-0.5	>0.5-1.0	>1.0-2.0	>2.0-3.0	>3.0-4.0	>4.0-5.0	>5.0	
Total Number of Patients	9 (5.7)	25 (15.8)	70 (44.3)	33 (20.9)	12 (7.6)	3 (1.9)	6 (3.8)	158 (100)
<1		2 (1.3)	10 (6.3)	4 (2.5)			1 (0.6)	17 (10.8)
1	2 (1.3)	4 (2.5)	6 (3.8)	3 (1.9)	1 (0.6)		1 (0.6)	17 (10.8)
2		2 (1.3)	10 (6.3)	4 (2.5)	3 (1.9)			19 (12.0)
3	2 (1.3)	3 (1.9)	5 (3.2)	4 (2.5)				14 (8.9)
4		5 (3.2)	10 (6.3)	6 (3.8)	1 (0.6)		1 (0.6)	23 (14.6)
5	2 (1.3)	2 (1.3)	7 (4.4)	3 (1.9)	1 (0.6)	1 (0.6)		16 (10.1)
6		2 (1.3)	7 (4.4)	3 (1.9)	3 (1.9)	1 (0.6)		16 (10.1)
7	2 (1.3)	2 (1.3)	5 (3.2)		1 (0.6)	1 (0.6)	1 (0.6)	12 (7.6)

^a Average dose=sum of all volumes times 1000 mg/mL divided by pre physical exam body weight divided by total number of minutes patient received argatroban infusion. Excludes patients where average dose could not be determined.
^b Duration of exposure=number of hours on drug divided by 24 hrs/day
 Reference Documentation Appendix 16.2.31

continued

Table 34 Number and Percentage of HIT Patients Receiving Argatroban According to Average Dose and Duration of Therapy (continued)

Duration of Exposure (Days) ^a	Average Dose (µg/kg/min) ^b							Total (Any Dose) N %
	0.1-0.5	>0.5-1.0	>1.0-2.0	>2.0-3.0	>3.0-4.0	>4.0-5.0	>5.0	
8			2 (1.3)	1 (0.6)	2 (1.3)			5 (3.2)
9			2 (1.3)	1 (0.6)				3 (1.9)
10			1 (0.6)					1 (0.6)
11			1 (0.6)	2 (1.3)			1 (0.6)	4 (2.5)
12		2 (1.3)	1 (0.6)				1 (0.6)	4 (2.5)
13			2 (1.3)	2 (1.3)				4 (2.5)
≥15	1 (0.6)	1 (0.6)	1 (0.6)					3 (1.9)
Overall Duration:								
Mean±SE	5.73±1.03	4.99±0.54	5.47±0.62	4.87±0.44	5.34±0.49	6.31±0.47	6.32±1.42	5.32±0.31
Median	5.23	4.28	4.45	4.36	5.84	6.00	5.73	4.46

^a Average dose=sum of all volumes times 1000 mg/mL divided by pre physical exam body weight divided by total number of minutes patient received argatroban infusion. Excludes patients where average dose could not be determined.
^b Duration of exposure=number of hours on drug divided by 24 hrs/day.
 Reference Documentation Appendix 16.2.31

Sponsor's table volume 28.10

The table below shows the average daily dose and duration for patients in the HITTS arm of Study ARG-911. Four patients are not included in this table because the average daily dose could not be determined. The majority of patients in the HITTS arm received an average daily dose of argatroban of greater than 1.0-2.0 µg/kg/min and had the drug infused for 4 or more days. The results above are consistent with the sponsor's planned use of argatroban in clinical practice.

Table 35 Number and Percentage of HITTS Patients Receiving Argatroban According to Average Dose and Duration of Therapy

Duration of Exposure (Days) ^a	Average Dose ^b (µg/kg/min)							Total (Any Dose)	
	0.1-0.5	>0.50-1.0	>1.0-2.0	>2.0-3.0	>3.0-4.0	>4.0-5.0	>5.0	N	%
Total Number of Patients	10 (7.1)	17 (12.1)	61 (43.6)	38 (27.1)	9 (6.4)	1 (0.7)	4 (2.9)	140	(100)
<1		1 (0.7)	9 (6.4)	2 (1.4)				12	(8.6)
1		3 (2.1)	4 (2.9)	2 (1.4)				9	(6.4)
2	1 (0.7)	2 (1.4)	5 (3.6)	1 (0.7)				9	(6.4)
3		2 (1.4)	1 (0.7)	3 (2.1)	1 (0.7)		1 (0.7)	8	(5.7)
4	2 (1.4)	3 (2.1)	8 (5.7)	5 (3.6)	1 (0.7)	1 (0.7)		20	(14.3)
5	4 (2.9)	1 (0.7)	9 (6.4)	3 (2.1)	4 (2.9)		2 (1.4)	23	(16.4)
6	2 (1.4)	2 (1.4)	7 (5.0)	9 (6.4)				20	(14.3)
7		1 (0.7)	4 (2.9)	4 (2.9)	2 (1.4)			11	(7.9)

^a Average dose=sum of all volumes times 1000 mg/mL divided by pre physical exam body weight divided by total number of minutes patient received argatroban infusion. Excludes patients where average dose could not be determined.
^b Duration of exposure=number of hours on drug divided by 24 hrs/day.
 Reference Documentation Appendix 16.2.32

continued

Table 35 Number and Percentage of HITTS Patients Receiving Argatroban According to Average Dose and Duration of Therapy (continued)

Duration of Exposure (Days) ^a	Average Dose ^b (µg/kg/min)							Total (Any Dose)	
	0.1-0.5	>0.50-1.0	>1.0-2.0	>2.0-3.0	>3.0-4.0	>4.0-5.0	>5.0	N	%
8		1 (0.7)	3 (2.1)	3 (2.1)				7	(5.0)
9			2 (1.4)					2	(1.4)
10		1 (0.7)	4 (2.9)	1 (0.7)				6	(4.3)
11			1 (0.7)	1 (0.7)			1 (0.7)	3	(2.1)
12				1 (0.7)				1	(0.7)
13			2 (1.4)	1 (0.7)				3	(2.1)
14			1 (0.7)	2 (1.4)	1 (0.7)			4	(2.9)
≥15	1 (0.7)		2 (1.4)	2 (1.4)	1 (0.7)			6	(4.3)
Overall Duration:									
Mean±SE	7.13±1.24	4.45±0.47	5.82±0.34	6.56±0.40	6.57±0.77	4.65±0.00	6.62±1.17	5.92±0.22	
Median	5.40	4.18	5.60	6.43	5.66	4.85	5.37	5.61	

^a Average dose=sum of all volumes times 1000 mg/mL divided by pre physical exam body weight divided by total number of minutes patient received argatroban infusion. Excludes patients where average dose could not be determined.
^b Duration of exposure=number of hours on drug divided by 24 hrs/day.
 Reference Documentation Appendix 16.2.32

Sponsor's table volume 28.10

Dosing Above 10 µg/kg/min

Several patients received greater than the intended maximum dose for argatroban.

- 1) Patient 002-010 received a maximum of 10.6 µg/kg/min as an intravenous infusion.
- 2) Patient 018-003 received 350 µg/kg bolus and an infusion of 10-12 µg/kg/min under an individual IND during an operation. Following the operation the drip rate returned to 1.2-2.0 µg/kg/min.
- 3) Patient 020-093 received a maximum of 20.0 µg/kg/min intravenous infusion. This patient was maintained on doses of argatroban between 15.0-20.0 µg/kg/min for 11 days when the infusion was discontinued.
- 4) All other patients in the ARG-911 study received 10.6 µg/kg/min or less.

Overall Adverse Events

The adverse event rate for the argatroban treated patients compared to the historical controls was not significantly different over the 37 day period (71% and 78%, respectively). The adverse event rate reflected the critically ill patient population. Below is a table of adverse events overall.

Overall Adverse Events for Study ARG-911

Patient number	New historical control /HIT	Argatroban/ HIT	New Historical Control / HITT	Argatroban/ HITT
Overall 37 day period	105/147 (71%)	125/160 (78%)	40/46 (87%)	123/144 (85%)
During infusion	N/A	101/160 (63%)	N/A	103/144 (72%)

Reviewer's table

Deaths

While death was a primary efficacy endpoint, it was also assessed for the safety of the drug. Fifty-three argatroban-treated patients (17%) and 45 historical control patients (23%) died during the study period of 0–37 days. The summary table below shows death information from Study ARG-911. There are an increased number of cardiovascular and respiratory deaths in the argatroban-treated patients compared to historical controls.

Death during the 37 day follow-up period for Study ARG-911

Type of Death	Argatroban treated (N=304)	New historical controls (N=193)
Cancer	1	1
Cardiovascular		
Cardiac Arrest	12	2
Cardiac / Circulatory Failure	5	8
Hypotension/Bradycardia	1	0
EKG abnormal	1	0
Myocardial infarction	2	1
Supraventricular Tachycardia	1	0
Ventricular Tachycardia	1	2
Cerebrovascular Disorder	0	3
Drug Abuse	1	0
Encephalopathy	1	1
Hemorrhage	2	1
Hepatic Failure	1	1
Inhalation Injury	0	1
Metabolic	1	0
Multiple System Organ Failure	8	1
Necrosis, Intestinal	0	2
Renal Failure, abnormal	1	1
Respiratory		
Apnea	10	3
Pleural effusion	1	0
Other respiratory	1	5
Sepsis	2	7
Thrombosis	0	4
Unknown	0	1

Reviewer's table

The top three causes of death for the argatroban and historical controls are listed below.

	Argatroban	New Historical control
Most frequent	Cardiac Arrest	Cardiac/Circulatory Failure
Second most frequent	Apnea	Sepsis
Third most frequent	Multiple system Organ failure	Other respiratory

Reviewer's table

Although the percentage of patients who die in the argatroban-treated group is less than those in the new historical controls there are important differences in the cause of death between patients treated group versus the new historical controls. These differences may relate either to difference in underlying medical conditions between treated and control groups, to adverse side effect of the drug, or to HIT/HITTS. All patients who died of cardiovascular causes had a cardiovascular history. The study design does not permit further analysis here.

Although an apparent discrepancy is noted in cardiac arrests, review of the preclinical pharmacology data by Dr. I. Antonipillai dated March 23, 1998 did not reveal any suggestion of propensity towards cardiac arrests or cardiac arrhythmias in chronic toxicity studies involving dogs and rats. Review of studies in healthy volunteers revealed that none of the 128 treated patients experienced a serious adverse event in studies ARG-100, ARG-101, ARG-102, ARG-105, ARG-108, ARG-109, and ARG-112. Similarly there were no serious adverse events in argatroban-treated patients in Study ARG-103 (renal-impairment study) or Study ARG-106 (hepatic impairment study). Review of the randomized trials Phase I and II trials (ARG-210, 230, 231, and 912) revealed that 28% of the argatroban-treated population experienced a serious adverse event compared to 24% of the placebo and 24% of the active control groups. These studies will be discussed later.

This reviewer's assessment of all deaths labeled cardiac arrests for the argatroban-treated population did not reveal any causal associated with the drug.

Adverse Events Leading to Withdrawal

Twenty-two patients withdrew from the study. Eleven in each argatroban arm withdrew. The table below shows the adverse events leading to withdrawal in Study ARG-911.

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Table 40 Adverse Events Leading to Withdrawal of Patients Receiving Argatroban

Adverse Event ^a	HIT		HITTS	
	AEs	Number of Patients (%)	AEs	Number of Patients (%)
Total Number Of Patients		160		144
Total Number Of Patients Who Withdrew		11 (7)		11 (8)
Anaemia	0	0 (0)	2	2 (1)
Anaemia Hypochromic	0	0 (0)	1	1 (1)
Anxiety	1	1 (1)	0	0 (0)
Bradycardia	1	1 (1)	0	0 (0)
Cardiac Arrest	0	0 (0)	1	1 (1)
Coagulation Disorder	2	2 (1)	0	0 (0)
Coagulation Factor Decreased	0	0 (0)	1	1 (1)
Multisystem Organ Failure	1	1 (1)	0	0 (0)
ECG Abnormal	1	1 (1)	0	0 (0)
ECG Abnormal Specific	1	1 (1)	0	0 (0)
Embolism Pulmonary	0	0 (0)	1	1 (1)
Encephalopathy	1	1 (1)	0	0 (0)
GI Haemorrhage	1	1 (1)	1	1 (1)
Haemorrhage NOS	1	1 (1)	3	2 (1)
Hepatic Failure	1	1 (1)	0	0 (0)
Hypertension Pulmonary	1	1 (1)	0	0 (0)
Peripheral Ischaemia	0	0 (0)	1	1 (1)
Phlebitis	1	1 (1)	0	0 (0)
Pulmonary Haemorrhage	0	0 (0)	1	1 (1)
Renal Function Abnormal	1	1 (1)	0	0 (0)
Tachycardia	1	1 (1)	0	0 (0)
Tachycardia Ventricular	1	1 (1)	0	0 (0)
Thrombosis	0	0 (0)	1	1 (1)

^aPatient counted once per event.

^bPreferred WHO term for MSOF is Death

Patients who discontinued study drug due to an adverse event were counted as completers.

Reference Documentation Appendix 1E2.37

Sponsor's table volume 28.10

The sponsor states that the majority of withdrawals for adverse events are due to anemia and hemorrhage. However other conclusions can be drawn. The table below shows another way of looking at the same data.

Reviewer's Adverse Events Leading to Withdrawal for Argatroban-treated Patients ARG-911

Category	HIT adverse events	HITTS adverse events	Total events
Endpoint failure (DVT/PE)	0	2	2
Hematologic ^a	4	9	13
Cardiac ^b	5	1	6
CNS/Psychiatric ^c	2	0	2
Systemic- Multiorgan system failure	1	0	1
GI- Hepatic failure	1	0	1
Pulmonary- Pulmonary Hypertension	1	0	1
Renal function	1	0	1
Vascular System ^d	1	1	2

a Includes anemia, anemia hypochromic, coagulation disorder, coagulation factor decreased, GI hemorrhage, Hemorrhage NOS, Pulmonary Hemorrhage.

b Includes bradycardia, cardiac arrest, ECG abnormal, ECG abnormal specific, Tachycardia, Tachycardia ventricular.

c Includes Anxiety and Encephalopathy.

d Includes Peripheral ischemia and Phlebitis.

Reviewer's table

Aside from endpoint failure and hematologic disorders, which are expected with an anticoagulant, the cardiac adverse events are the most prominent. The reason for the higher incidence in the HIT group is unclear since the baseline conditions involving the circulatory system were nearly equivalent between the two groups (HIT - 100% and HITTS - 98%).

Most Frequent Adverse Events Patients

The sponsor's table below compiles all adverse events for the HIT patients in decreasing order of occurrence. Those adverse events seen with a greater frequency in the HIT argatroban group are: diarrhea, hypotension, sepsis, chest pain, apnea, vomiting, dizziness, nausea, pain, fever, cardiac arrest, constipation, purpura, multisystem organ failure, rash, and abdominal pain.

Table 41 The Most Frequent Adverse Events Experienced by HIT Patients, by Decreasing Occurrences in the Argatroban Group, During the 37-Day Study Period

Adverse Event (By Coded Term)	Body System	HIT			
		Historical Control Number of		Argatroban Number of	
		AEs	Patients (%)	AEs	Patients (%)
Total Number of Patients		147		150	
Total Number of Events		380	105 (71)	422	125 (78)
Diarrhea	Gastro-Intestinal System Disorders	3	3 (2)	17	17 (11)
Dyspnea	Respiratory System Disorders	14	13 (9)	12	12 (8)
Hypotension	Cardiovascular Disorders, General	5	5 (3)	11	11 (7)
Sepsis	Resistance Mechanism Disorders	21	20 (14)	10	10 (6)
Chest Pain	Body as a Whole - General Disorders	3	3 (2)	10	9 (6)
Apnea	Respiratory System Disorders	12	8 (5)	9	9 (6)
Vomiting	Gastro-Intestinal System Disorders	0	0 (0)	9	8 (5)
Dizziness	Central & Peripheral Nervous System Disorders	0	0 (0)	8	8 (5)
Fibrillation, Atrial	Heart Rate and Rhythm Disorders	21	21 (14)	8	7 (4)
Nausea	Gastro-Intestinal System Disorders	0	0 (0)	8	7 (4)

AEs=Adverse events
 Patient counted once per event.
 Only serious adverse events reported after the infusion period.
 Reference Documentation Appendix 15.2.41

Continued

Table 41 The Most Frequent Adverse Events Experienced by HIT Patients, by Decreasing Occurrences in the Argatroban Group, During the 37-Day Study Period (Continued)

Adverse Event (By Coded Term)	Body System	HIT			
		Historical Control Number of		Argatroban Number of	
		AEs	Patients (%)	AEs	Patients (%)
Pain	Body as a Whole - General Disorders	5	4 (3)	7	7 (4)
Fever	Body as a Whole - General Disorders	3	3 (2)	7	7 (4)
Cardiac Arrest	Heart Rate and Rhythm Disorders	2	2 (1)	7	7 (4)
Constipation	Gastro-intestinal System Disorders	1	1 (1)	7	7 (4)
Purpura	Platelet, Bleeding & Clotting Disorders	1	1 (1)	7	7 (4)
Multisystem organ failure	Body as a Whole - General Disorders	0	0 (0)	7	7 (4)
Rash	Skin and Appendages Disorders	2	2 (1)	7	6 (4)
Abdominal Pain	Gastro-intestinal System Disorders	1	1 (1)	7	6 (4)
Thrombosis	Platelet, Bleeding & Clotting Disorders	9	7 (5)	7	5 (3)
Thrombophlebitis Deep	Vascular (Extracardiac) Disorders	18	17 (12)	6	6 (4)

AEs=Adverse events
 Patient counted once per event.
 Only serious adverse events reported after the infusion period.
 Reference Documentation Appendix 15.2.41

Sponsor's table volume 28.10

Reviewer's comment: The sponsor includes chest pain in the Body as A Whole system.

The etiology of chest pain is difficult and may involve other organ systems such as cardiac, pulmonary, or esophageal.

The sponsor's table below shows the most frequent adverse events for the HITTS patients. The adverse events seen with a greater frequency in the HITTS argatroban group are: pain, peripheral ischemia, hypotension, infection, apnea, vomiting, fever, urinary tract infection, constipation, thrombophlebitis, confusion, pleural effusion, peripheral gangrene, headache, and peripheral edema, and rash.

Table 42 The Most Frequent Adverse Events Experienced by HITTS Patients, by Decreasing Occurrences in the Argatroban Group, During the 37-Day Study Period

Adverse Event (By Coded Term)	Body System	HITTS					
		Historical Control			Argatroban		
		AEs	Number of Patients (%)		AEs	Number of Patients (%)	
Total Number Of Patients		46			144		
Total Number Of Events		143	40	(87)	517	123	(85)
Pain	Body as a Whole - General Disorders	2	2	(4)	16	13	(9)
Peripheral Ischaemia	Vascular (Extracardiac) Disorders	3	3	(7)	16	12	(8)
Hypotension	Cardiovascular Disorders, General	0	0	(0)	13	13	(9)
Constipation	Gastro-Intestinal System Disorders	1	1	(2)	13	12	(8)
Infection	Resistance Mechanism Disorders	2	2	(4)	13	10	(7)
Apnoea	Respiratory System Disorders	3	3	(7)	12	12	(8)
Fever	Body as a Whole - General Disorders	1	1	(2)	12	12	(8)
Cardiac Arrest	Heart Rate and Rhythm Disorders	4	4	(9)	12	11	(8)
Urinary Tract Infection	Urinary System Disorders	2	2	(4)	12	11	(8)

AEs=Adverse events
 Patient counted once per event.
 Only serious adverse events reported after the infusion period.
 Reference Documentation Appendix 16.2.42

Continued

Table 42 The Most Frequent Adverse Events Experienced by HITTS Patients, by Decreasing Occurrences in the Argatroban Group, During the 37-Day Study Period (continued)

Adverse Event (By Coded Term)	Body System	HITTS					
		Historical Control			Argatroban		
		AEs	Number of Patients (%)		AEs	Number of Patients (%)	
Embolism Pulmonary	Platelet, Bleeding & Clotting Disorders	8	8	(13)	12	10	(7)
Thrombophlebitis	Vascular (Extracardiac) Disorders	1	1	(2)	11	10	(7)
Rash	Skin and Appendages Disorders	1	1	(2)	10	10	(7)
Sepsis	Resistance Mechanism Disorders	8	4	(9)	9	9	(6)
Thrombophlebitis Deep	Vascular (Extracardiac) Disorders	12	7	(15)	8	8	(6)
Confusion	Psychiatric Disorders	0	0	(0)	8	8	(6)
Vomiting	Gastro-Intestinal System Disorders	0	0	(0)	8	8	(6)
Pleural Effusion	Respiratory System Disorders	4	2	(4)	7	7	(5)
Peripheral Gangrene	Vascular (Extracardiac) Disorders	2	2	(4)	7	7	(5)
Headache	Central & Peripheral Nervous System Disorders	0	0	(0)	7	6	(4)
Peripheral Edema	Body as a Whole - General Disorders	0	0	(0)	7	6	(4)

AEs=Adverse events
 Patient counted once per event.
 Only serious adverse events reported after the infusion period.
 Reference Documentation Appendix 16.2.42

Sponsor's table volume 28.10

Events common to both argatroban-treated groups with a higher frequency than the historical controls are:

- hypotension
- infection/sepsis

apnea
vomiting
pain
fever
constipation
rash

Drug Related Adverse Events

The sponsor provided a listing of drug-related adverse events. The events are listed by severity and drug relation for argatroban. These investigator-determined events are listed below. This table is included because of the complexity of the underlying conditions in many of these patients. Approximately 29 (18%) of argatroban-treated patients in the HIT and 39 (27%) of patients in the HITTS group experienced an event.

Investigator-Determined Drug Related Adverse Events for ARG-911^a (definitely, probably, and possibly related)

Adverse Event	HIT Patients- number and severity	HITTS Patients- number and severity
Skin and Appendages		
Alopecia	1 (moderate)	0
Bullous Eruption	0	1 (moderate)
Rash	1 (mild) 2 (moderate)	1 (mild) 1 (moderate)
Urticaria	1 (mild)	0
Skin disorder	0	1 (moderate)
Sweating Increased	0	1 (mild)
Musculoskeletal system		
Muscle Weakness	0	1 (mild)
Myalgia	1 (moderate)	0
Central and Peripheral Nervous System		
Dizziness	2 (mild)	1 (mild)
Headache	1 (mild)	1 (mild) 1 (moderate)
Hypotonia	1 (mild)	0
Speech disorder	0	1 (mild)
Vision disorders		
Abnormal Vision	0	1 (mild)
Hearing disorders		
Deafness	0	1 (mild)
Psychiatric Disorders		
Anorexia	1 (mild)	0
Confusion	0	1 (mild) 1 (moderate)
Gastrointestinal Disorder		
Constipation	1 (mild)	2 (mild)
Diarrhea	2 (moderate)	1 (moderate)
Dysphagia	0	1 (mild)
Gastritis	1 (moderate)	0
GI hemorrhage	1 (moderate)	0
Hiccup	1 (mild)	0
Nausea	1 (mild)	2 (mild) 1 (moderate)
Vomiting	1 (mild)	1 (mild) 1 (moderate)
Liver and Biliary System		
Hepatic Failure	0	1 (severe)
Hepatic Function, abnormal	1 (severe)	1 (mild)
Hepatomegaly	0	1 (mild)
Jaundice	0	1 (mild)
SGOT Increased	0	1 (mild)

SGPT Increased	0	1 (mild)
Metabolic and Nutritional Disorders		
Hyponatremia	0	1 (moderate)
Alkaline Phosphatase Increased	0	1 (mild)
Cardiovascular Disorders		
Atrial arrhythmia	1 (moderate)	0
Atrial fibrillation	2 (moderate)	0
Tachycardia	0	1 (mild)
Ventricular Tachycardia	0	1 (moderate)
Circulatory Failure	0	1 (severe)
Hypotension	0	1 (mild) 1 (moderate)
Myocardial, Endocardial, and Valve Disorders		
Pericardial Effusion	0	1 (moderate)
Vascular (extracardiac) Disorders		
Cerebrovascular disorder	0	1 (mild)
Peripheral Ischemia	0	1 (severe)
Phlebitis	1 (mild)	1 (moderate)
Thrombophlebitis	0	1 (moderate) 1 (severe)
Thrombophlebitis (deep)	1 (moderate)	3 (moderate) 1 (severe)
Respiratory System Disorders		
Dyspnea	1 (mild)	0
Hypoxia	0	1 (moderate) 1 (severe)
Pleural effusion	0	1 (severe)
Hematological Disorders		
Anemia	2 (mild)	1 (mild)
Leukopenia	1 (mild)	0
Platelet, Bleeding, and Clotting Disorder		
Coagulation Disorder	1 (moderate) 1 (severe)	1 (severe)
Coagulation Factor decreased	1 (moderate) 1 (severe)	1 (moderate)
Limb Embolism	0	1 (mild)
Pulmonary Embolism	1 (mild)	1 (severe)
Hemorrhage, NOS	3 (severe)	1 (moderate) 1 (severe)
Prothrombin time decreased	1 (moderate) 1 (severe)	1 (severe)
Purpura	3 (mild)	2 (mild)
Thrombosis	2 (moderate)	1 (severe)
Urinary System Disorders		
Hematuria	0	1 (moderate)
Urinary Tract Infection	0	2 (mild)
Body as a whole		
Death	1 (severe)	0
Fatigue	1 (mild)	1 (mild)
Fever	0	1 (mild) 1 (severe)
Peripheral edema	1 (moderate)	0
Pain	1 (mild)	0
Syncope	0	1 (mild) 1 (severe)
Application Site Disorders		
Application Site Reaction	0	1 (mild) 1 (severe)
Injection Site Reaction	0	1 (mild) 1 (severe)
Resistance Mechanism Disorders		
Infection	0	2 (moderate)
Infection Fungal	0	1 (mild)

a Each patient counted only once per system and once per event.
Reviewer's table

Bleeding was defined as major if it

- 1) was overt and resulted in a fall in hemoglobin level ≥ 2 g/dL
- 2) led to a transfusion of 2 unites or more
- 3) was retroperitoneal
- 4) occurred into a major prosthetic joint
- 5) was intracranial

Bleeding Episodes for Study ARG-911

The incidence of investigator-determined major and minor bleeds are shown in the sponsor's table below.

Table 47 Incidence of Major and Minor Bleeds

	HIT				HITTS			
	Historical Control		Argatroban		Historical Control		Argatroban	
		(%)		(%)		(%)		(%)
Total Number of Patients	147		160		46		144	
Patients with Major Bleeds	12	(8.2)	5	(3.1)	1	(2.2)	15	(10.4)
P-value ^a	0.0784				0.124			
Odds Ratio (95% CI)	2.76 (0.95 – 8.02)				0.19 (0.02 – 1.49)			
Patients with Minor Bleeds	80	(40.8)	64	(40.0)	19	(41.3)	60	(41.7)

^a P-value based on Fisher's exact test.

Patients having an event are counted once.

Reference Documentation Appendices 16.1.9 (Table 1A22 and 1B22) and 16.2.46.

Sponsor's table volume 28.10

There were more major bleeds in the argatroban-treated HITTS patients than in the historical control HITTS patients. However, only 8 bleeds in the argatroban group were adjudicated as major by the DMSC. During argatroban infusion there were 2 optic bleeds (mild) for HIT patients and 1 optic bleed (mild) for the HITTS patients.

Intracranial bleeds

One HITTS argatroban patient (029-003) suffered an intracranial bleed. This patient was not discovered during the in-house quality control process and was not reviewed by DMSC therefore does not appear in the statistics. The patient underwent CABG and post-operatively was noted to be thrombocytopenic on heparin. He was discharged home on steroids. He returned a few days later with severe peripheral edema. The patient was readmitted after extensive DVT was diagnosed. The patient received urokinase after the extensive clot extending from the popliteals bilaterally to the right atrium did not resolve on argatroban infusion and warfarin. The patient died several days later of an intracranial hemorrhage. The investigator did not think that the intracranial hemorrhage was related to study drug and wrote a letter to that effect which was included in the NDA (Appendix 16.2.46.1).

An intracranial bleed resulting in death was also seen in the historical controls. Patient L20-117 was admitted and found to have a pituitary tumor on March 31, 1992. She underwent resection of the mass and post-operatively was placed on heparin. Eleven days later when found to be HIPA positive, heparin was discontinued. Patient died twelve days post-operatively. CT scan revealed an infarction and hematoma.

Transfusions

The overall percentage of HIT and HITTS patients receiving blood transfusion was lower for the argatroban-treated groups compared to the historical controls. The data are shown in the following tables provided by the sponsor.

Table 51 Number and Percentage of HIT Patients Receiving a Blood Transfusion

	HIT					
	Historical Control			Argatroban		
	Number of		Transfusions	Number of		Transfusions
Transfusions	Patients ^a	Transfusions		Patients ^a		
	N	(%)	N	(%)		
Total Number of Patients	147		160			
During The Treatment Period						
Total Transfusions	496	98 (66.7)	177	59	(36.9)	
Blood Component Used:						
PRBC	212	80 (54.4)	116	52	(32.5)	
Platelets	117	60 (40.8)	20	8	(5.0)	
Fresh Frozen Plasma	75	42 (28.6)	27	10	(6.3)	
Other	72	31 (21.1)				
Cryoprecipitate	18	14 (9.5)	5	3	(1.9)	
Autotransfusion	2	2 (1.4)				
Whole Blood	2	1 (0.7)				
PRBC-Leukoreduced			4	1	(0.6)	
Plasma Protein Fraction			3	2	(1.3)	
Plasmanate			1	1	(0.6)	
Platelet Pheresis			1	1	(0.6)	

^a A patient is counted once per transfusion of blood component.

^b Through 30 days of follow-up for the argatroban patients.

Reference Documentation Appendix 16.2.50

continued

Table 51 Number and Percentage of HIT Patients Receiving a Blood Transfusion (continued)

	HIT					
	Historical Control			Argatroban		
	Number of		Transfusions	Number of		Transfusions
Transfusions	Patients ^a	Transfusions		Patients ^a		
	N	(%)	N	(%)		
Post Treatment ^b						
Total Transfusions			58	11	(6.9)	
Blood Component Used:						
PRBC			17	9	(5.6)	
Fresh Frozen Plasma			14	6	(3.8)	
PRBC-Leukoreduced			8	1	(0.6)	
Platelets			7	6	(3.8)	
Plasmanate			4	1	(0.6)	
Cryoprecipitate			3	3	(1.9)	
Plasma Protein Fraction			3	1	(0.6)	
Platelets-Leukoreduced			2	1	(0.6)	

^a A patient is counted once per transfusion of blood component.

^b Through 30 days of follow-up for the argatroban patients.

Reference Documentation Appendix 16.2.50

Table 52 Number and Percentage of HITTS Patients Receiving a Blood Transfusion

	HITTS				
	Historical Control			Argatroban	
	Number of		Patients ^a	Number of	
	Transfusions	N		Transfusions	Patients ^a
		(%)	N	(%)	
Total Number Of Patients		46		144	
During The Treatment Period					
Total Transfusions	119	31	(67.4)	209	69 (47.9)
Blood Component Used:					
Packed RBC	54	26	(56.5)	135	60 (41.7)
Platelets	32	18	(39.1)	16	12 (8.3)
Other	18	6	(13.0)		
Fresh Frozen Plasma	13	8	(17.4)	47	19 (13.2)
Cryoprecipitate	1	1	(2.2)	1	1 (0.7)
Albumin				5	3 (2.1)
Autotransfusion				3	2 (1.4)
Platelets, Single Donor				1	1 (0.7)
Unknown				1	1 (0.7)
IgG, Hi-Dose IV					
Antithrombin					
Erythropoietin					
Post Treatment ^b					
Total Transfusions	2	2	(4.4)	52	19 (13.2)
Blood Component Used:					
Packed RBC	2	2	(4.4)	29	16 (11.1)
Fresh Frozen Plasma				14	5 (3.5)
Antithrombin III				5	2 (1.4)
Platelets				2	2 (1.4)
Cryoprecipitate				1	1 (0.7)
Red Cell Additive				1	1 (0.7)

^a A patient is counted once per transfusion of blood component.
^b Through 30 days of follow-up for the argatroban patients.
 Reference Documentation Appendix 16.2.51

Sponsor's tables volume 28.10

During the treatment period, the historical control patients required more transfusions than the argatroban-treated patients. There was no information on the post-treatment period for the historical control HIT patients. Post-treatment argatroban treated HITTS patients required more transfusions than the historical control HITTS patients. The information on the post-treatment transfusion record for the historical control group may suffer from underreporting bias due to the retrospective data collection.

Clinical Laboratory Evaluation

The aPTT level was used to monitor anticoagulation in the argatroban-treated patients for Study ARG-911. With the first dose of argatroban at 2 µg/kg/min, 57% and 55% of the HIT and HITTS patients respectively had aPTT level between 45 and 90 seconds. Few patients had aPTT levels that were greater than 90 seconds, only 8% of the HIT and 12% of the HITTS patients reached that level.

Laboratory Parameters Adverse Events

Review of laboratory data did not reveal any particular toxicity in the significantly ill patient population treated with argatroban. Changes from baseline to post-infusion or discharge were not

significant between the historical control and argatroban treated patients for liver function tests, renal function tests or hemoglobin results. Patients in both groups received red blood cell and platelet transfusions.

No significant changes in vital signs such as blood pressure, heart rate or respiratory rate were noted between the historical control and argatroban treated group.

Study ARG-915

Drug Exposure for ARG-915

The majority of patients received an infusion rate of $< 3.0 \mu\text{g}/\text{kg}/\text{min}$. This is consistent with the sponsor's intended use of the drug.

PROTOCOL 915
AVERAGE DOSE OF ARGATROBAN ADMINISTERED OVER THE COURSE OF THE STUDY

AVERAGE DOSE (D) ($\mu\text{g}/\text{kg}/\text{min}$)	RTT	BITTS
	n (%)	n (%)
TOTAL NUMBER OF PATIENTS	125 (100%)	139 (100%)
0.1 - 0.5	7 (6%)	11 (8%)
>0.5 - 1.0	17 (14%)	22 (16%)
>1.0 - 2.0	46 (37%)	41 (29%)
>2.0 - 3.0	28 (22%)	26 (19%)
>3.0 - 4.0	2 (2%)	11 (8%)
>4.0 - 5.0	5 (4%)	4 (3%)
> 5.0	1 (1%)	3 (2%)
UNABLE TO CALCULATE	19 (15%)	21 (15%)
MEAN (SE)	1.8 (0.1)	1.9 (0.1)

Sponsor's table volume 28.42

The table below outlines the mean dosage and duration of the drug during Study ARG-915. The sponsor states that ten patients received heparin while on argatroban. The majority of patients who received heparin received the drug for less than one to two days or as a medication error. The majority of those patients who received heparin during this study experienced an endpoint.

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Table 7 Mean Dosage and Duration of Administration of Argatroban

Parameter	HIT (N = 125)	HITS (N = 139)
Mean Argatroban Dose ($\mu\text{g}/\text{kg}/\text{min}$) ^a	N = 106 1.8 \pm 0.1	N = 118 1.9 \pm 0.1
Mean Duration of Argatroban Therapy (days)	N = 118 5.1 \pm 0.4	N = 129 7.2 \pm 0.6
Days Since Heparin discontinuation ^b	N = 101 1.4 \pm 0.2	N = 124 2.2 \pm 0.3

Values are as mean \pm SE.

^a Average Dose=Sum of all volumes times 1000 $\mu\text{g}/\text{mL}$ divided by pre-physical exam body weight divided by total number of minutes patient received argatroban infusion. Excludes patients where average dose could not be determined.

^b Excludes 10 patients where heparin was administered after start of argatroban, 2 patients with missing heparin dates, and 27 patients who did not receive heparin.

Appendix 16.2.4.1

Sponsor's table volume 28.32

Overall Adverse Events for ARG-915

Patient number	New historical control /HIT	Argatroban/ HIT	New Historical Control / HITT	Argatroban/ HITT
Overall 37 day period	105/147 (71%)	81/125 (65%)	40/46 (87%)	101/138 (73%)

Reviewer's table

Deaths

The table below includes patients who died after the 37-day period.

Investigator's Determination of All-Known Death

Type of Death	Argatroban treated (N=264)	New historical controls (N=193)
Cancer	1	1
Cardiovascular		
Cardiac Arrest	12	2
Cardiac / Circulatory Failure	3	8
Myocardial infarction	3	1
Ventricular Tachycardia	0	2
Cerebrovascular Disorder	3	3
Disseminated Intravascular Coagulation	1	0
Encephalopathy	1	1
Gastrointestinal Perforation	1	0
Hemorrhage	0	1
Hepatic Failure	1	1
Inhalation Injury	0	1
Metabolic	1	0
Multiple System Organ Failure	1	1
Obstruction/Necrosis, Intestinal	3	2
Pancreatitis	1	0
Renal Failure, abnormal	2	1
Respiratory		
Apnea	0	3
Pleural effusion	0	0
Other respiratory	13	5
Sepsis	6	7
Thrombosis	2	4
Unknown/Unable to tell from records	7	1

Reviewer's table

Most Frequent Adverse Events for Study ARG-915

Five percent or more of the HIT patients experienced the following adverse events: dyspnea (9%), ventricular tachycardia (7%), nausea (6%), fever (6%), and hypotension (5%).

The table below outlines the most frequent adverse events experienced by > 5% of HITTS patients for Study ARG-915. These events are similar to those seen for Study ARG-911.

Table 15 The Most Frequent Adverse Events Experienced by ≥5% of HITTS Patients

Adverse Event	Body System	HITTS		
		Number of		
		AEs	Patients	(%)
Total Number of Patients ^a		136 ^c		
Total Number of Events ^b		460	101	(73)
Dyspnoea	Respiratory System Disorders	17	17	(12)
Fever	Body as a Whole - General Disorders	14	13	(9)
Cardiac Arrest	Heart Rate and Rhythm Disorders	13	11	(8)
Septis	Resistance Mechanism Disorders	12	11	(8)
Hypotension	Cardiovascular Disorders, General	11	11	(8)
Peripheral Ischaemia	Vascular (Extracardiac) Disorders	11	8	(6)
Diarrhoea	Gastro-Intestinal System Disorders	9	9	(7)
Nausea	Gastro-Intestinal System Disorders	8	8	(6)
Respiratory Insufficiency	Respiratory System Disorders	8	8	(6)
Renal Failure Acute	Urinary System Disorders	8	7	(5)
Pneumonia	Respiratory System Disorders	7	7	(5)
Tachycardia Ventricular	Heart Rate and Rhythm Disorders	7	7	(5)
Cardiac Failure	Cardiovascular Disorders, General	7	7	(5)

AEs=Adverse events through 30 days of follow-up.
^a Patient counted once per event.
^b Only serious adverse events reported after the infusion period.
^c An adverse event record was unavailable for one HITTS patient.
 Reference Documentation Appendices 16.2.13.2 and 16.4.1.1-16.4.1.8

Sponsor's table volume 28.32

The table below shows the investigator-determined adverse events for Study ARG-915. This table is presented because of the complex medical conditions present in the study patients.

Investigator's Determined of Adverse Events for Study ARG-915

Adverse Event	HIT Patients- number and severity	HITTS Patients- number and severity
Skin and Appendages		
Wound Drainage Increased	1 (moderate)	
Sweating Increased	1 (mild)	
Psychiatric Disorders		
Anorexia		1 (moderate)
Gastrointestinal Disorder		
Constipation		1 (mild)
Gastritis		1 (moderate)
GI hemorrhage	1 (mild)	
Hiccup		
Nausea	1 (mild) 1 (moderate)	
Vomiting		1 (moderate)
Liver and Biliary System		
Hepatic Function, abnormal		1 (mild)

		1 (moderate)
Metabolic and Nutritional Disorders		
Hypoglycemia		1 (moderate)
Renal Disorders		
Failure		1 (severe)
Cardiovascular Disorders		
Atrial arrhythmia		1 (severe)
Tachycardia	1 (mild)	
Circulatory Failure		
Myocardial Infarction		1 (severe)
Hypertension		1 (moderate)
Hypotension	1 (moderate)	
Vascular (extracardiac) Disorders		
Thrombophlebitis (deep)		1 (moderate)
Respiratory System Disorders		
Dyspnea		1 (severe)
Hypoxia		1 (severe)
Hematological Disorders		
Anemia	1 (mild)	
Platelet, Bleeding, and Clotting Disorder		
Coagulation Factor increased		2 (moderate)
Hemorrhage, NOS	1 (mild)	
Prothrombin time decreased		1 (moderate)
Thrombocytopenia	1 (mild) 1 (moderate)	1 (moderate)
Thrombosis	1 (moderate)	
Urinary System Disorders		
Hematuria	1 (moderate)	1 (moderate)
Body as a whole		
Fever	1 (moderate)	1 (moderate)
Insomnia		1 (moderate)
Pain		1 (moderate)
Resistance Mechanism Disorders		
Infection		1 (moderate)
Infection Fungal		1 (moderate)

Reviewer's table

Bleeding was defined as major if it:

- 1) was overt and resulted in a fall in hemoglobin level ≥ 2 g/dL
- 2) led to a transfusion of 2 unites or more
- 3) was retroperitoneal
- 4) occurred into a major prosthetic joint
- 5) was intracranial

Major Bleeding Episodes for Study ARG-915

Parameter	HIT/ Historical controls	HIT/ Argatroban-treated	HITTS/ Historical Controls	HITTS/ Argatroban-treated
Total number of patients	147	125	46	139
Major bleeding	12 (8.2%)	4 (3.2%)	1 (2.2%)	6 (4.3%)
Minor bleeding	60 (40.8%)	37 (29.6%)	19 (41.3%)	60 (43.5%)

Reviewer's table

Transfusions

The overall percentage of HIT and HITTS patients receiving a blood transfusion was lower for the argatroban-treated groups compared to the historical controls. The tables below show the transfusion rate for the argatroban-treated group. The rates are similar for the argatroban-treated

HIT patients in Study ARG-911 except for the increased platelet transfusions and fresh frozen plasma transfusions in Study ARG-915. There was a slightly higher use of transfusions for the argatroban-treated HITTS patients in Study ARG-911 compared to Study ARG-915.

Table 18 Number and Percentage of HIT and HITTS Patients Receiving a Blood Transfusion

	HIT		HITTS		TOTAL	
	Number of		Number of		Number of	
	Transfusions	Patients ^a (%)	Transfusions	Patients ^a (%)	Transfusions	Patients ^a (%)
Total Number of Patients	125		139		264	
During the Treatment Period						
Total Transfusions	148	45 (36.0)	219	73 (52.5)	367	118 (44.7)
Blood Component Used:						
PRBC	90	40 (32.0)	153	85 (48.8)	243	105 (39.8)
Platelets	24	13 (10.4)	34	15 (10.8)	58	28 (10.6)
Fresh Frozen Plasma	23	14 (11.2)	18	10 (7.2)	41	24 (9.1)
Cryoprecipitate	2	2 (1.6)	1	1 (0.7)	3	3 (1.1)
Autotransfusion	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)
Other, Unspecified	9	6 (4.8)	12	4 (2.9)	21	10 (3.8)
Post Treatment ^b						
Total Transfusions	4	4 (3.2)	8	5 (3.6)	12	9 (3.4)
Blood Component Used:						
PRBC	3	3 (2.4)	4	4 (2.9)	7	7 (2.7)
Fresh Frozen Plasma	1	1 (0.8)	3	1 (0.7)	4	2 (0.7)
Cryoprecipitate	0	0 (0.0)	1	1 (0.7)	1	1 (0.4)

^a A patient is counted once per transfusion of blood component.

^b Through 30 ± 7 days of follow-up.

Sponsor's table volume 28.32

During the treatment period, the historical control patients required more transfusions than the argatroban-treated patients. The sponsor did not provide information on the post-treatment period for the historical control HIT patients. Post-treatment argatroban-treated HITTS patients required more transfusions than the historical control HITTS patients. The information on the post-treatment transfusion record for the historical control group may suffer from underreporting bias due to the retrospective data collection. Because of the inadequacy of the data, no significant comparisons can be made between the historical control and the argatroban-treated patients.

Safety Evaluation from Other Clinical Trials (Including studies in healthy volunteers, specialized populations, randomized studies, and open-label studies)

Withdrawals

The table below shows withdrawals from all studies.

Table 3 Summary of Primary Reasons for Withdrawal for All Argatroban Subjects/Patients

Reason for Premature Discontinuation ^a	Argatroban Subjects/Patients							
	Studies in Healthy Volunteers ^b		Special Population Phase I Studies ^c		Randomized Studies ^d		Open-label Studies ^e	
	N	(%)	N	(%)	N	(%)	N	(%)
Total Number of Patients	128	(100)	41		817	(100)	653	(100)
Number of Patients Withdrawn	6	(4.7)	0	(0)	24	(2.9)	92	(14)
Significant Adverse Event	2	(1.8)	0	(0)	3	(0.4)	33	(5.1)
Surgery	0	(0)	0	(0)	0	(0)	11	(1.7)
Intercurrent Illness	0	(0)	0	(0)	0	(0)	4	(0.6)
Clinical Efficacy of Drug	0	(0)	0	(0)	15	(1.8)	2	(0.3)
Insufficient/Lacking								
Protocol Violation	1	(0.8)	0	(0)	0	(0)	1	(0.2)
Patient Request to Withdraw	1	(0.8)	0	(0)	6	(0.7)	4	(0.6)
Other					0	(0)	37	(5.7)
Elevated ACT or aPTT Levels	2	(1.6)	0	(0)	0	(0)	4	(0.6)

^a Patients may be included in more than one group.

^b Studies: ARG-100, 101, 102, 105, 108, 109, 112

^c Studies: ARG-103, 106

^d Studies: ARG-210, 230, 231, 912

^e Studies: ARG-216, 240, 310, 911, 915

Reference Documentation Appendix 19.1.4

Sponsor's table volume 28.55

One of the argatroban-treated withdrawals in the healthy population was due to a rash.

The table below shows the causes for premature discontinuation for the randomized clinical trial population.

Table 35 Treatment-Emergent Adverse Events Leading to Premature Discontinuation by Patients in Randomized Studies by Body System

Adverse Event ^{a,b}	Active Control		Placebo		Argatroban	
	N	(%)	N	(%)	N	(%)
Total Number of Patients	45	(100)	366	(100)	817	(100)
Number of Patients with an Event	8	(18)	28	(7.7)	90	(11)
Platelet, Bleeding and Clotting Disorders	6	(13)	2	(0.5)	9	(1.1)
Embolism Pulmonary	1	(2.2)	0	(0.0)	0	(0.0)
Gingival Bleeding	1	(2.2)	0	(0.0)	3	(0.4)
Haemorrhage NOS	3	(8.7)	1	(0.3)	3	(0.4)
Coagulation Factor Decreased	1	(2.2)	0	(0)	0	(0)
Epistaxis	0	(0)	0	(0)	2	(0.2)
Prothrombin Increased	0	(0)	0	(0)	1	(0.1)
Thrombocytopenia	0	(0)	1	(0.3)	1	(0.1)
Myo-Endo-Pericardial & Valve Disorders	2	(4.4)	11	(3.0)	29	(3.5)
Angina Pectoris	0	(0)	2	(0.5)	1	(0.1)
Coronary Artery Disorder	1	(2.2)	0	(0)	0	(0)
Myocardial Infarction	0	(0)	4	(1.1)	12	(1.5)
Myocardial Ischaemia	1	(2.2)	6	(1.6)	14	(1.7)
Thrombosis Coronary	0	(0)	0	(0)	3	(0.4)

Studies: ARG-210, 230, 231, 912

^a Patient counted once per body system and once per event.

^b WHO Term

Reference Documentation Appendix 19.1.55

Sponsor's table volume 28.55

Thirty-seven (5.7%) withdrawals occurred in the open-label studies. The table below shows selected premature discontinuations occurring in more than 1 patient in the open-label studies provided by the sponsor.

Withdrawals in Open-label studies

Event	Number
Platelet, Bleeding, and Clotting disorders	12 (1.8%)
Hemorrhage, NOS	3 (0.5%)
Coagulation Disorder	2 (0.3)
Coagulation Factor Decreased	1 (0.2%)
Coagulation Time Increased	1 (0.2%)
DIC	2 (0.3%)
Pulmonary Embolism	1 (0.2%)
Thrombocytopenia	2 (0.3%)
Thrombosis	1 (0.2%)
Heart rate and rhythm	6 (0.9%)
Cardiac Arrest	2 (0.3%)
Arrhythmia	1 (0.2%)
Bradycardia	1 (0.2%)
Tachycardia	1 (0.2%)
Ventricular tachycardia	1 (0.2%)
Anemia	2 (0.3%)
Death	2 (0.3%)

Reviewer's table

Deaths

No deaths were observed in healthy volunteers or the special population patients.

The table below shows incidence and cause of deaths from all the randomized studies. Cardiovascular causes are the most frequent. No conclusions can be drawn as the majority of patients in these trials had a pre-existing cardiac condition.

Table 25 Summary of Deaths for Patients in Randomized Studies

Treatment Cause of Death ^a	On Therapy		Post Therapy ≤37 Days	
	N	(%)	N	(%)
Argatroban				
Total Number of Patients	817	(100.0)	783	(100.0)
Number of Patients that Died	34	(4.2)	27	(3.4)
Cardiac Arrest	16	(2.0)	10	(1.3)
Circulatory Failure	15	(1.8)	10	(1.3)
Myocardial Infarction	5	(0.6)	5	(0.6)
Fibrillation Ventricular	5	(0.6)	0	(0.0)

Studies: ARG-210, 230, 231, 912

Patient no. 408-A69 from Study ARG-230 was not included in this table because he died >37 days post therapy.

^a A patient may have more than one cause of death.

Reference Documentation Appendix 19.1.34

Continued

Table 25 Summary of Deaths for Patients in Randomized Studies (Continued)

Treatment Cause of Death ^a	On Therapy		Post Therapy ≤37 Days	
	N	(%)	N	(%)
Argatroban (Continued)				
Apnea	2	(0.2)	1	(0.1)
Injection Site Reaction	2	(0.2)	0	(0.0)
Cerebrovascular Disorder	1	(0.1)	2	(0.3)
Dyspnea	1	(0.1)	2	(0.3)
Adams Stokes Syndrome	1	(0.1)	1	(0.1)
AV Block	1	(0.1)	1	(0.1)
Hemorrhage NOS	1	(0.1)	1	(0.1)
Acidosis	1	(0.1)	0	(0.0)
Bradycardia	1	(0.1)	0	(0.0)
Cardiac Failure Right	1	(0.1)	0	(0.0)
Gingival Bleeding	1	(0.1)	0	(0.0)
Hematuria	1	(0.1)	0	(0.0)
Hemoptysis	1	(0.1)	0	(0.0)
Heart Block	1	(0.1)	0	(0.0)
Hyperglycemia	1	(0.1)	0	(0.0)
Hypotension	1	(0.1)	0	(0.0)
Hypoventilation	1	(0.1)	0	(0.0)
Nervousness	1	(0.1)	0	(0.0)
Pericardial Effusion	1	(0.1)	0	(0.0)
Pulmonary Edema	1	(0.1)	0	(0.0)
Stupor	1	(0.1)	0	(0.0)
Tachycardia Ventricular	1	(0.1)	0	(0.0)
Renal Function Abnormal	0	(0.0)	2	(0.3)
Arrhythmia	0	(0.0)	1	(0.1)
BUN Increased	0	(0.0)	1	(0.1)
Cardiac Failure	0	(0.0)	1	(0.1)
Cyanosis	0	(0.0)	1	(0.1)
Death	0	(0.0)	1	(0.1)
Embolism Pulmonary	0	(0.0)	1	(0.1)

Studies: ARG-210, 230, 231, 912

Patient no. 408-A69 from Study ARG-230 was not included in this table because he died >37 days post therapy.

^a A patient may have more than one cause of death.

Reference Documentation Appendix 19.1.34

Continued

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Table 25 Summary of Deaths for Patients in Randomized Studies (Continued)

Treatment Cause of Death*	On Therapy		Post Therapy ≤37 Days	
	N	(%)	N	(%)
Argatroban (Continued)				
Fever	0	(0.0)	1	(0.1)
Fibrillation Atrial	0	(0.0)	1	(0.1)
NPN Increased	0	(0.0)	1	(0.1)
Pallor	0	(0.0)	1	(0.1)
Sepsis	0	(0.0)	1	(0.1)
Sepsis Secondary	0	(0.0)	1	(0.1)
Sweating Increased	0	(0.0)	1	(0.1)
Urinary Tract Infection	0	(0.0)	1	(0.1)

Studies: ARG-210, 230, 231, 912

Patient no. 408-A68 from Study ARG-230 was not included in this table because he died >37 days post therapy.

* A patient may have more than one cause of death.

Reference Documentation Appendix 19.1.34

Revised Sponsor's table volume 28.55

The table below shows the incidence and cause of deaths from the open-label studies.

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Table 26 Summary of Deaths for Argatroban Patients in Open-label Studies

Cause of Death ^a	Argatroban			
	On Therapy ^b		Post Therapy ^c ≤37 Days	
	N	(%)	N	(%)
Total Number of Patients	653	(100.0)	621	(100.0)
Number of Patients that Died	32	(4.9)	88	(14.2)
Cardiac Arrest	10	(1.5)	14	(2.3)
Death	4	(0.6)	13	(2.1)
Myocardial Infarction	2	(0.3)	3	(0.5)
Acidosis	2	(0.3)	0	(0.0)
Apnea	1	(0.2)	8	(1.3)
Sepsis	1	(0.2)	7	(1.1)
Circulatory Failure	1	(0.2)	2	(0.3)
Aspiration	1	(0.2)	1	(0.2)
Cardiomyopathy	1	(0.2)	1	(0.2)
Disseminated Intravascular Coagulation	1	(0.2)	1	(0.2)
Encephalopathy	1	(0.2)	1	(0.2)
Hypotension	1	(0.2)	1	(0.2)
Arrhythmia	1	(0.2)	0	(0.0)
ECG Abnormal	1	(0.2)	0	(0.0)

Studies: ARG-216, 240, 310, 911, 915

Patient nos. 059-007, 081-001, 129-001 from Study ARG-911 and patient nos. 150-001 and 114-007 from Study ARG-915 were not included in this table because their deaths were >37 days.

- ^a A patient may have more than one cause of death.
- ^b On treatment period = first week.
- ^c Post treatment=ensuing 30 days.

Reference Documentation Appendix 19.1.35

Continued

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Table 26 Summary of Deaths for Argatroban Patients in Open-label Studies
(Continued)

Cause of Death ^a	Argatroban			
	On Therapy ^b		Post Therapy ^c ≤37 Days	
	N	(%)	N	(%)
Fibrillation Ventricular	1	(0.2)	0	(0.0)
Hypertension Intracranial	1	(0.2)	0	(0.0)
Intestinal Necrosis	1	(0.2)	0	(0.0)
Pulmonary Edema	1	(0.2)	0	(0.0)
Respiratory Depression	1	(0.2)	0	(0.0)
Respiratory Insufficiency	0	(0.0)	5	(0.8)
Dyspnea	0	(0.0)	4	(0.6)
Pneumonia	0	(0.0)	3	(0.5)
Cardiac Failure Right	0	(0.0)	2	(0.3)
Hepatic Failure	0	(0.0)	2	(0.3)
Renal Function Abnormal	0	(0.0)	2	(0.3)
Respiratory Disorder	0	(0.0)	2	(0.3)
Adenocarcinoma NOS	0	(0.0)	1	(0.2)
Bradycardia	0	(0.0)	1	(0.2)
Cardiac Failure	0	(0.0)	1	(0.2)
Cerebrovascular Disorder	0	(0.0)	1	(0.2)
Colon Carcinoma	0	(0.0)	1	(0.2)
Convulsions	0	(0.0)	1	(0.2)
Drug Abuse	0	(0.0)	1	(0.2)
Duodenal Ulcer Perforated	0	(0.0)	1	(0.2)
Embolism Pulmonary	0	(0.0)	1	(0.2)
Hemorrhage Intracranial	0	(0.0)	1	(0.2)
Hemorrhage NOS	0	(0.0)	1	(0.2)
Intestinal Ischemia	0	(0.0)	1	(0.2)
Intestinal Obstruction	0	(0.0)	1	(0.2)

Table 26 Summary of Deaths for Argatroban Patients in Open-label Studies
(Continued)

Cause of Death ^a	Argatroban			
	On Therapy ^b		Post Therapy ^c ≤37 Days	
	N	(%)	N	(%)
Pancreatitis	0	(0.0)	1	(0.2)
Pleural Effusion	0	(0.0)	1	(0.2)
Pneumonitis	0	(0.0)	1	(0.2)
Renal Failure Acute	0	(0.0)	1	(0.2)
Sepsis Secondary	0	(0.0)	1	(0.2)
Tachycardia Supraventricular	0	(0.0)	1	(0.2)
Tachycardia Ventricular	0	(0.0)	1	(0.2)

Sponsor's table from volume 28.55

Serious Adverse Events

No serious adverse events were observed in healthy volunteers or the special population patients. Serious adverse events in randomized trials are listed below. These patients were all part of pilot cardiac intervention trials. The table below shows the increased percentages of argatroban-treated patients experiencing Cardiovascular Disorders in general, Myo Endo Pericardial and Valve disorders, and Heart Rate and Rhythm Disorders.

Table 31 Summary of Serious Adverse Events for Patients in Randomized Studies

Body System/Adverse Event ^{a, b}	Active Control		Placebo		Argatroban	
	N	(%)	N	(%)	N	(%)
Total Number of Patients	45		366		817	
Number of Patients with an Event	11	(24)	89	(24)	229	(28)
Cardiovascular Disorders, General	2	(4.4)	24	(6.6)	61	(7.5)
Myo Endo Pericardial & Valve Disorders	5	(11)	41	(11)	109	(13)
Myocardial Infarction	0	(0)	13	(3.6)	38	(4.7)
Myocardial Ischaemia	4	(8.9)	28	(7.7)	63	(7.7)
Heart Rate and Rhythm Disorders	2	(4.4)	14	(3.8)	49	(6.0)
Fibrillation Ventricular	2	(4.4)	5	(1.4)	14	(1.7)
Platelet, Bleeding & Clotting Disorders	2	(4.4)	13	(3.6)	19	(2.3)
Embolism Pulmonary	1	(2.2)	0	(0)	0	(0)

Studies: ARG-210, 230, 231, 912

^a Patient counted once per body system and once per event.

^b WHO Term

Reference Documentation Appendix 19.1.50

Sponsor's table volume 28.55

Serious adverse events in randomized trials are listed below. These patients had a high incidence of pre-existing cardiac disease. No further comparison can be made.

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Table 32 Summary of Serious Adverse Events (≥5%) for Patients in Open-label Studies

Serious Adverse Event ^{a,b,c}	Argatroban	
	N	(%)
Total Number of Patients	653	
Number of Patients with an Event	253	(39)
Heart Rate and Rhythm Disorders	45	(8.9)
Cardiac Arrest	33	(5.1)
Vascular (Extracardiac) Disorders	67	(10)
Respiratory System Disorders	56	(8.6)
Platelet, Bleeding & Clotting Disorders	46	(7.0)
Body as a Whole -General Disorders	37	(5.7)

Studies: ARG-216, 240, 310, 911, 915

^a Patient counted once per body system and once per event.

^b WHO Term

^c The data for historic controls were collected retrospectively and serious adverse events were not collected for this population.

Reference Documentation Appendix 19.1.51

Sponsor's table volume 28.55

Serious Adverse Events Outside the United States

A retrospective survey in Japan was collected from 1991 to March 1998. The overall incidence of adverse events is 4.42%. The highest incidence was observed in the liver and biliary system (1.45%) followed by platelet, clotting, and bleeding disorders (1.10%).

Safety Update

The sponsor has submitted a safety update for the period of March 1997 to August 1998 for the following studies: ARG-311 and 915X.

Study ARG-311

Fifty-four patients entered this study as of August 3, 1998. Seven of these patients repeated in this study. Five patients did not undergo a planned cardiovascular interventional procedure. There were no fatal events reported.

Seven serious adverse events were identified out of 61 exposures. The serious adverse events occurred with 11.5% of the exposures. They are listed in the table below.

Serious Adverse Events for Study ARG-311

ID number	Serious Adverse Event	Severity	Outcome	Sponsor's assessment of causality	FDA reviewer's assessment of causality
027-002	Reocclusion of proximal RCA	Severe	Resolved	Possible	Possible
012-004	Non-Q-wave Myocardial Infarction	Moderate	Resolved	Unlikely	Unlikely
024-002	Fever secondary to enterococcus	Moderate	Resolved	Unlikely	Unlikely but Case report not provided
010-001	Impending closure right PDA	Mild	Resolved	Unrelated	Unrelated
012-011	Gastrointestinal Esophageal Reflux Disease	Mild	Resolved	Unrelated	Unlikely
020-002	Dyspnea / EKG changes	Severe	Resolved	Unrelated	Unlikely
020-003	Severe internal carotid stenosis	Moderate	Resolved	Unrelated	Unrelated

Reviewer's table

There were no major bleeding events.

Study ARG-915X

One hundred and ninety two patients entered the study up until August 3, 1998. Twenty-two patients received at least one repeat course. A total of 214 patient exposures occurred.

Major bleeding was defined as:

- 1) overt and associated with a greater than 2 gram/dl decrease in hemoglobin
- 2) leading to a transfusion of 2 or more units of packed red blood cells
- 3) retroperitoneal, intracranial
- 4) into a major prosthetic joint

Information on bleeding events was collected during the argatroban infusion and over the thirty-day period after cessation of the administration of argatroban.

One hundred and one patients (91 primary and 10 retreated patients) experienced at least one serious adverse event. Thus there were at least 47.2 % serious adverse events among the 214 patient exposures.

Serious Adverse Events for Study ARG-915X

Serious Adverse Event	Primary Patient N=170 (patient number/percent)	Retreated Patient N=22 (patient number/percent)
Total	147 (86.5%)	12 (54.5%)
Major Bleeding	18	3
Deaths	40 (23.5%)	1 (4.5%)
Non-fatal	70 (41.2%)	8 (36.4%)
Multiple events	25 (14.7%)	1 (4.5%)

Reviewer's table

Review of Deaths for ARG-915X

ID number	Serious Adverse Event prior to Death	Site investigator's / Sponsor's assessment of causality (drug-related death)	FDA assessment of causality (drug-related death)	Critically ill
088-007	Multisystem organ failure	Possibly	Possibly	Yes
142-002	Bleeding/gastrointestinal	Possibly	Possibly	Yes, this patient had multiple causes for her death, GI bleed was only one of them
014-003	Multisystem organ failure (MSOF)	Unlikely	Unlikely	Yes
020-005	Cerebrovascular Accident (CVA)	Unlikely	Unlikely	Yes
022-001	Possible pulmonary embolus	Unlikely	Unlikely	Met cancer / hypercoagulable state
040-002	Adult Respiratory Distress Syndrome (ARDS)	Unlikely	Unlikely	Yes
113-009	Extensive Limb ischemia	Unlikely	No case synopsis provided	Unable to judge
145-001	Hepato-renal syndrome	Unlikely	Unlikely	Yes
153-001	Paroxysmal Nocturnal Hemoglobinuria	Unlikely	Unlikely	Yes, multiple causes for her death.
006-102	Cardiac arrhythmia	Unrelated	Unrelated	Yes
011-002	MSOF	Unrelated	Unrelated	Yes
015-002/102	Anoxic Brain Injury	Unrelated	Unrelated	
020-019	Enterobacter pneumonia	Unrelated	Unrelated	
029-002	Respiratory Arrest	Unrelated	Unlikely	Yes
037-204	HIT	Unrelated	Unlikely	Yes, had three prior treatments with argatroban successfully
039-001	Thermal Inhalation Injury	Unrelated	Unlikely	Yes
052-003	Coronary Artery Disease	Unrelated	Not enough information to judge	
052-004	Sepsis	Unrelated	Unlikely	Seriously but not critically
063-002	Cardiopulmonary Arrest	Unrelated	Unlikely	Yes
063-003	Cardiogenic Shock	Unrelated	Unlikely	Yes
066-002	Metastatic Cancer	Unrelated	Unlikely	
068-004	CVA	Unrelated	Unlikely	
069-002	Aspiration pneumonia	Unrelated	Unlikely	
088-005	Cardiopulmonary Arrest	Unrelated	Unlikely	
088-006	MSOF	Unrelated	Unlikely	

100-002	MSOF	Unrelated	Unlikely	Yes
113-007	Cardiogenic Shock	Unrelated	Unrelated	Yes
113-008	Sepsis	Unrelated	Not enough information to judge	
114-004	Sepsis	Unrelated	Not enough information to judge	
126-001	Sepsis	Unrelated	Unrelated	
126-004	MSOF	Unrelated	Unlikely	Yes
126-102	Endstage Renal Disease	Unrelated	Unrelated	
129-001	MSOF	Unrelated	Unrelated	Yes
130-001	Sepsis	Unrelated	Unrelated	Yes, and metastatic gastroesophageal cancer
130-002	Congestive Heart Failure	Unrelated	Unrelated	Yes
133-002	Possible myocardial rupture	Unrelated	Unrelated	Yes
133-005	Metastatic Cancer	Unrelated	Unrelated	
133-009	Cancer	Unrelated	Unlikely	
133-010	Acute Respiratory Failure	Unrelated	Unrelated	
150-001	MSOF	Unrelated	Unrelated	Yes
166-001	Cardiopulmonary Arrest	Unrelated	Unrelated	Yes

Reviewer's table

Other Serious Adverse Events

The investigators classified an event as a serious adverse if it was considered:

- 1) life-threatening
- 2) permanently disabling
- 3) a cause for prolonged hospitalization or rehospitalization.

Below is a table from the sponsor's submission. The sponsor did not alter the assessment made by the site investigator. The investigator/sponsor's assessment was that 82% of all non-fatal serious adverse events had no relationship to argatroban use.

Serious Adverse Events other than Death for Study ARG-915X

Event	Mild	Moderate	Severe
Allergic reaction, other drug			1
Amputation	1	1	23
Bleeding	1	7	16
Endocrine disturbance		1	
HCT drop			3
Cardiovascular collapse/bradycardia/arrest /hypotension/tachycardia		1	10
Chest pain		2	1
Coagulopathy			1
Dysphagia		1	
Elevated creatinine		1	
Multisystem organ failure			1
Myocardial infarction	2	1	
Pain		1	
Pericardial effusion		1	
Respiratory insufficiency		1	4
Sepsis/infection	1	3	3
Thrombosis	2	16	8

Transient ischemic attack		1	
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Reviewer's table

This reviewer assessed serious adverse events reported for 4 patients in Study ARG-915X

Patient 007-003 may have had worsening of pleural effusion due to use of argatroban however she had multiple other contributing factors as well. This reviewer considers causal relation to study drug possible.

Patient 020-003 had both gastrointestinal and retroperitoneal bleeding discovered within two days after argatroban infusion stopped. This reviewer consider causal relation to study drug likely

Patient 020-014 experienced severe gastrointestinal bleeding and cardiovascular collapse. This reviewer considers causal relation to study drug likely.

Patient 060-004 experienced bleeding while on argatroban infusion, which required a transfusion. The investigator felt this was unrelated. This reviewer considers causal relation to study drug possible.

Major Bleeding Events

The table below shows major bleeding events for Study ARG-915X. Site investigators thought that seventeen of the twenty-six (65.4%) major bleeding events were possibly or probably related to the argatroban infusion. Two fatal bleeds occurred.

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TABLE 3 MAJOR BLEEDING EVENTS IN PROTOCOL ARG-915X

Patient No.	Patient Initials	Age	Patient Gender	Clinical Description	Clinical Severity	Outcome	Relation to Study Drug
015-102	—	26	M	Bleeding, chest tube	Severe	Resolved	Probably
040-002	—	36	F	Bleeding, gastrointestinal	Severe	Resolved	Probably
052-004	—	78	M	Bleeding, gastrointestinal	Severe	Resolved	Probably
066-005	—	67	F	Bleeding, nasal/oral	Moderate	Resolved	Probably
068-002	—	65	M	Hematoma, left thigh	Moderate	Resolved	Probably
126-001	—	73	F	Bleeding, gastrointestinal	Severe	Resolved	Probably
126-001	—	73	F	Bleeding, IJ line site	Severe	Resolved	Probably
020-003	—	72	F	Bleeding, lower gastrointestinal	Moderate	Resolved	Possibly
020-003	—	72	F	Bleeding, retroperitoneal	Severe	Resolved	Possibly
020-014	—	63	M	Bleeding, gastrointestinal	Severe	Resolved	Possibly
020-015	—	74	M	Bleeding, pericardial effusion	Moderate	Resolved	Possibly
020-020	—	38	F	Bleeding, gastrointestinal	Moderate	Resolved	Possibly
037-002	—	71	M	Bleeding, gastrointestinal	Severe	Resolved	Possibly
043-006	—	68	M	Bleeding, pericardial tamponade	Moderate	Resolved	Possibly
088-007	—	79	F	Bleeding, gastrointestinal	Severe	Resolved	Possibly
114-002	—	73	M	Hgb/Hct drop	Severe	Resolved	Possibly
142-002	—	37	F	Bleeding, gastrointestinal	Severe	Fatal	Possibly
014-003	—	30	M	Bleeding, genito-urinary	Severe	Resolved	Unlikely
020-020	—	38	F	Bleeding, hemoperitoneal	Moderate	Resolved	Unlikely
039-001	—	34	F	Bleeding, vaginal	Severe	Resolved	Unlikely
039-001	—	34	F	Bloody drainage from wounds	Severe	Resolved	Unlikely
051-001	—	69	F	Bleeding, thymic vein	Severe	Resolved	Unlikely
051-001	—	69	F	Bleeding, aortotomy site	Severe	Resolved	Unlikely
142-101	—	20	M	Bleeding, intra-operative	Severe	Resolved	Unlikely
060-004	—	57	M	Spontaneous gross hematuria	Severe	Resolved	Unrelated
113-101	—	66	F	Hgb drop	Severe	Resolved	Unrelated

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE 3 MAJOR BLEEDING EVENTS IN PROTOCOL ARG-915X

Patient No.	Patient Initials	Age	Patient Gender	Clinical Description	Clinical Severity	Outcome	Relation to Study Drug
015-102		26	M	Bleeding, chest tube	Severe	Resolved	Probably
040-002		36	F	Bleeding, gastrointestinal	Severe	Resolved	Probably
052-004		78	M	Bleeding, gastrointestinal	Severe	Resolved	Probably
066-005		67	F	Bleeding, nasal/oral	Moderate	Resolved	Probably
068-002		65	M	Hematoma, left thigh	Moderate	Resolved	Probably
126-001		73	F	Bleeding, gastrointestinal	Severe	Resolved	Probably
126-001		73	F	Bleeding, U line site	Severe	Resolved	Probably
020-003		72	F	Bleeding, lower gastrointestinal	Moderate	Resolved	Possibly
020-003		72	F	Bleeding, retroperitoneal	Severe	Resolved	Possibly
020-014		63	M	Bleeding, gastrointestinal	Severe	Resolved	Possibly
020-015		74	M	Bleeding, pericardial effusion	Moderate	Resolved	Possibly
020-020		38	F	Bleeding, gastrointestinal	Moderate	Resolved	Possibly
037-002		71	M	Bleeding, gastrointestinal	Severe	Resolved	Possibly
043-006		68	M	Bleeding, pericardial tamponade	Moderate	Resolved	Possibly
088-007		79	F	Bleeding, gastrointestinal	Severe	Resolved	Possibly
114-002		73	M	Hgb/Hct drop	Severe	Resolved	Possibly
142-002		37	F	Bleeding, gastrointestinal	Severe	Fatal	Possibly
014-003		30	M	Bleeding, genito-urinary	Severe	Resolved	Unlikely
020-020		38	F	Bleeding, hemoperitoneal	Moderate	Resolved	Unlikely
039-001		14	F	Bleeding, vaginal	Severe	Resolved	Unlikely
039-001		34	F	Bloody drainage from wounds	Severe	Resolved	Unlikely
051-001		69	F	Bleeding, thymic vein	Severe	Resolved	Unlikely
051-001		69	F	Bleeding, aortotomy site	Severe	Resolved	Unlikely
142-101		20	M	Bleeding, intra-operative	Severe	Resolved	Unlikely
060-004		57	M	Spontaneous gross hematuria	Severe	Resolved	Unrelated
113-101		66	F	Hgb drop	Severe	Resolved	Unrelated

Sponsor's table volume 28.73

The major bleeding event for patient 020-020 occurred 12 days after the argatroban infusion was stopped. The major bleeding event for patient 051-001 occurred 23 days after the argatroban infusion was stopped.

The sponsor submitted a safety report for the following biopharmacologic protocols: SKF-001, SKF-002, and SKF-003.

Protocol SKF-001: This trial assessed the effect of argatroban alone and in combination with warfarin on the subject's INR. No deaths or serious adverse events were reported during this study. One patient was withdrawn from the study due to hematochezia.

Protocol SKF-002: This protocol was designed to assess the effects of erythromycin on the safety, tolerability, pharmacokinetics, and pharmacodynamics of argatroban in healthy volunteers. No deaths or serious adverse events occurred during this trial. There were no bleeding episodes during this trial.

Protocol SKF-003: This study was designed to assess the safety and tolerability of argatroban given concurrently with digoxin. No deaths were reported. Two patients experienced cardiac events while on the combination. One patient experienced atrial fibrillation and the other patient experienced a ventricular arrhythmia. There were two episodes of mild bleeding.

Pediatric Use

No information on pediatric use was presented in the NDA.

Geriatric Use

No trends were observed across age groups for both aPTT and the ACT. The safety analysis did suggest that older patients tended to have an increased incidence of events compared to younger patients; however, older patients had increased underlying conditions, which may predispose them to events. The studies were not sized appropriately to detect differences between age groups.

Gender/Race Analysis

The sponsor performed a gender and race analysis of adverse events in the integrated summary of safety and efficacy. No meaningful differences were noted in the gender analysis or in the racial analysis. The studies were not appropriately sized to make meaningful conclusions for other racial groups besides Caucasian. Below is a table of racial participation in all studies combined.

Racial Participation in Argatroban studies

Race	Numbers/Percentage of Patients
	1639 (100%)
Caucasian	1383 (84%)
Hispanic	163 (9.9%)
Black	65 (4%)
Other	17 (1%)
Asian	11 (0.7%)

Reviewer's table

Foreign Marketing History

Argatroban received its initial approval in Japan on June 5, 1990 for the treatment of chronic arterial occlusion. The English translation of the initial indication is shown below:

Indication 1. Argatroban is indicated for: Improvement of ulcers, resting pain, or feelings of coldness in the extremities in chronic arterial occlusion (Buerger's Disease, arteriosclerosis obliterans).

Argatroban received the second and third indications on May 7, 1996 as listed below:

Indication 2. Argatroban is also indicated for: Improvement of neurological symptoms (motor paralysis) and ADL [Activities of Daily Living] (walking, standing, sustaining the sitting position and eating) in acute cerebral thrombosis within 48 hours from onset (lacunar type excluded).

Indication 3. Prevention of clotting during hemodialysis in the following patients: Patients with antithrombin III deficiency; Patients with decreased antithrombin III levels (in whom antithrombin levels have decreased to 70% or less of the normal level, and the use of sodium heparin or calcium heparin is judged not to improve clotting (residual blood in the circuit)).

Sponsor's text volume 28.1

Discussion

The sponsor has resubmitted NDA 20-883 for argatroban in heparin-induced thrombocytopenia with one pivotal (ARG-911) and one supportive (ARG-915) studies and a small pilot cardiovascular study (ARG-310). The ARG-911 and ARG-915 trials are similar with respect to design (multicenter, open-label), inclusion/exclusion criteria, dosing regimen, efficacy and safety outcome. The patients in these trials are compared with historical controls.

The majority of historical control patients are from the same sites as the argatroban-treated patients. The inclusion and exclusion criteria for Studies ARG-911 and ARG-915 were applied to the historical control subjects as well as the argatroban-treated patients. The currently accepted definition of HIT and HITTS were used. The IMRP determined eligibility, classification as HIT or HITTS, and determined the efficacy endpoints such as new thrombosis, amputation, death, or bleeding (major or minor) for the both groups. The IMRP adjudication of the historical control group strengthens their validity. The event rates seen in the historical control group are comparable to those in the literature overview provided by the sponsor and other published literature.⁹ The new historical control group is an adequate comparison group for the argatroban-treated patients.

The primary efficacy endpoint was a composite endpoint of new thrombosis, amputation, or death for both studies. The sponsor provided categorical (primary) and time-to-event analyses (secondary). Additional supporting analyses for Study ARG-911 were provided using the evaluable and the seropositive populations and cumulative time-to-event analyses.

Analyses for pivotal Study ARG-911

Categorical analyses

For the ITT, the statistically significant results were seen for the HIT patients compared to the historical controls for the composite endpoint ($p=0.014$) and for the development of new thrombosis ($p=0.027$). There was a numerical difference for the HITTS patients but the result was not statistically significant ($p=0.131$). These results are further supported by the statistically significant results for the argatroban-treated HIT patients compared to historical controls for the composite endpoint seen in the evaluable ($p=0.006$) and seropositive ($p=0.004$) populations. Similarly, the results for the HITTS patients for the composite endpoint are statistically significant for the evaluable ($p=0.039$) and seropositive ($p=0.018$) populations.

The statistically significant results in the evaluable and seropositive populations are provide substantial support.

Time-to-event analyses

A statistically significant result was observed for both the HIT ($p=0.007$) and HITTS ($p=0.018$) populations in the Kaplan-Meier Time-to Event Analyses for the composite endpoint. The log rank and Wilcoxon results similarly are supportive to the categorical analyses.

Analyses for supportive Study ARG-915

Categorical analyses

Statistically significant differences were seen for the HIT patients compared to the historical controls for the composite endpoint ($p=0.021$). Statistically significant results were seen for the HIT and HITTS patients compared to the historical controls for the development of new thrombosis ($p=0.004$ and $p=0.003$, respectively). There was a trend towards statistically significant results for the composite endpoint for the HITTS patients ($p=0.067$).

Time-to-event analyses

A statistically significant result was observed for both the HIT ($p=0.022$) and HITTS ($p=0.012$) populations in the Kaplan-Meier Time-to Event Analyses for the composite endpoint.

Criticisms of the results obtained in these studies include:

There were differences between the historical control population and the argatroban-treated population for Studies ARG-911 and ARG-915. There were differences in the following:

1. patients with a previous diagnosis of HIT or HITTS in the absence of current thrombocytopenia and Prior heparin exposure within six weeks prior to baseline - These patients are an appropriate subgroup of the HIT patients as these individuals will develop HIT with re-exposure to heparin or low molecular weight heparin. Currently there is no data about when patients who have previously developed HIT can safely be exposed to heparin again. These argatroban-treated cases were reviewed and the majority of these patients were patients with an underlying cardiac condition. Six of them participated in other cardiac argatroban trials (PTCA, stent placement, and cardiac defibrillator surgery).
2. Demographics (sex and test positive population for ARG-911) - These differences are not known to have any clinical significance in terms of morbidity or mortality.
3. Baseline platelet counts between groups - For ARG-911, the argatroban-treated populations had lower median platelet counts than the historical control patients. The clinical definition of heparin-induced thrombocytopenia is not defined strictly by a platelet count but by a greater than 50% percent decrease from baseline. Warkentin¹⁰ and others have described patients with HIT and HITTS who have normal platelet counts.
4. Prior medical conditions and prior medication- The patients in the argatroban-treated population in both trials appeared to include sicker patients when the prior medical conditions and prior medication information is viewed. However, it must be noted that the retrospective collection of data for the historical controls may be incomplete. However, review of the literature and the covariate analyses provided in this NDA did not suggest any consistent relationship between prior medical conditions/medication and outcome for HIT or HITTS.
5. Lack of homogeneity among patients tested for HIPA and SRA - Likely the patients tested were not a random sample because of the difficulty conducting the tests. These tests have variability and accuracy, even when performed at the best institutions the sensitivity ranges from 50% to 90%. Not all centers especially the smaller centers have the knowledge, equipment, and personnel to accurately perform this test.
6. Lack of homogeneity in results for the pooled center analysis - The usefulness of the pooled center analysis is difficult to validate. The majority of the historical control patients came from Center A with the majority of the argatroban-treated patients coming from center C. The greatest difference in results between the historical control and the argatroban treated patients are seen for Center A. This result is not surprising given the fact that Center A (Loyola Medical Center) is a major research center for HIT. There would be significant concern if the greatest difference in outcome were not at Center A but at another center.
7. Failure of resolution of thrombocytopenia in the historical control group compared to the improvement in thrombocytopenia in the argatroban treated population. Heparin-induced thrombocytopenia is a complex disorder. Both treatment groups had their heparin stopped. Stopping the heparin decreased the stimulus for development of further heparin-PF4 antibodies. However, the historical control groups did not necessarily receive any additional anticoagulant, thus any subclinical or clinical clots would have continued to propagate in the absence of an anticoagulant. Published research suggest a procoagulant effect may exist temporarily after heparin is discontinued.⁸
8. Lack of benefit for amputation -The lack of a benefit for amputation may reflect the nature and severity of the pathophysiologic process.^{3,5,6} This drug is a direct thrombin inhibitor and would be useful in stopping the propagation of a clot but would not have significant affect on an already formed clot. Arterial thromboses are less likely to respond to anticoagulant therapy.

Study ARG-310

This pilot study demonstrated the successful use of a particular dosing regimen of argatroban as an anticoagulant for HIT patients requiring stent placement, PTCA, or atherectomy.

Review of the Efficacy Results with other Scientific Literature

Other historical control registries exist such as the one used for approval for lepirudin. The tables below compare the argatroban-treated patients with selected papers from the sponsor's literature overview and historical controls from the NDA. Overall the outcome results demonstrate that argatroban is active as an anticoagulant and provides benefit in the HIT population.

Comparison of Percent Event Rates for HIT patients for Study ARG-911 and ARG-915 with HIT/HITTS and literature overview

Percentages of New thromboses, Amputation, and Death for HIT patients

Event	Literature overview ^a	Historical Controls for Argatroban	ARG-911	ARG-915
Composite Endpoint	42.3	38.8	25.6	25.6
New thrombosis	36	15	6.9	4
Amputation	6	2	1.9	4.8
All-cause Death	20.2	21.8	16.9	16.8

^a population includes HIT/HITTS patients (not separated by author/sponsor)

^b not all-cause death

Reviewer's table

Comparison of Events for HITTS patients in Study ARG-911 and ARG-915 with literature Overview for HITTS patients

Percentages of New thromboses, Amputation, and Death for HITTS patients

Event	Literature Overview	Historical controls for argatroban	ARG-911	ARG-915
Composite Endpoint	63.6	56.5	43.8	41
New thrombosis	96	19.6	14.6	4.3
Amputation	52.1	8.7	11.1	11.5
Death	23.9	28.3	16.9	16.8

Reviewer's table

Clearly argatroban-treated patients had lower incidences of events compared to the others reported in the literature.

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Comparison of HIT/HITTS Event Rates (excluding Nand paper)

Percentages of New thromboses, Amputation, and Death for HIT/HITTS patients

Event	Literature overview ^b	Historical controls for argatroban	ARG-911	ARG-915
Composite Endpoint	47.4 ^c	43	34.2	33.7
New thrombosis	48.8	16.1	10.9	4.2
Amputation	13.5	3.6	6.25	8.3
All-cause Death	20.2 ^c	23.3	17.4	21.2

^a Most severe endpoint

^b Rates recalculated to exclude Nand paper

^c Not all-cause mortality

Reviewer's table

Although the event rates in the combined population depend on the frequencies of HIT and HITTS patients, the table above suggests that argatroban is active as an anticoagulant in this patient population.

Alternative options

Other alternatives exist for patients with heparin-induced thrombocytopenia, however argatroban clearly has additional merit.

The following treatment options exist:

- 1) stopping heparin
- 2) use of lepirudin (only drug approved in the US)
- 3) use of ancrod (not approved in the US, only approved in France)
- 4) use of warfarin
- 5) use of low molecular weight heparin
- 6) off-label use of danaparoid

Stopping heparin may not be a viable alternative for the patient needing anticoagulation for a DVT, PE, cardiac catheterization, PTCA, stent placement, or CABG.

Lepirudin is the only approved drug for heparin-induced thrombocytopenia with thrombosis. Lepirudin is not approved for prophylactic use in the United States. Antibodies are formed in approximately 40% of HIT patients. Lepirudin is renally excreted and significant dosage adjustment must be made for renal impaired patients. Lepirudin cannot be given to patients with HIT/HITTS who are in renal failure or who develop renal failure. There is a steep lepirudin dose/aPTT ratio such that minor dose adjustments can result in suprathereapeutic aPTTs. Re-exposure information is only known for 13 patients.

Published information available demonstrates that the use of ancrod or warfarin alone or in combination in patients with heparin-induced thrombocytopenia actually increases thrombin formation.¹² Warfarin and ancrod use in HIT patients also increase the risk of developing Venous Limb Gangrene Syndrome. Antibodies to ancrod can develop.

Heparin-induced thrombocytopenia and thrombosis can develop with the use of low molecular weight heparins.¹²

Danaparoid is not currently approved for HIT in the U.S. There is some concern about the cross-reactivity with HIT antibodies observed in patients on danaparoid.

Additional known merits of argatroban:

- 1) has clearly demonstrated its efficacy to be used prophylactically for patients with HIT no dosage adjustment needed for renal impairment thus has the potential to be used in dialysis patients
- 2) no antibodies formed with repeat dosing and no cross-reactivity with heparin antibodies
- 3) easier argatroban dose adjustment to achieve and maintain aPTT
- 4) up to 40 patients have received repeat exposure without significant adverse reactions
- 5) pilot study (ARG-310) has successfully demonstrated a dosing regimen for cardiac interventions

Argatroban should be approved for the indication as written. The separation of patients into HIT and HITTS is artificial because the study population of HIT patients likely included HITTS patients with subclinical thromboses. The study did not require that patients undergo venography, duplex scans, spiral CT scans, ventilation/perfusion studies, or pulmonary angiography prior to entry. When the HIT and HITTS populations are combined the argatroban-treated population for the composite endpoint is nearly statistically significant for ARG-911 ($p=0.06$) and is statistically significant for ARG-915 ($p=0.05$).

This decision is based on the totality of evidence presented in the NDA, review of scientific literature on heparin-induced thrombocytopenia, and review of alternatives available to the patient with heparin-induced thrombocytopenia.

Safety Update and overall safety review of Drug

The safety profile for this drug is similar to that for other coagulants with bleeding being the major safety concern, however there was a slight difference in the cause of death for the historical control compared to the argatroban-treated population.

Review of the pivotal (Study ARG-911) and supportive (ARG-915) study did not reveal any specific drug-related causality for death. This reviewer is concerned that in Study ARG-911 trial there were 5 patients who withdrew early from the trial because of cardiac arrhythmia. Additionally, a one percent higher cardiac cause of death for the argatroban-treated (7.23%) compared to historical control (6.21%) in ARG-911 was observed. This difference was not seen in Study ARG-915. The difficulty with the review of these two trials is that some of these patients were critically ill and greater than 85% of argatroban-treated patients in both studies had an underlying cardiac condition. The pilot cardiac intervention study, ARG-310, did not have any fatal events nor any indication of arrhythmia.

Review of the studies including healthy volunteers, special population, and cardiac patients revealed that for serious adverse events, there was an increased percentage of patients in the randomized studies who had serious cardiac events compared to both the active control and placebo groups. The numbers of patients are not enough to make a statement about statistical significance.

The sponsor included retrospectively collected information about Japan's post-marketing adverse events. Review of this data did not suggest any additional concerns.

No information about pediatric use was submitted.

Final Conclusions and Recommendations

The efficacy results from this NDA submission demonstrate that the drug is active as an anticoagulant for patients with heparin-induced thrombocytopenia and reduces the combined risk of the new thrombosis, amputation and death. The drug should be approved for the sponsor's indication. The following phase IV commitments should be undertaken by the sponsor

- 1) further cardiac testing - in vitro electrophysiologic testing, in cardiac compromised animal models, and the collection of information on cardiac adverse events
- 2) information about the use of the drug in the pediatric population.

/S/

Ann T. Farrell, M.D.

1-18-2000

cc:

NDA 20-883

HFD-180

HFD-180/LTalarico

HFD-180/SAurecchia

HFD-180/KRobie-Suh

HFD-180/AFarrell

HFD-181/PM

HFD-180/JChoudary

HFD-180/LZhou

f/t 1/18/00 jgw

/S/

1-20-00

Appendix 1-Investigator/Site

Argatroban-treated

APPENDIX 16.4.4.2
TEXAS BIOTECHNOLOGY CORPORATION
PROTOCOL 911

NUMBER OF PATIENTS PER INVESTIGATOR
GROUP-ARGATROBAN TREATED

SITE	INVESTIGATOR	NUMBER OF PATIENTS
001	ARABIA, P.	1
002	BARTHOLOMEW, J.	10
003	BERNHAM, S.	3
006	CHEDIAK, J.	6
007	COHEN, M.	2
009	DUIGUID, D.	1
011	FRANCIS, J.	4
012	GABRIEL, D.	3
013	GERUNSHIEMER, T.	1
014	GRAY, R./PAULSON, R.	4
015	MASSELL, K.	3
016	HILD, D.	5
017	JANG, I.	7
018	KESSLER, C.	4
020	LEWIS, B.	43
021	LYONS, R.	3
023	MCCLURKEN, J.	1

APPENDIX 16.4.4.3
TEXAS BIOTECHNOLOGY CORPORATION
PROTOCOL 911

NUMBER OF PATIENTS PER INVESTIGATOR
GROUP-ARGATROBAN TREATED

SITE	INVESTIGATOR	NUMBER OF PATIENTS
024	MENA, R.	1
025	PENNER, J.	4
026	PERRY, J.	3
028	REHMAN, K.	2
029	RICE, L.	5
031	SHUMAN, M.	1
032	SIEGEL, J.	2
034	SOFF, G.	4
036	ZEHNDER, J.	5
037	ZIEGLER, Z.	9
039	ANDES, W.	3
040	AYALA, K.	6
041	BHANJI, B.	2
042	BAYNES, R.	2
043	BENGTSON, J.	4
047	BROWN, A.	2
048	CHANG, J.	1

APPENDIX 16.4.4.2
TEXAS BIOTECHNOLOGY CORPORATION
PROTOCOL 911

NUMBER OF PATIENTS PER INVESTIGATOR
GROUP-ARGATROBAN TREATED

SITE	INVESTIGATOR	NUMBER OF PATIENTS
052	FRANCIS, C.	4
053	HACK, T.	3
055	JUCKETT, M.	2
059	MATTHAI, W.	13
060	OLSON, J.	10
062	REEVES, J.	1
063	RUBIN, J.	3
066	WILLIAMS, E.	3
067	AKERS, D.	3
068	KRY, C.	3
069	FRIED, W.	2
070	DRENO, E.	2
072	LEVITT, L.	1
073	SANTIAGO, M.	1
074	BUTCHINS, M.	1
075	TELFER, M.	1
077	BOWA, R.	1

APPENDIX 16.4.4.2
TEXAS BIOTECHNOLOGY CORPORATION
PROTOCOL 911

NUMBER OF PATIENTS PER INVESTIGATOR
GROUP-ARGATROBAN TREATED

SITE	INVESTIGATOR	NUMBER OF PATIENTS
078	SOBEL, M.	1
079	RUSTAGI, P.	8
080	BOKER, M.	4
081	RIFKIN, S.	7
082	AND, Y.	6
083	HARR, T.	2
084	FAIG, D.	2
085	LUTERMAN, A.	1
086	IRANI, M.	3
087	MCGEE, W.	1
088	ORTEGA, G.	2
089	HAIRE, W.	1
091	KONKE, B.	3
092	ZIMMERMAN, M.	1
093	TROWBRIDGE, A.	1
094	SCHACT, M.	1
096	MACPARKANE, E.	3

APPENDIX 16.4.4.3
TEXAS BIOTECHNOLOGY CORPORATION
PROTOCOL 911

NUMBER OF PATIENTS PER INVESTIGATOR
GROUP-ARGATROBAN TREATED

SITE	INVESTIGATOR	NUMBER OF PATIENTS
100	MORAR, J.	6
102	JUBELIER, S.	1
103	BIANCO, A.	1
106	COMEN, A.	1
107	STASZESKI, M.	1
111	ALVING, B.	3
113	LEHNER, R.	4
114	WISDMAN, A.	4
115	AZAR, M.	1
117	STRONG, J.	1
118	ELLIOT, C.	2
119	RICHSON, E.	1
121	BERKOWITZ, B.	3
123	BARTON, J.	4
126	CUSIDAN, M.	1
127	BLASKOWSKY, L.	2
129	COCKHAM, D.	1

APPENDIX 16.4.4.3
TEXAS BIOTECHNOLOGY CORPORATION
PROTOCOL 911

NUMBER OF PATIENTS PER INVESTIGATOR
GROUP-ARGATROBAN TREATED

SITE	INVESTIGATOR	NUMBER OF PATIENTS
130	SHURAF, M.	1
133	MCKENNA, R.	4
135	KHAN, A.	1
137	SHOPNICK, R.	1
138	MAKARY, A.	4
141	NORWE, M.	1
142	SIMAIER, A.	2

Historical Control

NUMBER OF PATIENTS PER INVESTIGATOR
GROUP-HISTORIC CONTROL

SITE	INVESTIGATOR	NUMBER OF PATIENTS
001	ARABIA, F.	1
002	BARTHOLOMEW, J.	27
003	BERDMAN, S.	1
014	GRAY, R./PAULSON, B.	1
016	MILD, D.	0
018	KESSELER, C.	1
025	PENNER, J.	2
037	EIDLER, E.	4
040	AYALA, E.	1
042	BAYNES, R.	1
052	FRANCIS, C.	10
059	MATTHIAS, M.	1
060	OLSON, J.	16
063	RUBIN, J.	1
066	WILLIAMS, E.	2
067	ACOLS, D.	1
068	ZBY, C.	1

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NUMBER OF PATIENTS PER INVESTIGATOR
GROUP-HISTORIC CONTROL

SITE	INVESTIGATOR	NUMBER OF PATIENTS
082	ANN, Y.	2
086	IRANI, M.	1
091	ROMKLE, B.	4
093	TROWBRIDGE, A.	3
113	LEWIS, R.	14
115	ASAR, M.	1
L20	L20	93

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Appendix 2- Articles used in Literature Analysis

#	Title	Author	Journal, Year, Volume & Pages
1	Heparin-induced thrombocytopenia, thrombosis and hemorrhage	D. Silver	Ann. Surg. 1983, 198:301-306
2	Heparin-associated thrombocytopenia and thrombosis: a serious clinical problem and potential solution	R.G. Makhoul	J. Vasc. Surg. 1986, 4: 522-528
3	The heparin-induced thrombocytopenia syndrome: An update	J. Laster	Surgery 1987, 102:763-770
4	Diagnostic & therapeutic strategies of white clot syndrome	A.F. AbuRahma	Amer J. Surg. 1991, 162:175-179
5	Heparin-induced thrombocytopenia in open heart surgical patients: sequelae of late recognition	J.T. Walls	Ann Thorac. Surg. 1992, 53:787-791
6	Heparin-induced thrombocytopenia in patients undergoing intra-aortic balloon pumping after open heart surgery	J.T. Walls	ASAIO J. 1992, M574-M576 (Poster)
7	Complications from heparin-induced thrombocytopenia in patients undergoing cardiopulmonary bypass	R.L. Singer	Chest 1993, 104:1436-1440
8	Heparin-induced thrombocytopenia	R. DeMasi	Amer. Surg. 1994, 60:26-29
9	A 14-year study of heparin-induced thrombocytopenia	T.E. Warkentin	Amer. J. Med. 1996, 101:502-507
10	Heparin-induced thrombocytopenia with thrombosis: incidence, analysis of risk factors, and clinical outcomes in 108 consecutive patients treated at a single institution	Sucha Nand	Amer. J. Hematol. 1997, 56:12-16

Table 1: Summary of the articles that met the inclusion/exclusion criteria.

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Appendix 5 - References

1. Januzzi, JL and Jang, IK. Heparin-Induced Thrombocytopenia: Diagnosis and Contemporary Antithrombin Management. *Journal of Thrombosis and Thrombolysis*. 1999; 7:259-264.
2. Alving, BM and Krishnamurti, C. Recognition and Management of Heparin-Induced Thrombocytopenia (HIT) and Thrombosis. *Seminars in Hemostasis and Thrombosis*. 1997; 23(6):569-574.
3. Visentin, GP. Heparin-Induced Thrombocytopenia: Molecular Pathogenesis. *Thrombosis and Haemostasis*. 1999 August; 82(2):448-456.
4. Warkentin, TE; Sikov, WM; Lillicrap, DP. Multicentric Warfarin-Induced Skin Necrosis Complicating Heparin-Induced Thrombocytopenia. *American Journal of Hematology*. 1999; 62:44-48.
5. Warkentin, TE. Heparin-Induced Thrombocytopenia: A Clinicopathologic Syndrome. *Thrombosis and Haemostasis*. 1999 August; 82(2):439-447.
6. Warkentin, TE. Heparin-Induced Thrombocytopenia: IgG-Mediated Platelet Activation, Platelet Microparticle generation, and Altered Procoagulant/Anticoagulant Balance in the Pathogenesis of Thrombosis and Venous Limb Gangrene Complicating Heparin-Induced Thrombocytopenia. *Transfusion Medicine Reviews*. 1996 October; X(4):249-258.
7. Spadone, D; Clark F; James E; Laster J; Hoch J; Silver D. Heparin-Induced Thrombocytopenia in the Newborn. *Journal of Vascular Surgery* 1992 Feb; 15(2):306-311; discussion 311-2.
8. Wallis, DE; Workman, DL; Lewis BE, Steen, L; Pifarre, R; Moran, JF. Failure of Early Heparin Cessation as Treatment for Heparin-induced Thrombocytopenia. *The American Journal of Medicine*. 1999 June; 106:629-635.
9. Magnani, HN. Heparin-Induced Thrombocytopenia (HIT): An Overview of 230 Patients Treated with Orgaran (Org 10172). *Thrombosis and Haemostasis* 1993; 70(4):554-561.
10. Warkentin TE. Clinical Presentation of Heparin-Induced Thrombocytopenia. *Seminars in Hematology*. 1998 October ; 35(4):9-16.
11. Talarico, L. FDA Medical Officer's Review NDA 20-807. August 19, 1997.
12. Warkentin TE. Limitations of Conventional Treatment Options for Heparin-Induced Thrombocytopenia. *Seminars in Hematology*. 1998 October; 35(4):17-25.