Treatment Odds Ratios and Risk Ratios for Adjusted and Unadjusted All-Cause Mortality

	Odds Ratio (95% C.I.)	P-Value	Risk Ratio (95% C.I.)	P-Value
HIT[a]				
Unadjusted[b]	1.71 (0.76, 3.96)	0.197	1.65 (0.76, 3.57)	0.202
Adjusted (Multivariate)[c]	1.88 (0.75,4.96)	0.185	1.83 (0.76, 4.37)	0.175
Adjusted (Stepwise)[d]	1.87 (0.78, 4.52)	0.163	1.71 (0.77, 3.78)	0.189
HITTS[a]				
Unadjusted[b]	1.47 (0.70, 3.12)	0.305	1.49 (0.76, 2.92)	0.250
Adjusted (Multivariate)[c]	–	–	1.22 (0.58, 2.69)	0.600
Adjusted (Stepwise)[d]	1.18 (0.53, 2.62)	0.685	1.12 (0.55, 2.29)	0.762
HIT/HITTS Combined[e]				
Unadjusted[b]	1.58 (0.91, 2.75)	0.104	1.57 (0.95, 2.60)	0.082
Adjusted (Multivariate)[c]	1.53 (0.83, 2.86)	0.173	1.49 (0.85, 2.60)	0.164
Adjusted (Stepwise)[d]	1.47 (0.82, 2.63)	0.194	1.40 (0.83, 2.36)	0.204

[a] All models done separately for HIT and HITTS.
[b] Model includes the factor treatment.
[c] Model includes the factor treatment and a Yes/No indicator variable for each of the 5 predictive baseline covariates (renal impairment, respiratory distress syndrome, sepsis, ventilation, and hemodialysis).
[d] Covariates (renal impairment, respiratory distress syndrome) used in this model were identified from a previous model which included the factors for treatment, population and Yes/No indicator variables for 11 baseline covariates analyzed in a forward stepwise process.

Note that when the magnitude of the above p-values are examined, starting with no adjustment, then following adjustment for 2 covariates, and then following adjustment for 5 covariates; either a small decrease is observed (e.g., RR p-values for HIT patients), an initial decrease followed by an increase is observed (e.g., OR p-value for HIT patients), or an initial increase is observed (e.g., OR and RR p-values for HITTS, and Combined HIT/HITTS patients).

In summary, increases in the magnitude of p-values in the above analyses, as an increasing number of covariates (i.e., predictors of all-cause mortality) are adjusted for, do NOT support the efficacy of argatroban with respect to the reduction of all-cause mortality, in HIT or HITTS patients.

Secondary Efficacy Outcome Results

Resolution of Thrombocytopenia

For HIT patients, the median platelet count increased from 82K/mm3 prior to drug administration, to 113K/mm3 by day 3, to

144K/mm3 at the conclusion of argatroban therapy. For HITTS patients, the median platelet count increased from 59K/mm3 prior to drug administration, to 133K/mm3 by day 3, to 179K/mm3 at the conclusion of argatroban therapy. Note that the mean duration of argatroban therapy was 4.9 days in HIT patients, and 7.3 days in HITTS patients.

APTT Values

For HIT patients, the median APTT increased from 30 seconds at baseline to 67 seconds at 12 hours. For HITTS patients, the median APTT increased from 30 seconds at baseline to 69 seconds at 12 hours. All patients were subsequently well-maintained in the target APTT range of 45-90 seconds, for the subsequent 72 hours examined.

SAFETY ANALYSIS

Deaths

All deaths that occurred in study ARG-915 were reconstructed from case report forms, and are tabulated in **Appendix 2** of this review. Particular attention was paid to patient medical history, timing of heparin and argatroban administration, platelet count profile, HIT antibody status (not required to be collected in the study), clinical and objective evidence of thrombosis, on-site investigator assessment of clinical course and cause of death, and autopsy results whenever available.

Note that study ARG-915 enrolled a total of 271 patients. Results from the first 174 patients were provided by the sponsor for review. Case report forms for 6 deaths that were NOT included in the endpoint tabulations for the results from the first 174 patients, were included with this application and are reviewed in Appendix 2 of this review. These patients include 5 HITTS patients and 1 HIT patient, and are listed below (vol. 12.7, p. 297).

Deaths NOT included in Endpoint Tabulations for the First 174 Patients Enrolled in Study ARG-915

Patient Identification	HIT/HITTS Status
017-001	HITTS
088-001	HITTS
089-001	HITTS
116-002	HIT
133-001	HITTS
146-001	HITTS

In addition, there have been 26 deaths reported so far, for the remaining 97 patients enrolled in ARG-915. Case report forms have not yet been provided for these patients. A summary of these patients, and the cause of death (as per the sponsor) is shown below (vol. 12.7, p. 297).

Deaths Reported to Date for the Remaining 97 Patients Enrolled in Study ARG-915

Patient Identification	Cause of Death (per sponsor)
012-004	Hypertension
020-004	Multisystem organ failure
020-106	Multisystem organ failure
020-012	Ischemic Cardiomyopathy
020-021	Metabolic Acidosis
020-022	Acute Renal Failure
020-024	Multiple CVAs
020-027	Ventricular Fibrillation
020-028	Sepsis
020-032	Respiratory Failure
032-005	Ventricular Tachycardia
036-009	Multiorgan failure
041-002	Pneumonia
041-003	Pancreatitis
100-002	Cardiac Arrest
113-018	Pulmonary Embolism
113-019	Pneumonia

121-006	Electromechanical Dissociation
123-006	Cardiac Arrest
123-007	Multiorgan failure
126-006	Sepsis
129-003	Multisystem failure
133-005	Ventricular tachycardia
144-003	Respiratory Failure
150-002	ARDS/Stroke
157-002	Cardiac Arrest

Note that 26 deaths of the 97 remaining argatroban-treated patients enrolled in study ARG-915, is a mortality rate of 27%.

Adverse Events Leading to Withdrawal

A total of 5(6%) HIT patients, and 7(8%) HITTS argatroban-treated patients withdrew from ARG-915 for an adverse event. Similar rates were seen in study ARG-911. One HIT patient, and two HITTS patients each discontined due to cardiac arrest and death, respectively. Adverse events leading to study withdrawal are summarized below (Table 14, vol. 12.1, p. 49).

Adverse Events Leading to Study Withdrawal

	HIT		HITTS	
	Number of		Number of	
Adverse Event[a]	AEs	Patients (%)	AEs	Patients (%)
Total Number Of Patients		85		89
Total Number Of Patients Who Withdrew		5 (6)		7 (8)
Bleeding From Multiple Sites		1 (1)		0 (0)
Cardiac Arrest		1 (1)		2 (2)
Death[1]		1 (1)		2 (2)
DIC		0 0		1 (1)
Decreased Platelet Count		1 (1)		0 0
PTT Elevated		0 0		1 (1)
Sepsis		1 (1)		0 0
Transtentorial Brain Herniation		0 0		1 (1)

[1] Deaths due to multisystem failure (146-001), respiratory depression/cardiac dissociation (012-001), and ventricular arrhythmia (149-001).

Most Frequent Adverse Events

A summary of those adverse events that occurred more often in argatroban-treated HIT patients, by a difference of ≥ 3%, is shown in the table below (vol. 12.8, pp. 180-190).

Adverse Events That Occurred More Often in Argatroban-Treated HIT Patients By a Difference of ≥ 3%

EVENT Total Number of Patients	Historical Control Patients (%) 108	Argatroban Patients (%) 85
Dyspnea	4(4)	7(8)
Sepsis	4(4)	6(7)
Nausea	0(0)	8(9)
Fever	2(2)	5(6)
Ventricular Tachycardia	2(2)	9(11)
Anemia	1(1)	3(4)

A total of 72(66%) historical control, and 70(79%) argatroban-treated HITTS patients experienced an adverse event. A summary of those adverse events that occurred more often in argatroban-treated HITTS patients, by a difference of ≥ 3%, is shown below (vol. 12.8, pp. 191-204).

Adverse Events That Occurred More Often in Argatroban-Treated HITTS Patients By a Difference of ≥ 3%

EVENT Total Number of Patients	Historical Control Patients (%) 109	Argatroban Patients (%) 89
Hypotension	3(3)	5(6)
Cardiac Arrest	4(4)	7(8)
Ventricular Tachycardia	1(1)	7(8)
Cardiac Failure, Right	1(1)	4(4)
Bradycardia	0(0)	3(3)
Sepsis	1(1)	4(4)
Acute Renal Failure	1(1)	5(6)
Purpura	1(1)	4(4)
Anemia	0(0)	3(3)
Fever	2(2)	10(11)
Dyspnea	7(6)	10(11)
Diarrhea	2(2)	5(6)
Nausea	2(2)	5(6)
Anorexia	0(0)	3(3)
Insomnia	1(1)	4(4)

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 in a major prosthetic joint. Bleeding was considered **minor** if it was reported but did not require more than 2 units PRBCs.

The incidences of major bleeding were 8.2% and 12.3% in argatroban-treated HIT and HITTS patients, respectively. These rates are higher than the major bleeding rates seen in argatroban-treated patients in study ARG-911 (3.1% and 10.4% in HIT and HITTS patients, respectively), and not significantly different than those reported for historical control patients.

A summary of the incidences of major and minor bleeding that occurred in ARG-915 is shown below (Table 15, vol. 12.1, p. 51).

Description of Major Bleeding Events in Argatroban-Treated HIT and HITTS Patients

PATIENT ID	BLEEDING SITE	TIME*	PRBC's in Units (dates)	DRUG exposure	COMMENTS
012-003 HITTS	Low H & H	Pre	2U PRBC 03/17/97	03/15/97-03/19/97	Chronic low H & H. Complicated insulin-dependent diabetes mellitus.
017-002 HIT	Left BKA stump Low H & H Vaginal Bleed	pre pre 2+	3U PRBC 12/14/96 3U PRBC 12/15/96 1U PRBC 12/16/96 2U PRBC 12/20/96 1U PRBC 12/21/96 2U PRBC 12/23/96	12/13/96-12/27/96	Patient was amputated prior to treatment and receiv PRBC post surgery at the stump (BKA). Vaginal/menstrual bleed was severe and requested blood transfusion for low H & H.
017-003 HIT	GI through NG tube Abdominal incision Urethra Central line Mouth	2+ 2+ post post post	1U PRBC 12/15/96 1U PRBC 12/18/96 2U PRBC 12/19/96 1U PRBC 12/20/96	12/13/96-12/20/96	Investigator classified this as a major bleed. Howev patient was post surgery for debridement with sepsi: Post-thoracotomy and renal failure.
020-014 HITTS	GI bleed	6+	2U PRBC 04/23/97 2U PRBC 04/26/97 2U PRBC 04/29/97	04/23/97-05/03/97	Patient had a large tarry stool. EGD performed sho diffuse gastritis, 8mm ulcer in the pre-pyloric area ar superficial erosions in the bulb.
022-001 HITTS	CABG wound	1	2U PRBC 03/12/97 1U PRBC 03/16/97	03/11/97-03/18/97	The patient received blood transfusions for oozing f sternal wound post-CABG. H & H dropped from 9.4 to 8.5/23.5. Major bleed per investigator.
025-001 HITTS	Bilateral hips Tracheotomy	2 9+	2U PRBC 05/16/97 2U PRBC 05/26/97	05/13/97-05/26/97	S/p CABG and MVR, ventilator dependent, gangrenc and fever. Had hematoma on the hips with anemia requesting transfusion. He also presented some bleeding around tracheotomy.
029-002 HITTS	IABP rupture	1+	2UPRBC 02/28/97 3UPRBC 03/01/97 2UPRBC 03/02/97	02/28/97-03/02/97	IABP rupture post argatroban treatment received blo for anemia
032-002 HITTS	Low H&H	7	2UPRBC 05/14/97	05/08/97-05/24/97	Post-Angioplasty – Sepsis
036-004 HITTS	Bleed from NG tube Hemorrhoids Bloody stool Small bleed stump	3+ 4 4 6+	2U PRBC 03/27/97 2U PRBC 04/02/97	03/25/97-04/04/97	The NG tube bleed was the only one to be classified major. Alcoholic, sepsis with endocarditis and pneumonia and acute MI, she underwent BKA on 03/31/97.
037-001 HITTS	Right Groin Hematuria Low H&H Hip surgery Right Hip	2 2+ 8+ 2 7+	2U PRBC 11/14/96 2U PRBC 11/16/96	11/06/96-11/16/96	Polycythemia vera and recurrent DVT with Antiphospholipid syndrome, myelodysplastic syndron History of breast carcinoma. She was transfused for low H&H. She underwent hip surgery for hip fracture during study treatment.
043-001 HITTS	Left calf fasciotomy Hematoma cath. site Epistaxis Line sites Surgery	2+ 2+ 2+ 2+ 2	3U PRBC 12/05/96	12/04/96-12/05/96	Bleeding during surgery: calf fasciotomy. DIC five ho after surgery.
043-008 HIT	Brachial	2	2UPRBC 04/10/97	04/09/97-04/13/97	Attempted cardiac catheterization, hematuria, oozing form right brachial catheterization
052-002 HIT	Low H&H	5	2U PRBC 02/12/97	02/08/97-02/13/97	Large cell non-Hodgkin's Lymphoma. Chest tube placement, for left pleural effusion. Chronic anemia. Classified major bleed by site coordinator.
052-004 HIT	Low H & H	5	2UPRBC 03/13/97	03/08/97-03/17/97	History of Tetralogy of Fallot, cleansing of pacemaker pocket, surgical bleed
052-005 HIT	Low H&H	1+	3U PRBC 04/15/97 1U PBRC 04/16/97 2U PBRC 04/17/97	04/15/97-04/17/97	Post MVR and redo CABG with IABP placement. Pos surgical bleed. Sepsis, renal failure, anasarca and requirement for ventilatory support. No bleeding site reported.
079-002 HIT	Low H & H	5	2UPRBC 05/03/97	04/29/97-05/05/97	Carcinoma of the Bladder. No bleeding site
113-010 HITTS	Chest tube site	3+	Only platelets	04/09/97-04/17/97	Post CABG and MVR. Post surgical anemia, no PRB given classified major bleed by PI.
149-001 HITTS	GI on NG tube	3	None	02/22/97-02/24/97	Re-do CABG; argatroban was discontinued, no transfusion

* Day number from onset of treatment.

During the treatment period, 30(35%) HIT patients, and 40(45%) HITTS argatroban-treated patients, underwent a total of 91 and 114 transfusions, respectively. Packed red blood cells were the predominant transfused blood product, accounting for 33% of HIT patients, and 38% of HITTS patients. By comparison, more transfusions were required in historical control patients; 54% of HIT, and 51% of HITTS patients. Packed red blood cells were also the predominant transfused blood product in historical control patients, accounting for 44% of HIT, and 45% of HITTS patients. Platelets were transfused more often in historical control patients (20% of HIT, and 15% of historical control HITTS patients; compared to 8% of HIT, and 11% of argatroban-treated HITTS patients). Blood product transfusion requirements were similar for argatroban-treated patients in studies ARG-911 and ARG 915.

OTHER ARGATROBAN STUDIES

Dosing guidelines were the same for all patients in the ARG-911 protocol, including those with underlying renal or liver disease. Studies ARG-103 and ARG-106 (completed after study ARG-911 had begun enrollment) examined the safety and pharmacokinetics of argatroban in patients with renal and liver disease, respectively.

Study ARG-103

In study **ARG-103** (vol. 81, p. 1 ff.), a total of 24 volunteers were stratified into 4 groups based on their creatinine clearance (in ml/min/1.73 m2): normal (Clcr > 80), mild impairment (Clcr 50-80), moderate impairment (Clcr 30-49) or severe impairment (Clcr ≤ 29). Subjects were given a continuous i.v. infusion of 5 µg/kg/min for 4 hours. A total of 19 male and 5 female subjects, of age 30-75 years of age, weighing 56-106 kg, and height 61-74 inches were enrolled. The baseline medical history was similar between the 4 treatment groups, although subjects with decreased renal function tended (expectedly) to have a higher frequency of cardiovascular and genitourinary disease.

There were no dropouts or serious adverse events. A total of 5 (21%) subjects reported 6 adverse events. These events included headache, fever, and tiredness; all were mild and

An approximate 4-fold decrease in the total body clearance of argatroban in patients with hepatic disease compared to healthy subjects was seen, while the volume of distribution did not change. The mean terminal elimination half-life of argatroban was also increased from 1 hour in healthy subjects to 3 hours in subjects with hepatic disease. The steady-state plasma argatroban concentration, estimated from the infusion dose divided by the clearance, was predicted to be approximately 4x higher in hepatically impaired patients for a given dose. This increased plasma concentration was reflected in the proportionally higher ACT and APTT values observed. Thus, it is recommended in the proposed labeling for argatroban that, "For hepatic impaired patients with Child's scores > 6, an initial dose of 0.5 µg/kg/min is recommended (rather than 2 µg/kg/min for non-hepatically impaired patients), based on the approximate four-fold decrease in argatroban clearance relative to those with normal hepatic function."

Study ARG-310

Study title: An open-label study of NOVASTAN® (brand of argatroban) evaluating safety and efficacy in patients with heparin-induced thrombocytopenia/thrombosis undergoing percutaneous transluminal coronary antioplasty, atherectomy or stent implantation.

Study ARG-310 was an open-label, non-randomized, historically-controlled, prospective study of 30 patients with HIT/HITTS who required percutaneous transluminal coronary angioplasty (PTCA), atherectomy, or stent implantation. The primary efficacy endpoint was the acute procedural success rate, defined as the percentage of HIT/HITTS patients who were able to undergo the clinically indicated coronary interventional procedure without any of the following adverse outcomes: death, need for rescue coronary artery bypass graft(CABG) surgery, or Q-wave myocardial infarction (QwMI). The acute procedural success rate for the argatroban-treated HIT/HITTS patients was compared to that from a historical control population of patients undergoing coronary interventional procedures and anticoagulated with unfractionated heparin (from the Cleveland Clinic Foundation Interventional Registry).

Secondary efficacy endpoints were 1) the investigator's qualitative clinical assessment of the achievement of adequate anticoagulation during the interventional procedure, and 2) acute angiographic success (i.e. the ability to successfully dilate the

Efficacy and Major Bleeding Results for ARG-310

Endpoint	Argatroban	Control	P-Value
Acute Procedural Success (%)[a]	100.0 (30/30)	94.3 (5352/5676)	0.002[e]
Acute Angiographic Success[b]	11.9 ± 2.4 (N = 45)	85.6 ± 1.6 (N = 45)	< 0.001[f]
Achievement of Adequate Anticoagulation (%)[c]	100.0 (30/30)	—	—
Major Bleeding (%)[d]	3.3 (1/30)	3.1 (29/939)	NS[e]

[a] Acute Procedural Success = no death, rescue CABG or Q-wave MI. Historical control is the Cleveland Clinic Registry.
[b] % stenosis of culprit lesion after procedure (argatroban) vs. % stenosis of culprit lesion before procedure (control). N = number of lesions. A patient could have more than one lesion.
[c] No historical control data were available for this endpoint.
[d] Historical control is the heparin arm of the EPILOG study.
[e] Z-test
[f] T-test

The efficacy of argatroban over heparin in the performance of coronary interventional procedures in patients with HIT/HITTS was seen in the prespecified secondary endpoint of acute angiographic success. No significant difference between treatment groups for the primary endpoint of acute procedural success, which was 30(100%) in the argatroban group compared to 5352(94%) in the heparin historical control group (p= 0.413*). The incidence of major bleeding was 3.3% in the argatroban group and 3.1% in the heparin group (p= N.S.).

* two-sided Fisher's Exact Test

INTEGRATED SUMMARY OF SAFETY

A summary of the 1340 patients included in the Integrated Summary of Safety who received argatroban is shown below:

Clinical Studies Included in the ISS

Phase	Study Type	Number of Argatroban-treated Patients
I	Healthy Volunteers (ARG-100, 101, 102, 105, 108, 109, 112)	128
	Special Populations	41
	ARG-103 Renal Disease (creat clearance <80 ml/min/1.73 m2)	24
	ARG-106 Hepatic Disease (Child's score > 6)	17
II/III	Randomized Studies	731
	ARG-210 PTCA	5
	ARG-230 Acute MI (Adjunctive therapy to Streptokinase; argatroban vs. placebo)	725
	ARG-912 HIT/HITTS	1
	Open-Label Studies	327
	ARG-216 PTCA	21
	ARG-240 HIT/HITTS	2
	ARG-911 HIT/HITTS (Pivotal Study)	304
	Ongoing Studies	112
	ARG-231 Acute MI (Adjunctive therapy to r-TPA)	85
	ARG-310 HIT/HITTS in Setting of PTCA	27

Of the 1340 subjects/patients who received argatroban, 68% were male, 83% were Caucasian, 12% were Hispanic, the mean age was 58 years, and the mean weight was 78 kg.

A total of 63% of patients received 1 to 7 days of argatroban therapy; 23% received 12 hours or less, and 1% received > 14 days of therapy. The majority (70%) of patients who received < 1 day of argatroban, received argatroban for a PTCA procedure. All 9 patients who received argatroban for > 14 days were being treated for HIT/HITTS.

The most frequent concomitant medications in patients from all studies included in the ISS were antithrombotic agents(81%) and cardiac medications(77%). A total of 72% of patients received concomitant aspirin, 16% received warfarin, and 10% received diabetic medications.

There were no deaths reported for **normal volunteers or special population patients.**

For patients who received argatroban in **randomized studies**, 32(4%) died on therapy, compared to 11(3%) of placebo patients. The number of patients who received an active control was small (n=5); 1 patient who received Ancrod died in study ARG-912. On therapy causes of death were similar in argatroban-treated and placebo patients, and were cardiovascular in origin (cardiac arrest, circulatory failure, myocardial infarction, and ventricular fibrillation).

For patients who received argatroban in **open-label studies**, 11(3%) died on therapy, compared to 18(8%) of historical control patients. On therapy causes of deaths that occurred with a greater incidence in argatroban-treated than historical control patients were single events in the categories of Acidosis, DIC, ECG Abnormal, and Encephalopathy.

For patients who received argatroban in **ongoing studies**, 2(2%) died on therapy, compared to 0(0%) active control patients. On therapy causes of death in argatroban-treated patients were cardiovascular in origin.

One patient of 128 argatroban-treated **healthy volunteers** prematurely withdrew due to a rash. No **special population** patients withdrew due to an adverse event.

For patients who received argatroban in **randomized studies**, 90(12%) patients experienced a treatment-emergent adverse event leading to premature study withdrawal, compared to 33(9%) of placebo patients. Adverse events that occurred more often in argatroban-treated than placebo patients, by a difference of ≥ 0.5%, were: circulatory failure (1.4% of argatroban-treated patients compared to 0.8% of placebo patients), hematuria (0.8% of argatroban-treated patients compared to 0.3% of placebo patients), and injection site reactions (0.8% of argatroban-treated patients compared to 0.3% of placebo patients).

For patients who received argatroban in **open-label studies**, 24(7%) experienced a treatment-emergent adverse event leading to premature study withdrawal, compared to 1(0.5%) historical control patient. Adverse events that occurred more often in argatroban-treated patients by a difference of ≥ 0.5% were: GI hemorrhage (0.6% of argatroban-treated patients compared to 0.0% of historical control patients), anemia (0.6% of argatroban-treated patients compared to 0.0% of historical control patients), coagulation disorder (0.6% of argatroban-treated

patients compared to 0.0% of historical control patients), and hemorrhage NOS (0.9% of argatroban-treated patients compared to 0.0% of historical control patients).

For patients who received argatroban in **ongoing studies**, 8(7%) experienced a treatment-emergent adverse event leading to premature study withdrawal, compared to 4(10%) of active control patients. Adverse events that occurred more often in argatroban-treated patients, by a difference of ≥ 0.5% were: stupor (0.9% of argatroban-treated patients compared to 0.0% of active control patients), ventricular fibrillation (0.9% of argatroban-treated patients compared to 0.0% of active control patients), vascular disorder (1.8% of argatroban-treated patients compared to 0.0% of active control patients), anemia (0.9% of argatroban-treated patients compared to 0.0% of active control patients), and increased prothrombin time (0.9% of argatroban-treated patients compared to 0.0% of active control patients).

No argatroban-treated **healthy volunteers** or **special population patients** experienced a serious adverse event.

For patients who received argatroban in **randomized studies**, 214(29%) experienced a serious adverse event, compared to 87(24%) of placebo patients. Serious adverse events that occurred more often in argatroban-treated patients, with a difference of ≥ 1% were: cardiac failure (1.8% of argatroban-treated patients compared to 0.5% of placebo patients), circulatory failure (3.7% of argatroban-treated patients compared to 2.5% of placebo patients), and myocardial infarction (5.1% of argatroban-treated patients compared to 3.3% of placebo patients). Note that the excess of these adverse events may represent a lack of efficacy of argatroban (in patients with an acute MI, as adjunctive therapy to [redacted].

A total of 142(43%) argatroban-treated patients in **open-label studies** experienced a serious adverse event. Serious adverse events were **not** specifically identified in the case report forms for historical control patients. Serious adverse events that occurred with a frequency of ≥ 1% were: hypotension (1%), cardiac arrest (5%), cerebrovascular disorder (2%), peripheral gangrene (2%), peripheral ischemia (4%), thrombophlebitis (3%), DVT (3%), apnea (6%), pulmonary embolism (3%), thrombosis (2%), and sepsis (2%).

A total of 13(12%) argatroban-treated patients, compared to 9(23%) active control patients in **ongoing studies** experienced a

serious adverse event. The serious adverse event that occurred more often in argatroban-treated patients, with a difference of ≥ 1.0% was cardiac arrest (1.8% of argatroban-treated patients compared to 0.0% of active control patients).

A total of 49(38%) argatroban-treated, compared to 14(39%) active control subjects experienced a treatment-emergent adverse event in **studies in healthy volunteers**. (The active control medications were heparin, warfarin, or no therapy.) The adverse event that occurred more frequently in argatroban-treated subjects, with a difference of ≥ 5%, was dizziness (11% in argatroban-treated subjects compared to 6% in active control subjects).

A total of 671(92%) argatroban-treated, compared to 330(90%) placebo patients experienced a treatment-emergent adverse event in **randomized studies**. Adverse events that occurred more frequently in argatroban-treated than placebo patients, by a difference of ≥ 2.0%, were: depression (3.3% of argatroban-treated patients compared to 1.1% of placebo patients), abdominal pain (8.9% of argatroban-treated patients compared to 5.5% of placebo patients), hematuria (4.5% of argatroban-treated patients compared to 2.5% of placebo patients), and injection site reactions (26% of argatroban-treated patients compared to 24% of placebo patients).

A total of 261(80%) argatroban-treated, and 121(56%) historical control patients experienced treatment-emergent adverse events in **open-label studies**. Adverse events that occurred more frequently in argatroban-treated than historical control patients in open-label studies, by a difference of ≥ 2.0%, are tabulated below:

Treatment-Emergent Adverse Events That Occurred More Often in Argatroban-Treated Patients, by a difference of ≥ 2.0%, in OPEN-LABEL STUDIES

ADVERSE EVENT	ARGATROBAN-TREATED PATIENTS (%)	HISTORICAL CONTROL PATIENTS (%)
Rash	5.2	1.4
Dizziness	3.4	0.5
Headache	3.4	0.5
Anorexia	2.1	0.0
Confusion	3.4	0.9
Depression	3.1	0.9
Constipation	5.8	0.5
Diarrhea	7.0	3.2
Nausea	4.3	0.9
Vomiting	5.5	2.8
Hypotension	8.3	3.7
Cardiac Arrest	5.8	2.8
Atrial Fibrillation	3.1	0.5
Tachycardia	2.1	0.0
Ventricular Tachycardia	3.4	1.4
Apnea	6.4	3.7
Pleural Effusion	2.8	0.5
Purpura	3.7	0.5
Urinary Tract Infection	4.6	1.8
Back Pain	2.4	0.0
Fatigue	2.1	0.0
Fever	6.1	1.8
Infection	4.3	0.9
Sepsis	5.8	2.3

A total of 73(65%) argatroban-treated, and 30(75%) active control patients in **ongoing studies** experienced a treatment-emergent adverse event. Treatment-emergent adverse events that occurred more frequently in argatroban-treated patients, by a difference of ≥ 2.0%, were: diarrhea (3.6% in argatroban-treated,

compared to 0.0% in active control patients), nausea (4.5% in argatroban-treated, compared to 2.5% in active control patients), hypotension (9.8% in argatroban-treated, compared to 5.0% in active control patients), bradycardia (2.7% in argatroban-treated, compared to 0.0% in active control patients), back pain (12.0% in argatroban-treated, compared to 5.0% in active control patients), and fever (5.4% in argatroban-treated, compared to 2.5% in active control patients).

"Fetal Disorder" adverse events reported in studies ARG-911 (HIT/HITTS) and ARG-230 (Acute MI) were newly diagnosed hiatal hernias, aneurysms, or an arterio-venous fistula found in adult patients. Newly diagnosed neoplasms during the study period of the same studies as above included two cases of colon cancer, three cases of thrombocythemia, a lung neoplasm, an ovarian cyst, and a breast mass.

Of the 1340 patients exposed to argatroban in the ISS, 68% were males and 32% were females. A total of 78% of male and 81% of female subject/patients reported an adverse event. Those body system categories that occurred with a difference in frequency of ≥ 5% were: Gastrointestinal System Disorders (29% in females compared to 24% in males), Platelet, Bleeding & Clotting Disorders (18% in females compared to 13% in males), and MYO ENDO Pericardial & Valve Disorders (19% in males compared to 14% in females). No individual adverse event occurred with a difference in frequency of ≥ 5%.

Of the argatroban-treated population, 83% were Caucasians, 12% were Hispanic, and 4% were Black. A total of 78% of Caucasian and 85% of Hispanic patients/subjects reported an adverse event. Those body system categories that occurred with a difference in frequency of ≥ 10% were: Central & Peripheral Nervous System Disorders (21% for Caucasian patients compared to 8% for Hispanic patients), Psychiatric Disorders (18% for Caucasian patients compared to 7% for Hispanic patients), and Cardiovascular Disorders - General (19% for Caucasian patients compared to 39% for Hispanic patients). The individual adverse event which occurred with a difference in frequency of ≥ 10% was hypotension (13% in Caucasian patients compared to 27% in Hispanic patients). Note that the greater incidence of cardiovascular adverse events in Hispanic patients may reflect the greater proportion of Hispanic patients who participated in cardiovascular trials. For example, Hispanic patients made up 16% and 27% of randomized and ongoing studies (primarily cardiovascular trials), respectively; compared to 2% of open-label studies (primarily HIT/HITTS trials).

Of the 1340 argatroban-exposed patients included in the ISS, **5%** were <30 years, **15%** were 30-45 years, **46%** were 46-65 years, and **35%** were >65 years of age. Those body system categories that occurred more frequently in patients >65 years than patients age 30-45 years, by a difference of ≥ 10% were: Heart Rate and Rhythm Disorders (7% compared to 17%), Respiratory System Disorders (14% compared to 26%), and Urinary System Disorders (6% compared to 17%). The Body as a Whole category occurred in 33% of patients age 30-45 years compared to 46% of patients age 46-65 years.

Of the 1340 argatroban-exposed patients, **50%** were enrolled in the United States, **32%** were enrolled in Canada, and **20%** were enrolled in South America. Canadian patients reported a significantly greater incidence of adverse events (by ≥ 20%) compared to patients enrolled in the United States and/or South America, for the following body system categories: Skin and Appendages Disorders, Central & Peripheral Nervous System Disorders, Psychiatric Disorders, MYO ENDO Pericardial & Valve Disorders, Respiratory System Disorders, Body as a Whole, and Application Site Disorders. South American patients reported a significantly greater incidence of adverse events (by ≥ 20%) compared to patients enrolled in the United States for the following body system categories: Cardiovascular System Disorders-General and Body as a Whole.

No unanticipated clinically significant changes in vital signs or clinical hematology, coagulation, chemistry, or urinanalysis parameters were reported in argatroban-treated patients.

Foreign Labeling and Post-Marketing Safety Experience in Japan

Japanese Labeling

Argatroban has been approved in Japan for the following indications:

•*Improvement of ulcers, rest pain, or feelings of coldness in the extremities in chronic arterial occlusion (Buerger's disease, arteriosclerosis obliterans).*

This indication was approved in 1990 at a recommended dose is 10 mg i.v. infused over 2-3 hours, twice daily.

•Improvement of neurological symptoms (motor paralysis) and ADL (walking, standing, sustaining the sitting position and eating) in acute cerebral thrombosis within 48 hours from onset (lacunar type excluded).

This indication was approved in 1996 at a recommended dose is 60 mg i.v. infused over 24 hours for 2 days, THEN 10 mg i.v. infused over 3 hours, twice daily for the next 5 days.

•Prevention of clotting during hemodialysis in patients with 1) antithrombin III deficiency, and 2) decreased antithrombin III levels in whom antithrombin levels have decreased to 70% or less of the normal level, and the use of heparin is judged not to improve clotting.

This indication was approved in 1996 at a recommended dose of 10 mg at the start of hemodialysis followed by 5-40 mg per hour during dialysis.

The ADVERSE REACTIONS section of the Japanese labeling for argatroban reports the adverse events listed below. Note that "**rarely**" = <0.1%, and "**infrequently**" = 0.1% to < 5%.

1) Clinically significant adverse reactions: Hemorrhagic cerebral infarction, cerebral hemorrhage, and digestive tract bleeding.

Hemorrhagic cerebral infarction may occur infrequently, and cerebral hemorrhage and digestive tract bleeding may occur rarely.

2) Other adverse reactions

A. Hematologic: Abnormal prolongation of coagulation time, hemorrhage, hematuria, anemia, or an increase or decrease in WBC may occur infrequently.

B. Hypersensitivity: Erythematous rash may occur infrequently. Itching may occur rarely.

C. Vascular: Vascular pain and vasculitis may occur infrequently.

D. Hepatic: An increase in SGOT, SGPT, Alk Phos, LDH or total bilirubin may occur infrequently.

E. Renal: An increase in BUN or creatinine may occur infrequently.

F. Gastrointestinal: Nausea, anorexia, abdominal pain, and diarrhea may occur infrequently.

G. Others: Pain of numbness of extremities, light-headedness, headache, arrhythmia, palpitations, feeling of warmth/flushing, rigors, fever, chest pain, hyperventilation, dyspnea, hypertension, edema or swelling may occur infrequently.

3) Use in the Elderly

The incidence of adverse reactions was 5% (11/221) in clinical studies in patients more than 65 years of age with acute cerebral thrombosis, and 3.4%(117/3392) in postmarketing surveillance in patients with chronic arterial occlusion.

4) Use in Pregnancy or Lactation

The safety of argatroban in pregnant women has not been established. Animal studies have shown that the drug is excreted in breast milk.

5) Pediatric Use

Use of argatroban in children has not been established.

Safety information from the CLINICAL STUDIES section of the Japanese label is shown below. Note that a mandatory post-marketing survey is required in Japan, in order to renew the marketing license for a new molecular entity beyond 6 years. As a result post-marketing for argatroban is available for 5019 patients with chronic arterial occlusion as summarized below.

1) Studies in Chronic Arterial Occlusion

Notably, transaminase elevations were reported in argatroban-treated patients with acute cerebral thrombosis in 4.4%-5.4% of patients; total bilirubin increases were reported in 1.8% of patients; and increases in alkaline phosphatase were reported in 2.7% of patients.

Japanese Post-Marketing Survey

Post-marketing information from 3791 patients from 620 institutions in Japan for the period 1/90 to 1/94 was included with this application. A total of 3326(88%) of these patients received argatroban for chronic arterial occlusion. The incidence of adverse events was 13.3% before approval and 3.2% post-approval. A total of 27 serious adverse events were reported in 20 patients and are summarized below (Table 6-1, vol. 151A, pp. 265-66).

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Serious Adverse Events

Classification by organ	Name of adverse reaction reported by company	Name of adverse reaction by Subcommittee on Drug Adverse Reactions	Time to onset (days)	Outcome	Measures taken by Subcommittee on Drug Adverse Reactions, matter to be informed, etc
Skin and appendages disorder	Ulcer of lower extremities aggravated	Skin ulceration	1	Not recovered	Nothing of note
Central and peripheral nervous system disorder	Severe headache beginning in the course of infusion	Headache	1	Recovered	Nothing of note
Gastro-intestinal system disorder	Intestinal obstruction	Eliminated	8	Died	Probably not related to NOVASTAN
	Diarrhea	Diarrhea	4	Recovered	Nothing of note
Liver and biliary system disorder	Hepatic function disorder	File sheet not returned	36	Relieved	
	Hepatitis acute	File sheet not returned	9	Recovered	
	Al-P increased	File sheet not returned	70	Recovered	
Cardiovascular system disorder (general)	Shock hemorrhagic	Death (body as a whole-general disorder)	5	Died	Nothing of note
	Edema	Edema	9	Recovered	Nothing of note
	Shock-like symptom	Shock	8	Died	Unlikely relationship to NOVASTAN
					Nothing of note
	ECG abnormal (ST decreased)	Eliminated	2	Recovered	Nothing of note
	Edema generalized	Edema (generalized)	9	Recovered	
Myo-, endo-, pericardial and valve disorder	Coronary artery spasm	Angina at rest	2	Recovered	Nothing of note
Myo-, endo-, pericardial and valve disorder					
Vascular (extracardiac) disorder	Apoplexy suspected	Sudden death	13	Died	Nothing of note
Respiratory system disorder	Pneumonia interstitial	Pneumonia interstitial	15	Sequela seen	Nothing of note
Platelet, bleeding and clotting disorder	Hematemesis/ melena	Hemorrhage of upper digestive tract	5	Died	Nothing of note
	Stool tarry	Stool tarry	12	Recovered	Nothing of note
	Cerebral hemorrhage (relapse)	Cerebral hemorrhage	20	Relieved	Nothing of note
	Hemorrhage (from anastomotic artificial blood vessel)	Hemorrhage (suture site)	2	Recovered	Nothing of note
	Urinary tract bleeding	Urinary tract hemorrhage	9	Recovered	Nothing of note
	Pancytopenia	File sheet not returned	76	Died	
	DIC	File sheet not returned	76	Died	
	Melena	Melena/blood pressure decreased	1	Not recovered	Nothing of note
	Cerebral hemorrhage	Cerebral hemorrhage	4	Died	Nothing of note
	Nasal hemorrhage	File sheet not returned	5	Died	
	Hemorrhage		5	Died	
Body as a whole-general disorder	Chest discomfort	Chest discomfort	9	Recovered	Nothing of note

A summary of the incidences of both pre- and post-approval adverse events from the Japanese post-marketing survey, are summarized below (Annex Form 2, vol. 151A, pp. 240-243).

Pre- and Post-Approval Adverse Events Reported for Argatroban in Japan

ADVERSE EVENTS	Argatroban-Treated Patients N(%)
Total Number of Patients Surveyed	3971
Total Number of Patients With Adverse Reactions	147
Total Number of Adverse Reactions	208
Platelet, Bleeding and Clotting Disorders	**41(1.0%)**
Coagulation Time Increased	7(0.2%)
Hemorrhage	9(0.2%)
Nasal Hemorrhage	1(0.0%)
Hematuria	11(0.3%)
Vaginal Hemorrhage	1(0.0%)
Cerebral Hemorrhage	2(0.1%)
Subcutaneous Hemorrhage	1(0.0%)
Hemoptysis	1(0.0%)
Hematemesis	3(0.1%)
Melena	2(0.1%)
Tarry Stool	1(0.0%)
Hematoma	2(0.1%)
Thrombocytopenia	2(0.1%)
Pancytopenia	2(0.1%)
DIC	1(0.0%)
Liver and Biliary System Disorders	**25(0.6%)**
Abnormal Hepatic Function	9(0.2%)
Hepatic Damage	1(0.0%)
SGOT Increased	12(0.3%)
SGPT Increased	13(0.3%)
LDH Increased	3(0.1%)
Gastrointestinal System Disorders	**22(0.6%)**
Nausea	10(0.3%)
Vomiting	5(0.1%)
Diarrhea	7(0.2%)
Anorexia	6(0.2%)
Abdominal Pain	2(0.1%)
Upper Abdominal Pain	1(0.0%)
Epigastric Pain	1(0.0%)
Skin and Appendages Disorders	**16(0.4%)**
Skin Exfoliation	1(0.0%)
Erythema	1(0.0%)
Rash	2(0.1%)
Rash, Erythematous	1(0.0%)
Bullous Eruption	1(0.0%)
Eruption	2(0.1%)
Drug Eruption	1(0.0%)
Eczema	1(0.0%)
Itching	5(0.1%)
Skin Ulceration	1(0.0%)

Central and Peripheral Nervous System Disorders	14(0.4%)
Headache	8(0.2%)
Inarticulateness	1(0.0%)
Disturbed Consciousness	1(0.0%)
Sensory Abnormality of Extremities	1(0.0%)
Coldness	1(0.0%)
Motor Neuropathy	1(0.0%)
Numbness of Lower Extremities	2(0.1%)
Numbness of Fingers	1(0.0%)
Body as a Whole - General	15(0.4%)
Pain of Lower Extremities	3(0.1%)
Pain	3(0.1%)
Fever	3(0.1%)
Hot Feeling, Generalized	2(0.1%)
Hot Feeling, Extremities	1(0.0%)
Chest discomfort	2(0.1%)
Rigors	1(0.0%)
Malaise	1(0.0%)

In summary, the Japanese postmarketing experience supports the overall safety of the use of argatroban. Note however, that the average daily, and cumulative 7-day doses of argatroban used in studies ARG-911 and ARG-915, were approximately 100x and 10x higher respectively, than those used in Japan.

SUMMARY AND CONCLUSIONS

Introduction

The principal efficacy results for the Intention-to-Treat population of the pivotal study ARG-911 are summarized below.

Primary Efficacy Outcomes for 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

Note that although statistical significance for the prespecified primary endpoints (of all-cause death, amputation, or new thromboses for HIT patients, and death or amputation for HITTS patients) were not seen, highly significant reductions in new thrombotic events in argatroban-treated HIT and HITTS

patients were shown. A significant reduction of the overall composite endpoint (of new thromboses, amputation, or all-cause death) was not seen in HIT or HITTS patients, due to the numerically higher all-cause death rate seen in argatroban-treated patients. This higher death rate was attributed to gross imbalances in patient characteristics, with argatroban-treated patients being more compromised at baseline.

The following issues will subsequently be discussed:

- An analysis of the causes of death in study ARG-911
- The comparability of patient baseline characteristics in study ARG-911, including explanations for these imbalances, and the results of adjustment for covariates that predicted all-cause mortality
- A comparison of the efficacy outcomes of studies ARG-911 and ARG-915
- An analysis of the causes of death in study ARG-915
- Patient baseline characteristics in study ARG-915
- The validity of the "new thrombosis" endpoint
- An assessment of the overall safety experience with argatroban
- Overall conclusions

The Classification of Deaths as "Due to Thrombosis," or "Due to Underlying Disease."

Study ARG-911

A numerically greater incidence of 30-day all-cause mortality in argatroban-treated HIT and HITTS patients, compared to historical control patients, was seen in study ARG-911. When deaths were subclassified by the sponsor as "due to thrombosis" or "due to underlying disease," significantly more deaths due to thrombosis were found for historical control patients for both the HIT and HITTS populations. This is summarized in the table below:

Sponsor's Subclassification of Deaths

DEATHS Total # Patients	HIT			HITTS		
	Hist Ctrl 108	Argat 160	P-value*	Hist Ctrl 109	Argat 144	P-value*
Due to Thrombosis	4(4%)	0(0%)	0.026	8(7%)	1(1%)	0.006
Treatment-Emergent	0(0%)	2(1%)	0.517	0(0%)	1(1%)	N.S.
Due to Underlying Disease	8(7%)	27(17%)	0.027	8(7%)	24(17%)	0.035
* two-sided Fisher's Exact Test						

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

In order to further evaluate the clinical validity of the subclassification of the cause of death as "thrombotic" or "due to underlying disease," ALL deaths that occurred in study ARG-911 were reconstructed from case report forms and relevant patient listings, and presented 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 assessments of the clinical course and cause of death, and autopsy findings whenever available. The results of this analysis are subsequently discussed.

With respect to deaths that occurred in **historical control HIT patients**, 7/12(58%) were positive for a heparin-induced antibody test, 4/12(33%) were negative, and 1(8%) did not have such a test performed. Of these 12 deaths, 4 were attributed to thrombosis, and 8 were attributed to underlying disease.

Of the 4 **historical control HIT deaths** attributed to thrombosis, 1 was confirmed on autopsy and the remaining 3 deaths were based on a high clinical suspicion by the Investigator, particularly as they occurred in the setting of ongoing thrombosis.

Of the 8 **historical control HIT deaths** attributed to underlying disease, 1 patient (081-H01) died of a "myocardial infarction with cardiogenic shock" in the setting of ongoing thrombosis. No thrombotic component was identified in the

remaining 7 deaths; there were confirmatory autopsy results for 2 of these patients (patients 201-H14, and 022-H02), and the causes of the remaining 5 deaths are tabulated below:

Patient	Timing and Cause of observed death
016-H04	Died as a consequence of endotracheal tube mucous plug obstruction
018-H01	Died as a consequence of gram negative sepsis
016-H06	Died 37 days following the discontinuation of heparin of multi-system failure
020-H18	Died 24 days following the discontinuation of heparin of hepatic and renal failure
201-H16	Died 17 days following the discontinuation of heparin of sepsis

In summary, with regard to the classification of **historical control HIT patients**, one death attributed to underlying disease (patient 081-H01 who died of an MI with cardiogenic shock in the setting of ongoing thrombosis) should be reclassified as a death due to thrombosis. As a result, there were 5 historical control HIT deaths due to thrombosis, and 7 for which a thrombotic component was not identified.

With regard to deaths that occurred in **argatroban-treated HIT patients**, 16/30(53%) were positive for a heparin-induced antibody test, 8/30(27%) were negative, and 6(20%) did not have such a test performed. Of these 30 deaths, 0 were attributed to thrombosis, 29 were attributed to underlying disease, and 1 was treatment-emergent. No argatroban-treated HIT patients had autopsy results. (Note that although case report forms were provided for 30 deaths in argatroban-treated HIT patients in study ARG-911, only 29 were included in the sponsor's efficacy analyses).

The single **treatment-emergent death in an argatroban-treated HIT patient** (077-001), and one argatroban-treated HIT death (048-001) listed as due to underlying disease, were attributed by the on-site investigators as due to thrombosis. These deaths should be classified as thrombotic deaths..

Eight **argatroban-treated HIT deaths attributed to underlying disease** had no reported objective or clinical evidence of ongoing thrombosis at or before their death, as well as prolonged periods of time between their HIT diagnosis and occurrence of death. These deaths are tabulated below.

Patient	Timing and Cause of observed death
012-003	Died 30 days following the discontinuation of heparin of right heart failure, renal failure, and hepatic encephalopathy
017-004	Died 26 days following the discontinuation of heparin of acute respiratory distress
039-002	Died 24 days following the discontinuation of heparin of COPD
040-006	Died 48 days following the discontinuation of heparin of respiratory arrest
059-007	Died 97 days following the discontinuation of heparin of multi-system compromise
103-001	Died 29 days following the discontinuation of heparin of renal failure
121-002	Died 50 days following the discontinuation of heparin of neutropenic sepsis
126-001	Died 21 days following discontinuation of heparin with "no evidence of bleeding or thrombosis" as per investigator

Of the remaining 20 deaths in **argatroban-treated HIT deaths** attributed to underlying disease, 16/20(80%) had available comparative objective or clinical information regarding ongoing thrombosis near the time of death. Of these 16 patients, 5 had significant evidence of ongoing thrombosis at the time of death. These cases are tabulated below.

Patient	Ongoing Thrombotic Event(s) at the time of Death
017-007	Non-QwMI and progressive neurologic deterioration
020-034	Embolization to both feet
036-003	Pulmonary Embolus and progression of bilateral LE thromboses
074-001	CVA
090-001	DVT and PE

In summary, 7 deaths in **argatroban-treated HIT patients** should be considered thrombotic: Patients 077-001 (the single treatment emergent death), 048-001 (attributed to "pulmonary emboli" by the on-site investigator), and the 5 patients with objective evidence of ongoing thrombosis around the time of death (listed above). As a result, there were 7 argatroban-treated HIT deaths due to thrombosis, 8 deaths likely due to underlying disease (given the prolonged period between the diagnosis of HIT and the occurrence of death), 11 deaths with no objective evidence of ongoing thrombosis around the time of death, and 4 deaths with incomplete information to assess ongoing thrombosis.

Overall, given the available clinical data as outlined above, there were 5(5%) thrombotic deaths in historical control HIT patients, and 7(4%) thrombotic deaths in argatroban-treated HIT patients. There were 7(6%) historical control, and 19(12%) argatroban-treated HIT deaths for which a thrombotic component was not identified. A total of 4(3%) argatroban-treated HIT patients had incomplete information to assess ongoing thrombosis.

With regard to deaths that occurred in **historical control HITTS patients**, 14/16(88%) were positive for a heparin-induced antibody test, 0(0%) were negative, and 2(13%) did not have such a test performed. Of these 16 deaths, 8 were attributed to thrombosis, and 8 were attributed to underlying disease.

Of the 8 **historical control HITTS deaths** attributed to thrombosis, 4 were confirmed on autopsy and the remaining 4 deaths were based on a high clinical suspicion by the on-site investigator, particularly as they occurred in the setting of ongoing thrombosis.

Of the 8 **historical control HITTS deaths** attributed to underlying disease, 1 patient (113-H21) died from an "acute myocardial infarction" as per the on-site investigator, 12 days following the discontinuation of heparin. Another 2 deaths occurred in the setting of significant ongoing thrombosis:

Patient	Ongoing Thrombotic Event(s) at the time of Death
128-H02	CVA and Acute MI
200-H19	Progression of LE DVT and a PE

In addition, 1 death (016-H03) occurred following heparin being continued for 17 days following the onset of SRA-positive HIT, in the setting of ongoing thrombosis (R LE arterial thrombi).

Of the remaining 4 **historical control HITTS deaths** attributed to underlying disease, a thrombotic component was not identified for the following 2 deaths:

Patient	Timing and Cause of observed death
115-H01	Died 22 days following the discontinuation of heparin of sepsis/multi-organ failure
200-H26	Died 22 days following the discontinuation of heparin of pulmonary hemorrhage

In addition, 1 patient (200-H29) had an autopsy, which confirmed the absence of new thromboses. The remaining death in this group of patients (050-H01) had incomplete information (no pulmonary angiogram results), so that an assessment of ongoing thrombosis could not be performed.

In summary, with regard to the classification of **historical control HITTS patients**, 4 deaths attributed to underlying disease (patients 113-H21, 128-H02, 200-H19, and 016-H03) should be reclassified as a death due to thrombosis for the reasons cited above. As a result, there were 12 historical control HIT deaths due to thrombosis, 3 for which a thrombotic component was not identified, and 1 for which ongoing thrombosis could not adequately be assessed due to missing information.

With regard to deaths that occurred in **argatroban-treated HITTS patients**, 20/26(77%) were positive for a heparin-induced antibody test, 3/26(12%) were negative, and 3/26(12%) did not have such a test performed. Of these 26 deaths, 1 was attributed to thrombosis, 23 were attributed to underlying disease, and 2 were treatment-emergent. Three argatroban-treated HITTS patients had autopsy results.

The single **argatroban-treated HITTS death** attributed to thrombosis (020-008), occurred in the setting of ongoing thrombosis (R Iliac arterial thrombi and probable PE) and was attributed to an acute myocardial infarction.

One of the **argatroban-treated treatment-emergent HITTS deaths** (066-003) occurred in the setting of sepsis, diffuse intravascular coagulation, and generalized bleeding, with an autopsy which confirmed the absence of new thromboses. The second treatment-emergent death (020-009) was also secondary to diffuse intravascular coagulation (and therapy-induced anticoagulation) and generalized bleeding.

Of the 23 **argatroban-treated HITTS deaths** attributed to underlying disease, 2 patients had autopsies; one of which (080-002) confirmed the absence of new thrombotic events, and one which confirmed the presence of a new myocardial infarction (138-001). The latter death was also attributed by the on-site investigator to an acute myocardial infarction. Two additional deaths were also attributed by the on-site investigator to HITTS: 1) 037-007; "The final cause of death was multiorgan system

failure secondary to HITTS", and 2) 118-001; "Support was terminated due to multiple complications of HITTS-related thrombosis."

Argatroban-treated HITTS deaths attributed to underlying disease, for which no evidence of ongoing thrombosis during the peri-death period was found, are tabulated below:

Patient	Cause of observed death
002-007	Death due to "respiratory failure secondary to lung fibrosis"
007-001	Death following respiratory failure, renal failure, fever, GI bleeding, and DIC, due to "cardiopulmonary collapse"
016-004	Death "with nonprogressing arterial lesions in the lower extremities with demarcation, with an open chest wound and sepsis"
017-006	Death "on a Morphine drip"
020-006	Death associated with pneumonia, arrhythmia, and respiratory failure
020-017	Death following cardiopulmonary resuscitation for Electromechanical Dissociation
029-003	Death following an intracranial bleed following a urokinase infusion
036-004	Death associated with gram negative sepsis
036-005	Death due to reintubation following tracheostomy complications
081-001	Death 73 days following the discontinuation of heparin of respiratory failure
115-003	Death following witnessed aspiration of food

Incomplete information was provided for 2 patients (052-003 and 137-001) to assess whether there was ongoing thrombosis during the peri-death period.

The 6 remaining argatroban-treated HITTS deaths attributed to underlying disease had objective and/or subjective evidence of ongoing thrombosis during the peri-death period. These cases are tabulated below.

Patient	Cause and circumstances of death
002-006	Death associated with becoming "increasingly short of breath at rest," in the setting of an objectively documented PE
012-002	Death "following a brief episode of respiratory distress," in the setting of an objectively documented PE
075-001	Death following an episode of increased respiratory rate and then unresponsiveness, in the setting of a recent CVA and LE arterial thrombi; VQ scans were not performed
082-002	Death following cardiac arrest in the setting of LE DVTs and worsening VQ scan results following an 11 day argatroban infusion. As per the on-site investigator the day before the patient died: "There is no clinical improvement and worsening of thrombus throughout the study."
082-003	Death following cardiac arrest in the setting of new extremity DVTs and new pulmonary thromboemboli following 7 days of argatroban
114-003	Death of a patient who became suddenly tachypneic and desaturated while on a ventilator; 4 hours later the patient experienced Electro-Mechanical Dissociation and died.

In summary, 10 deaths in **argatroban-treated HITTS patients** should be considered thrombotic: the single argatroban-treated HITTS death attributed to thrombosis (020-008), the patient who died of an acute MI as per autopsy findings (138-001), two deaths attributed by the on-site investigator to HITTS (037-007 and 118-001), and six patients for whom objective and/or subjective clinical evidence was identified in the peri-death period.

Of the remaining 16 **argatroban-treated HITTS patients**, a thrombotic component was not identified in 14 patients: the 2 treatment-emergent deaths (066-003 and 020-009), the patient with an autopsy which confirmed the absence of new thrombotic events (080-002), and the 11 patients for whom no objective evidence of ongoing peri-death thrombosis was identified (002-007, 007-001, 016-004, 017-006, 020-006, 020-017, 029-003, 036-004, 036-005, 081-001, and 115-003). Incomplete information was available for two patients (052-003 and 137-001) to assess ongoing thrombosis in the peri-death period.

Overall, given the available clinical data as outlined above, there were 12(11%) thrombotic deaths in historical control HITTS patients, and 10(7%) thrombotic deaths in argatroban-treated HITTS patients. There were 3(3%) historical control, and 14(10%) argatroban-treated HITTS deaths for which a thrombotic component was not identified. One historical control, and 2 argatroban-treated HITTS deaths could not be assessed for ongoing thrombosis during the peri-death period.

In summary, an equal (for HIT patients), or somewhat greater (for HITTS patients), incidence of thrombotic deaths were seen following the reconstruction and reclassification of deaths from case report form data. Deaths for which a thrombotic component was not identified were numerically greater for argatroban-treated HIT and HITTS patients. This observation was attributed by the sponsor to the more compromised health status of argatroban-treated patients at baseline. The comparability of patient baseline characteristics, including explanations for these imbalances, and the results of adjustment for covariates that predicted mortality, are subsequently discussed.

Imbalances in Patient Baseline Characteristics in Study ARG-911

Explanations for Observed Imbalances

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

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(%) 160	p-value*	Histor. Control N(%) 109	Argatro-ban N(%) 144	p-value*
Circulatory System	96(89)	160(100)	<0.0001	104(95)	142(99)	0.144
Symptoms, Signs, and Ill-Defined Conditions	58(54)	128 (80)	<0.0001	55(51)	119(83)	<0.0001
Endocrine, Nutritional, Metabolic, and Immunity	50(46)	108 (66)	0.0006	52(48)	103(72)	0.0002
Injury and Poisoning	46(43)	70 (44)	N.S.	37(34)	78(54)	0.0015
Respiratory System	40(37)	94 (59)	0.0007	38(35)	89(62)	<0.0001
Digestive System	39(36)	95 (59)	0.0003	33(30)	71(49)	0.003
Blood and Blood-Forming Organs	36(33)	107 (67)	<0.0001	52(48)	98(68)	0.0013

Genitourinary System	31(29)	87 (54)	<0.0001	22(20)	69(48)	<0.0001
Musculoskeletal and Connective Tissue Systems	29(27)	52 (33)	N.S.	51(47)	62(43)	N.S.
Nervous System and Sense Organs	27(25)	40 (25)	N.S.	14(13)	52(36)	<0.0001
Infectious Diseases	15(14)	38 (24)	0.06	11(10)	33(23)	0.0076
Mental Disorders	23(21)	65 (41)	0.0009	42(39)	50(35)	N.S.
Neoplasms	14(13)	41 (26)	0.0135	22(20)	32(22)	N.S.
Skin and Subcutaneous Tissue	8 (7)	31 (19)	0.0076	9 (8)	21(15)	N.S.
Congenital Anomalies	5 (5)	9 (6)	N.S.	4 (4)	7 (5)	N.S.
Pregnancy, Childbirth, and Puerperium	1 (1)	6 (4)	N.S.	2 (2)	2 (1)	N.S.
Other Factors Influencing Health Status	15(14)	2 (1)	<0.0001	15(14)	5 (4)	0.0039

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

Adapted from Sponsor's Table 2S, vol. 105, p. 304

Significant imbalances were noted in patient characteristics, with argatroban-treated patients being more compromised at baseline.

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 Medical/Surgical/Invasive Procedure History by Body System and Surgeries

	HIT			HITTS		
TYPE OF SURGERIES Total Number of Patients	Histor. Control N(%) 108	Argatro-ban N(%) 160	p-value*	Histor. Control N(%) 109	Argatro-ban N(%) 144	p-value*
Cardiovascular System	86(80)	130(81)	N.S.	82(75)	129(90)	0.003
Misc. Diagnostic and Therapeutic Procedures	56(52)	80(50)	N.S.	51(47)	76(53)	0.375
Digestive System	52(48)	63(39)	0.168	51(47)	61(42)	N.S.
Respiratory System	35(32)	42(26)	0.335	19(17)	31(22)	N.S.
Musculoskeletal System	28(26)	33(21)	0.373	33(30)	36(25)	0.393
Female Genital Organs	21(19)	43(27)	0.189	25(23)	26(18)	0.347
Integumentary System	14(13)	26(16)	N.S.	3(3)	18(13)	0.005
ENT	11(10)	19(12)	N.S.	14(13)	17(12)	N.S.
Male Genital Organs	11(10)	14(9)	N.S.	7(6)	10(7)	N.S.
Urinary System	11(10)	18(11)	N.S.	3(3)	19(13)	0.003
Nervous System	5(5)	8(5)	N.S.	7(6)	10(7)	N.S.
Obstetrical Procedures	5(5)	10(6)	N.S.	1(1)	4(3)	N.S.
Heme and Lymph System	1(1)	12(8)	0.017	2(2)	6(4)	N.S.
* two-sided Fisher's Exact Test						

Adapted from Sponsor's Table 2S, vol. 105, p. 303

There were significantly greater heme and lymph system surgeries in argatroban-treated HIT patients; and significantly greater cardiovascular, integumentary, and urinary system surgeries in argatroban-treated HITTS patients, compared to historical control patients.

A summary table for patient medical/surgical/invasive procedure history by **medical history** is shown below (Table 11, vol. 105, p. 97).

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	160		109	144	
Cancer	10 (9.3)	29 (18.1)	0.052	17 (15.6)	25 (17.4)	0.736
Renal Impairment	14 (13.0)	46 (28.8)	0.003	6 (5.5)	37 (25.7)	<0.001
Hepatic Impairment	5 (4.6)	15 (9.4)	0.164	1 (0.9)	15 (10.4)	0.001
Diabetes	28 (25.9)	45 (28.1)	0.780	27 (24.8)	50 (34.7)	0.099
Sepsis	6 (5.6)	19 (11.9)	0.090	3 (2.8)	17 (11.8)	0.009
Lupus Erythematosus	2 (1.9)	6 (3.8)	0.481	1 (0.9)	8 (5.6)	0.082
Respiratory Distress Syndrome	19 (17.6)	29 (18.1)	1.00	12 (11.0)	29 (20.1)	0.059
Ongoing Procedures						
Receiving Hemodialysis	4 (3.7)	22 (13.8)	0.006	1 (0.9)	10 (6.9)	0.026
On Circulatory Assist Device	7 (6.5)	19 (11.9)	0.206	2 (1.8)	19 (13.2)	0.001
Undergoing Ventilation	13 (12.0)	9 (5.6)	0.071	9 (8.3)	11 (7.6)	1.00
Previous Surgery						
Previous CABG	39 (36.1)	46 (28.8)	0.229	26 (23.9)	71 (49.3)	<0.001

Statistical comparisons made with Fisher's Exact Test.

In summary, significant differences in patient characteristics between the argatroban and historical control HIT and HITTS patients were seen, with argatroban-treated patients being substantially more compromised at baseline. The sponsor's explanation for these imbalances is reproduced below (vol. 105, p. 167):

Although the reasons for the imbalance in the disease severity between the argatroban and historical control groups cannot be conclusively established, it is likely due to selection bias(es) caused by the influence of the investigational therapy (i.e. argatroban) on clinical decision-making and selection of treatment options for the patients in the argatroban group, and which are not present in the historical control group. There is a well-known tendency for physicians to withhold treatment with an investigational agent until the patient's clinical condition, as well as prognosis, have become severe, and very often the investigational agent is regarded as a "treatment of last resort". The availability of argatroban as a treatment option may have encouraged pbysicians to adopt a "watchful waiting" approach for patients with a diagnosis of HIT or HITTS, electing to carefully monitor the patient's condition for a possible resolution of the thrombocytopenia. However, if the patient's condition did not resolve, or if serious clinical complications became apparent, the clinical decision-making process would be expected to increase the priority of treatment with argatroban as an acceptable option. These considerations could not be expected to have influenced the historical control group, since patients receiving investigational agents, including anticoagulant and antithrombotic agents, were excluded from this group.

The above explanation for unbalanced patient baseline characteristics seems implausible. In an institution with an available (and likely advertised) protocol and investigational agent for a potentially life-threatening condition for which there was no approved therapy, there was likely to be 1) greater insight into the diagnosis and management of the disease itself, and 2) increased and more rapid implementation of the investigational agent. "Watchful waiting" would more likely be employed where no investigational agent was available, and where procurement of such an agent were difficult and time-consuming. Further, even if "watchful waiting" were employed in argatroban-treated patients, it is not clear why mortality would be greater in this group compared to the historical control group where NO (or no efficacious) antithrombotic therapy was employed.

The sponsor also stated that the 30-day mortality rate for the historical control group (11% in HIT patients, and 15% in HITTS patients) was significantly lower than the death rate found for other HIT/HITTS cohorts reported in the literature. This is shown below (Table 30, vol. 105, p. 169).

Comparison of the 30-Day Mortality in ARG-911 Historical Control HIT/HITTS Patients With Other Published Reports

Report	Number of Patients	30-Day Mortality
ARG-911 Historical Control Groups	217	12.9% (28/217)
Published Reports		
Walls JT et al *Ann Thorac Surg* (1992) 53: 787-791	82	28.0% (23/82)
Warkentin TE and Kelton JG *Am J Med* (1996) 101: 502-507	127	20.5% (26/127)
European Agency for the Evaluation of Medicinal Products *European Public Assessment Report for Lepirudin* (1997)	120	17.5% (21/120)
All Three Published Reports (Pooled)	329	21.3% (70/329)

However, note that the 30-day mortality rate quoted for Lepirudin is not consistent with the incidence reported in the NDA 20-807 (MOR 8/10/97, p. 44), which was 12% at 60 days:

Efficacy Outcomes for Lepirudin (NDA 20-807)

Study B7		Study NR13		Historical controls	
No.of Patients (%)	82(100)	No.of Patients (%)	116(100)	No. of Patients (%)	91(100)
Deaths	6(7.3)	Deaths	11(9.5)	Deaths	11(12.1)
Amputations	3(3.7)	Amputations	10(8.6)	Amputations	8(8.8)
TECs	8(9.8)	TECs	20(17.2)	TECs	25(27.5)
Patients with Comb.Endpoint	15(18.3)	Patients with Comb.Endpoint	33(28.4)	Patients with Comb. Endpoint	39(42.9)

In summary, the death rate in historical control patients in study ARG-911 is NOT uniquely low, as it is similar to that reported for historical control patients in the Lepirudin study.

Methods and criteria used in the initial identification of historical control cases played an important role in the observed imbalances in patient baseline characteristics of control and treatment groups in study ARG-911. Specifically, oncology patients and more medically compromised patients were excluded from inclusion in the historical control, in part due to the interpretation of the exclusion criteria #1, which excluded patients with "clinically significant or uncontrolled endocrine, hepatic, renal, pulmonary, gastrointestinal, or psychiatric disorder for which antithrombin therapy would be contraindicated in the opinion of the investigator." In fact, 14% of patients screened for inclusion in the historical control were excluded for a pre-existing diagnosis of cancer, sepsis, renal failure, multisystem failure, or AIDS. An additional 39% of patients screened for inclusion in the historical control were excluded for failure to meet inclusion/exclusion criteria (not further specified).

Further, one of the recommendations provided by the sponsor for the identification of potential historical control cases was to start with patients who had been diagnosed with a DVT or PE (vol. 4.5, p. 41). This recommendation could have enriched the historical control population with HIT patients who already experienced a new thrombotic event. Note however, that any enrichment of historical control patients with new thrombotic events was not reflected in higher death or amputation rates.

Finally, investigators may have been reluctant to forward cases of retrospectively identified HIT/HITTS cases for medico-legal considerations.

Another problem with the collection of the historical control for study ARG-911 was that 45% of historical control patients, and no argatroban-treated patients, were provided by a single investigator (Dr. Warkentin) from 3 study centers in Canada (Study sites 200, 201, and 202). These centers accounted for 3 of the 7 largest centers (that enrolled ≥ 10 patients each). The event rates for the **overall composite endpoint** for these **7 largest centers** (namely sites 020, 059, 060, 113, 200, 201, and 202), the **4 of these 7 centers** that enrolled BOTH argatroban-treated and historical control patients, the **3 of these 7 centers** that enrolled ONLY historical control patients (sites 200, 201, and 202), and the **96 remaining sites** that each enrolled < 10 patients are summarized below.

Treatment-by-Center Analysis of the Incidence of the Overall Composite Endpoint

	HIT			HITTS		
	Argat	Hist Ctrl	P-value*	Argat	Hist Ctrl	P-value*
7 largest centers; enrolled ≥10 patients per site	5/36(14%)	28/77(36%)	0.015	9/33(27%)	41/81(51%)	0.037
4 centers; enrolled BOTH Argat and HC patients	5/36(14%)	4/45(9%)	0.501	9/33(27%)	11/16(69%)	0.012
3 centers; enrolled ONLY HC patients	0/0(0%)	24/32(75%)	--	0/0(0%)	30/65(46%)	--
96 sites; enrolled <10 patients per site	38/124(31%)	8/31(26%)	0.666	53/111(48%)	18/28(64%)	0.141
* two-sided Fisher's Exact Test						

Table adapted from Table 9a of Biometrics Review of NDA 20-883

Note that the incidence of the overall composite endpoint in historical control patients enrolled from the 3 Canadian sites which contributed 45% of all historical control patients (and no argatroban-treated patients) was **75% in HIT** patients and **46% in HITTS** patients. These rates should be compared to a much lower rate in other centers that enrolled HIT patients **(9%-26%)**, and a higher rate for the range seen in other centers that enrolled HITTS patients **(64%-69%)**. Thus, the disproportionate contribution of 3 centers (200, 201, and 202) to patients

included in the historical control, resulted in a isproportiately higher overall composite event rate in historical control HIT (but not HITTS) patients.

Impact of Imbalances in Patient Baseline Characteristics on Efficacy Outcomes in Study ARG-911

Statistical Analyses

A summary of the imbalances of baseline characteristics between argatroban-treated and historical control patients is shown below (Table 11, vol. 105, p. 97).

Summary of Medical/Surgical/Invasive Procedure History (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	160		109	144	
Cancer	10 (9.3)	29 (18.1)	0.052	17 (15.6)	25 (17.4)	0.736
Renal Impairment	14 (13.0)	46 (28.8)	0.003	6 (5.5)	37 (25.7)	<0.001
Hepatic Impairment	5 (4.6)	15 (9.4)	0.164	1 (0.9)	15 (10.4)	0.001
Diabetes	28 (25.9)	45 (28.1)	0.780	27 (24.8)	50 (34.7)	0.099
Sepsis	6 (5.6)	19 (11.9)	0.090	3 (2.8)	17 (11.8)	0.009
Lupus Erythematosus	2 (1.9)	6 (3.8)	0.481	1 (0.9)	8 (5.6)	0.082
Respiratory Distress Syndrome	19 (17.6)	29 (18.1)	1.00	12 (11.0)	29 (20.1)	0.059
Ongoing Procedures						
Receiving Hemodialysis	4 (3.7)	22 (13.8)	0.006	1 (0.9)	10 (6.9)	0.026
On Circulatory Assist Device	7 (6.5)	19 (11.9)	0.206	2 (1.8)	19 (13.2)	0.001
Undergoing Ventilation	13 (12.0)	9 (5.6)	0.071	9 (8.3)	11 (7.6)	1.00
Previous Surgery						
Previous CABG	39 (36.1)	46 (28.8)	0.229	26 (23.9)	71 (49.3)	<0.001

Statistical comparisons made with Fisher's Exact Test.

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. The results of these analyses are shown below (Tables 19S and 20S, vol. 105, pp. 323-24).

Logistic Regression Analysis of Patient Baseline Covariates Which Predicted All-Cause Mortality

	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, 3.285)
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.

Cox Proportional Hazards Analysis of Patient Baseline Covariates Which Predicted All-Cause Mortality

	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 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-CAUSE 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) ;
|7: model results adjusted for imbalances in cancer, renal, RDS, sepsis, Cardiac assist device, ventilation, and dialysis

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 follcwing 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 inconsistent." 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.

Comparison of the Efficacy Outcomes of Studies ARG-911 and ARG-915

Study ARG-915

Study ARG-915 was a compassionate-use, open-label, multicenter 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 were 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.

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.

A comparison of primary efficacy outcomes for studies ARG-915 and ARG-911 are shown below. Note that study ARG-915 was a compassionate-use, safety study which was not designed to demonstrate the overall efficacy of argatroban in patients with HIT/HITTS. The primary focus of the efficacy analysis of study ARG-915 however, was to further investigate the incidences and causes of deaths.

Primary Efficacy Outcomes for 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

Primary Efficacy Outcomes for 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

As is shown above, the incidence of all-cause death was greater in study ARG-915 than in study ARG-911. As was done for study ARG-911, all deaths that occurred in study ARG-915 were reconstructed from case report form data, and presented in the **Appendix 2** of this NDA review. Particular attention paid to medical history, timing of heparin and argatroban administration, platelet count, HIT antibody status (not required to be collected/documented in study ARG-915), clinical and objective evidence of ongoing thrombosis, on-site investigator assessment of clinical course and cause of death, and autopsy results whenever available. The results of this analysis are subsequently discussed.

Analysis of Deaths in Study ARG-915

HIT Patients

For the 13 deaths in HIT patients, for which case report forms were provided, 6(46%) were positive for a heparin-induced antibody test, 1(8%) was negative, and 6(46%) were not done/documented. (Note that heparin-induced antibody tests were not required in study ARG-915). Autopsy results were available for 2 patients. Of the 13 deaths that occurred in HIT patients, 1 was attributed to thrombosis and 12 were attributed to underlying disease by the sponsor.

Deaths in argatroban-treated HIT patients, which occurred in the setting of ongoing thrombosis, are tabulated below.

Patient	Ongoing Thrombotic Event(s) at Time of Death
014-002	Myocardial infarction
017-001	Bilateral LE ischemia and sudden onset of hypotension
017-004	Patient became "increasingly coagulopathic" near time of death; classified by sponsor as death due to myocardial infarction
036-007	"Intravascular thrombosis in the pulmonary tree"

Deaths in argatroban-treated HIT patients, for which ongoing thrombosis was not identified, are tabulated below.

Patient	Cause of Death
017-003	Candidemia, hepatic and renal failure
036-004	Sepsis
039-002	Multisystem failure
039-003	Metastatic lung cancer
052-004	Cardiac arrest
052-005	Respiratory failure
116-002	Metastatic adenocarcinoma
126-004	Sepsis
145-001	Pulmonary edema, renal failure, and myocardial infarction

As discussed in the analysis of deaths for study ARG-911, 5(5%) deaths in **historical control HIT patients** occurred in the setting of ongoing thrombosis, while no thrombotic component was identified for the remaining 7(6%) patients. By comparison, 4(5%) deaths in **argatroban-treated HIT patients** in study ARG-915 occurred in the setting of ongoing thrombosis, while no thrombotic component was identified for the remaining 9(11%) patients.

HITTS Patients

For the 23 deaths in HITTS patients, for which case report forms were provided, 5(22%) were positive for a heparin-induced antibody test, 0(0%) was negative, and 18(78%) were not done/documented. (Note that heparin-induced antibody tests were not required in study ARG-915). Autopsy results were available for 3 patients. Of the 23 deaths that occurred in HITTS patients, 2 were attributed to thrombosis, 1 was classified as treatment-emergent, and 20 were attributed to underlying disease by the sponsor.

Deaths in argatroban-treated HITTS patients, which occurred in the setting of ongoing thrombosis, are tabulated below.

Patint	Ongoing Thrombotic Event(s) at Time of Death
012-001	CVA
020-009	CVA
024-002	Bilateral UE and LE ischemia and myocardial infarction
025-001	Mesenteric ischemia and possible PE (Classified as thrombotic death by sponsor)
039-106	Mesenteric thromboemboli
043-001	Pulmonary emboli and infarcts
079-001	"Possible infection/sepsis, heart disease, and multiple thrombotic events"
081-003	Acute MI
115-003	CHF, pneumonia, azotemia, and "multiple embolic strokes vs. brainstem infarction."
122-001	ARDS, sepsis, and acute abdomen "with probable mesenteric infarction"
146-001	Renal and hepatic failure, and worsening UE and LE thromboemboli
149-001	Acute MI

Deaths in argatroban-treated HITTS patients, for which ongoing thrombosis was not identified, are tabulated below.

Patient	Cause of Death
007-001	Aspiration
020-002	Cardiac arrest
020-018	Cardiac arrest
036-002	Duodenal perforation
037-002	Multiorgan failure
088-001	Cardiorespiratory arrest
089-001	Bleeding, ARDS
114-007	Sepsis
121-204	Dilated cardiomyopathy
133-001	Anoxic encephalopathy
143-001	Renal failure

As discussed in the analysis of deaths for study ARG-911, 12(11%) deaths in **historical control HITTS patients** occurred in the setting of ongoing thrombosis, while no thrombotic component was identified for the remaining 4(4%) patients. By comparison, 12(13%) deaths in **argatroban-treated HITTS patients** in study ARG-915 occurred in the setting of ongoing thrombosis, while no thrombotic component was identified for the remaining 11(12%) patients.

In summary, the incidences of thrombotic deaths were essentially the same for historical control and argatroban-treated HIT and HITTS patients. Ongoing thrombosis was not identified in the remainder of deaths, and many of these were not likely related to a thrombotic complication of HIT/HITTS. However, a numerical excess of non-thrombotic deaths in argatroban-treated patients was again observed (and greater than that seen in study ARG-911). In addition, a 27% mortality rate in the 97 remaining HIT/HITTS patients was also reported. To further investigate the numerically greater death rate in argatroban-treated patients in study ARG-915, baseline characteristics were examined, and are subsequently discussed.

Patient Baseline Characteristics in Study ARG-915

With regard to baseline patient characteristics, a summary of medical/surgical/invasive procedure history of patients (by ICD-9 coded terms) by body system and **diseases** is shown below.

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 **medical history**, is shown below. (Table 8, vol. 12.1, p. 23)

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.

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.**