Comparing the 31 argatroban-treated patients with a HISTORY of a positive laboratory test for HIT/HITTS ("Non-Active" patients) to "Active" HIT patients in the historical control, statistically significant reductions in the incidence of **new thromboses** (6% of argatroban-treated patients compared to 24% of historical control patients, p= 0.040*), and the **overall composite endpoint** (10% of argatroban-treated patients compared to 33% of historical control patients, p= 0.012*). A trend in **all-cause mortality** was also seen in favor of argatroban (0% in argatroban-treated patients compared to 11% in historical control patients, p= 0.068*).

* two-sided Fisher's Exact Test

Statistical Adjustments for Patient Baseline Characteristic Imbalances

One of the assumptions of the primary analyses was that the argatroban patients and historical controls had comparable baseline characteristics. The protocol indicated logistic regression models would be used to adjust for any known baseline covariate imbalances or in predictive risk factors. Because it was revealed the argatroban patients and historical controls did not have comparable baseline characteristics with respect to medical history or surgical/invasive procedures, logistic regression and Cox proportional hazards models were used to adjust treatment effects for these baseline imbalances as follows:

To increase the power of the analyses, data for the HIT and HITTS populations were combined, since the imbalances in baseline characteristics appeared to be consistent between these populations. Logistic regression was used on the incidence of death over entire study period. The model included effects for treatment, population (HIT or HITTS) and a yes/no indicator variable for the baseline covariate. This was done for each of the eleven baseline covariates, separately. If the P-value for the baseline covariate was less than 0.050, the baseline covariate was considered to have a significant influence on death.

A forward stepwise regression approach was also performed. The model included effects for treatment, population (HIT or HITTS) and a yes/no indicator variable for all 11 baseline covariates. The effects for treatment and population were required to be in the model at all times. Parameters for variables forced into the model were estimated first. Next, the procedure computed the adjusted chi-square statistics for each baseline covariate not in the model and examined the largest of these statistics. If it met the significance entry level=0.050, the variable was added to the model. Once a baseline covariate was entered into the model, it was never removed from the model. The process was repeated until none of the remaining baseline covariates met the 0.050 significance level for entry.

After identifying the significant baseline covariates, logistic regression was performed using a multivariate model that included effects for treatment and all the significant baseline covariates identified. This model was done for HIT and HITTS, separately. This model was also done including an effect for population (HIT/HITTS).

The same process and models were repeated for time-to-death using Cox proportional hazards models.

The baseline covariates having an influence on death were used to determine the corresponding influence on the composite endpoint. Both logistic regression and Cox Proportional Hazards analyses were done using a multivariate model that included effects for treatment and all the significant baseline covariates having a significant influence on death. This model was done for HIT and HITTS, separately. This model was also done including an effect for population (HIT/HITTS).

A summary of the results of the Logistic Regression and Cox Proportional Hazards Analyses designed to identify baseline patient characteristic covariates which had a influence on death are shown below (Table 19S, vol. 105, p. 323, and Table 20S, vol. 105, p. 324).

Results of the Logistic Regression Analysis Designed to Identify Patient Baseline Covariates Which had an Influence on Death

	Treatment			Covariate		
	P-value	Odds Ratio (95% CI)		P-value	Odds Ratio (95% CI)	
No Covariate (Unadjusted)[a]						
Treatment	.109	1.50	(.92, 2.48)	–	–	
Single Covariate[b]						
Cancer	.147	1.444	(.886, 2.398)	.029	1.895	(1.048, 3.321)
Renal Impairment	.823	1.062	(.628, 1.812)	<.001	4.555	(2.683, 7.754)
Hepatic Impairment	.177	1.411	(.862, 2.350)	.082	2.001	(.878, 4.255)
Lupus	.112	1.494	(.918, 2.479)	.966	1.028	(.232, 3.265)
Cardiac Assist. Device	.194	1.394	(.851, 2.323)	.043	2.053	(.991, 4.044)
Respiratory Distress Syndrome	.176	1.414	(.862, 2.360)	<.001	3.087	(1.800, 5.231)
Sepsis	.195	1.392	(.850, 2.319)	.028	2.203	(1.060, 4.361)
Diabetes	.117	1.485	(.913, 2.462)	.664	1.120	(.663, 1.850)
Ventilation	.074	0.456	(-.035, .968)	.005	1.024	(.288, 1.718)
CABG	.113	1.493	(.917, 2.478)	.945	1.018	(.615, 1.659)
Dialysis	.295	1.311	(.795, 2.195)	.001	3.542	(1.670, 7.319)
Stepwise Model[c]						
Cancer	.898	0.97	(.56, 1.67)	.010	2.23	(1.19, 4.09)
Renal		See Above		<.001	4.29	(2.48, 7.43)
Respiratory Distress Syndrome		See Above		<.001	2.91	(1.64, 5.11)

[a] Model included the factors treatment and population (HIT/HITTS).
[b] Model included the factor treatment, population and a Yes/No indicator for the covariate. Each covariate was analyzed separately.
[c] Model chosen when factors for treatment, population and a Yes/No indicator for the 11 baseline covariates was used in a forward stepwise process.

Results of the Cox Proportional Hazards Analysis Designed to Identify Patient Baseline Covariates Which had an Influence on Death

	Treatment			Covariate		
	P-value	Risk Ratio (95% CI)		P-value	Risk Ratio (95% CI)	
No Covariate (Unadjusted)[a]						
Treatment	.125	1.430	(.906, 2.256)	–	–	
Single Covariate[b]						
Cancer	.172	1.376	(.87, 2.176)	.031	1.742	(1.051, 2.887)
Renal Impairment	.918	1.025	(.635, 1.655)	<.001	3.895	(2.462, 6.163)
Hepatic Impairment	.194	1.359	(.856, 2.158)	.102	1.752	(.895, 3.425)
Lupus	.127	1.429	(.904, 2.261)	.995	1.004	(.315, 3.197)
Cardiac Assist. Device	.217	1.338	(.843, 2.125)	.023	2.011	(1.103, 3.665)
Respiratory Distress Syndrome	.204	1.345	(.851, 2.126)	<.001	2.713	(1.718, 4.284)
Sepsis	.219	1.337	(.842, 2.123)	.026	1.987	(1.088, 3.63)
Diabetes	.134	1.419	(.898, 2.242)	.661	1.110	(.697, 1.768)
Ventilation	.077	1.513	(.956, 2.395)	.003	2.439	(1.343, 4.430)
CABG	.128	1.427	(.903, 2.256)	.924	1.022	(.651, 1.606)
Dialysis	.347	1.252	(.784, 2.001)	<.001	3.000	(1.652, 5.449)
Stepwise Model[c]						
Cancer	.798	0.94	(.58, 1.52)	.029	1.76	(1.06, 2.93)
Renal		See Above		<.001	3.50	(2.19, 5.59)
Respiratory Distress Syndrome		See Above		<.001	2.40	(1.51, 3.81)

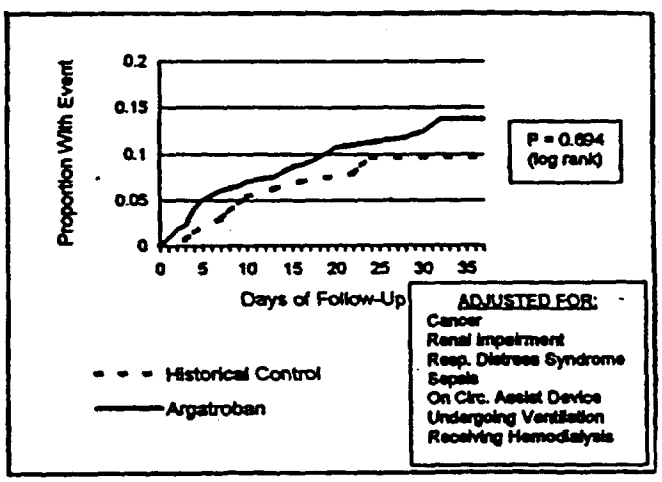
[a] Model included the factors treatment and population (HIT/HITTS).
[b] Model included the factor treatment, population and a Yes/No indicator for the covariate. Each covariate was analyzed separately.
[c] Model chosen when factors for treatment, population and a Yes/No indicator for the 11 baseline covariates was used in a forward stepwise process.

A baseline diagnosis of cancer, renal impairment, sepsis, or respiratory distress syndrome, as well as whether the patient was undergoing hemodialysis, mechanical ventilation, or was on a circulatory assist device were determined to be statistically significant predictors of all-cause mortality by logistic regression and Cox Proportional Hazards models. Of these 7 characteristics, 3 were determined from stepwise regression to be the most influential (independent) predictors of all-cause death; namely, cancer, renal impairment, or respiratory distress syndrome. Based on the results of these analyses, **the time-to-event data for all-cause mortality and the overall composite endpoint are presented following adjustment for the differences between the argatroban and historical control groups for the following seven covariates: cancer, renal impairment, sepsis, respiratory distress syndrome, ongoing hemodialysis, mechanical ventilation, or on a circulatory assist device.**

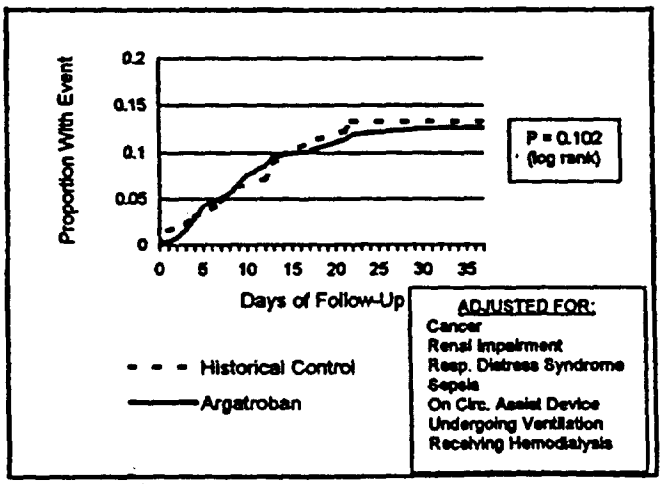
Statistical Analysis of All-Cause Death

Kaplan-Meier curves comparing time-to-death (for all-cause death) for argatroban-treated and historical control intention-to-treat HIT and HITTS patients using multivariate adjustment (using the Cox Proportional Hazards Model) for the covariates of cancer, renal impairment, respiratory distress syndrome, sepsis, undergoing hemodialysis, mechanical ventilation, or on a circulatory assist device are shown below (Figures 7-9, vol. 105, pp. 127-8).

Kaplan-Meier Survival Curve (All-Cause Mortality)
Patients with HIT
(Adjusted Using Cox Proportional Hazards Model)



**Kaplan-Meier Survival Curve (All-Cause Mortality)
Patients with HITTS
(Adjusted Using Cox Proportional Hazards Model)**

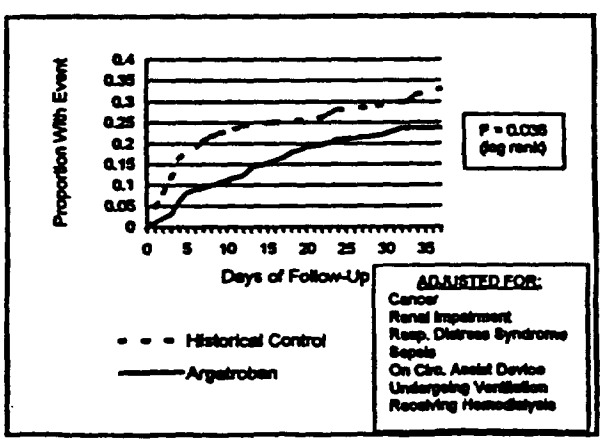


No statistically significant differences in survival were seen when Kaplan-Meier estimates are adjusted for the above covariates. However, a trend toward greater all-cause mortality in argatroban-treated HIT patients was seen.

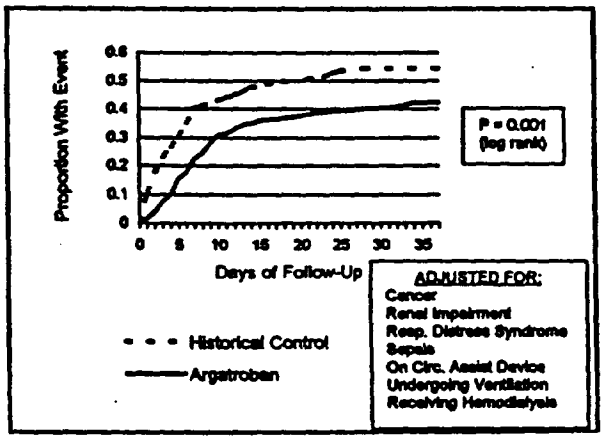
Statistical Analysis of the Overall Composite Endpoint

The time-to-overall composite endpoint (equivalent to time-to-first event) for argatroban-treated and historical control intention-to-treat HIT and HITTS patients, using multivariate adjustment (using the Cox Proportional Hazards Model) for the covariates of cancer, renal impairment, respiratory distress syndrome, sepsis, undergoing hemodialysis, mechanical ventilation, or on a circulatory assist device are shown below (vol. 105, pp. 111).

**Time-to-Overall Composite Endpoint
Patients with HIT
(Adjusted Using Cox Proportional Hazards Model)**



Time-to-Overall Composite Endpoint
Patients with HITTS
(Adjusted Using Cox Proportional Hazards Model)



Statistically significant reductions the the overall composite endpoint were seen for HIT and HITTS patients following multivariate adjustment for those baseline characteristics that were found to significantly impact on the occurrence of death.

A summary of the sponsor's logistic regression and Cox Proportional Hazards model analyses on the incidence of **all-cause death** and the **overall composite** (new thromboses, amputation, or all-cause death) endpoints for HIT and HITTS patients, when adjusted for **NONE**, the 3 most influential covariates as identified from stepwise regression as predictors of all-cause mortality (i.e., cancer, renal impairment and respiratory distress syndrome), and the 7 covariates which predicted all-cause mortality by logistic regression and Cox Hazards Proportional Model analyses (i.e., cancer, renal impairment, sepsis, respiratory distress syndrome, ongoing hemodialysis, mechanical ventilation, or on a circulatory assist device), are shown below (Table 7, Biometrics Review).

Sponsor's Logistic Regression and Cox Proportional Hazards Model
Analyses of the incidence of the
OVERALL COMPOSITE ENDPOINT and ALL-CASE DEATH
(when adjusted for 0, 3, or 7 Predictors of all-cause mortality)

Disease Category:	HIT		HITTS	
Time Interval	OR/RR; 95% CI ; p-	OR/RR; 95% CI ; p-	OR/RR; 95% CI ; p-	OR/RR; 95% CI; p-
Model |*Covariates*:	Composite	Death	Composite	Death
Logistic|None	0.74; (.43, 1.25); .256	1.77; (.88, 3.77); .121	0.64; (.39, 1.06); .082	1.28; (.66,2.57); .48
Logistic|3	0.62; (.35, 1.10); .101	1.34; (.62, 3.02); .459	0.54; (.32, .92); .023	0.65; (.29, 1.44); .29
Logistic|7	0.60; (.33, 1.08); .091	1.24; (.56, 2.89); .610	0.44; (.25, .77); .005	0.51; (.21, 1.19); .13
Hazard|None	0.70; (.45, 1.10); .123	1.62; (.82, 3.18); .166	0.66; (.46, .95); .025	1.27; (.68,2.36); .46
Hazard|3	0.62; (.39, .99); .044	1.25; (.62, 2.55); .535	0.57; (.38, .84); .005	0.61; (.30, 1.26); .19
Hazard|7	0.60; (.37, .97); .038	1.16; (.55, 2.43); .694	0.48; (.32, .73); <.001	0.54; (.25, 1.13); .10

Data from sponsor Appendix 16.1.9.3.4 of Volumes 154 & 154a; |None: indicates model results unadjusted for covariate imbalance; |3: model results adjusted for cancer, renal impairment (Renal) & respiratory distress syndrome (RDS) ;

Note that when the incidence of the **overall composite endpoint** for **HITTS** patients was adjusted in the logistic regression model for NONE, 3, and 7 of the above covariates, corresponding p-values (which reflect the difference in outcome between argatroban-treated and historical control patients) of 0.082, 0.023, and 0.005 were found. Importantly, these p-values decrease in magnitude when more covariates were adjusted for, and the latter two were statistically significant. Similar results were seen using the Cox Proportional Hazards model, with the exception that all 3 p-values were statistically significant using this analysis.

Similarly, when the incidence of **all-cause death** in **HITTS** patients (for which the study was not sized) was adjusted for NONE, 3, and 7 of the above covariates using the logistic regression model, corresponding (and decreasing) p-values 0.48, 0.29, and 0.13 were found. Equivalent results were seen using the Cox Proportional Hazards model.

As per Dr. Sankoh's Biometrics Review, "for **HITTS** patients, the (above) covariate analysis results show a significant and consistent covariate effect for the overall composite endpoint, and a robust positive (although not significant) effect on all-cause mortality." Thus, the efficacy of argatroban in HITTS patients is supported by this analysis.

When the incidence of the **overall composite endpoint** for **HIT** patients was adjusted in the logistic regression model for NONE, 3, and 7 of the above covariates, corresponding p-values of 0.256, 0.101, and 0.091 were found. Similar results were seen for p-values obtained using the Cox Proportional Hazards model; namely, p-values of 0.123, 0.044, and 0.038, following adjustment for 0, 3, and 7 of the above covariates, respectively.

When the incidence of **all-cause death** for **HIT** patients was adjusted for NONE, 3, and 7 of the above covariates using the logistic regression model, corresponding p-values of 0.121, 0.459, and 0.610 were found. Note that these p-values increase as more covariates were adjusted for; namely p-values of 0.121, 0.459, and 0.610 were seen following adjustment for 0, 3, and 7 of the above covariates respectively, in the logistic regression analysis; while p-values of 0.166, 0.535, and 0.694 were seen following adjustment for 0, 3, and 7 of the above covariates respectively, in the Cox Proportional Hazards analysis.

As per Dr. Sankoh's Biometrics Review, "for HIT patients,

while the results for the overall composite endpoint suggest robust covariate effects (i.e. the logistic regression and Cox Proportional Hazards model results indicate similar argatroban effectiveness direction-wise, although the logistic regression results are at best borderline), the results for all-cause mortality are consistent." In particular, increasing p-values for all-cause death, following adjustment of an increasing number of covariates, do NOT support the overall efficacy of argatroban in HIT patients.

Secondary Efficacy Outcome Results

Resolution of Thrombocytopenia for Argatroban-treated patients

For HIT patients, the median platelet count increased from 81 K/mm3 prior to drug administration, to 132 K/mm3 by day 3 of therapy, to 186 K/mm3 at the conclusion of therapy (mean duration of therapy was 5.3 days). For HITTS patients, the median platelet count increased from 66 K/mm3 prior to drug administration, to 120 K/mm3 by day 3, to 198 K/mm3 at the conclusion of therapy (mean duration of therapy was 5.9 days). A total of 104/129* or 81% of HIT patients, and 100/144 or 69% of HITTS patients achieved a resolution of their platelet counts to baseline values or above. (* Does not include the 31 of the 160 total HIT patients with a documented history of a positive HIT antibody who did not enter with thrombocytopenia or thrombosis).

Resolution of Thrombocytopenia for Historical Control patients

For HIT patients, the median platelet count increased from 81 K/mm3 at the time of diagnosis, to 92 K/mm3 at day 3 following the discontinuation of heparin, to 167 K/mm3 at day 7. For HITTS patients, the median platelet count increased from 72 K/mm3 at

the time of diagnosis, to 100 K/mm3 at day 3 following the discontinuation of heparin, to 216 K/mm3 at day 7 (vol. 5.1, p. 289).

APTT Levels for Argatroban-treated patients

For HIT patients, the median APTT increased from 30 seconds at baseline to 60 seconds at 12 hours post-infusion. For HITTS patients, the median APTT increased from 30 seconds at baseline to 68 seconds at 12 hours post-infusion. APTT values were subsequently well-maintained in the target APTT range of 45-90 seconds (i.e. 1.5 - 3.0 x control). A total of 133/160 or 83% of HIT patients, and 135/144 or 94% of HITTS patients achieved an APTT in the target range.

Types of Thrombotic Complications (TECs)

A summary of the types of thromboembolic complications (TECs) in the intention-to-treat population is shown below (Table 18, vol. 105, p. 116).

Types of Thromboembolic Complications (TECs)

	HIT				HITTS			
	Historical Control		Argatroban		Historical Control		Argatroban	
	N	(%)	N	(%)	N	(%)	N	(%)
Total Number of Patients	108		160		109		144	
Number of Patients with TEC	25	(23)	10	(6)	45	(41)	27	(19)
Number of TECs[a]	38	(35)	13	(8)	65	(60)	38	(26)
Venous	25	(23)	12	(8)	48	(44)	32	(22)
Venous Thrombosis	21	(19)	10	(6)	33	(30)	23	(16)
Pulmonary Embolism	4	(4)	2	(1)	15	(14)	9	(6)
Arterial	13	(12)	1	(1)	17	(16)	6	(4)
Limb Artery Thrombosis	4	(4)	1	(1)	14	(13)	1	(1)
Thrombotic Stroke/CVA	4	(4)	0	(0)	1	(1)	1	(1)
Myocardial Infarction	2	(2)	0	(0)	0	(0)	1	(1)
Other	3	(3)	0	(0)	2	(2)	3	(2)

[a] Patients could have more than one TEC.

The majority of TECs were venous in origin and all (diagnosed) events occurred much less frequently in the argatroban-treated patients, except in the HITTS patients where there was 1 thrombotic stroke/CVA event in each of the argatroban and historical control groups, 1 myocardial infarction in the

argatroban group compared to 0 in the historical control, and 3 "other" arterial thromboses in the argatroban group compared to 2 "other" arterial thromboses in the historical control group.

The ratio of new TECs per patient was 1.5 for historical control, and 1.3 for argatroban-treated HIT patients; and 1.4 for both historical control and argatroban-treated HITTS patients. More pulmonary emboli and arterial TECs occurred in historical control patients.

Drug Interactions Between Argatroban and Warfarin

Breslow-Day Tests were performed to test the effect of warfarin on the development of the overall composite outcome, all-cause mortality, new thrombosis, thrombotic composite outcome, and death due to thrombosis, in argatroban-treated and historical control HIT and HITTS patients. No significant interaction of warfarin therapy was found.

Treatment-by-Center Interaction Assessment

This study was conducted at 103 investigative sites in the United States and Canada. Historical control data were collected from 36 centers. Study sites which enrolled >= 10 patients for the argatroban and historical control groups is shown below (Appendix 16.4.4.2, vol. 129 and Section 8A, vol. 70, pp. 1-40).

Study Sites with 10 or Greater Patients

HISTORICAL CONTROL			ARGATROBAN-TREATED		
Investigator	Study Site	No. Patients	Investigator	Study Site	No. Patients
Lewis, B	020	35	Lewis, B	020	43
Olson, J	060	16	Olson, J	060	10
Lerner, R	113	24	Bartholomew, J	002	10
Warkentin, T	200	47	Mattai, W	059	13
Warkentin, T	201	24			
Warkentin, T	202	26			

Note that patients enrolled in the historical control by Dr. Warkentin were from a registry of HIT/HITTS patients treated at one of three study sites in Canada (sites 200, 201, and 202).

The majority of centers enrolled less than 3 patients; 7 centers enrolled ≥ 10 patients (sites 020, 059, 060, 113, 200, 201, and 202). Data from centers other than the center with the highest total patient enrollment were combined to create five "pseudo-centers" using a computer-generated randomization scheme. No treatment-by-center interactions were reported. The incidence of the overall composite endpoint was reported to be higher for historical control than for argatroban-treated HIT patients (except for Center 3), and HITTS patients (except for Center 2).

SAFETY ANALYSIS

Deaths

The primary causes of death in both argatroban-treated and historical control patients were thrombosis and organ system failure (cardiac, respiratory, and renal). Note that **14%** and **27%** of deaths in argatroban-treated HIT and HITTS patients, respectively, occurred during the argatroban infusion period, while **67%** and **75%** of deaths for HIT and HITTS patients, respectively, occurred during the equivalent period in historical control patients.

All deaths that occurred in study ARG-911 were reconstructed from case report forms and relevant patient listings, and are tabulated in **Appendix 1** of this review. Particular attention was paid to patient medical history, timing of heparin and argatroban administration, platelet count profile, HIT antibody status, clinical and objective evidence of thrombosis, on-site investigator assessment of clinical course and cause of death, and autopsy results whenever available.

Adverse Events Leading to Withdrawal

Adverse events were categorized according to System Organ Class and WHO Preferred Terms. A summary of adverse events of HIT and HITTS patients receiving argatroban leading to patient withdrawal is shown below (Table 38, vol. 105, p. 192).

Adverse Events Leading to Withdrawal of Patients Receiving Argatroban

	HIT			HITTS		
Adverse Event[a]	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)
Death	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)

[a] Patient counted once per event.
Patients who discontinued study drug due to an adverse event were counted as completers.

A total of 11(7%) of HIT patients and 11(8%) HITTS patients receiving argatroban withdrew from the study. Among the HIT patients, 2 patients withdrew due to hemorrhage and 2 due to a "coagulation disorder". Among HITTS patients, 8 patients withdrew secondary to hemorrhage or anemia, and 3 patients withdrew due to a thrombotic event.

Serious Adverse Events

Serious adverse events were NOT specifically identified in the case report forms for historical control patients. Serious adverse events reported for HIT and HITTS argatroban-treated patients are summarized below (vol. 106, pp. 150-361). Most serious adverse events in argatroban-treated HIT/HITTS patients were related to thrombosis or bleeding.

Serious Adverse Events
Argatroban-Treated HIT and HITTS Patients

Patient Number	Adverse Event
002-004	Internal Jugular Vein Thrombosis Transmetatarsal amputation
002-007	Drop in Hemoglobin (required 4 units prbc) (Death)
002-008	Amputation of Forearm due to Ischemia and Gangrene
002-010	New Thrombus of R Distal Iliac and R Common Femoral Vein New Pulmonary Embolus
003-001	New Thrombosis Leading to R BKA
006-002	Respiratory Failure Renal Failure Ventricular Fibrillation Bleeding Duodenal Ulcer
006-006	DVT of L Common, L Femoral, and L Saphenous Veins
011-001	DVT of L arm resulting in ischemic L Hand and leading to Amputation
011-002	L AKA
011-003	L Ventricle Thrombus New L Posterior Tibial Vein Thrombosis Pulmonary Embolus New Thromboses of multiple veins of R Lower Extremity
011-004	Jugular Vein Thrombus
012-001	Pneumonia MI
014-002	Thrombotic Stroke
014-001	Thrombosis of R Leg leading to amputation
015-001	DVT
015-002	Seizure
016-002	Drop in Hemoglobin (of 3 g/dl) Shortness of Breath
017-002	New Bilateral DVT
017-003	Decreased Hemoglobin/Guiac Positive Stool L AKA
017-005	CABG and AVR Hypotension secondary to removal of pacing wire Acute Respiratory Distress
018-001	Fever with chills
018-002	New L Upper and R Lower Extremity DVTs
018-003	Re-occlusion of Profunda Femoral Artery
020-015	DVT of R Femoral and Popliteal Veins

020-029	Ischemia of L Foot leading to amputation
020-091	Asystole
020-092	Cerebral infarct
020-103	Ischemia of R Leg leading to amputation
020-105	Cardiopulmonary Arrest
021-002	Chest Pain
025-001	L Leg DVT
025-003	Major bleeding during ventricular embolectomy
029-002	New Bilateral Lower Extremity Thromboses
029-005	GU Bleeding
032-001	Drop in Hematocrit
032-002	L Toe amputation
034-001	L AKA Adrenal insufficiency R Foot ischemia leading to amputation
037-002	New LE Thrombosis
037-005	Bleeding (requiring 2 units of prbcs) New Bilateral Lower Extremity DVTs Bilateral Foot gangrene leading to amputation
039-001	GI bleeding Gross hematuria
040-005	New Lower Extremity Thromboses
042-002	ST Segment Elevation and Increase in PA Pressure During CABG Tachycardia
043-001	Unstable Angina MI
043-002	Congestive Heart Failure Atrial Fibrillation
043-003	Ischemic Bowel resulting in colectomy Gangrenous Gall Bladder
052-001	Drop in Hematocrit requiring prbc transfusion
052-002	Infection of Groin Incision Site
053-003	Pulmonary Embolism
055-002	Hemoptysis Dysphagia Dehydration Orthostatis hypotension Bilateral adrenal hemorrhage
059-006	Acute respiratory failure
059-008	Acute respiratory failure Drop in Hematocrit
059-009	Cerebral Infarction

059-010	Abdominal pain
059-011	Acute respiratory failure
060-002	L BKA R Transmetatarsal amputation
060-004	Bleeding requiring transfusion x 2 Right-sided chest pain Hemoptysis
060-009	Drop in Hematocrit (requiring transfusion)
060-010	New Thromboses in the IVC, external iliac, and common femoral arteries
066-001	Pulmonary hemorrhage
067-002	INR of 10.4 on warfarin
067-003	R Hand Wound infection R Hand gangrene leading to amputation
070-001	R DVT
072-001	Anemia requiring transfusion
073-001	Inferior and Lateral T-wave inversions following a sural nerve biopsy Over-anticoagulation with warfarin Bilateral lower extremity gangrene
079-001	Ischemia of L Lower Extremity, leading to amputation Ischemia of fingers bilaterally, leading to amputation
079-003	CVA
079-007	New R Popliteal Vein Thrombosis
080-001	Bilateral Lower Extremity Ischemia leading to bilateral BKAs
081-007	Severe peripheral thromboses leading to amputation
082-001	Bilateral gangrene of the feet, leading to amputation
082-004	Thrombosis of R Common Femoral Vein
085-001	Progressive Peripheral Arterial Occlusive Disease leading to a BKA
086-002	Pulmonary Embolism
088-001	Syncope x 2 R Leg DVT . Wound Abscess
091-003	Blood loss during CABG surgery R BKA due to occlusive thrombi L AKA due to occlusive thrombi
100-001	Operative and Post-operative (CABG) bleeding Respiratory failure Chest pain
100-003	GI bleeding x 2 Hyotension
107-001	GU bleeding New Pulmonary Embolus

111-001	R Common Femoral Vein thrombus
113-004	Pulmonary Embolus
114-001	L Femoral Thrombus
115-002	L Ventricular Thrombus Bilateral Internal Jugular Vein Thromboses
118-002	Adenocarcinoma of the Bowel New R Superficial Femoral Vein Thrombosis
121-001	Sepsis Ventricular tachycardia/cardiac arrest
121-003	Pneumonia
123-001	Pulmonary embolus
123-003	R Upper Extremity Hematoma
123-004	Lower Extremity Cellulitis Lower Extremity Edema
130-001	Respiratory Distress
135-001	Vasovagal syncope

Adverse Events Occurring During the Argatroban Infusion Period

A summary of emergent (for the historical control patients) and adverse events (for argatroban-treated patients) experienced by 5% or more of HIT/HITTS patients **during the period of argatroban infusion** are shown below (Table 40, vol. 105, pp. 201-203).

Emergent (Historical Control) and Adverse Events Experienced by ≥5% of Patients During the Argatroban Infusion Period

	HIT				HITTS			
	Historical Control		Argatroban		Historical Control		Argatroban	
	Number of		Number of		Number of		Number of	
Event[a]	EEs	Patients (%)	AEs	Patients (%)	EEs	Patients (%)	AEs	Patients (%)
Total Number of Patients		108		160		109		144
Total Number of Events	143	49 (45)	282	101 (63)	191	72 (66)	352	105 (73)
Skin and Appendages Disorders	6	5 (5)	13	10 (6)	11	10 (9)	23	18 (13)
Rash	0	0 (0)	7	6 (4)	3	3 (3)	7	7 (5)
Central and Peripheral Nervous System Disorders	4	3 (3)	16	13 (8)	4	4 (4)	16	13 (9)
Psychiatric Disorders	1	1 (1)	14	11 (7)	5	5 (5)	19	14 (10)
Confusion	0	0 (0)	3	3 (2)	2	2 (2)	7	7 (5)
Gastro-intestinal System Disorders	14	9 (8)	55	37 (23)	14	11 (10)	45	28 (19)
Constipation	1	1 (1)	6	6 (4)	0	0 (0)	11	10 (7)
Diarrhoea	5	5 (5)	15	15 (9)	2	2 (2)	4	4 (3)
Metabolic & Nutritional Disorders	2	2 (2)	11	8 (5)	3	3 (3)	11	10 (7)
Cardiovascular Disorders, General	8	7 (6)	16	14 (9)	9	7 (6)	15	12 (8)
Hypotension	5	5 (5)	10	10 (6)	3	3 (3)	10	10 (7)
Heart Rate and Rhythm Disorders	7	7 (6)	20	15 (9)	7	7 (6)	28	20 (14)
Cardiac Arrest	2	2 (2)	1	1 (1)	4	4 (4)	7	7 (5)
Vascular (Extracardiac) Disorders	18	13 (12)	5	5 (3)	31	24 (22)	25	19 (13)
Peripheral Ischaemia	2	2 (2)	0	0 (0)	6	5 (5)	7	5 (3)
Thrombophlebitis Deep	10	7 (6)	2	2 (1)	12	12 (11)	6	6 (4)
Respiratory System Disorders	31	14 (13)	34	28 (18)	26	20 (18)	30	24 (17)
Dyspnoea	5	4 (4)	8	8 (5)	7	7 (6)	4	4 (3)
Platelet, Bleeding and Clotting Disorders	8	8 (7)	23	18 (11)	21	18 (17)	27	20 (14)
Embolism Pulmonary	3	3 (3)	1	1 (1)	8	7 (6)	8	7 (5)
Urinary System Disorders	7	6 (6)	13	11 (7)	7	7 (6)	22	19 (13)
Urinary Tract Infection	2	2 (2)	4	4 (3)	2	2 (2)	12	11 (8)
Body as a Whole-General Disorders	14	10 (9)	40	30 (19)	38	25 (23)	43	30 (21)
Chest Pain	1	1 (1)	6	5 (3)	7	6 (6)	4	3 (2)
Fever	2	2 (2)	5	5 (3)	2	2 (2)	9	9 (6)
Oedema	2	2 (2)	0	0 (0)	8	8 (7)	1	1 (1)
Pain	4	3 (3)	4	4 (3)	10	10 (9)	10	9 (6)
Application Site Disorders	3	3 (3)	4	4 (3)	5	5 (5)	6	5 (3)
Resistance Mechanism Disorders	10	10 (9)	7	7 (4)	4	3 (3)	19	15 (10)

EEs=Emergent events during observation period.

[a] Patient counted once per body system and once per event.

For HIT patients, a total of 101(63%) argatroban-treated patients and 49(45%) historical control patients experienced adverse or emergent (defined as first 7 days of observation) adverse events, respectively. For HITTS patients, a total of 105(73%) argatroban-treated and 72(66%) historical control patients experienced adverse and emergent events, respectively.

Those body system categories that occurred more frequently in argatroban-treated than historical control HIT patients (by a difference of 5% or greater) are tabulated below. Body system categories are expanded to include specific contributing adverse events as per information from Appendix 16.2.39, volume 128. Note that the total number of contributing adverse events often exceeds the corresponding body system total since patients were counted only once per body system and once per adverse event.

Adverse Events (by Body System Category) That Occurred More Frequently in Argatroban-Treated Than Historical Control HIT Patients (by a difference of 5% or greater) DURING THE ARGATROBAN INFUSION

EVENT	Historical Control Patients (%)	Argatroban Patients (%)
Total Number of Patients	108	160
Central and Peripheral Nervous System Disorders	**3(3%)**	**13(8%)**
Coma	1(1%)	0(0%)
Convulsions	1(1%)	2(1%)
Dizziness	0(0%)	7(4%)
Encephalopathy	0(0%)	1(1%)
Fecal Incontinence	0(0%)	1(1%)
Headache	0(0%)	2(1%)
Hypoaesthesia	0(0%)	1(1%)
Hypotonia	1(1%)	0(0%)
Muscle Contractions Involuntary	0(0%)	1(1%)
Stupor	1(1%)	0(0%)
Psychiatric Disorders	**1(1%)**	**11(7%)**
Anorexia	0(0%)	2(1%)
Anxiety	0(0%)	1(1%)
Confusion	0(0%)	3(2%)
Depression	0(0%)	4(3%)
Insomnia	0(0%)	2(1%)
Somnolence	0(0%)	1(1%)
Thinking Abnormal	1(1%)	1(1%)

Gastrointestinal System Disorders	9(8%)	37(23%)
Abdominal Pain	1(1%)	5(3%)
Amylase Increased	0(0%)	1(1%)
Constipation	1(1%)	6(4%)
Diarrhea	5(5%)	15(9%)
Dyspepsia	0(0%)	1(1%)
Dysphagia	2(2%)	0(0%)
Flatulence	0(0%)	2(1%)
Gastritis	0(0%)	1(1%)
GI Hemorrhage	1(1%)	1(1%)
Hiccup	0(0%)	2(1%)
Ileus	0(0%)	1(1%)
Melena	1(1%)	1(1%)
Nausea	0(0%)	6(4%)
Esophageal Ulceration	0(0%)	1(1%)
Pancreatitis	0(0%)	1(1%)
Peritonitis	0(0%)	1(1%)
Rectal Disorder	1(1%)	1(1%)
Vomiting	2(2%)	6(4%)
Respiratory System Disorders	14(13%)	28(18%)
Apnea	4(4%)	4(3%)
Coughing	2(2%)	5(3%)
Dyspnea	4(4%)	8(5%)
Emphysema	1(1%)	0(0%)
Hemoptysis	3(3%)	0(0%)
Hyperventilation	1(1%)	0(0%)
Hypoventilation	0(0%)	1(1%)
Hypoxia	2(2%)	3(2%)
Pharyngitis	0(0%)	2(1%)
Pleural Effusion	0(0%)	1(1%)
Pneumonia	3(3%)	2(1%)
Pneumothorax	2(2%)	1(1%)
Pulmonary Edema	1(1%)	0(0%)
Respiratory Disorder	2(2%)	5(3%)
Respiratory Insufficiency	1(1%)	1(1%)
Sputum Increased	0(0%)	1(1%)
Body as a Whole - General	10(9%)	30(19%)
Abdomen Enlarged	0(0%)	3(2%)
Ascites	0(0%)	1(1%)
Asthenia	1(1%)	0(0%)
Back Pain	0(0%)	4(3%)
Chest Pain	1(1%)	5(3%)
Death	2(2%)	2(1%)
Fatigue	0(0%)	3(2%)
Fever	2(2%)	5(3%)
Hypothermia	0(0%)	1(1%)
Edema	2(2%)	0(0%)
Edema Genital	0(0%)	1(1%)
Edema Peripheral	1(1%)	6(4%)
Pain	3(3%)	4(3%)
Rigors	0(0%)	2(1%)
Sudden Death	1(1%)	0(0%)
Syncope	0(0%)	1(1%)

More "platelet, bleeding, and clotting disorders" events were reported in the argatroban-treated patients: 18(11%) patients in the argatroban group compared to 8(7%) patients in the historical control group. This body system category and component adverse events is shown below (Appendix 16.2.39, vol. 128).

Platelet, Bleeding & Clotting Disorders

EVENT Total Number of Patients	Historical Control Patients (%) 108	Argatroban Patients (%) 160
Platelet, Bleeding & Clotting Disorders	**8(7%)**	**18(11%)**
Coagulation Disorder	0(0%)	2(1%)
Coagulation Factor Decreased	0(0%)	1(1%)
Embolism Pulmonary	3(3%)	1(1%)
Hemorrhage NOS	1(1%)	4(3%)
Prothrombin Decreased	0(0%)	1(1%)
Purpura	0(0%)	7(4%)
Thrombocytopenia	0(0%)	2(1%)
Thrombosis	1(1%)	3(2%)
Thrombosis Arterial	1(1%)	0(0%)
Thrombosis Arterial Leg	2(2%)	0(0%)

The body system category that occurred more frequently in historical control patients (by a difference of 5% or greater) than argatroban-treated HIT patients was the "vascular(extracardiac) disorders" category: 5(3%) patients in the argatroban group compared to 13(12%) in the historical control group. This category is broken down into component adverse events and shown below (Appendix 16.2.39, vol. 128).

Vascular (Extracardiac) Disorders

EVENT Total Number of Patients	Historical Control Patients (%) 108	Argatroban Patients (%) 160
Vascular (Extracardiac) Disorders	**13(12%)**	**5(3%)**
Cerebral Hemorrhage	1(1%)	0(0%)
Cerebrovascular Disorder	3(3%)	0(0%)
Peripheral Gangrene	0(0%)	1(1%)
Peripheral Ischemia	2(2%)	0(0%)
Phlebitis	0(0%)	1(1%)
Thrombophlebitis	2(2%)	1(1%)
Thrombophlebitis Deep	7(6%)	2(1%)

Those body system categories that occurred more frequently in argatroban-treated than historical control HITTS patients (by a difference of 5% or greater) are tabulated below. Body system categories are expanded to include specific contributing adverse events as per information from Appendix 16.2.39, volume 128. Note that the total number of contributing adverse events often exceeds the corresponding body system total since patients were counted only once per body system and once per adverse event.

Adverse Events (by Body System Category) That Occurred More Frequently in Argatroban-Treated Than Historical Control HITTS Patients
(by a difference of 5% or greater)
DURING THE ARGATROBAN INFUSION

EVENT Total Number of Patients	Historical Control Patients (%) 109	Argatroban Patients (%) 144
Psychiatric Disorders	**5(5%)**	**14(10%)**
Agitation	0(0%)	3(2%)
Anorexia	0(0%)	2(1%)
Anxiety	0(0%)	1(1%)
Confusion	2(2%)	7(5%)
Depersonalization	0(0%)	1(1%)
Depression	2(2%)	3(2%)
Insomnia	1(1%)	0(0%)
Nervousness	0(0%)	1(1%)
Gastrointestinal System Disorders	**11(10%)**	**28(19%)**
Abdominal Pain	3(3%)	4(3%)
Constipation	0(0%)	10(7%)
Diarrhea	2(2%)	4(3%)
Duodenal Ulcer	0(0%)	1(1%)
Duodenal Ulcer Hemorrhagic	0(0%)	1(1%)
Dyspepsia	0(0%)	1(1%)
Dysphagia	0(0%)	2(1%)
Eructation	0(0%)	1(1%)
Flatulence	0(0%)	1(1%)
Gastric Ulcer	0(0%)	1(1%)
Gastritis	1(1%)	0(0%)
GI Hemorrhage	0(0%)	1(1%)
Hematemesis	1(1%)	0(0%)
Ileus	0(0%)	2(1%)
Nausea	2(2%)	5(3%)
Esophagitis	1(1%)	1(1%)
Saliva Increased	0(0%)	1(1%)
Stomatitis Ulcerative	0(0%)	1(1%)
Tongue Disorder	0(0%)	1(1%)
Vomiting	4(4%)	6(4%)

209). Note that for the argatroban group, listed events include **all** events that occurred during the infusion period, and only **serious** adverse events that occurred after the infusion period. Also note that that for the historical control, "emergent events" are those events that occurred during the first 7 days of observation only.

Adverse Events Experienced by ≥ 5% of HIT Patients

	HIT					
	Historical Control			Argatroban		
Adverse Event[a, b]	EEs	Number of Patients	(%)	AEs	Number of Patients	(%)
Total Number of Patients		108			160	
Total Number of Events	143	49	(45)	422	125	(78)
Diarrhoea	5	5	(5)	17	17	(11)
Dyspnoea	5	4	(4)	12	12	(8)
Hypotension	5	5	(5)	11	11	(7)
Sepsis	4	4	(4)	10	10	(6)
Chest Pain	1	1	(1)	10	9	(6)
Apnoea	4	4	(4)	9	9	(6)
Vomiting	2	2	(2)	9	8	(5)
Dizziness	0	0	(0)	8	8	(5)
Thrombophlebitis Deep	10	7	(6)	6	6	(4)

EEs=Emergent events during observation period.
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.

APPEARS THIS WAY
ON ORIGINAL

Adverse Events Experienced by ≥ 5% of HITTS Patients

	HITTS					
	Historical Control			Argatroban		
Adverse Event[a,b]	EEs	Number of Patients (%)		AEs	Number of Patients (%)	
Total Number Of Patients		109			144	
Total Number Of Events	191	72	(66)	517	123	(85)
Pain	10	10	(9)	16	13	(9)
Peripheral Ischaemia	6	5	(5)	16	12	(8)
Hypotension	3	3	(3)	13	13	(9)
Constipation	0	0	(0)	13	12	(8)
Infection	0	0	(0)	13	10	(7)
Apnoea	4	4	(4)	12	12	(8)
Fever	2	2	(2)	12	12	(8)
Cardiac Arrest	4	4	(4)	12	11	(8)
Urinary Tract Infection	2	2	(2)	12	11	(8)
Embolism Pulmonary	8	7	(6)	12	10	(7)
Thrombophlebitis	3	2	(2)	11	10	(7)
Rash	3	3	(3)	10	10	(7)
Sepsis	1	1	(1)	9	9	(6)
Thrombophlebitis Deep	12	12	(11)	8	8	(6)
Vomiting	4	4	(4)	8	8	(6)
Confusion	2	2	(2)	8	8	(6)
Peripheral Gangrene	1	1	(1)	7	7	(5)
Pleural Effusion	1	1	(1)	7	7	(5)
Dyspnoea	7	7	(6)	6	6	(4)
Chest Pain	7	6	(6)	4	3	(2)
Oedema	8	8	(7)	1	1	(1)

EEs=Emergent events during observation period.
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.

Those adverse events that occurred more frequently in argatroban-treated than historical control HIT patients (by a difference of 5% or greater) are tabulated below.

Adverse Events That Occurred More Frequently in Argatroban-Treated Than Historical Control HIT Patients (by a difference of 5% or greater) FROM THE MOST FREQUENT ADVERSE EVENTS

EVENT Total Number of Patients	Historical Control Patients (%) 108	Argatroban Patients (%) 160
Diarrhea	5(5%)	17(11%)
Chest Pain	1(1%)	9(6%)
Dizziness	0(0%)	8(5%)

Those adverse events that occurred more frequently in argatroban-treated than historical control HITTS patients (by a difference of 5% or greater) are tabulated below.

Adverse Events That Occurred More Frequently in Argatroban-Treated Than Historical Control HITTS Patients (by a difference of 5% or greater) FROM THE MOST FREQUENT ADVERSE EVENTS

EVENT Total Number of Patients	Historical Control Patients (%) 109	Argatroban Patients (%) 144
Hypotension	3(3%)	13(9%)
Constipation	0(0%)	12(8%)
Infection	0(0%)	10(7%)
Fever	2(2%)	12(8%)
Urinary Tract Infection	2(2%)	11(8%)
Thrombophlebitis	2(2%)	10(7%)
Sepsis	1(1%)	9(6%)

Adverse events that occurred more frequently in historical control patients (by a difference of 5% or greater) in HITTS patients were "thrombophlebitis, deep": 8(6%) patients in the argatroban group compared to 12(11%) in the historical control group, and "edema": 1(1%) patient in the argatroban group compared to 8(7%) patients in the historical control group.

Bleeding Events

Major bleeding was defined as bleeding which was overt AND 1) was associated with a decrease in hemoglobin of ≥ 2 g/dL, 2) led to a transfusion of ≥ 2 units PRBCs, OR 3) was intracranial, retroperitoneal, or occurred into a major prosthetic joint. Bleeding was considered **minor** if it was reported but did not require more than 2 units of PRBCs. "Bleeds which did not require more than 2 units of blood were considered **insignificant** if they occurred prior to any exposure to argatroban or had no clinical relevance and no impact on the patient's condition." Bleeding events occuring six weeks or less prior to exposure to argatroban were recorded but not counted as major bleeds on treatment.

Note that significantly more argatroban-treated HIT patients received concomitant antithrombotic therapy (other than heparin): 134(84%) patients in the argatroban group compared to 76(70%) patients in the historical control group (p= 0.029*). Significantly fewer argatroban-treated HITTS patients received concomitant antithrombotic therapy (other than heparin): 122(85%) patients in the argatroban group compared to 105(96%) patients in the historical control group (p= 0.003*).

A summary of major and minor bleeding event rates is shown below (Table 47, vol. 105, p. 220).

Incidence of Major and Minor Bleeding

	HIT				HITTS			
	Historical Control		Argatroban[a]		Historical Control		Argatroban[a]	
Bleeding Site		(%)		(%)		(%)		(%)
Total Number of Patients	108		160		109		144	
Total Number of Bleeds								
Major Bleeds	7	(6.5)	5	(3.1)	10	(9.2)	15	(10.4)
P-value[b]		0.202				0.743		
Minor Bleeds	13	(12.0)	64	(40.0)	18	(16.5)	60	(41.7)

Number of patients having an event are counted once.
[a] Bleeding was recorded for 6 weeks prior to the study and during the study. The odds ratios (95% C.I). were 0.47 (0.14, 1.50) and 1.15 (0,50, 2.75) for the HIT and HITTS groups, respectively.
[b] P-value based on logistic regression modeling for the effect treatment.

No statistically significant difference in the rates of major bleeding were seen between argatroban and historical control groups for HIT or HITTS patients. The incidence of major bleeding in argatroban-treated patients was 3.1% in HIT patients, and 10.4% in HITTS patients.

* two-sided Fisher's Exact Test

Note that all major bleeding events, except one case in the HITTS historical control group, and ≥ 89% of all minor bleeding, occurred in the first 14 days following the discontinuation of heparin (vol. 5.1, p. 303).

Description of Major Bleeding Events

Argatroban-Treated Patients

A summary of major bleeding events that occurred in HIT and HITTS argatroban-treated patients is shown below (Table 49, vol. 105, pp. 223-225).

APPEARS THIS WAY
ON ORIGINAL

Description of Major Bleeding Events in Argatroban-treated Patients

PATIENT ID	BLEEDING SITE	TIME[a]	PRBC's in Units (dates)	DRUG exposure	COMMENTS[b]
002-007 HITTS	GI & Hgb & Hct Drop	0	3U (08/19-20/96)	08/18-19/96	Transfusions for low Hgb & Hct possibly related and argatroban was discontinued. Tarry stools 3 days after drug discontinuation, unlikely related. Patient on chemotherapy.
012-001 HITTS	Hematuria GI	5 15	2U (08/10/95) 2U (08/10/96)	07/26-08/11/96	Hematuria occurred on argatroban and urokinase possibly related. Drug was discontinued on 08/11/96 for mild bleeding possibly related. Other transfusions were given "to increase tissue oxygenation because of respiratory failure" (Investigator's comment).
015-001 HIT	GU	5	2U (06/19/96)	06/14-20/96	Investigator's comment: PRBCs given for low Hgb & Hct due to accidental discontinuation of Foley catheter. Not specifically for bleeding and unrelated. Drug was discontinued. Patient met criteria.
017-004 HIT	GI	2	2U (11/21/95)	11/18-21/95	Bright red blood per rectum. Drug was discontinued. Possibly related.
018-003 HITTS	Vascular surgery	4	5U (04/29/96)	04/25-05/04/96	Surgical bleeding during vascular surgery performed on argatroban on private IND. Drug was continued. Other prior transfusions given for anemia post-CABG.
020-009 HITTS	Multisystem hemorrhage	4	Multiple (between 07/04-05/95)	06/30-07/04/95	Coagulopathy, DIC occurring on multiple anticoagulants. She was also on warfarin, and was put on streptokinase concomitantly. Argatroban was increased up to 10 µg/kg/min according to record. Probably related. Death related to bleed.
029-005 HITTS	GU	9	2U (10/22-23/96)	10/23-28/96	Transfusion was given due to pre-existing anemia (SLE treated with steroids and cyclophosphamid). Mild vaginal bleed on 10/30 self terminating while on warfarin. Unrelated.
036-004 HITTS	Limb/ surgical procedures	2 & 3	5U (09/25/96) 3U (09/26/96)	09/23-27/96	Multiple cardiovascular surgical procedures with sepsis. Received transfusions post-surgery to maintain Hgb & Hct. He met criteria. Probably related to study drug.
037-002 HITTS	Limb	2	None	02/29-03/06/96	Mild bleed but no transfusion. Probably related.
037-005 HITTS	Fasciotomy	1	2U (05/28/96) Transfusions were given w/o bleeding	05/27-06/12/96	Bleeding at fasciotomy reported on 05/28 related to study drug. Other transfusions given in patient with post-CABG anemia, sepsis and debridement of infected mediastinostomy. She also had amputations post argatroban.
039-001 HITTS	GI & hematuria	3	2U (08/27/96)	08/24-27/95	Patient was on argatroban and warfarin. Argatroban was discontinued after gross bloody diarrhea and gross hematuria possibly related to study drug.
059-008 HIT	Hgb & Hct drop	1	None	03/07-16/96	Patient met criteria w/o bleeding site, possibly related. However, the patient received transfusions prior to study drug for severe anemia/malnutrition.
059-009 HITTS	GI	1	2U (06/19/97)	06/18-07/04/96	Patient with severe trauma, large cerebellar infarct (+ventriculostomy), gastrotomy feeding tube and tracheostomy. Drug was only discontinued on 07/04. Possibly related.

[a] Number of days on argatroban.
[b] Relationship with drug according to investigator.

Description of Major Bleeding Events in Argatroban-treated Patients continued...

PATIENT ID	BLEEDING SITE	TIME[a]	PRBC's In Units (dates)	DRUG exposure	COMMENTS[b]
063-003 HIT	DIC/sepsis with multiple sites	1	Multiple (03/16-19/96)	03/15-17/96	Multiple bleeding sites in DIC due to sepsis with other blood derivatives. Patient was also transfused prior to study entry. Drug was discontinued. Possibly related.
066-001 HITTS	Pulmonary hemorrhage	0	2U (04/14/96)	04/12/96	One hour after argatroban initiation, the patient experienced pulmonary hemorrhage on repeat suctioning. Drug was discontinued. Probably related.
077-001 HIT	GI	0	2U (03/18/96)	03/18/96	On argatroban for 6 hours, she became hypotensive probably GI bleeding. She had liver impairment suggesting ischemic hepatitis/enteritis. Drug was discontinued. Possibly related.
114-003 HITTS	GI	0	2U (09/17/96)	09/16-19/96	Underwent percutaneous endoscopic gastrotomy and had bleeding. Drug was continued. Post-procedural bleeding
130-001 HITTS	Hematuria (07/26/96)	7	2U (07/25/96) 2U (07/30/96)	07/19-08/04/96	No other bleeding events. Transfusions reported for anemia. Unrelated to study drug. Met criteria.
133-001 HITTS	GI	2	1U (08/17/96)	08/15-17/96	Bright red stools for which argatroban was discontinued. She received prior transfusions for anemia. Bleeding event possibly related.
138-001 HITTS	GI & Intra-aortic balloon pump	3	2 U post-treatment at amputation	09/05-09/96	Coagulopathy receiving procoagulant products. Mild GI bleed possibly related.

[a] Number of days on argatroban.
[b] Relationship with drug according to investigator.

APPEARS THIS WAY
ON ORIGINAL

Historical Control Patients

A summary of major bleeding events that occurred in HIT and HITTS historical control patients is shown below (Table 50, vol. 105, pp. 227-229).

Description of Major Bleeding Events in Historical Control Patients

PATIENT ID	BLEEDING SITE	TIME[a]	PRBC's in Units (dates)	DRUG exposure	COMMENTS[b]
001-H01 HITTS	GIx2	-	2U (11/28/95) 2U (12/09/95)	Warfarin	Mesenteric venous thrombosis was converted to warfarin on 12/07. Possible antiphospholipid antibody syndrome and mild DIC.
003-H01 HITTS	Hgb & Hct drop	-	9U (07/13/94) 5U (07/14/94)	Warfarin	Metastatic lung cancer. He underwent thrombectomy of the left leg and experienced severe bleedings at this site and IV site for central line. Fasciotomy was also performed. Patient was converted to warfarin.
015-H01 HIT	Hgb & Hct drop	-	2U (06/09/95) 2U (06/10/95) 2U (06/12/95)	Heparin	Quadriplegia underwent posterior decompression of the cervical spine on warfarin. She experienced sepsis and had many procedures.
020-H02 HIT	Hgb & Hct	-	3U (07/11/94)	Heparin	Post-CABG and anemia due to bleeding at the catheterization site. Pleural effusion.
020-H18 HIT	GI	-	Multiple transfusions (08/16-09/03/93)	Heparin	Patient underwent CABG and had pleural and pericardial effusions. Her Hgb & Hct dropped probably due to GI blood loss. She also had some melanotic stools probably due to arteriovenous malformation.
022-H02 HIT	Hgb & Hct drop Intracranial bleeding	-	FFP's only	Heparin and warfarin	Intracranial bleeding after re-exposure to heparin requiring ventricular drain.
040-H03 HITTS	GI	-	20U (07/14-31/94)	Warfarin and urokinase	Post-CABG on heparin and warfarin. Warfarin was continued and urokinase was tried. He had severe GI bleed requiring many transfusions. He underwent vagotomy and pyloroplasty.
056-H08 HIT	GU	-	Multiple transfusions (08/28-10/05/94)	Heparin	Necrotizing fasciitis underwent multiple debridements. Hemodialysis was started for acute tubular necrosis. She also received multiple transfusions for uterine and other sites during and post-heparin.
063-H01 HITTS	Groin and Hgb & Hct drop	-	3U (08/25/94)	Heparin and [redacted]	Patient experienced major bleeding at the groin while on heparin for acute MI undergoing PTCA and pacemaker placement. She also received streptokinase for her massive pulmonary embolism on 08/24 and 25.
091-H03 HIT	Hgb & Hct drop	-	3U (12/11/95) 1U (12/12/95) 5U (12/13/95)	Heparin	Traumatic leg wound (MVA) with sepsis. Underwent procedures on bone and muscles on heparin and developed DVT for which heparin was still prescribed. Platelet transfusions were also given. Patient was amputated (BKA) on 12/13.
140-H02 HITTS	Post-catheterization bleed	-	Multiple transfusions (05/20-23/96)	Heparin and urokinase	Patient with complex medical story including subdural hematoma and aortic aneurysm repair with possible MI underwent angiography on heparin. Hemostasis of right femoral artery was complicated. Patient also had thrombosis and ischemia right leg and had thrombectomy, then bypass with urokinase.
200-H26 HITTS	Pulmonary hemorrhage	-	2U (01/28/94) 2U (02/02/94)	[redacted]	Multiple injuries (MVA) Spinal fusion, DVT on heparin requiring [redacted] filter occurred on 01/17, and sepsis on 01/18. She was put on ancrod on 01/25 and developed pulmonary and vaginal bleeding on 01/27 and 02/02-04.

[a] Number of days on argatroban.
[b] Relationship with drug according to investigator.

Description of Major Bleeding Events in Historical Control Patients cont...

PATIENT ID	BLEEDING SITE	TIME[a]	PRBC's in Units (dates)	DRUG exposure	COMMENTS[b]
200-H33 HITTS	Retroperitoneal	-	4U (04/17/93)	[redacted]	Metastatic lung cancer with DIC was initially treated with heparin, was converted to warfarin and switched to ancrod before being finally switched to danaproid. He developed retroperitoneal bleeding and danaproid was temporarily suspended.
200-H42 HITTS	Hematemesis	-	4U (05/01-02/92)	[redacted] warfarin	Patient underwent thrombectomy for leg ischemia and developed Thrombocytopenia and DIC initially treated with IV IgG. He was treated with ancrod (04/29-05/03) and warfarin was added from 04/30 on. He had hematemesis on 05/02.
200-H45 HIT	Hemoptysis	-	3U (02/17/93) 1U (02/18/93)	[redacted]	Knee surgery for which he received prophylactic heparin. He was treated with ancrod and warfarin for PE for 7 days. Hemoptysis and H & H drop occurred on 02/17-22.
201-H13 HITTS	Hematemesis	-	No PRBC's	warfarin	Metastatic carcinoma was treated with heparin and warfarin was added on until INR became therapeutic. At that time, the patient had severe hematemesis treated with platelet transfusions.
202-H06 HITTS	Pulmonary artery hemorrhage	-	4U (12/19/94)	[redacted]	Crohn's disease receiving prophylactic heparin after intestinal resection. At the end of heparin treatment while patient presented HITTS, she was switched to ancrod and a Swanz-Ganz was inserted leading to pulmonary artery hemorrhage.

[a] Number of days on argatroban.
[b] Relationship with drug according to investigator.

Most major bleeding sites were gastrointestinal, genitourinary, or related to a procedure or surgery. In the historical control group, there was a intracranial bleed (on heparin and warfarin) and a retroperitoneal bleed (on [redacted].

A summary of the occurrence of major bleeding in argatroban-treated patients and their corresponding APTT values is shown below (Table 48, vol. 105, p. 221).

Occurrence of Major Bleeding and APTT Values in Argatroban-Treated Patients

	HIT		HITTS	
	Major Bleed.		Major Bleed	
	Yes	No	Yes	No
aPTT Levels[a]	N (%)	N (%)	N (%)	N (%)
Total Number of Patients	157		142	
≤ 3 x Baseline	2 (1)	105 (67)	5 (4)	67 (47)
>3 x Baseline	3 (2)	47 (30)	10 (7)	60 (42)

For HIT patients: 020-021, 020-033, 138-003, and for HITTS patients: 052-003, 133-004, the baseline or maximum aPTT is not available.
[a] Maximum aPTT level per patient during the initial 14 days of treatment.

Of the 5 HIT patients who experienced a major bleed, 3 (or 60%) of these patients had a treatment APTT of > 3x baseline. Of the 15 HITTS patients, 10 (or 67%) had a treatment APTT of > 3x baseline.

A summary of blood or blood component use **during the argatroban infusion period** for HIT and HITTS patients is shown below (Tables 52 and 53, vol. 105, pp. 236-240).

Blood and Blood Component Transfusions for HIT Patients

	HIT					
	Historical Control			Argatroban		
	Number of Transfusions	Number of Patients[a]		Number of Transfusions	Number of Patients[a]	
		N	(%)		N	(%)
Total Number of Patients		108			160	
During the Study						
Total Transfusions	209	58	(53.7)	177	59	(36.9)
Blood Component Used:						
PRBC	128	48	(44.4)	116	52	(32.5)
Platelets	35	22	(20.4)	20	8	(5.0)
Fresh Frozen Plasma	31	13	(12.0)	27	10	(6.3)
Pladsol	7	1	(0.9)			
Albumin	2	2	(1.9)			
Colloid-5% Albumin	2	1	(0.9)			
Platelet Pheresis	1	1	(0.9)	1	1	(0.6)
Autotransfusion	1	1	(0.9)			
Anti-Rhesus (D)	1	1	(0.9)			
Other, Unspecified	1	1	(0.9)			
Cryoprecipitate				5	3	(1.9)
PRBC-Leukoreduced				4	1	(0.6)
Plasma Protein Fraction				3	2	(1.3)
Plasmanate				1	1	(0.6)

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

APPEARS THIS WAY
ON ORIGINAL

Blood and Blood Component Transfusions for HITTS Patients

	HITTS					
	Historical Control			Argatroban		
	Number of Transfusions	Patients[a] N	(%)	Number of Transfusions	Patients[a] N	(%)
During The Study						
Total Transfusions	154	55	(50.5)	209	69	(47.9)
Blood Component Used:						
PRBC	83	49	(45.0)	135	60	(41.7)
Platelets	32	16	(14.7)	16	12	(8.3)
Fresh Frozen Plasma	24	17	(15.6)	47	19	(13.2)
Erythropoietin	5	1	(0.9)			
Albumin	3	2	(1.8)	5	3	(2.1)
Cryoprecipitate	3	3	(2.8)	1	1	(0.7)
IgG, Hi-Dose IV	3	1	(0.9)			
Antithrombin	1	1	(0.9)			
Autotransfusion				3	2	(1.4)
Platelets, Single Donor				1	1	(0.7)
Unknown				1	1	(0.7)

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

Total transfusions in the HIT population were significantly greater in the historical control patients: 59(37%) argatroban-treated patients compared to 58(54%) historical control patients (p= 0.008*). This observation was due in part to greater PRBC transfusions: 52(33%) argatroban-treated patients compared to 48(44%) historical control patients (p= 0.054*), and significantly more platelet transfusions: 8(5%) argatroban-treated patients compared to 22(20%) historical control patients (p= 0.0001*), seen in the historical control group.

Total transfusions, including PRBC and platelet transfusions, were not significantly different between argatroban-treated and historical control patients in the HITTS population.

* two-sided Fisher's Exact Test

Minor Bleeding Events

Minor bleeding, recorded for 6 weeks **prior to**, and **during** the study for argatroban-treated patients, was significantly higher in the argatroban group. The relevance of this comparison

is unclear. Further, the sponsor stated that **"minor bleeds were heavily biased against test drug because there was no way of retrospectively identifying minor bleeds in the historical control group"** (vol. 105, p. 235). A description of the types of minor bleeding seen in argatroban-treated patients is shown below. Note that if patients had more than one minor bleed, only the first bleed after the initiation of treatment or discontinuation of heparin is listed (vol. 4.5, p. 4).

Characterization of Minor Bleeding (Transfusion Requiring)

Type of Bleed	HIT		HITTS	
	Hist Control n=108	Argatroban n=160	Hist Control n=109	Argatroban n=144
GI	2(2%)	1(1%)	0(0%)	5(3%)
GU*	1(1%)	2(1%)	0(0%)	0(0%)
Limb sites**	0(0%)	0(0%)	2(2%)	2(1%)
Thoracic	1(1%)	3(2%)	0(0%)	2(1%)
Hematuria	0(0%)	0(0%)	1(1%)	1(1%)
Hemoptysis	1(1%)	0(0%)	0(0%)	1(1%)
Abdominal	0(0%)	3(2%)	0(0%)	0(0%)
CABG	0(0%)	3(2%)	1(1%)	2(1%)

* includes catheterizations and instrumentation in the groin
** includes injection and infusion sites in the extremities

**Characterization of Minor Bleeding
(NON-Transfusion Requiring)**

Type of Bleed	HIT		HITTS	
	Hist Control n=108	Argatroban n=160	Hist Control n=109	Argatroban n=144
GI	1(1%)	10(6%)	1(1%)	11(8%)
GU*	3(3%)	14(9%)	2(2%)	8(6%)
Limb sites**	1(1%)	8(5%)	0(0%)	8(6%)
Thoracic	0(0%)	3(2%)	1(1%)	1(1%)
Hematuria	1(1%)	5(3%)	1(1%)	2(1%)
Hemoptysis	0(0%)	11(7%)	2(2%)	3(2%)
Abdominal	0(0%)	2(1%)	2(2%)	0(0%)
CABG	0(0%)	0(0%)	1(1%)	0(0%)
Brachial	1(1%)	0(0%)	1(1%)	2(1%)
Oral	1(1%)	0(0%)	0(0%)	3(2%)
Epistaxis	0(0%)	2(1%)	1(1%)	1(1%)
Other	0(0%)	0(0%)	0(0%)	2(1%)
Hematemesis	0(0%)	0(0%)	1(1%)	1(1%)
Optic	0(0%)	1(1%)	0(0%)	0(0%)

* includes catheterizations and instrumentation in the groin
** includes injection and infusion sites in the extremities

The highest rate of transfusion-requiring minor bleeding for argatroban-treated HIT patients was a 2% incidence of GU-, Thoracic-, Abdominal-, and CABG-related bleeding. The highest rate of transfusion-requiring minor bleeding for argatroban-treated HITTS patients was a 3% incidence of GI bleeding.

The highest rates of non-transfusion-requiring minor bleeding for argatroban-treated HIT patients were: GI (6%), GU (9%), Limb sites (5%), and Hemopytsis (7%). The highest rates of non-transfusion-requiring minor bleeding for argatroban-treated HITTS patients were: GI (8%), GU (6%), and Limb sites (6%).

Evaluation of Laboratory Parameters

APTT Values

A summary of mean and median APTT values in the first 72 hours following argatroban administration for HIT and HITTS patients is shown below (Appendix 16.2.65 vol. 128).

APTT Values in the First 72 Hours Following Argatroban Administration

POPULATION	TIME (HRS) (a)	N	Mean	MEDIAN	MINIMUM	MAXIMUM
HIT	BASELINE	154	37.4	29.9		
	<=12 HRS	154	65.3	60.4		
	>12 - <=24 HRS	115	65.9	61.1		
	>24 - <=36 HRS	103	60.7	57.8		
	>36 - <=48 HRS	95	61.2	58.0		
	>48 - <=60 HRS	85	57.7	56.9		
	>60 - <=72 HRS	76	59.0	57.4		
HITTS	BASELINE	139	34.4	29.9		
	<=12 HRS	136	71.3	67.5		
	>12 - <=24 HRS	106	72.2	69.5		
	>24 - <=36 HRS	109	69.7	66.0		
	>36 - <=48 HRS	92	65.8	63.7		
	>48 - <=60 HRS	90	64.1	63.1		
	>69 - <=72 HRS	92	61.1	60.3		

Note that an APTT value in the target range of 45-90 seconds (or 1.5-3.0 x control) was obtained by the first 12 hours of argatroban administration in both HIT and HITTS patients. APTT values in the target therapeutic range were maintained for the duration of study therapy for both HIT and HITTS patients.

INR Values

The maximum International Normalization Ratio (INR) values for HIT and HITTS patients prior to argatroban administration, prior to the start of warfarin, while on argatroban and warfarin, and after argatroban was stopped (and warfarin continued), are summarized below (Table 61, vol. 105, pp. 269-70).

Maximum INR Values for Argatroban-Treated Patients Who Received Concurrent Warfarin

	HIT				HITTS			
Average Dose Group[a]	Prestudy[b]	Argatroban[c]	Argatroban +Warfarin[d]	Warfarin[e]	Prestudy[b]	Argatroban[c]	Argatroban +Warfarin[d]	Warfarin[e]
0.1 - 0.5								
N	1	7	7	4	2	7	7	8
Median	3	6	4.4	4	3.4	5.2	5.3	2.7
Interquartile Range								
>0.5 - 1.0								
N	4	11	13	13	3	7	8	8
Median	1.8	7.7	4.7	3.1	1	6.1	6	3.8
Interquartile Range								
>1.0 - 2.0								
N	13	36	42	37	11	27	37	28
Median	1.8	4.8	5	2.5	1.3	4.2	6.4	2.8
Interquartile Range								
>2.0 - 3.0								
N	7	16	20	16	8	24	28	20
Median	1.1	3.9	4.5	2	1.2	4.4	6.3	2.7
Interquartile Range								
>3.0 - 4.0								
N	2	7	9	8	1	7	9	7
Median	1.2	2.7	4.2	2.6	2	6.2	6.5	2.5
Interquartile Range								
>4.0 - 5.0								
N		1	2	2	1		1	
Median		4.4	5.9	2	1.5		5.4	
Interquartile Range								
> 5.0								
N		1	1	1		2	3	1
Median		2.8	3.2	2.4		6.8	2.9	1.9
Interquartile Range								

[a] Average Dose=Sum of all volumes times 1000 mg/mL divided by pre physical exam body weight divided by total number of maximum platelet response argatroban infusion. Excludes patients where average dose could not be determined.
[b] Baseline INR prior to the initiation of the argatroban infusion.
[c] Maximum INR while patient on argatroban prior to the start of warfarin.
[d] Maximum INR while patient on argatroban and warfarin.
[e] Maximum INR after patient stopped argatroban.

Note that median INR values of as high as 7.7 were seen in argatroban-only treated patients. Thus, monitoring the INR to assess the degree of anticoagulation secondary to warfarin given concurrently with argatroban will not be appropriate.

Clinical Laboratory Chemistry Parameters

The only notable changes from baseline in laboratory chemistry values (including liver function tests) in argatroban-treated patients were small median increases in Alkaline Phosphatase values from 87 U/L at baseline to 99 U/L (within 24 hours post-infusion or at discharge) in HIT patients, and 98 U/L to 104 U/L in HITTS patients. No significant concomitant changes in SGOT, SGPT, bilirubin, or GGT values were noted (Appendix

16.2.54, vol. 128). No significant changes from baseline in renal function tests or uric acid values were seen.

Clinical Laboratory Hematology Parameters

No clinically significant changes from baseline in laboratory hematology values were noted for argatroban-treated patients except for platelet counts, which are shown below (Appendix 16.2.57, vol. 128).

Platelet Counts at Baseline and Post-Infusion

Parameter	HIT		HITTS	
	Historical Control	Argatroban	Historical Control	Argatroban
Platelet (thou/mcL)				
Baseline				
N	100	86	99	94
Median	81	86	72	69
Interquartile Range				
Post Infusion[a]				
N	100	86	99	94
Median	166.5	188	215	200.5
Interquartile Range				
Change from Baseline				
N	100	86	99	94
Median	79.5	89.5	139	122.5
Interquartile Range				

Smith-Kline data used where both baseline and post available, otherwise local lab data used where both baseline and post available

[a] Within 24 hours post infusion or at discharge.

Vital Signs

No clinically significant changes in blood pressure or respiratory rate were seen in argatroban-treated patients.

APPEARS THIS WAY
ON ORIGINAL

STUDY ARG-915

Introduction

Study ARG-915 was a compassionate-use, open-label study that was initiated following the completion of study ARG-911. The study enrolled 271 patients between 11/96 and 10/97, and results from the first 174 patients are now submitted to support the results of the pivotal study ARG-911. Safety and efficacy outcomes for patients enrolled in study ARG-915, were compared to the same historical control group used in study ARG-911.

Study ARG-915 was conducted at 62 of the same sites employed in study ARG-911. Study sites which enrolled greater than 5 patients are shown below (vol. 4.7, pp. 40-3).

Study Sites with ≥ 5 Patients

Investigator	Site Number	Number of Patients Enrolled
Bartholomew, J	002	8
Lewis, B	020	8
Zehnder, J	036	8
Zeigler, Z	037	6
Andes, WA	039	6
Bengston, J	043	8
Lerner, R	113	13
Wiseman, A	114	9

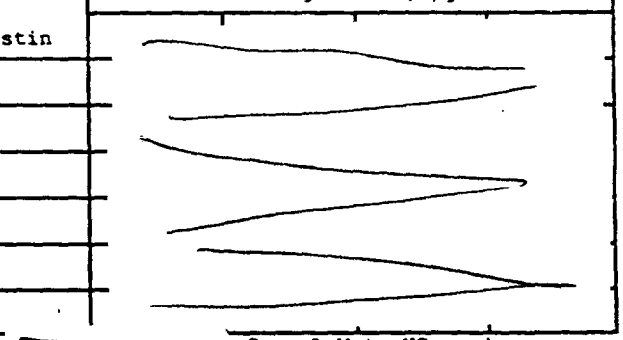
The original protocol for study ARG-195 was dated 9/9/96. Protocols for ARG-911 and ARG-915 were compared (Section 16.1.1.3, vol. 107, pp. 90ff, and vol. 12.1, pp. 85ff). Notable differences were: 1) The following exclusion criteria were included in study ARG-915, and not in study ARG-911: "terminally ill patients with a life expectancy of less than 2 weeks," and "anticipated long-term (more than 2 weeks) use of a thrombin inhibitor," and 2) It is stated in study ARG-915 that, "No sample population size needs to be predefined since the main objective is to continue to offer argatroban to patients requiring the drug during the regulatory review cycle." It is further stated in study ARG-915 that, "the primary efficacy measures will be to obtain adequate anticoagulation to prevent new thrombosis, limb amputation, or death."

Amendment #1 to study ARG-915, dated 9/12/97, introduced specific dosing instructions for patients with hepatic impairment, and changed the primary efficacy endpoint to "the incidence of new thrombosis, limb amputation due to ischemic complications secondary to HIT/HITTS, and/or death due to thrombosis."

Amendment #2, dated 10/13/97, named the continuation of study ARG-915 as ARG-915X(Extension), and introduced the following information regarding the concomitant use of argatroban and warfarin: "If the patient needs to transition to oral anticoagulant therapy then the investigator should be aware that the concomitant use of argatroban and warfarin results in prolongation of the prothrombin time and INR." "Minimize the combined effects on the PT and INR by using a thromboplastin reagent with a low ISI (i.e. close to 1.0) and/or by decreasing the plasma argatroban concentration (i.e., lowering the argatroban dose), as shown below (Appendix D, vol. 12.1, p. 147).

Effects of Plasma Argatroban and Thromboplastin ISI on the INR

Degree of Warfarinization	ISI* of Thromboplastin	Plasma Argatroban, µg/mL**
None (Normal pool)	1.05	
	2.01	
Low (Pool "A")	1.05	
	2.01	
Higher (Pool "B")	1.05	
	2.01	



* For a photo-optical instrument; Coag-A-Mate XC used.
** Concentrations typical for NOVASTAN® doses of 0, 1, 2.5, and 5 µg/kg/min.

Patient Disposition

All patients enrolled in study ARG-915 were included in the intention-to-treat, evaluable, and safety populations. There were 70 HIT patients, 89 HITTS patients, and 15 patients with a previous diagnosis of HIT or HITTS. Heparin-induced antibody serology was not consistently collected/required for patients in this study, so that an SRA-positive population was not available.

A total of 20% of HIT patients and 18% of HITTS patients prematurely discontinued argatroban therapy in study ARG-915. By comparison, 13% of HIT, and 6% of HITTS patients prematurely discontinued argatroban therapy in study ARG-911. A total of 6% of HIT and 8% of HITTS patients in study ARG-915 discontinued due to an adverse event. A summary of the reasons for premature discontinuation of patients enrolled in study ARG-915 is shown below (Table 3, vol. 12.1, p. 14).

Patients Prematurely Discontinuing Argatroban in Study ARG-915

Reason for Premature Discontinuation	HIT N	HIT (%)	HITTS N	HITTS (%)
Total Number of Patients	85	(100)	89	(100)
Total Number Discontinued	17	(20)	16	(18)
Discontinued*				
Adverse Event	5	(6)	7	(8)
Surgery	3	(4)	3	(3)
Patient request to withdraw	0		1	(1)
Other	9	(11)	5	(6)

* Patients may be included in more than one group.

Patient Demographics

No significant differences between argatroban-treated and historical control HIT and HITTS patients were reported. Patients were mean age 65 years, 49% were male, 91% were Caucasian, mean weight was 79 kg, and mean height was 168 cm.

Mean Dose, Duration, and Delay of Argatroban Administration

The mean argatroban dose was 1.9 mcg/kg/min in HIT patients, and 2.5 mcg/kg/min in HITTS patients enrolled in study ARG-915. By comparison, the mean argatroban dose in study ARG-911 was 2.0 mcg/kg/min and 1.9 mcg/kg/min in HIT and HITTS patients, respectively.

The mean duration of argatroban therapy was 4.9 days in HIT patients and 7.3 days in HITTS patients in study ARG-915. By comparison, the mean duration in study ARG-911 was 5.3 days and 5.9 days in HIT and HITTS, respectively.

The mean number of days from discontinuation of heparin to intiation of argatroban therapy was 1.6 days in HIT patients and 2.4 days in HITTS patients enrolled in study ARG-915. By comparison, the mean delay in study ARG-911 was 1.0 days and 3.1 days in HIT and HITTS patients, respectively.

Patient Baseline Characteristics

A summary of medical/surgical/invasive procedure history of patients (by ICD-9 coded terms) by body system and **diseases** is shown below.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Baseline Medical/Surgical/Invasive Procedure History by Body System and Disease

	HIT			HITTS		
Body System** Total Number of Patients	Histor. Control N(%) 108	Argatro-ban N(%) 85	p-value*	Histor. Control N(%) 109	Argatro-ban N(%) 89	p-value*
Circulatory System	96(89)	81(95)	0.123	104(95)	82(92)	0.381
Symptoms, Signs, and Ill-Defined Conditions	58(54)	42(49)	0.565	55(51)	46(52)	N.S.
Endocrine, Nutritional, Metabolic, and Immunity	50(46)	50(59)	0.110	52(48)	62(70)	0.002
Injury and Poisoning	46(43)	22(26)	0.023	37(34)	28(32)	N.S.
Respiratory System	40(37)	35(41)	0.656	38(35)	40(45)	0.188
Digestive System	39(36)	30(35)	N.S.	33(30)	34(38)	0.291
Blood and Blood-Forming Organs	36(33)	28(33)	N.S.	52(48)	46(52)	0.668
Genitourinary System	31(29)	40(47)	0.011	22(20)	33(37)	0.011
Musculoskeletal and Connective Tissue Systems	29(27)	22(26)	N.S.	51(47)	24(27)	0.005
Nervous System and Sense Organs	27(25)	12(14)	0.072	14(13)	17(19)	0.244
Infectious Diseases	15(14)	16(19)	0.431	11(10)	10(11)	N.S.
Mental Disorders	23(21)	23(27)	0.397	42(39)	14(16)	0.0004
Neoplasms	14(13)	8(9)	0.500	22(20)	7(8)	0.016
Skin and Subcutaneous Tissue	8 (7)	9(11)	0.455	9 (8)	11(12)	0.355
Congenital Anomalies	5 (5)	8(9)	N.S.	4 (4)	8(9)	0.142
Pregnancy, Childbirth, and Puerperium	1 (1)	0(0)	N.S.	2 (2)	0(0)	N.S.
Other Factors Influencing Health Status	15(14)	3(4)	0.023	15(14)	1(1)	0.001

* two-sided Fisher's Exact Test
** Patients are counted once per body system

Adapted from Sponsor's Table 7, vol. 12.1, p. 20-1

Statistically significant differences in the baseline disease status of argatroban-treated and historical control HIT patients included greater incidences of "injury and poisoning" and "other factors influencing health status" in **historical control patients.** There was a greater incidence of "genitourinary system disease" in **argatroban-treated HIT patients.**

For HITTS patients, significantly greater incidences of "musculoskeletal and connective tissue system diseases," "mental disorders," and "neoplasms" were seen in **historical control patients.** Significantly greater incidences of "endocrine, nutritional, metabolic, and immunity disorders," and "genitourinary system disorders" were seen in **argatroban-treated HITTS patients.**

The baseline medical/surgical/invasive procedure history of patients (by ICD-9 coded terms) by body system and **surgeries** (including ongoing procedures or previous surgery) is summarized below.

Baseline Surgeries for Study ARG-915

	HIT			HITTS		
TYPE OF SURGERIES Total Number of Patients	Histor. Control N(%) 108	Argatro-ban N(%) 85	p-value*	Histor. Control N(%) 109	Argatro-ban N(%) 89	p-value*
Cardiovascular System	86(80)	75(88)	0.123	82(75)	80(90)	0.001
Misc. Diagnostic and Therapeutic Procedures	56(52)	38(45)	0.384	51(47)	38(43)	N.S.
Digestive System	52(48)	36(42)	0.468	51(47)	36(41)	N.S.
Respiratory System	35(32)	24(28)	0.637	19(17)	17(19)	N.S.
Musculoskeletal System	28(26)	12(14)	0.050	33(30)	14(16)	0.019
Female Genital Organs	21(19)	15(18)	N.S.	25(23)	14(16)	0.215
Integumentary System	14(13)	8(9)	0.500	3(3)	6(7)	0.304
ENT	11(10)	10(12)	N.S.	14(13)	12(14)	N.S.
Male Genital Organs	11(10)	4(5)	0.185	7(6)	4(5)	N.S.
Urinary System	11(10)	6(7)	0.610	3(3)	8(9)	0.067
Nervous System	5(5)	4(5)	N.S.	7(6)	3(3)	N.S.
Obstetrical Procedures	5(5)	1(1)	0.231	1(1)	3(3)	N.S.
Heme and Lymph System	1(1)	4(5)	0.171	2(2)	3(3)	N.S.
* two-sided Fisher's Exact Test						

Adapted from Sponsor's Table 7, vol. 12.1, p. 19

For HIT and HITTS patients, musculoskeletal system surgeries were significantly greater in **historical control patients.** Cardiovascular system-related surgeries were more frequent in **argatroban-treated HITTS patients.**

A summary of patient medical/surgical/invasive procedure history by **body system** and **medical history**, is shown below. (Tables 6 and 8, vol. 12.1, pp.18 and 23)

Summary of Medical/Surgical/Invasive Procedure History (from ICD-9 coded terms) by Body System

	HIT				HITTS			
	Historical Control		Argatroban		Historical Control		Argatroban	
Body System[a]	N	(%)	N	(%)	P-value	N	(%)	N	(%)	P-value
Total Number of Patients	108		85			109		89		
Cardiovascular	102	(94)	85	(100)	0.035	108	(99)	86	(98)	0.587
Miscellaneous/Ill Defined	83	(77)	58	(68)	0.194	79	(73)	66	(75)	0.746
Neuromuscular	70	(65)	52	(61)	0.653	87	(80)	48	(55)	<0.001
Digestive	64	(59)	47	(55)	0.660	62	(57)	53	(60)	0.665
Respiratory	62	(57)	47	(55)	0.772	54	(50)	49	(56)	0.473
Genito-Urinary	62	(57)	54	(64)	0.459	49	(45)	50	(57)	0.115
Diabetes/Endocrine	52	(48)	50	(59)	0.149	53	(49)	63	(72)	0.001
Injury and Poisoning	46	(43)	22	(26)	0.022	37	(34)	28	(32)	0.763
Oncology & Hematology	44	(41)	36	(42)	0.883	64	(59)	50	(57)	0.885
Dermatology	20	(19)	15	(18)	1.00	12	(11)	17	(19)	0.110
Infectious/Parasitic Diseases	15	(14)	16	(19)	0.431	11	(10)	10	(11)	0.819

A patient is counted once per body system.
[a] Recoded using ICD-9
Statistical comparisons made with Fisher's Exact Test.

APPEARS THIS WAY
ON ORIGINAL

Summary of Medical/Surgical/Invasive Procedure History (from ICD-9 coded terms) by Medical History

	HIT			HITTS		
	Historical Control	Argatroban		Historical Control	Argatroban	
Medical History	N (%)	N (%)	P-value	N (%)	N (%)	P-value
Total Number of Patients	108	85		109	89	
Cancer	10 (9.3)	8 (9.4)	1.00	17 (15.6)	3 (3.4)	0.004
Renal Impairment	14 (13.0)	22 (25.9)	0.026	6 (5.5)	15 (16.8)	0.011
Hepatic Impairment	5 (4.6)	2 (2.3)	0.468	1 (0.9)	6 (6.7)	0.047
Diabetes	28 (25.9)	19 (22.3)	0.615	27 (24.8)	33 (37.1)	0.065
Sepsis	6 (5.6)	9 (10.6)	0.279	3 (2.8)	7 (7.9)	0.116
Lupus Erythematosus	2 (1.9)	0 (0.0)	0.505	1 (0.9)	2 (2.2)	0.589
Respiratory Distress Syndrome	19 (17.6)	7 (8.2)	0.088	12 (11.0)	8 (9.0)	0.813
Ongoing Procedures						
Receiving Hemodialysis	4 (3.7)	2 (2.3)	0.696	1 (0.9)	0 (0.0)	1.00
On Circulatory Assist Device	7 (6.5)	13 (15.3)	0.058	2 (1.8)	15 (16.8)	<0.001
Undergoing Ventilation	13 (12.0)	0 (0.0)	<0.001	9 (8.3)	2 (2.2)	0.116
Previous Surgery						
Previous CABG	39 (36.1)	27 (31.8)	0.545	26 (23.9)	45 (50.6)	<0.001

Statistical comparisons made with Fisher's Exact Test.

APPEARS THIS WAY ON ORIGINAL

When the baseline patient characteristics were organized by medical history, significantly greater renal impairment was seen in both HIT and HITTS **argatroban-treated patients.** A greater incidence of hepatic impairment, being on a circulatory assist device, and a history of a previous CABG were seen in **argatroban-treated HITTS patients.** For **historical control patients,** a significantly greater incidence of cancer (in HITTS patients), and ongoing mechanical ventilation (in HIT patients) were reported. A numerically greater incidence of diabetes (in HITTS patients), and being on a circulatory assist device (in HIT patients) were seen for **argatroban-treated patients** compared to historical control patients. The incidence of the respiratory distress syndrome was numerically greater in **historical control HIT patients.**

Note that, compared to the imbalances in baseline characteristics of patients enrolled in study ARG-911, (where argatroban-treated patients were uniformly more compromised than historical control patients), study populations were much more similar in study ARG-915, with historical control patients often

Concomitant Medications

Concomitant medications (other than heparin) are listed below by the Anatomical/Therapeutic/Chemical (ATC) classification scheme (Table 9, vol. 12.1, pp. 25-6).

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Concomitant Medications (Other than Heparin)

ATC Classification	HIT		HITTS	
	Historical Control N (%)	Argatroban N (%)	Historical Control N (%)	Argatroban N (%)
Any Medication	108	85	109	89
Antacids, Drugs for Treatment of Peptic Ulcer and Flatulence	78 (72.2)	68 (80.0)	81 (74.3)	71 (79.8)
Psycholeptics	66 (61.1)	50 (58.8)	71 (65.1)	62 (69.7)
Analgesics	91 (84.3)	65 (76.5)	93 (85.3)	74 (83.2)
Cardiac Therapy	69 (63.9)	48 (56.5)	55 (50.5)	62 (69.7)
Mineral Supplements	59 (54.6)	44 (51.8)	39 (35.8)	43 (48.3)
Antibacterials for Systemic Use	77 (71.3)	51 (60.0)	65 (59.6)	66 (74.2)
Diuretics	61 (56.5)	44 (51.8)	49 (45.0)	63 (70.8)
Antithrombotic Agents	76 (70.4)	65 (76.5)	105 (96.3)	73 (82.0)
Laxatives	60 (55.6)	32 (37.7)	64 (58.7)	49 (55.1)
Calcium Channel Blockers	38 (35.2)	29 (34.1)	24 (22.0)	23 (25.8)
Drugs Used in Diabetes	34 (31.5)	29 (34.1)	32 (29.4)	37 (41.6)
Plasma Substitutes and Perfusion Solutions	24 (22.2)	8 (9.4)	15 (13.8)	12 (13.5)
Agents Acting on the Renin-Angiotensin System	25 (23.2)	29 (34.1)	15 (13.8)	30 (33.7)
Beta Blocking Agents	30 (27.8)	25 (29.4)	27 (24.8)	32 (36.0)
Antispasmodic and Anticholinergic Agents and Propulsive	18 (16.7)	19 (22.4)	21 (19.3)	19 (21.4)
Anesthetics	16 (14.8)	12 (14.1)	23 (21.1)	14 (15.7)
Antianemic Preparations	34 (31.5)	22 (25.9)	21 (19.3)	20 (22.5)
Antipruritics, Including Antihistamine, Anesthetic, etc.	17 (15.7)	14 (16.5)	20 (18.4)	20 (22.5)
Anti-Asthmatics	37 (34.3)	22 (25.9)	32 (29.4)	18 (20.2)
Vitamins	17 (15.7)	16 (18.8)	15 (13.8)	13 (14.6)
Corticosteroids for Systemic Use	17 (15.7)	17 (20.0)	18 (16.5)	14 (15.7)
Muscle Relaxants	14 (13.0)	4 (4.7)	15 (13.8)	6 (6.7)
Antidiarrhea, Intestinal Antiinflammatory/ Antiinfection Agents	20 (18.5)	16 (18.8)	13 (11.9)	17 (19.1)
Antihemorrhagics	15 (13.9)	12 (14.1)	16 (14.7)	13 (14.6)
Thyroid Therapy	8 (7.4)	8 (9.4)	6 (5.5)	12 (13.5)
Psychoanaleptics	7 (6.5)	9 (10.6)	9 (8.3)	7 (7.9)
Cough and Cold Preparations	5 (4.6)	4 (4.7)	5 (4.6)	4 (4.5)
Unable to be Classified	26 (24.1)	76 (89.4)	19 (17.4)	74 (83.2)
Antihistamines for Systemic Use	11 (10.2)	5 (5.9)	25 (22.9)	2 (2.3)
Antihy;ertensives	17 (15.7)	8 (9.4)	10 (9.2)	9 (10.1)
Antiinflammatory and Antirheumatic Products	14 (13.0)	3 (3.5)	10 (9.2)	3 (3.4)
Ophthalmologicals	13 (12.0)	5 (5.9)	11 (10.1)	3 (3.4)
Other Hematological Agents	9 (8.3)	0 (0.0)	30 (27.5)	0 (0.0)

For HIT patients, significantly greater use of concomitant laxatives (p=0.014*), plasma substitutes and perfusion solutions (p=0.020*), antiinflammatory and antirheumatic products (p=0.023*), and other hematologic agents (p=0.005*) were reported in historical control patients.

For HITTS patients, significantly greater use of concomitant antithrombotic (p=0.001*), systemic antihistamines (p <0.0001*), and other hematologic agents (p <0.0001*) were reported in historical control patients. Significantly greater use of concomitant cardiac medications (p=0.009*), systemic antibacterials (p=0.035*), diuretics p=0.0003*), and renin-angiotensin inhibitors (p=0.001*) were reported in argatroban-treated patients.

* two-sided Fisher's Exact Test

Concomitant Antithrombotic Medications

A summary of concomitant antithrombotic medications is summarized below (vol. 12.1, p. 27).

Concomitant Antithrombotic Medications

	HIT		HITTS	
	Historical Controls	Argatroban 915	Historical Controls	Argatroban 915
Warfarin sodium	24	32	54	28
Acetylsalicyclic Acid	15	3	12	4
Urokinase	3	0	1	1
Ticlopidine	1	0	0	0
Heparin	7	3	0	1
Heparin Fraction, Na salt	0	0	3	0
Dipyridamole	0	0	1	0
LMH	0	0	0	1
Warfarin + acetylsalicyclic acid	3	7	3	7
Warfarin + Urokinase	0	1	0	2
Warfarin + Ticlopidine	1	1	0	0
Warfarin + Heparin Fraction	4	4	2	4
Warfarin + PA	0	1	0	0
ASA + Ticlopidine	1	0	0	0
ASA + Dipyridamole	0	0	1	0
ASA + Heparin	7	1	3	0
Warfarin + ASA + Urokinase	0	0	1	2
Warfarin + Urokinase + Heparin fr	2	0	0	0
Warfarin + Heparin + ASA	2	1	3	0
Warfarin + Heparin + ASA + Dextran 6%	0	0	0	1

Of argtroban-treated HIT patients who received concomitant antithrombotic and/or thrombolytic medications, 85% received warfarin, and 24% received aspirin; alone or in combination. Of argatroban-treated HITTS patients who received concomitant antithrombotic and/or thrombolytic medications, 86% received warfarin, and 27% received aspirin; alone or in combination.

Of historical control HIT patients who received concomitant antithrombotic and/or thrombolytic medications, 47% received warfarin, and 38% received aspirin; alone or in combination. Of historical control HITTS patients who received concomitant antithrombotic and/or thrombolytic medications, 60% received warfarin, and 26% received aspirin; alone or in combination.

Primary Efficacy Outcome Results

Primary efficacy outcome results for HIT and HITTS patients are summarized below (Tables 11 and 12, vol. 12.1, pp. 31-2).

Primary Efficacy Outcomes for HIT Patients

	HIT								
	Historical Control[a]			Argatroban[b]			Treatment		
Parameter	N	% (95% CI)		N	% (95% CI)		P-value[c]	Odds Ratio	(95% CI)	P-value[d]
Total Number of Patients	108	100	–	85	100	–	–	–	–	–
New Thrombosis	25	23	(15,31)	3	4	(0,7)	<0.001	0.1	(0.0, 0.4)	0.001
Amputation:										
All cause amputation	4	4	(0,7)	6	7	(2,13)	0.101	2.0	(0.5, 7.9)	0.304
Due to ischemic complication[e]	2	2	(-1,4)	3	4	(0,7)	0.251	1.9	(0.3,15.0)	0.474
Due to other reasons	2	2	(-1,4)	3	4	(0,7)	0.251	1.9	(0.3,15.0)	0.474
Death:										
Due to thrombosis	4	4	(0,7)	1	1	(-1,3)	0.217	0.3	(0.0,2.1)	0.298
Treatment-Emergent	0	0	(0,0)	0	0	(0,0)	–	–	–	–
Due to Pre-existing Conditions	8	7	(2,12)	14	16	(9,24)	0.001	2.5	(1.0, 6.5)	0.055
Thrombotic Composite Outcome[f]	28	26	(18,34)	6	7	(2,13)	<0.001	0.2	(0.1, 0.5)	0.001
Composite Outcome[g]	36	33	(24,42)	21	25	(15,34)	0.091	0.7	(0.4, 1.2)	0.193

[a] Study period was −37 days.
[b] Infusion period was 1 to 14 days.
[c] Based on the Z-statistic from the 1-sample Normalization Test.
[d] 2-sample test based on logistic regression, modeling for the effect treatment.
[e] Secondary to HIT/HITTS.
[f] Any occurrence of new thrombosis, amputation due to HIT/HITTS, or death due to thrombosis.
[g] Any occurrence of new thrombosis, amputation or death.

Primary Efficacy Outcomes for HITTS Patients

	HITTS							
	Historical Control[a]		Argatroban[b]			Treatment Odds		
Parameter	N	% (95% CI)	N	% (95% CI)	P-value[c]	Ratio	(95% CI)	P-value[d]
Total Number of Patients	109	100 –	89	100 –	–	–	–	–
New Thrombosis	45	41 (32,51)	8	9 (3,15)	<0.001	0.1	(0.06,0.3)	<0.001
Amputation:								
All cause amputation	13	12 (6,18)	13	15 (7,22)	0.435	1.3	(0.5, 2.9)	0.579
Due to ischemic complication[e]	12	11 (5,17)	10	11 (5,18)	0.946	1.0	(0.4, 2.5)	0.980
Due to other reasons	1	1 (-1,3)	3	3 (0,7)	0.015	3.8	(0.4,76.9)	0.254
Death:								
Due to thrombosis	8	7 (2,12)	2	2 (-1,5)	0.065	0.3	(0.0, 1.2)	0.124
Treatment-Emergent	0	0 (0,0)	1	1 (-1,3)	–	–	–	–
Due to Pre-existing Conditions	8	7 (2,12)	15	17 (9,25)	<0.001	2.6	(1.1,6.7)	0.043
Thrombotic Composite Outcome[f]	54	50 (40,59)	16	18 (10,26)	<0.001	0.2	(0.1, 0.4)	<0.001
Composite Outcome[g]	59	54 (45,63)	33	37 (27,47)	0.001	0.5	(0.3,0.9)	0.017

[a] Study period was ~37 days.
[b] Infusion period was 1 to 14 days.
[c] Based on the Z-statistic from the 1-sample Normalization Test.
[d] 2-sample test based on logistic regression, modeling for the effect treatment.
[e] Secondary to HIT/HITTS.
[f] Any occurrence of new thrombosis, amputation due to HIT/HITTS, or death due to thrombosis.
[g] Any occurrence of new thrombosis, amputation or death.

A summary table of the primary efficacy outcome results for study ARG-915 is shown below. Note that there were 6 additional deaths in argatroban-treated patients (1 HIT and 5 HITTS patients) that were NOT included in the initial case report tabulations for study ARG-915 (vol. 12.7, p. 297). These deaths are included in the summary table below.

Summary Table of Primary Efficacy Outcomes
Study ARG-915

Efficacy Outcomes	HIT			HITTS		
	Hist Ctrl 108	Argatro 85	P-value*	Hist Ctrl 109	Argatro 89	P-value*
New Thromboses	25(23%)	3(4%)	0.0001	45(41%)	8(9%)	<0.0001
Amputation	4(4%)	6(7%)	0.340	13(12%)	13(15%)	0.531
All-cause Death	12(11%)	16(19%)	0.152	16(15%)	23(26%)	0.072
Overall Composite	36(33%)	21(25%)	0.207	59(54%)	33(37%)	0.031
* two-sided Fisher's Exact Test						

Adapted from Sponsor's Tables 11 and 12, vol. 12.1, pp. 31-2, and information from vol. 12.7, p. 297

For comparison, a summary table for the primary efficacy outcome results for study ARG-911 is shown below:

Summary Table of Primary Efficacy Outcomes
Study ARG-911

Efficacy Outcomes	HIT			HITTS		
	Hist Ctrl 108	Argatro 160	P-value*	Hist Ctrl 109	Argatro 144	P-value*
New Thromboses	25(23%)	10(6%)	0.0001	45(41%)	27(19%)	0.0001
Amputation	4(4%)	4(3%)	N.S.	13(12%)	18(13%)	N.S.
All-cause Death	12(11%)	29(18%)	0.124	16(15%)	26(18%)	0.500
Overall Composite	36(33%)	43(27%)	0.276	59(54%)	62(43%)	0.099
* two-sided Fisher's Exact Test						

Adapted from Tables 15 and 16, vol. 105, pp. 107-8

Similar primary efficacy outcomes for patients in studies ARG-911 and ARG-915 were seen. For argatroban-treated HIT and HITTS patients, significant reductions in the incidence of new thromboses were seen. Notably, as was seen for study ARG-911, a numerically greater all-cause death rate was also found for argatroban-treated HIT and HITTS patients in study ARG-915.

Statistical Analyses of Primary Efficacy Outcome Results

A baseline diagnosis of renal impairment, sepsis, respiratory distress syndrome, receiving hemodialysis, or undergoing mechanical ventilation were determined to be statistically significant predictors of all-cause mortality by logistic regression and Cox Proportional Hazards models. This is summarized in the table below (Table 10, vol. 12.1, pg. 28).

Baseline Predictors of All-Cause Mortality from Logistic Regression and Cox Proportional Hazards Models

	Logistic Regression[a]		Cox Proportional Hazards Model[a]	
	P-Value	Odds Ratio (95% C.I.)	P-Value	Risk Ratio (95% C.I.)
Cancer	0.487	1.37 (0.53, 3.14)	0.506	1.31 (0.59, 2.89)
Renal Impairment	0.001	3.12 (1.58, 6.06)	<0.001	2.99 (1.67, 5.35)
Hepatic Impairment	0.220	2.13 (0.56, 6.68)	0.241	1.84 (0.66, 5.11)
Diabetes	0.321	0.72 (0.36, 1.35)	0.349	0.75 (0.41, 1.37)
Sepsis	0.008	3.28 (1.31, 7.80)	0.005	2.81 (1.37, 5.77)
Lupus Erythmatosus	0.158	3.74 (0.48, 23.5)	0.122	3.05 (0.74, 12.6)
Respiratory Distress Syndrome	0.007	2.71 (1.28, 5.53)	0.006	2.38 (1.29, 4.42)
Receiving Hemodialysis	0.037	5.25 (0.99, 25.3)	0.013	4.58 (1.38, 15.2)
On Circulatory Assist Device	0.462	1.38 (0.55, 3.14)	0.382	1.40 (0.66, 3.01)
Undergoing Ventilation	0.022	3.13 (1.12, 8.05)	0.033	2.45 (1.08, 5.57)
Previous CABG Surgery	0.806	1.07 (0.60, 1.89)	0.620	1.14 (0.68, 1.93)

[a] Results from a model that included factors for the effects treatment, population, and a yes/no indicator for the baseline covariate. Each covariate was analyzed separately.

Of the above 5 covariates identified above, 2 were determined from stepwise regression to be the most influential (independent) predictors of all-cause mortality, namely renal impairment and respiratory distress syndrome.

A summary of the sponsor's logistic regression and Cox Proportional Hazards model analyses of the incidence of all-cause mortality, when adjusted for **NONE**, the **5** covariates which predicted all-cause mortality, and the **2** most influential of these 5 covariates identified from stepwise regression, is shown below (Table 13, vol. 12.1, p. 43).

APPEARS THIS WAY
ON ORIGINAL