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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

APR 30 1998

NDA: 20-883

Sponsor: Texas Biotechnology Corp.

Drug: Novastan® (Argatroban)

Class: Antithrombin

Indication: Anticoagulant therapy in patients
with heparin-induced
thrombocytopenia

Date of submission: 8/15/97

Amendments: 10/31/97, 11/17/97, 11/21/97,
12/11/97, 12/19/97, and 2/9/98

Medical Reviewer: Kurt Sizer, M.D.

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TABLE OF CONTENTS

	<u>Page</u>
INTRODUCTION AND BACKGROUND.....	4
STUDY ARG-911 (PIVOTAL STUDY)	
Study Protocol.....	8
Protocol Amendments.....	13
Study Administration.....	13
Collection of Cases Included in the Historical Control.....	15
Statistical Analysis Plan.....	16
Study Results.....	21
Patient Disposition.....	21
Patient Demographics.....	27
Dose, Duration, and Delay of Argatroban Therapy.....	28
Patient Baseline Characteristics.....	31
Baseline and Concomitant Medications.....	34
Primary Efficacy Outcome Results.....	42
Intent-to-Treat Population.....	42
SRA Positive Population.....	47
Population with a History of Positive HIT Serology.....	49
Statistical Adjustments for Baseline Predictors of Death.....	51
Secondary Efficacy Outcome Results.....	57
Safety Analysis.....	60
Deaths.....	60
Adverse Events Leading to Study Withdrawal.....	60
Serious Adverse Events.....	61
Treatment Emergent Adverse Events.....	65
Most Frequent Adverse Events.....	71
Bleeding Events.....	75
Clinical Laboratory Parameters and Vital Signs.....	85
STUDY ARG-915 (Continuation study of ARG-911)	
Introduction.....	88
Patient Disposition.....	89
Patient Demographics.....	90
Dose, Duration, and Delay of Argatroban Therapy.....	90
Patient Baseline Characteristics.....	91
Concomitant Medications.....	97
Primary Efficacy Outcome Results.....	100
Statistical Adjustments for Baseline Predictors of Death.....	102
Secondary Efficacy Outcome Results.....	104
Safety Analysis.....	105
Deaths.....	105
Adverse Events Leading to Study Withdrawal.....	107
Most Frequent Adverse Events.....	108
Bleeding Events.....	109
OTHER STUDIES	
Study ARG-103 (Patients with Renal Disease).....	113
Study ARG-106 (Patients with Liver Disease).....	114
Study ARG-310 (Patients with HIT/HITTS undergoing PTCA).....	115
INTEGRATED SUMMARY OF SAFETY.....	118

TABLE OF CONTENTS CONTINUED

	<u>Page</u>
Foreign Labeling and Post-Marketing Safety Experience (Japan).....	124
SUMMARY AND CONCLUSIONS	
Introduction.....	131
Analysis of Causes of Death in Study ARG-911.....	132
Imbalances in Patient Baseline Characteristics and Their Impact on the Efficacy Outcomes of Study ARG-911.....	147
Analysis of Causes of Death in Study ARG-915.....	153
Comparison of Efficacy Outcomes in Studies ARG-911 and ARG-915.....	151
Patient Baseline Characteristics in Study ARG-915.....	155
Validity of the New Thrombosis Endpoint.....	159
Overall Safety Experience with Argatroban.....	161
Overall Conclusions.....	168
APPENDIX 1: Analysis of Deaths that Occurred in Study ARG-911.....	170
APPENDIX 2: Analysis of Deaths that Occurred in Study ARG-915.....	196

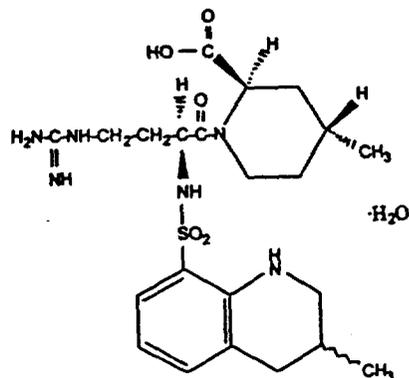
Introduction and Background

Thrombocytopenia is a well-recognized complication of heparin therapy. Two distinct forms of heparin-induced thrombocytopenia (HIT) have been described: 1) Type I HIT is early (usually occurs in the first 1 or 2 days following the initiation of heparin therapy), benign, nonimmune thrombocytopenia which often normalizes despite continued heparin administration, and 2) Type II HIT is a late (usually occurs 5-10 days following the initiation of heparin therapy), immune-mediated thrombocytopenia, which confers an increased risk of subsequent thrombotic complications.

Type II HIT is mediated by the formation of an antibody which recognizes Platelet Factor 4 (PF4) bound to heparin. PF4 is a positively charged protein found in platelet α -granules which binds to heparin with high affinity. The heparin-dependent antibody reacts with a cryptic epitope on PF4 that emerges only after the protein binds to heparin. The antibody-PF4-heparin complex then binds to platelets via platelet Fc γ receptors. Subsequent crosslinking of these Fc γ receptors results in platelet activation, release of platelet-derived microparticles, and platelet aggregation. The platelet-derived microparticles are believed to play a significant role in thrombotic complications associated with Type II HIT. In addition, the heparin-dependent antibody can also bind to and injure endothelial cell surfaces.

A total of 10-60% of patients who are exposed to heparin will make antibodies against the heparin:PF4 complex. A smaller proportion of patients (3-5%) will develop the antibody **and** thrombocytopenia, and as many as a third of these patients will develop HIT-associated thromboses (HITTS: Heparin-induced thrombocytopenia with thrombosis syndrome). Thrombotic complications can be either venous or arterial, and the location is highly influenced by the underlying disease state. For example, patients who have undergone cardiovascular surgery or have peripheral arterial occlusive disease, are more likely to get thrombi in heart or limb arteries, respectively. In contrast, patients who have undergone recent orthopedic or generally surgery are more likely to sustain a DVT or PE. Further, HIT-associated thromboses are often clinically very severe, and include PE, DVT, CVA, mesenteric and renal artery occlusion, and coronary artery and bypass graft occlusion. Limb amputation and death can result. Importantly, the incidence of developing a thrombotic event following the diagnosis of HIT, despite the discontinuation of heparin and recovery of the

Argatroban is a synthetic, direct thrombin inhibitor derived from L-arginine. It has a molecular weight of 527, and is a mixture of R and S stereoisomers at a ratio of approximately 65:35. Its structural formula is shown below:



Argatroban selectively and reversibly binds to the active site of thrombin in an "inhibitor-like" fashion, characterized by X-ray crystallography as a close interaction with hydrophobic groups and no direct interaction with the oxyanion hole. The 2R,4R isomer of argatroban has been observed to be the most potent inhibitor of thrombin, with a 10-fold greater K_i than the 2R,4S isomer, 100-fold greater K_i than the 2S,4R isomer, and a 15,000-fold greater K_i than the 2S,4S isomer.

Argatroban is primarily metabolized in the liver by hydroxylation and aromatization of the 3-methyl-tetrahydroquinoline ring. The resulting major metabolite has 3- to 5-fold less anticoagulant activity than the parent compound; other metabolites are found only in extremely low concentrations. In healthy subjects, approximately 22% of radioactively-tagged argatroban was recovered in the urine, and 65% was recovered in the stool.

Argatroban is 54% bound to serum proteins, including 20% to albumin, and 34% to α_1 -glycoprotein. Steady-state levels are achieved within 1-3 hours following an i.v. infusion. Dose-dependent increases in APTT, PT, ACT, and TT values are reported in healthy subjects in i.v. infusion doses up to 40 $\mu\text{g}/\text{kg}/\text{min}$. The α and β elimination half-lives following discontinuation of an i.v. infusion are 7 minutes and 54 minutes, respectively. The disposition of argatroban is reported to be unaffected by renal dysfunction. Hepatic impairment is associated with decreased clearance and an increased half-life (to 152 minutes for patients with a Child's score of > 6).

Beyond the known pharmacologic action of argatroban, no major preclinical toxicologic adverse effects have yet been described. In addition, argatroban has not been found to result in antibody formation following repeated exposure in animals.

Argatroban has been studied in over 1300 patients in sponsor-conducted trials, including studies in acute MI, PTCA, and HIT/HITTS. In addition, Argatroban has been marketed in Japan since 1990 for peripheral arterial disease, and since 1996 for acute thrombotic stroke, and the prevention of clotting during hemodialysis in patients with decreased antithrombin III levels (in whom heparin has proved inadequate). A total of approximately 30,000 patients in Japan received Argatroban in 1996. The primary adverse event associated with Argatroban administration is bleeding.

The IND for Novastan® (Argatroban) was submitted by Genentech Inc. in 1988, and transferred to its present sponsor Texas Biotechnology Corporation in 1993. Meetings regarding the development of Argatroban for patients with HIT/HITTS were held with the sponsor on 2/2/95, 2/26/97 (CMC), 4/2/96, 1/7/97, and 5/21/97, with a follow-up Telecon on 7/18/97. NDA 20-883 was submitted on 8/15/97 for the approval of Argatroban as "anticoagulant therapy in patients with heparin-induced thrombocytopenia." ARG-911, a single, multicenter, historically-controlled, open-label, prospective trial of a total of 304 patients with HIT/HITTS was submitted to support this indication. Reviewable information for the first 174 of 271 patients who completed Study ARG-915 - an open-label, compassionate-use, continuation study of ARG-911 - was submitted on 2/9/98.

STUDY ARG-911

Study Title: An Historical Control Study of NOVASTAN® (brand of argatroban) in Patients with Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS).

This was a multicenter, open-label, historically-controlled, prospective study of patients with HIT or HITTS given argatroban 2 mcg/kg/min - 10 mcg/kg/min (for a target APTT of 1.5 - 3.0 x baseline), until clinical resolution of the underlying condition, appropriate anticoagulation was provided with other agents, or until treatment was continued up to 14 days. Primary efficacy endpoints were amputation, death, and new thrombosis.

Study Protocol

Elements of the study protocol from the NDA Study Report (vol. 105) were compared (where appropriate) to the **original** study protocol from IND . The original study protocol was dated 12/12/94 and a second protocol dated 1/13/95 which included 4 out of a total of 6 amendments is also cited. The two final amendments (dated 7/19/96 and 12/30/96) were also acknowledged.

Definition of HIT and HITTS

- **HIT** - This arm consisted of all patients with a diagnosis of HIT, defined as *thrombocytopenia that occurs after the initiation of heparin without new thrombosis formation after the initiation of heparin*. These patients may have had active thrombosis at baseline that was cause for their heparin therapy but did not show any obvious signs of new thrombosis occurring on heparin. This arm also included patients with a documented history of a positive laboratory test for HIT or HITTS (e.g., heparin-induced platelet aggregation, Serotonin Release Assay, etc.).
- **HITTS** - This arm consisted of all patients with a diagnosis of HITTS, defined as *thrombocytopenia after the initiation of heparin that is accompanied by new thrombus formation after the initiation of heparin*.

Primary Efficacy Endpoints as per the Original Study Protocol Which Determined the Sample Size of the Study ("Final Protocol" dated 1/7/97, vol. 107, p. 103)

"For the HIT portion of the study, the primary event is death, amputation, or development of a new thrombosis."

"For the HITTS portion of the study, the primary event is the frequency of death or limb amputation."

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ON ORIGINAL**

Primary Efficacy Endpoints as per the NDA Study Report

- Development of new (i.e., not present at baseline) thrombosis;
- Amputation (all causes) as well as amputation due to ischemic complications of HIT or HITTS and amputation due to other reasons;
- Death (all causes) as well as death due to thrombosis, treatment-emergent deaths, and deaths due to underlying disease and pre-existing conditions.

The overall composite outcome endpoint was derived by determining the number of patients who experienced one or more of the following: (1) development of new thrombosis, (2) all-cause death, and (3) all-cause amputation. This composite endpoint makes no assumptions regarding the cause or nature of the clinical outcomes observed. It includes all events, including those resulting from clinical conditions present prior to drug administration which are unrelated to argatroban administration.

The thrombotic composite outcome endpoint was derived by determining the number of patients who experienced one or more of the following: (1) development of new thrombosis, (2) death due to thrombosis, and (3) amputation due to ischemic complications of HIT or HITTS. This composite endpoint evaluates the efficacy of argatroban to reduce both the development of new thrombosis and the expected adverse outcomes associated with thromboembolic complications.

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Secondary Endpoints

Secondary efficacy endpoints were the same in the original protocol (Protocol dated 1/13/95, pp. 21-22) and in the final study report and are shown below.

- Pulmonary embolism
 - V/Q scan
 - Presence or absence of shortness of breath
 - Presence or absence of chest X-ray changes (if X-ray was obtained)
 - iv. Presence or absence of chest pain
- Venous thrombosis
 - Comparison of the diameter of the affected limb (10 cm proximal to the medial malleolus in the foot or the anatomic snuff box in the arm) and at the most swollen point of the affected limb to the unaffected extremity
 - Presence or absence of pain in the affected limb
 - Presence or absence of heat in the affected limb
- Presence or absence of acute myocardial infarction secondary to HITTS
- Presence or absence of stroke secondary to HITTS
- Presence or absence of other arterial thrombosis
- Arterial and venous Doppler of the upper and lower extremities

Negative heparin-induced platelet aggregation test at study end

Resolution of thrombocytopenia as evidenced by normalization of the platelet count

An obtained anticoagulant effect as evidenced by increased treatment aPTT

Inclusion Criteria

Inclusion criteria were male or non-pregnant female patients age ≥ 18 years and ≤ 80 years, with documented heparin-induced thrombocytopenia with or without thrombosis, or a history of a positive heparin-induced antibody test.

Exclusion Criteria

- 1) any condition which, in the investigator's opinion, contraindicated the use of argatroban or endangered the patient if he/she participated in this trial
- 2) clinically significant or uncontrolled endocrine, hepatic, renal, pulmonary, gastrointestinal, or psychiatric disorder of sufficient severity that the investigator deemed antithrombotic therapy with argatroban to be contraindicated
- 3) unexplained aPTT > 200% of control at baseline
- 4) documented coagulation disorder or bleeding diathesis unrelated to HITTS
- 5) lumbar puncture within the past 7 days
- 6) history of previous aneurysm, hemorrhagic stroke, or recent thrombotic stroke (within past 6 months) unrelated to HITTS
- 7) prothrombin time of greater than 16 seconds at screen in the absence of COUMADIN®
- 8) known clinical site of bleeding (e.g., gastrointestinal (GI) bleed, hematuria, hemorrhagic cerebrovascular accident (CVA), retroperitoneal hematoma, diabetic retinopathy, hemorrhagic pericardial effusion, or hemorrhagic pleural effusion).

Patients with a known clinical site of bleeding could be enrolled if the investigator deemed the risk of continued thrombosis outweighed the potential bleeding risk.
- 9) females of known or suspected pregnancy
- 10) breastfeeding females
- 11) participation in other clinical drug trials within the past 30 days
- 12) history of hypersensitivity to argatroban
- 13) concomitant use of cimetidine
- 14) previous participation in this trial

Withdrawal Criteria

For safety reasons (e.g. adverse event, sensitivity, severely decreased platelet count, etc.), the infusion may have been interrupted for up to 24 hours. If the infusion was interrupted for more than 24 consecutive hours, the patient was discontinued from the study. Infusion was terminated immediately if clinically significant bleeding unresponsive to usual clinical interventions occurred. In addition, the infusion was discontinued at least 30 minutes before any surgical procedure. The argatroban infusion could be reinstated post operatively as soon as hemostatic control was achieved. Patients could not undergo percutaneous transluminal coronary angioplasty (PTCA) or any surgical procedure on argatroban. Patients were also withdrawn from the study if an intercurrent illness, at the discretion of the investigator, affected assessments of clinical status. In addition, patients were also withdrawn for non-compliance or the patient's request to withdraw.

Study Drug Administration

Patients were administered a drug infusion of argatroban at a dose of 2 µg/kg/min. An aPTT was evaluated 2 hours after initiating the infusion. The argatroban dose was adjusted as clinically indicated according to dosing guidelines in the protocol; however, the dose was not to exceed 10 µg/kg/min. The aPTT was checked 2 hours after each dosing change until the aPTT was in the desired therapeutic range. Once a therapeutic aPTT (between 1.5 and 3 times the patient baseline; if the baseline was abnormal, aPTT was not to exceed 100 seconds) was achieved, patients remained on this infusion until clinical resolution of their underlying condition, appropriate anticoagulation was provided with other agents or until treatment was continued for up to fourteen days. Anticoagulation testing (aPTT) was performed at least once per day after the aPTT had been stabilized.

Study Assessments

A summary of study assessments is reproduced below (vol. 105, pp. 59-60)

Study Assessments

Procedure	Pre treatment	Treatment Period (Infusion may not be continued for more than 14 days)							Within 24 Hours Post Infusion or at Discharge	30 Day Follow-Up
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7 ^a		
History	X ^b									
Physical Exam	X ^c								X	X ^d
Vital Signs	X	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X	
CBC w/ Platelet Count	X ^f			X ^g					X	
SMA-20 or Equivalent	X ^f			X ^g					X	
Urinalysis	X ^f			X ^g					X	
Urine HCG	X ^f									
Heparin-Induced Platelet Aggregation Test	X			X					X	X ^d

- ^a The infusion may be continued up to fourteen days.
- ^b Within one week before initiating treatment.
- ^c Within 72 hours before initiating treatment, including height and weight.
- ^d This is only if the patient returns to the study site.
- ^e Vital signs recorded at least once per day and as clinically indicated.
- ^f Should be performed no more than 12 hours before initiating treatment infusion.
- ^g Obtained between 8 am and 12 noon daily.
- ^h Patients will be evaluated daily for signs and symptoms of clinical ischemic syndromes. If a thrombotic complication is documented, it will be monitored daily to resolution or until argatroban therapy is stopped.
- ⁱ A positive arterial or venous duplex Doppler study will be confirmed by arteriography or venography when clinically indicated.
- ^j Arterial and/or venous duplex Doppler studies will be performed as appropriate for those patients who develop thrombosis while receiving argatroban infusion.
- ^k V/Q scanning will be performed for those patients who develop new pulmonary embolism while receiving argatroban infusion.
- ^l Evaluated at least once per day and 2 hours after each dose change.

Study Assessments continued

Procedure	Pre treatment	Treatment Period (Infusion may not be continued for more than 14 days)							Within 24 Hours Post Infusion or at Discharge	30 Day Follow-Up
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7 ^a		
Signs and Symptoms of Clinical ischemic Syndromes	X	X ^h	X ^h	X ^h	X ^h	X ^h	X ^h	X ^h	X	
Arterial & Venous Doppler ⁱ	X	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X ^j	X	
V/Q Scan	X	X ^k	X ^k	X ^k	X ^k	X ^k	X ^k	X ^k	X	
ECG	X								X	
aPTT	X	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X ^l	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	
Summary of Patient's Clinical Course									X	

- ^a The infusion may be continued up to fourteen days.
- ^b Within one week before initiating treatment.
- ^c Within 72 hours before initiating treatment, including height and weight.
- ^d This is only if the patient returns to the study site.
- ^e Vital signs recorded at least once per day and as clinically indicated.
- ^f Should be performed no more than 12 hours before initiating treatment infusion.
- ^g Obtained between 8 am and 12 noon daily.
- ^h Patients will be evaluated daily for signs and symptoms of clinical ischemic syndromes. If a thrombotic complication is documented, it will be monitored daily to resolution or until argatroban therapy is stopped.
- ⁱ A positive arterial or venous duplex Doppler study will be confirmed by arteriography or venography when clinically indicated.
- ^j Arterial and/or venous duplex Doppler studies will be performed as appropriate for those patients who develop thrombosis while receiving argatroban infusion.
- ^k V/Q scanning will be performed for those patients who develop new pulmonary embolism while receiving argatroban infusion.
- ^l Evaluated at least once per day and 2 hours after each dose change.

Protocol Amendments

Amendment #1: March 28, 1995

The number of patients to be treated under the protocol was increased from 100 patients diagnosed with heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) or heparin-induced thrombocytopenia (HIT) to approximately 300 patients consisting of approximately 150 patients diagnosed with HITTS constituting a "treatment population" and approximately 150 patients diagnosed with HIT constituting a "prophylactic population". In addition, the protocol was changed to include a historical control population with data to be collected from centers participating in the study as well as other centers where appropriate.

Amendment #2: May 1, 1995

This amendment allowed patients to be enrolled in the absence of heparin challenge or thrombocytopenia if they had a documented history of a positive heparin-induced platelet aggregation test. Patients had been allowed to enroll in the absence of heparin challenge or thrombocytopenia if they have documented evidence of a positive heparin-induced platelet aggregation test within the past 12 months.

Amendment #3: September 15, 1995

This amendment detailed fully the historical control population. Patients diagnosed with either HIT or HITTS "after January 1, 1990" were screened was changed to read "after January 1, 1993." This amendment also described the inclusion/exclusion criteria used for patient screening, which was the same for the prospective study. Data from patients who met these criteria were collected on data forms similar to those used to collect data during the conduct of the ARG-911 study.

Amendment #4: September 22, 1995

This amendment clarified several sections of the protocol. First, the inclusion criteria were clarified by removing most references to the heparin-induced platelet aggregation test.

Exclusion criterion number 2 under the protocol was also clarified. The original intent of this criterion had been for the investigator to assess the concomitant clinical conditions present in the patient with regard to their clinical significance to the patient being treated with argatroban. The timing of some of the procedures and evaluations required are also clarified. The amendment requests that every effort be made to obtain duplex Doppler and/or V/Q studies 24 hours prior to initiating the infusion but allow a 48 hour window after initiation when this is not possible.

A 30 day follow-up visit was added. It was an office visit, is possible, or a telephone contact.

Amendment #5: July 19, 1996

This amendment extended the maximum amount of the time a patient was treated from 7 days up to 14 days.

Amendment #6: December 30, 1996

Because of the relative rarity of HITTS cases and because of the need to collect positive serotonin release assay tests from historical controls for comparison with prospective SRA-positive patients, additional historical control cases were collected with diagnosis after January 1, 1985.

Study Administration

ARG-911 was conducted at 103 investigative sites in the United States and Canada. Historical control data were collected from 36 centers. Study sites which enrolled ≥ 10 patients for the

argatroban and historical control groups are shown below (Appendix 16.4.4.2, vol. 129 and Section 8A, vol. 70, pp. 1-40, and Biometrics Review, Table 9a).

Study Sites with 10 or Greater Patients

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

Note that patients enrolled in the historical control by Dr. Warkentin were from a registry of HIT/HITTS patients treated at three study sites in Canada.

Case report form data were reviewed against source documents at the study sites by Texas Biotechnology Corporation study monitors. The CRF data were entered and audited by the _____

_____ The regulatory documentation on file with the sponsor for selected sites (including IRB approval and consent forms) was inspected by the Department of Quality Assurance and _____, to assure that this documentation was complete and in compliance with regulatory guidelines. Randomly selected CRFs were audited for consistency with source documents, protocol adherence, and regulatory compliance.

The Data Safety Monitoring Committee (DSMC) reviewed the eligibility and HIT/HITTS diagnoses of both historical control and argatroban-treated patients. In addition, this committee conducted the interim analyses and determined which cases collected by on-site investigators were included in the historical control. None of the members of this committee were investigators in the ARG-911 study, and none were affiliated with the sponsor. Members of the DSMC are shown below.

David DeMets, Ph.D.
University of Wisconsin
K6/446 Clinical Science Center
Madison, Wisconsin

James Ferguson, M.D.
Texas Heart Institute
Houston, Texas

Graham Pineo, M.D. (as of 5/96)
The Calgary General Hospital
Calgary, Alberta

Hau Kwaan, M.D. (resigned)
VA Hospital
Chicago, Illinois

Thomas Massey
Coromed Inc.
Troy, NY

Harry Messmore, M.D.
Loyola Univ Med Center
Chicago, Illinois

Dr. Jean Claude Becker, Senior Director, Clinical Development for Texas Biotechnology Corporation, presented data and summaries to the committee but had no vote. Mr. Massey of Coromed Inc. was the recording secretary and a non-voting member.

Collection of Cases Included in the Historical Control

Historical control cases were solicited primarily from investigators participating in the ARG-911 study (although Dr. Warkentin provided 45% of historical control patients and NONE of the argatroban-treated patients from 4 centers in Canada). The initial screening was conducted by the investigator (or the investigator's study coordinator) using criteria contained in several newsletters published by the sponsor. These newsletters (dated 1/96, 6/96, and 9/96) suggested specific strategies for the identification of historical control HIT/HITTS patients, and are summarized below (vol. 4.5, pp. 40-41).

- Search only records from January 1993 forward (later amended to 1985 forward).
- Search records for patients diagnosed with thrombocytopenia (ICD9 code 287.5). From this list eliminate pediatric patients and patients with leukemia, lymphoma, or other oncologic diagnoses.
- Search records for patients diagnosed with deep vein thrombosis or pulmonary embolism (ICD9 code 415.1). Then check for heparin use.
- Search for records for patients who received Ancrod.
- Ask pharmacists whether they have reported any heparin-associated adverse events to the heparin manufacturer, and then review the data on those patients.

- Determine whether your institution's pharmacy can supply you and/or the laboratory with a list of patients currently being treated with heparin; then have these patients' platelet counts monitored for decreases.
- Ask your medical records or admissions department to provide you with a list of patients admitted with thrombi or other related diagnoses.
- Conduct Grand Rounds on the subject of HIT and its serious consequences.
- All study sites should keep careful records as to how the patients were identified and how the data were collected. Sites must also keep a log of the historic patients that were excluded from their final cohort.

All eligible patients had to meet the inclusion/exclusion criteria of the ARG-911 protocol. Case report forms for eligible cases were then completed by the investigator and forwarded to the Data Safety Management Committee for final review.

Statistical Analysis Plan

Primary Efficacy Analysis

All analyses were based on the intention-to-treat HIT and HITTS populations, and compared the incidence rates for

- development of a new thrombosis
- limb amputation and limb amputation due to ischemic complications secondary to HIT/HITTS
- death and death due to thrombosis
- the composite and thrombotic composite endpoint

between the argatroban patients and the historical control population, separately for the HIT and HITTS populations, over the entire study period.

A one-sample normal approximation test was used to test the null hypothesis that the incidence rates for argatroban patients, from the time of infusion until the end of the 30 day follow-up period, were no different than the incidence rates for the historical control population during the 37 day period.

Logistic regression was conducted to test the null hypothesis that over the entire study period, there was no increased risk of the outcome event associated with argatroban. The assumptions for this analysis are:

- o Patients are treated with argatroban for 1 to 14 days and then have a follow-up assessment 30 days later, resulting in 31 to 44 days of observation
- o The historical control data are observed over a 37 day period
- o The loss of follow-up in both groups is low
- o **The argatroban patients and historical controls have comparable baseline characteristics**

Secondary Efficacy Analysis

Survival curves for outcome events (development of a new thrombosis, (any) limb amputation, (any) death, the composite and thrombotic composite) were generated for the HIT and HITTS populations. Survival curves were calculated using Kaplan-Meier estimates, and were compared by the log rank test (to detect differences between the argatroban and historical control curves late in the study), and the Wilcoxon test (to detect differences between the argatroban and historical control curves early in the study).

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

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

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

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

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

The baseline covariates having an influence on death were used to

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

Safety Analysis

The primary evaluation of safety was based on:

- the occurrence of major bleeding
- the change from baseline to the lowest treatment value in hematocrit
- the occurrence of intracranial bleeding
- blood transfusion data
- aPTT data

Incidence rates for major bleeding and intracranial bleeding were presented and compared between the argatroban and historic control groups using logistic regression analysis modeling for the effect treatment. Odds ratios and 95% confidence intervals were calculated.

The change from baseline to the lowest treatment value in hematocrit and blood transfusion data were summarized.

aPTT data for the argatroban treatment group was summarized:

- over time
- for the 1st aPTT after infusion started (i.e. aPTT at initial dose of 2 µg/kg/min)
- for the 'maximum' aPTT that occurred during the patient's infusion and the related argatroban dose
- for the 'average' aPTT.

To determine if a correlation existed between 'high' aPTT levels and bleeding, incidence rates for major bleeding were calculated for all argatroban patients who had a treatment aPTT greater than 3X their baseline aPTT at any time during their infusion. Finally, the Pearson product moment correlation coefficient was determined to evaluate if any correlation existed between aPTT measurements obtained from Loyola and those obtained from local labs. the aPTT measurements used for this evaluation were those taken at baseline and the first treatment aPTT.

Adverse events rates were summarized for each treatment according to System Organ Class and Preferred terms using the WHO Adverse Reaction Dictionary.

Covariate Analysis

The following covariates were used in the evaluation of the incidence rate for the composite endpoint:

- age stratified as < 65 years and >= 65 years
- sex
- mean argatroban dose over the length of the infusion, stratified into the intervals < 1.0, 1.0-2.0, and > 2 units
- renal impairment
- hepatic impairment

- use of the 3 most common concurrent medications (determined to be furosemide, potassium chloride, paracetamol) as well as warfarin and aspirin
- medical history with an emphasis on oncology, sepsis, ARDS, diabetes, and lupus
- body weight
- use of a cardiac assist device
- need for dialysis
- if the patient was ventilated
- if the patient had previous CABG surgery

A logistic regression analysis which modeled the effects of treatment and the covariate was performed. The Breslow-Day test was done to test for treatment-by-covariate interactions.

Patient Population Definitions

The Intention-to-Treat population consisted of all patients who received at least one dose of drug, and all historical control patients meeting the protocol inclusion/exclusion criteria.

Evaluable patients were defined as all patients who 1) received argatroban or were in the historical control population, and 2) were determined by the DSMC to have a clinical diagnosis of HIT or HITTS.

The "previously diagnosed patient population" consisted of patients who had documented evidence of a positive laboratory test for HIT or HITTS in the absence of thrombosis or thrombocytopenia. These patients were included in the HIT population.

The "Serotonin Release Assay (SRA) positive population" consisted of argatroban-treated patients who were positive for HIT by SRA conducted at the Loyola University Medical Center, and the historical control population patients who had a baseline SRA test performed and were positive.

Determination of Sample Size as per the Study Report

Approximately 150 patients diagnosed with HITTS and approximately 150 patients diagnosed with HIT were administered argatroban.

Since the study was an historical control design, Appendix B of the protocol shows a sample size formula for the comparison of two event rates which allows the number of patients in the historical control arm and the argatroban arm to be different or unequal. The study is designed for a two-sided significance level of 0.01 and power of 0.90.

For the HITTS population, the primary event was the frequency of death, limb amputation, or development of new thrombosis. The event rate for the historical control population (p_c) was estimated to be in the range of 0.40 to 0.50. The event rate for the argatroban group (p_t) was estimated to be in the range of 0.10 to 0.20. Hence, the absolute difference between the argatroban group event rate and the historical control population event rate was expected to be large. To have a 90% power to detect an absolute difference of 0.20 to 0.30, at a 1% significance level, 50 historical control patients were required.

For the HIT population, the primary event was the frequency of death, limb amputation or development of a new thrombosis. The event rate for the historical control population (p_c) was estimated to be in the range of 0.30 to 0.35. The event rate for the argatroban group (p_t) was estimated to be 0.10 or less. Again, the absolute difference between the argatroban group event rate and the historical control population event rate was expected to be large. To have a 90% power to detect an absolute difference ≥ 0.20 , at a 1% significance level, a minimum of 60 historical control patients were required.

Determination of Sample Size as per the Original Protocol (Protocol dated 1/7/97, vol. 107, p. 103)

Since the study is an historical control design, we have derived in Appendix B a sample size formula for the comparison of two event rates which allows the number of patients in the control arm and Novastan® arm to be different or unequal. The study is designed for a two-sided significance level (α) of 0.01 and power of 0.90.

For the HITTS portion of the study, the primary event is the frequency of death or limb amputation. The control event rate (p_c) is estimated to range between 0.4 and 0.5. The treatment effect is estimated to be large where the treatment group event rate p_t to be with range 0.1 or 0.2. That is, the absolute difference ($\Delta = p_c - p_t$) is large. Based on this, we have shown in Appendix B that 150 treated patients and 50 control patients would provide 90% power to detect differences of this magnitude.

For the HIT portion of the study, the primary event is death, amputation or development of a new thrombosis. In this setting, the estimated event rate (p_c) in the control arm is in the range of 0.3 to 0.35. Again, a large treatment effect is expected so that the event rate will be reduced to 0.1 or less, making the absolute difference in event rates large. Again, as shown in Appendix B, a sample of 150 HIT treated patients and a minimum of 60 control patients are required to have a 90% power to detect clinically important differences at the 1% significance level.

Interim Analyses

(From vol. 105, p. 79)

"The Data Safety Monitoring Committee met on 3 occasions (12/95, 3/96, and 9/96). **Efficacy** and safety data were presented. Historical control data were not available for the first 2 meetings. Summary results of **efficacy** and safety were presented at all meetings. Although interim analyses were planned, no formal hypothesis testing was actually performed."

In response to a requested clarification of the nature of interim analyses performed, the sponsor reported (NDA Supplement of 12/16/97) that while the data were examined on 3 occasions (for safety monitoring only) by the DSMC, no formal hypothesis testing was carried out. Formal comparative efficacy analyses were conducted on 7/24/97.

STUDY RESULTS

Patient Disposition

A total of 304 patients (160 with HIT and 144 with HITTS) were entered into the argatroban group, and 217 patients (108 with HIT and 109 with HITTS) were entered into the historical control group. Included in the 160 patients with HIT in the argatroban group were 31 patients with a documented history of a positive laboratory test for HIT/HITTS who required anticoagulation. These patients were considered as part of the HIT patient population in subsequent analyses. Two such patients were also included in the HIT historical control group.

A total of 1061 patients were initially screened by 34 investigators for inclusion in the historical control. Of these, 249 (23%) were determined by the contributing investigator to be eligible HIT/HITTS patients. These patients were then forwarded to the Data Safety Management Committee for final review. The initial screening criteria used for collection of the historical control differed by study site: some sites first identified patients who had had serum samples sent for HIPA testing; others used SRA positive patients, and others identified patients with thrombocytopenia on heparin from medical or pharmacy records. A summary of all patients screened for inclusion in the historical control (except from 6 investigators who enrolled 9 patients for which information is not available), and reasons for patient exclusion is shown below (vol. 4.6, pp. 4-7).

**APPEARS THIS WAY
ON ORIGINAL**

**Patients Initially Screened for Inclusion in the Historical
Control, and Reasons for Exclusion**

Investigator	Patients Screened	Eligible Patients	Reasons for Exclusion
Akers	15 screened 2 referrals	2	15 failed to meet inclusion/exclusion criteria
Arabia	5 screened	1	4 had a history of cancer
Ayala	4 screened	3	1 failed to meet inclusion/exclusion criteria
Azar	10 HIPA tested	1	8 failed to meet inclusion/exclusion criteria 1 taking another test drug
Baynes	12 HIT Ab tested	4	8 HIT Ab negative
Berkman	3 screened	1	2 unable to give informed consent
Eby	33 SRA positive	1	29 outside hospitals 3 failed to meet inclusion/exclusion criteria
Ellis	6 med records 1 referral	1	3 no heparin exposure 2 failed to meet inclusion/exclusion criteria 1 unknown
Gray/Paulson	8 screened	2	6 failed to meet inclusion/exclusion criteria
Hassell	2 screened	1	1 insufficient information
Hild	23 HIPA tested	5	12 HIPA negative 1 diagnosed with DIC 2 sepsis/renal failure 1 multisystem organ failure
Hutchins	4 screened	1	2 failed to meet inclusion/exclusion criteria 1 occurred before 1993
Konkle	63 SRA tested	7	24 without HIT/HITTS 8 charts not available 17 multiple medical problems 7 failed to meet inclusion/exclusion criteria
Kruse	18 with thrombocytopenia	8	10 failed to meet inclusion/exclusion criteria
Lerner	114 screened	24	90 failed to meet inclusion/exclusion criteria
Lewis	199 had thrombocytopenia and associated heparin use	35	17 had a diagnosis of cancer 12 pediatric patients 1 diagnosed at another hospital 1 diagnosed trauma, fractures, and death 1 diagnosed with HIV 7 active or recent bleeding 3 heart transplant/vascular graft 1 orthopedic patient 1 post-surgical thrombocytopenia 1 pernicious anemia 1 sepsis 118 charts incomplete or unavailable
Matthai	7 screened	1	6 not done/inadequate manpower
Penner	9 screened	1	7 HIPA negative 1 did not require anticoagulation

Rifkin	2 screened	2	
Runyon	5 screened	4	1 No heparin received
Haas/Sham	33 screened	8	25 failed to meet inclusion/exclusion criteria
Shane	35 screened	17	8 failed to meet inclusion/exclusion criteria 3 were pre-1993 1 abnormal clotting time at baseline 1 received ancrod 4 diagnosis of HITTS not understood 1 unknown
Trowbridge	76 screened	3	32 no thrombocytopenia 1 no heparin exposure 2 HIPA negative 23 failed to meet inclusion/exclusion criteria 9 with ongoing bleeding 3 with concomitant use of cimetidine 3 unknown
Warkentin	211 SRA Positive	100	23 no thrombocytopenia 20 "eliminated for location" 1 chart not available 3 HIT diagnosis after death 1 HIT diagnosis uncertain 11 newly acceptable, not used 52 unknown
Williams	39 screened	1	38 no thrombocytopenia or no heparin use
Yunus	9 screened	3	6 no thrombocytopenia
Zeigler	34 screened	2	15 no records available 2 no thrombocytopenia 5 no heparin use 3 age > 80 years 4 active bleeding 1 recent CVA 1 patient in critical condition 1 received ATIII
Zuckerman	79 screened	1	71 eliminated with cancer, known coagulation factor disorders, AIDS, pregnancy, active bleeding, etc. 4 probable HIT but no case report form completed 2 not HIT/HITTS or unclear diagnosis 1 illegible medical record
Total Patients	1061	240	

The most frequent reason for exclusion was failure to meet inclusion/exclusion criteria (39% of patients). The next most frequent reason was failure to meet the study definition of thrombocytopenia at baseline (13% of patients). A total of 110 (or 14%) patients were eliminated due to a pre-existing diagnosis of cancer, sepsis, renal failure, multisystem failure, or AIDS. One hundred forty one (14%) patients were not available for review.

A total of 32 of the 249 patients who were forwarded to the Data Safety Management Committee for final review were excluded for the reasons summarized below (vol. 5.1, p. 302).

Patients Screened and Excluded from the Historical Control

Reason for Exclusion	Study Site-Patient Number
No Thrombocytopenia	002-H03 081-H02 020-H17 113-H05 032-H01 113-H18
Discharge Summary - No Evidence of HIT	020-H28 056-H04 140-H01
Inadequate Documentation	113-H02 113-H06
Inadequate follow-up (less than 30 days)	014-H02 042-H02 016-H01 042-H04 016-H02 056-H02 020-H31 056-H05 040-H02 067-H02 042-H01 091-H05 091-H05
Alternative Causes for Thrombocytopenia Other etiology, not specified	040-H01 113-H14 113-H23 056-H06
No heparin treatment	113-H01
Pre-existing thrombocytopenia	113-H11
Related to Surgery	113-H20
Post-CABG	113-H19
Pancytopenia due to other causes	

Evaluable patients were defined as all patients who 1) received argatroban or were in the historical control population, and 2) were determined by the DSMC to have a clinical diagnosis of HIT or HITTS. A total of 280 of the 304 patients (92%) in the argatroban group were evaluable; 24 patients were determined by the DSMC to have violated the protocol for the following reasons: no thrombocytopenia (12 patients), thrombocytopenia due to sepsis (5 patients), thrombocytopenia due to systemic lupus erythematosus with antiphospholipid syndrome (3 patients), chronic thrombocytopenia due to another cause without any change related to heparin exposure (3 patients), and thrombocytopenia not due to heparin as per the investigator (1 patient).

The "positive Serotonin Release Assay (SRA) population" consisted of argatroban patients who were positive for HIT by SRA conducted at the Loyola University Medical Center, and the historical control population patients who had a baseline SRA test performed and were positive. Overall, the positive SRA population was 51% in the argatroban group and 49% in the historical group.

Patient disposition is summarized below. (Table 1, Appendix 16.2.1, vol. 128, p. 2)

Patient Disposition

POPULATION	HIT		HITTS		PREVIOUSLY DIAGNOSED FOR HIT/HITTS	
	HISTORIC CONTROL	ARGATROBAN	HISTORIC CONTROL	ARGATROBAN	HISTORIC CONTROL	ARGATROBAN
	INTENT-TO-TREAT	106	129	109	144	2
EVALUABLE	106	117	109	134	2	29
SAFETY	106	129	109	144	2	31
SRA POSITIVE	35	58	72	86	0	12

Patients were given argatroban until clinical resolution of their anticoagulation-requiring underlying condition, appropriate anticoagulation was provided with other agents, or until treatment was continued up to 14 days. A summary of the number of patients completing the Argatroban infusion is shown below (Table 3, vol. 105, p. 86).

Patients Completing Argatroban Infusion

Patient Disposition	HIT		HITTS	
	N	(%)	N	(%)
Total Number of Patients	160	(100)	144	(100)
Total Number Completed	139	(87)	135	(94)
Completed: ^a				
Up To Maximum Time Argatroban Infusion Allowed	20	(13)	34	(24)
Resolution of Underlying Condition	18	(11)	10	(7)
Transferred to Warfarin	100	(63)	102	(71)
Transferred to Other Oral Anticoagulant Therapy	1	(1)	5	(3)

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

A total of 139 (87%) patients in the HIT group, and 135 (94%) patients in the HITTS group completed the argatroban infusion. The majority of patients were switched to warfarin in both groups; a mean of approximately 10% of patients experienced a resolution of their underlying condition (while hospitalized), and a mean of approximately 20% of patients continued argatroban for the maximum-allowed time (which was 7 days from the beginning of the study of 2/12/95, until 7/19/96 when the protocol was amended to allow a total of 14 days of therapy).

The number of patients who prematurely discontinued Argatroban is summarized below (Table 4, vol. 105, p. 87).

Patients Prematurely Discontinuing Argatroban

Reason for Premature Discontinuation	HIT N (%)	HITTS N (%)
Total Number of Patients	160 (100)	144 (100)
Total Number Discontinued	21 (13)	9 (6)
Discontinued: ^a		
Surgery	5 (3)	1 (1)
Patient request to withdraw	1 (1)	2 (1)
Other	15 (9)	6 (4)

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

The majority of patients in both HIT and HITTS patients who discontinued therapy prematurely did so for "other" reasons. These reasons were tabulated from patient line listings (Appendix 16.4.1, vol. 129, p. 3-29) and are shown below.

"Other" Reasons for Premature Discontinuation of Argatroban

"OTHER" REASONS	Number of Patients
Elevated coagulation tests	4
Switched to Low Molecular Weight Heparin	1
Transferred to another argatroban (PTCA) study	2
Transferred to another hospital	2
Patient withdrawn by attending physician	3
PTCA	2
Patient made DNR	3
Intravenous catheter infection	1
Need for additional surgery	1
Unable to maintain i.v. access due to patient disorientation	1

No patients were lost to follow-up.

Efficacy Evaluation**Data Sets Analyzed**

The efficacy analysis was conducted on the intention-to-treat population, which included all patients who received at least one dose of drug, and all historical control patients meeting the protocol inclusion/exclusion criteria.

Patient Demographics

Baseline demographic characteristics for the 217 historical control and 304 argatroban patients are summarized below (Table 5, vol. 105, p. 89).

Patient Demographics

Parameter	HIT		HITTS	
	Historical Control (N = 108)	Argatroban (N = 160)	Historical Control (N = 109)	Argatroban (N = 144)
Age, N	108	160	109	144
Mean (y)±SD	65.1±11.4	61.3±13.5	65.1±9.9	61.5±12.7
Range(y)	33-84	24-86	34-81	18-81
P-value ^a	0.025		0.053	
Sex, N (%)	108 (100)	160 (100)	109(100)	144(100)
Male	54 (50)	68 (43)	56 (51)	72 (50)
Female	54 (50)	92 (58)	53 (49)	72 (50)
P-value ^b	0.261		0.899	
Race, N (%)	108 (100)	160 (100)	109(100)	144(100)
Asian	0 (0)	2 (1)	0 (0)	3 (2)
Caucasian	99 (92)	142 (89)	102 (94)	123 (85)
Black	5 (5)	10 (6)	6 (6)	14 (10)
Hispanic	3 (3)	4 (3)	0 (0)	3 (2)
Other	1 (1)	2 (1)	1 (1)	1 (1)
P-value ^b	0.897		0.163	
Weight, N	86	160	68	144
Mean (kg)±SD	79.0±24.2	78.9±18.6	84.2±20.2	83.0±20.5
Range (kg)	39-158	44-127	39-155	45-161
P-value ^a	0.401		0.511	
Height, N	77	153	61	129
Mean (cm)±SD	167.9±10.9	167.9±12.0	167.2±10.1	168.5±9.6
Range (cm)	147-193	131-211	141-191	140-203
P-value ^a	0.978		0.610	

^a Based on Wilcoxon Rank Sum Test.

^b Based on Fisher's Exact Test.

Most patients were Caucasian, in their early to mid-60's, with an approximately equal number of males and females. Note that HIT

patients were significantly younger in the argatroban group (mean age 61 years in the argatroban group compared to a mean age of 65 years in the historical control group, $p=0.025$), with a similar trend seen in the HITTS patients (mean age of 62 years in the argatroban group compared to a mean age of 65 years in the historical control group, $p=0.053$).

Mean Dose, Duration, and Delay in Argatroban Administration

The mean dosage and duration of Argatroban administration is shown below (Table 6, vol. 105, p. 90).

Mean Dosage, Duration, and Delay in Initiation of Argatroban Therapy

Parameter	HIT		HITTS	
	Historical Control (N = 108)	Argatroban (N = 160)	Historical Control (N = 109)	Argatroban (N = 144)
Mean Argatroban Dose ($\mu\text{g}/\text{kg}/\text{min}$)	—	2.0 \pm 0.1	—	1.9 \pm 0.1
Mean Duration of Argatroban Therapy (days)	—	5.3 \pm 0.3	—	5.9 \pm 0.2
Time since Heparin D/C to Initiation of Argatroban or to Follow-Up (days)	N = 108 1.0 (3.7)	N = 139 1.0 (1.7)	N = 109 0.5 (1.9)	N = 140 3.1 (4.6)

Values are as mean \pm SE.

The mean dose of argatroban administered was 2.0 mcg/kg/min in the HIT and HITTS groups, for a mean duration of 5.3 days (median of 4.5 days) in the HIT group and 5.9 days (median of 5.6 days) in the HITTS group. The mean delay from discontinuation of heparin to treatment with argatroban (or follow-up in the historical control patients) was longer for HITTS patients (3.1 days for the argatroban group compared to 0.5 days for the historical control group).

A breakdown of the duration of argatroban therapy for HIT and HITTS patients is shown below (Tables 32,33, vol. 105, pp. 175-179).

**Daily Breakdown of Duration of Argatroban Administration
for HIT Patients**

Duration of Exposure (Days)	Total (Any Dose)	
	N	%
Total Number of Patients	158	(100)
<1	17	(10.8)
1	17	(10.8)
2	19	(12.0)
3	14	(8.9)
4	23	(14.6)
5	16	(10.1)
6	16	(10.1)
7	12	(7.6)
8	5	(3.2)
9	3	(1.9)
10	1	(0.6)
11	4	(2.5)
12	4	(2.5)
13	4	(2.5)
≥15	3	(1.9)
Overall Duration:		
Mean±SE	5.32±0.31	
Median	4.46	

**Daily Breakdown of Duration of Argatroban Administration
for HITTS Patients**

Duration of Exposure (Days)	Total (Any Dose)	
	N	%
Total Number of Patients	140	(100)
<1	12	(8.6)
1	9	(6.4)
2	9	(6.4)
3	8	(5.7)
4	20	(14.3)
5	23	(16.4)
6	20	(14.3)
7	11	(7.9)
8	7	(5.0)
9	2	(1.4)
10	6	(4.3)
11	3	(2.1)
12	1	(0.7)
13	3	(2.1)
≥15	6	(4.3)
Overall Duration:		
Mean±SE	5.92±0.22	
Median	5.61	

The average dose of argatroban administered during the study is shown below (Table 34, vol. 105, p. 181).

Average Dose of Argatroban Administered

Average Dose ^a (µg/kg/min)	HIT		HITTS	
	N	(%)	N	(%)
Total Number of Patients	158	(100)	140	(100)
0.1 - 0.5	9	(6)	10	(7)
>0.5 - 1.0	25	(16)	17	(12)
>1.0 - 2.0	70	(44)	61	(42)
>2.0 - 3.0	33	(21)	38	(26)
>3.0 - 4.0	12	(8)	9	(6)
>4.0 - 5.0	3	(2)	1	(1)
> 5.0	6	(4)	4	(3)
Mean±SE	2.0±0.1		1.9±0.1	

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

The baseline platelet count (prior to the initiation of therapy) is shown below (Table 8, vol. 105, p. 93).

Baseline Platelet Counts

Parameter	HIT		HITTS	
	Historical Control (N=108)	Argatroban (N=160)	Historical Control (N=109)	Argatroban (N=144)
Baseline Platelet Count (x10 ³ /cu mm)				
N	104	138	103	132
Median	84.00	82.00	72.00	66.50
Interquartile Range				

Patient Baseline Characteristics

A summary of medical/surgical/invasive procedure history of patients (by ICD-9 coded terms) by body system and diseases is shown below (Table 2S, vol. 105, p. 304).

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

Body System** Total Number of Patients	HIT			HITTS		
	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.

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						

Sponsor's table with p-values calculated and added by reviewer

Statistically significant differences in the baseline disease status of argatroban-treated and historical control patients are noted, with the argatroban-treated patients generally more compromised.

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 (Table 2S, vol. 105, p. 303).

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

TYPE OF SURGERIES	HIT			HITTS		
	Histor. Control N(%)	Argatroban N(%)	p-value*	Histor. Control N(%)	Argatroban N(%)	p-value*
Total Number of Patients	108	160		109	144	
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.

Summary tables for patient medical/surgical/invasive procedure history by **body system**, and **medical history**, are shown below. (Table 10, vol. 105, p. 95, and Table 11, vol. 105, p. 97)

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

Body System ^a	HIT			HITTS				
	Historical Control		P-value	Historical Control		P-value		
	N	(%)		N	(%)			
Total Number of Patients	108		160		109	144		
Cardiovascular	102	(94)	160	(100)	0.004	108 (99)	143 (99)	1.000
Miscellaneous/ill Defined	83	(77)	140	(88)	0.030	79 (72)	124 (86)	0.010
Neuromuscular	70	(65)	113	(71)	0.350	87 (80)	120 (83)	0.512
Digestive	64	(59)	112	(70)	0.088	62 (57)	89 (62)	0.440
Respiratory	62	(57)	106	(66)	0.158	54 (50)	101 (70)	0.001
Genito-Urinary	62	(57)	114	(71)	0.026	49 (45)	92 (64)	0.003
Diabetes/Endocrine	52	(48)	108	(68)	0.002	53 (49)	103 (72)	<0.001
Injury and Poisoning	46	(43)	70	(44)	0.900	37 (34)	78 (54)	0.001
Oncology & Hematology	44	(41)	120	(75)	<0.001	64 (59)	107 (74)	0.010
Dermatology	20	(19)	48	(30)	0.045	12 (11)	32 (22)	0.029
Infectious/Parasitic Diseases	15	(14)	39	(24)	0.043	11 (10)	33 (23)	0.008

^a A patient is counted once per body system.

^b Recoded using ICD 9

Statistical comparisons made with Fisher's Exact Test.

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

Medical History	HIT			HITTS						
	Historical Control		P-value	Historical Control		P-value				
	N	(%)		N	(%)					
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	8	(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 general, the above tables reiterate the significant differences in the argatroban and historical control HIT and HITTS patients, with argatroban-treated patients having a substantially more compromised medical/surgical status. In addition, and in contrast to patients in the historical control group, more HIT patients in the argatroban group were undergoing hemodialysis or were on mechanical ventilation, and more HITTS patients were undergoing hemodialysis, were on a circulatory assist device, or had undergone prior CABG surgery.

Baseline and Concomitant Medications

Baseline Medications

Prior medications other than heparin taken by HIT/HITTS patients within 2 weeks prior to study admission are summarized below (Table 12, vol. 105, p. 100).

Prior Medications taken within 2 Weeks of Study Admission Listed
by Anatomic/Therapeutic/Chemical (ATC) Classification

ATC Classification	HIT		HITTS	
	Historical Control N (%)	Argatroban N (%)	Historical Control N (%)	Argatroban N (%)
Total Number of Patients	108	160	109	144
Any Medication	100 (92.6)	151 (94.4)	98 (89.9)	140 (97.2)
Antithrombotic Agents	30 (27.8)	93 (58.1)	25 (22.9)	87 (60.4)
Analgesics	56 (51.9)	90 (56.3)	68 (62.4)	103 (71.5)
Psycholeptics	58 (53.7)	89 (55.6)	53 (48.6)	103 (71.5)
Cardiac Therapy	55 (50.9)	86 (53.8)	36 (33.0)	87 (60.4)
Antibacterials for Systemic Use	61 (56.5)	82 (51.3)	71 (65.1)	99 (68.8)
Diuretics	32 (29.6)	74 (46.3)	29 (26.6)	76 (52.8)
Antacids, Drugs for Treatment of Peptic Ulcer and Flatulence	32 (29.6)	73 (45.6)	29 (26.6)	79 (54.9)
Mineral Supplements	36 (33.3)	67 (41.9)	25 (22.9)	79 (54.9)
Plasma Substitutes and Perfusion Solutions	23 (21.3)	55 (34.4)	7 (6.4)	44 (30.6)
Antipruritics, Including Antihistamine, Anesthetic, etc.	19 (17.6)	40 (25.0)	14 (12.8)	43 (29.9)
Laxatives	25 (23.2)	36 (22.5)	35 (32.1)	41 (28.5)
Calcium Channel Blockers	18 (16.7)	35 (21.9)	26 (23.9)	47 (32.6)
Antihemorrhagics	8 (7.4)	35 (21.9)	13 (11.9)	34 (23.6)
Agents Acting on the Renin-Angiotensin System	11 (10.2)	31 (19.4)	9 (8.3)	30 (20.8)
Antispasmodic and Anticholinergic Agents and Propulsive	19 (17.6)	29 (18.1)	17 (15.6)	28 (19.4)
Anesthetics	27 (25.0)	28 (17.5)	34 (31.2)	45 (31.3)
Beta Blocking Agents	15 (13.9)	28 (17.5)	13 (11.9)	42 (29.2)
Muscle Relaxants	15 (13.9)	25 (15.6)	21 (19.3)	25 (17.4)
All Other Therapeutic Products	12 (11.1)	24 (15.0)	12 (11.0)	22 (15.3)
Drugs Used in Diabetes	7 (6.5)	22 (13.8)	6 (5.5)	34 (23.6)
Antihypertensives	11 (10.2)	18 (11.3)	14 (12.8)	14 (9.7)
Corticosteroids for Systemic Use	6 (5.6)	17 (10.6)	9 (8.3)	33 (22.9)

For HIT patients, notable medication imbalances include:
antithrombotic agents: 93(58%) patients in the argatroban group compared to 30(28%) patients in the historical control group, p=<0.0001*

*two-sided Fisher's Exact Test

antihemorrhagics: 35(22%) patients in argatroban group compared to 8(7%) patients in the historical control group, $p= 0.002^*$
plasma substitutes: 55(34%) patients in the argatroban group compared to 23(21%) patients in the historical group, $p= 0.028^*$
diuretics: 74(46%) patients in the argatroban group compared to 32(30%) patients in the historical control group, $p= 0.008^*$
antacids, drugs for treatment of peptic ulcer and flatulence: 73(46%) patients in the argatroban group compared to 32(30%) patients in the historical control group, $p= 0.011^*$

For HITTS patients, notable medication imbalances include:

antithrombotic agents: 87(60%) patients in the argatroban group compared to 25(23%) patients in the historical control group, $p= <0.0001^*$
antihemorrhagics: 34(24%) patients in the argatroban group compared to 13(12%) patients in the historical control group, $p= 0.022^*$
plasma substitutes: 44(31%) patients in the argatroban group compared to 7(6%) patients in the historical control group, $p= <0.0001^*$
systemic corticosteroids: 33(23%) patients in the argatroban group compared to 9(8%) patients in the historical control group, $p= 0.002^*$
cardiac therapy: 87(60%) patients in the argatroban group compared to 36(33%) patients in the historical control group, $p= <0.0001^*$
drugs used in diabetes: 34(24%) patients in the argatroban group compared to 6(6%) patients in the historical control group, $p= 0.0001^*$
beta blockers: 42(29%) patients in the argatroban group compared to 13(12%) patients in the historical control group, $p= 0.001^*$
renin-angiotensin agents: 30(21%) patients in the argatroban group compared to 9(8%) patients in the historical control group, $p= 0.008^*$
diuretics: 76(53%) patients in the argatroban group compared to 29(27%) patients in the historical control group, $p= <0.0001^*$
antacids, drugs for treatment of peptic ulcer and flatulence: 79(55%) patients in the argatroban group compared to 29(27%) patients in the historical control group, $p= <0.0001^*$

In general, argatroban-treated patients received a greater number of prior medications from multiple drug classes than patients in the historical control. This observation is consistent with the significantly increased underlying medical disease in the argatroban-treated patients discussed previously.

* two-sided Fisher's Exact Test

Baseline Antithrombotic (or thrombolytic) Medications

For HIT patients, 93(58%) patients in the argatroban group, and 30(28%) patients in the historical control group received antithrombotic (or thrombolytic) medications within 2 weeks prior to study enrollment. For HITTS patients, 87(60%) patients in the argatroban group, and 25(23%) patients in the historical control group received antithrombotic (or thrombolytic) medications. Specific medications are shown below (vol. 4.6, p.8).

Baseline Antithrombotic (or thrombolytic) Medications

	HIT		HITT	
	Historical Controls	Argatroban Treated	Historical Controls	Argatroban Treated
Warfarin sodium	2	34	2	24
Acetylsalicylic acid	13	20	9	20
Urokinase	0	6	1	4
Atteplase	0	4	1	0
Ticlopidine	1	2	1	3
Heparin	6	2	2	4
Heparin fraction, Na salt	1	1	0	1
Streptokinase	0	1	1	0
Dipyridamole	2	1	2	1
ABCIXIMAB	1	1	0	0
Warfarin + acetylsalicylic acid	0	5	2	9
Warfarin + Urokinase	0	4	0	4
Warfarin + Ticlopidine	0	1	0	0
Warfarin + Heparin fraction	0	0	0	2
Warfarin + streptokinase	0	1	0	0
ASA + Urokinase	0	1	0	2
ASA + Alteplase	0	1	1	1
ASA + Ticlopidine	0	0	1	2
ASA + Heparin	2	2	0	0
ASA + Dipyridamole	1	0	1	3
ASA + ABCIXIMAB	0	1	0	0
Urokinase + Alteplase	0	1	0	0
Urokinase + ABCIXIMAB	0	0	0	1
Alteplase + Ticlopidine	0	1	0	0
Ticlopidine + ABCIXIMAB	0	0	0	1
Heparin + Dipyridamole	1	0	0	0
Dipyridamole + Asasantin	0	0	1	0
Warfarin + ASA + Urokinase	0	0	0	2
Warfarin + ASA + Alteplase	0	1	0	0
Warfarin + Urokinase + Heparin fraction	0	0	0	2
Warfarin + Urokinase + Alteplase	0	0	0	1
ASA + Ticlopidine + Alteplase	0	1	0	0
ASA + Ticlopidine + Heparin	0	1	0	0

Of the argatroban-treated HIT patients who received baseline antithrombotic and/or thrombolytic medications, 49% received

warfarin, and 35% received aspirin; alone or in combination. Of the argatroban-treated HITTS patients who received baseline antithrombotic and/or thrombolytic medications, 51% received warfarin, and 34% received aspirin; alone or in combination.

Of the historical control HIT patients who received baseline antithrombotic and/or thrombolytic medications, 7% received warfarin, and 53% received aspirin; alone or in combination. Of the argatroban-treated HITTS patients who received baseline antithrombotic and/or thrombolytic medications, 16% received warfarin, and 56% received aspirin; alone or in combination.

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Concomitant Medications

Concomitant medications other than heparin (received while hospitalized) are summarized below (Table 13, vol. 105, pp. 101-2).

Concomitant Medications Listed by Anatomical/Therapeutic/
Chemical (ATC) Classification

	HIT		HITTS	
	Historical Control N (%)	Argatroban N (%)	Historical Control N (%)	Argatroban N (%)
Any Medication	108	160	109	144
Antacids, Drugs for Treatment of Peptic Ulcer and Flatulence	78 (72.2)	121 (75.6)	81 (74.3)	109 (75.7)
Psycholeptics	66 (61.1)	118 (73.8)	71 (65.1)	100 (69.4)
Analgesics	91 (84.3)	117 (73.1)	93 (85.3)	125 (88.8)
Cardiac Therapy	69 (63.9)	102 (63.8)	55 (50.5)	86 (59.7)
Mineral Supplements	59 (54.6)	95 (59.4)	39 (35.8)	81 (56.3)
Antibacterials for Systemic Use	77 (71.3)	93 (58.1)	65 (59.6)	105 (72.9)
Diuretics	61 (56.5)	84 (52.5)	49 (45.0)	84 (58.3)
Antithrombotic Agents	76 (70.4)	134 (83.8)	105 (96.3)	122 (84.7)
Laxatives	60 (55.6)	66 (41.3)	64 (58.7)	71 (49.3)
Calcium Channel Blockers	38 (35.2)	49 (30.6)	24 (22.0)	50 (34.7)
Drugs Used in Diabetes	34 (31.5)	43 (26.9)	32 (29.4)	63 (43.8)
Plasma Substitutes and Perfusion Solutions	24 (22.2)	42 (26.3)	15 (13.8)	44 (30.6)
Agents Acting on the Renin-Angiotensin System	25 (23.2)	42 (26.3)	15 (13.8)	39 (27.1)
Beta Blocking Agents	30 (27.8)	38 (36.3)	27 (24.8)	47 (32.8)
Antispasmodic and Anticholinergic agents and Propulsive	18 (16.7)	38 (23.8)	21 (19.3)	33 (22.9)
Anesthetics	16 (14.8)	35 (21.9)	23 (21.1)	39 (27.1)
Antianemic Preparations	34 (31.5)	35 (21.9)	21 (19.3)	23 (16.0)
Antipruritics, Including Antihistamine, Anesthetic, etc.	17 (15.7)	34 (21.3)	20 (18.4)	39 (27.1)
Anti-Asthmatics	37 (34.3)	33 (20.6)	32 (29.4)	40 (27.8)
Vitamins	17 (15.7)	33 (20.6)	15 (13.8)	25 (17.4)
Corticosteroids for Systemic Use	17 (15.7)	31 (19.4)	18 (16.5)	31 (21.5)
Muscle Relaxants	14 (13.0)	28 (17.5)	15 (13.8)	32 (22.2)
Antidiarrhea, Intestinal Antiinflammatory/ Antiinfection Agents	20 (18.5)	27 (16.9)	13 (11.9)	29 (20.1)
Antihemorrhagics	15 (13.9)	23 (14.4)	16 (14.7)	25 (17.4)
Thyroid Therapy	8 (7.4)	20 (12.5)	6 (5.5)	9 (6.3)
Psychoanaleptics	7 (6.5)	17 (10.6)	9 (8.3)	17 (11.8)
Cough and Cold Preparations	5 (4.6)	16 (10.0)	5 (4.6)	8 (5.6)
Unable to be Classified	26 (24.1)	15 (9.4)	19 (17.4)	20 (13.9)
Antihistamines for Systemic Use	11 (10.2)	15 (9.4)	25 (22.9)	12 (8.3)
Antihypertensives	17 (15.7)	13 (8.1)	10 (9.2)	15 (10.4)
Antiinflammatory and Antirheumatic Products	14 (13.0)	10 (6.3)	10 (9.2)	4 (2.8)
Ophthalmologicals	13 (12.0)	9 (5.6)	11 (10.1)	10 (6.9)
Other Hematological Agents	9 (8.3)	0 (0.0)	30 (27.5)	0 (0.0)

In general, and in contrast to what was described previously for baseline medications, concomitant medications were more similar in argatroban-treated and historical control HIT and HITTS

patients. Notable imbalances for HIT patients included more antithrombotic medication administered to argatroban patients, and more systemic antibiotic use in historical control patients:

antithrombotic agents: 134(84%) patients in the argatroban group compared to 76(70%) patients in the historical control group, p= 0.029*

antibacterials for systemic use: 93(58%) patients in the argatroban group compared to 77(71%) patients in the historical control group, p= 0.010*

Notable imbalances in HITTS patients included more systemic antibiotic, antihypertensive, diuretic, plasma substitute, and diabetic medications given to argatroban-treated patients, and more antithrombotic therapy given to historical control patients:

antithrombotic agents: 122(85%) patients in the argatroban group compared to 105(96%) patients in the historical control group, p= 0.003*

antibacterials for systemic use: 105(73%) patients in the argatroban group compared to 65(60%) patients in the historical control group, p= 0.031*

plasma substitutes: 44(31%) patients in the argatroban group compared to 15(14%) patients in the historical control group, p= 0.002*

drugs used in diabetes: 63(44%) patients in the argatroban group compared to 32(29%) patients in the historical control group, p= 0.026*

diuretics: 84(58%) patients in the argatroban group compared to 49(45%) patients in the historical control group, p= 0.042*

calcium channel blockers: 50(35%) patients in the argatroban group compared to 24(22%) patients in the historical control group, p= 0.036*

renin-angiotensin drugs: 39(27%) patients in the argatroban group compared to 15(14%) patients in the historical control group, p= 0.013*

* two-sided Fisher's Exact Test

Concomitant Antithrombotic (or thrombolytic) Medications

For HIT patients, 134(84%) patients in the argatroban group, and 76(70%) patients in the historical control group received concomitant antithrombotic (or thrombolytic) medications. For HITTS patients, 122(85%) patients in the argatroban group, and 105(96%) patients in the historical control group received concomitant antithrombotic (or thrombolytic) medications. Specific medications are shown below (vol. 4.6, p.9).

Concomitant Antithrombotic (or thrombolytic) Medications

	HIT		HITTS	
	Historical Controls	Argatroban Patients	Historical Controls	Argatroban Patients
Warfarin sodium	24	69	54	51
Acetylsalicylic acid	15	16	12	9
Urokinase	3	3	1	4
Ticlopidine	1	1	0	1
Heparin	7	0	0	1
Heparin fraction. Na salt	0	0	3	1
Dipyridamole	0	0	1	0
Warfarin + acetylsalicylic acid	3	26	3	31
Warfarin + Urokinase	0	0	0	8
Warfarin + Ticlopidine	1	0	0	1
Warfarin + Heparin fraction	4	2	2	0
Warfarin + Dipyridamole	0	0	0	1
ASA + Urokinase	0	1	0	2
ASA + Alteplase	0	1	0	1
ASA + Ticlopidine	1	5	0	0
ASA + epoprosterol	0	2	0	0
ASA + Dipyridamole	0	1	1	0
ASA + Heparin	7	0	3	0
Warfarin + ASA + Urokinase	0	0	1	1
Warfarin + ASA + Alteplase	0	0	0	0
Warfarin + Urokinase + Heparin fr	2	1	0	2
Warfarin + ASA + Dipyridamole	0	2	0	1
Warfarin + Urokinase + Dipyridamole	0	0	0	1
Warfarin + Heparin + ASA	2	0	3	0
Warfarin + Heparin + Dipyridamole	0	0	0	0
ASA + Ticlopidine + Urokinase	0	2	0	0
ASA + Ticlopidine + Warfarin	0	1	0	3

Of the argatroban-treated HIT patients who received concomitant antithrombotic and/or thrombolytic medications, 76% received warfarin, and 43% received aspirin; alone or in combination. Of

the argatroban-treated HITTS patients who received concomitant antithrombotic and/or thrombolytic medications, 84% received warfarin, and 42% received aspirin; alone or in combination.

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

Primary Efficacy Outcome Results

Intention-to-treat population

The rates of new thrombosis, amputation, death, and the composite outcome endpoint (any occurrence of new thrombosis, amputation, or death) over the study period (i.e. 31 to 44 days for the argatroban group and 37 days for the historical control group) for the intention-to-treat HIT and HITTS patient populations are shown below (Table 15, vol. 105, p. 107, and Table 16, vol. 105, p.108).

Development of New Thrombosis, Amputation, Death, and Composite Outcome Endpoint for HIT Patients

Parameter	Historical Control ^a		Argatroban ^b		HIT		Treatment		P-value ^d
	N	% (95% CI)	N	% (95% CI)	P-value ^c	Odds Ratio	(95% CI)		
Total Number of Patients	108	100	160	100	-	-	-	-	-
New Thrombosis	25	23 (15,31)	10	6 (2,10)	<0.001	0.2	(0.1, 0.5)	<0.001	
Amputation:									
All cause amputation	4	4 (0,7)	4	3 (0,5)	0.420	0.7	(0.2, 2.9)	0.573	
Due to ischemic complication ^e	2	2 (-1,4)	1	1 (-1,2)	0.250	0.3	(0.0, 3.5)	0.372	
Due to other reasons	2	2 (-1,4)	3	2 (0,4)	0.983	1.0	(0.2, 7.8)	0.989	
Death:									
Due to thrombosis	4	4 (0,7)	0	0 (0,0)	0.013	-	-	-	
Treatment-Emergent	0	0 (0,0)	2	1 (0,3)	-	-	-	-	
Due to Pre-existing Conditions	8	7 (2,12)	27	17 (11,23)	<0.001	2.5	(1.2, 6.2)	0.028	
Thrombotic Composite Outcome ^f	28	26 (18,34)	11	7 (3,11)	<0.001	0.2	(0.1, 0.4)	<0.001	
Composite Outcome ^g	36	33 (24,42)	43	27 (20,34)	0.083	0.7	(0.4, 1.3)	0.256	

^a Study period was ~37 days.
^b Infusion period was 1 to 14 days.
^c Based on the Z-statistic from the 1-sample Normalization Test.
^d 2-sample test based on logistic regression, modeling for the effect treatment.
^e Secondary to HIT/HITTS.
^f Any occurrence of new thrombosis, amputation due to HIT/HITTS, or death due to thrombosis.
^g Any occurrence of new thrombosis, amputation or death.
 P<0.050 indicating statistical significance.

**Development of New Thrombosis, Amputation, Death, and Composite Outcome
Endpoint for HITTS Patients**

Parameter	HITTS							
	Historical Control ^a		Argatroban ^b		P-value ^c	Treatment		
	N	% (95% CI)	N	% (95% CI)		Odds Ratio	(95% CI)	P-value ^d
Total Number of Patients	109	100	144	100	-	-	-	-
New Thrombosis	45	41 (32,51)	27	19 (12,25)	<0.001	0.3	(0.2, 0.6)	<0.001
Amputation:								
All cause amputation	13	12 (6,18)	18	13 (7,18)	0.832	1.1	(0.5, 2.3)	0.891
Due to ischemic complication ^e	12	11 (5,17)	15	10 (5,15)	0.820	0.9	(0.4, 2.1)	0.880
Due to other reasons	1	1 (-1,3)	4	3 (0,5)	0.019	3.1	(0.4, 60.8)	0.317
Death:								
Due to thrombosis	8	7 (2,12)	1	1 (-1,2)	0.002	0.1	(0.0, 0.5)	0.023
Treatment-Emergent	0	0 (0,0)	1	1 (-1,2)	-	-	-	-
Due to Pre-existing Conditions	8	7 (2,12)	24	17 (11,23)	<0.001	2.5	(1.1, 6.2)	0.031
Thrombotic Composite Outcome ^f	54	50 (40,59)	40	28 (20,35)	<0.001	0.4	(0.2, 0.7)	<0.001
Composite Outcome ^g	59	54 (45,63)	62	43 (35,51)	0.008	0.6	(0.4, 1.1)	0.082

^a Study period was ~37 days.

^b Infusion period was 1 to 14 days.

^c Based on the Z-statistic from the 1-sample Normalization Test.

^d 2-sample test based on logistic regression, modeling for the effect treatment.

^e Secondary to HIT/HITTS.

^f Any occurrence of new thrombosis, amputation due to HIT/HITTS, or death due to thrombosis.

^g Any occurrence of new thrombosis, amputation or death.

P<0.050 indicating statistical significance.

Statistically significant reductions in new thromboses were seen for both HIT and HITTS patients. For HIT patients, 10(6%) patients in the argatroban group compared to 25(23%) patients in the historical control group experienced a new thrombosis ($p < 0.001$, 2-sample logistic regression). For HITTS patients, 27(19%) patients in the argatroban group compared to 45(41%) patients in the historical control group experienced a new thrombosis ($p < 0.001$, 2-sample logistic regression).

No statistically significant differences in the incidence of amputation was seen between the argatroban-treated and historical control HIT or HITTS patients.

Numerical differences in the incidence of all-cause mortality (not statistically significant) were seen between the argatroban-treated and historical control HIT or HITTS patients. For HIT patients, 29(18%) patients in the argatroban group compared to 12(11%) patients in the historical control group died ($p = 0.124$, 2-sided Fisher's Exact Test). For HITTS patients, 26(18%) in the argatroban group compared to 16(15%) patients in the historical control group died ($p = 0.500$, 2-sided Fisher's Exact Test).

When deaths were further classified by the sponsor as "due to thrombosis" or "due to pre-existing conditions," significantly more deaths due to pre-existing conditions were reported for argatroban-treated patients, and significantly more deaths due to thrombosis were found for historical control patients, for both the HIT and HITTS populations. Specifically, for HIT patients, 27(17%) patients in the argatroban group compared to 8(7%) patients in the historical control group were determined to die due to pre-existing conditions ($p= 0.028$, 2-sample logistic regression), and 0(0%) patients in the argatroban group compared to 4(4%) patients in the historical control group were determined to die due to thrombosis ($p= 0.026$, 2-sided Fisher's Exact Test). For HITTS patients, 24(17%) patients in the argatroban group compared to 8(7%) patients in the historical control group were determined to die due to pre-existing conditions ($p= 0.031$, 2-sample logistic regression), and 1(1%) patients in the argatroban group compared to 8(7%) patients in the historical control group were determined to die due to thrombosis ($p= 0.023$, 2-sample logistic regression).

The incidence of the composite endpoint of new thrombosis, amputation, or death was not significantly different between treatment groups for HIT patients, or for HITTS patients (using 2-sample logistic regression or 2-sided Fisher's Exact Test statistics)

The incidence of the "thrombotic composite endpoint" of new thrombosis, amputation due to HIT/HITTS (listed as "amputation due to ischemic complications in the above tables), or death due to thrombosis was significantly reduced for argatroban-treated compared to historical control patients in HIT and HITTS patients. In the HIT group, 11(7%) patients in the argatroban group compared to 28(26%) patients in the historical control group experienced a component of the thrombotic composite endpoint ($p= <0.001$, 2-sample logistic regression). In the HITTS group, 40(28%) patients in the argatroban group compared to 54(50%) patients in the historical control group experienced a component of the thrombotic composite endpoint ($p= <0.001$, 2-sample logistic regression).

Primary Efficacy Outcome Results During the Argatroban Infusion and the Period Following the Argatroban Infusion

The majority of primary outcome events for argatroban-treated HIT patients occurred in the post-infusion period. Specifically, 3/10 or 30% of new thromboses, 1/4 or 25% of amputations, 4/29 or 14% of all-deaths, and 8/43 or 19% of overall composite endpoint

events occurred during the argatroban infusion period in HIT patients. More events tended to occur during the argatroban infusion in HITTS patients: 16/28 or 57% of new thromboses, 8/20 or 40% of amputations, 7/26 or 27% of all-deaths, and 30/68 or 44% of overall composite endpoint events occurred during the argatroban infusion period. These results are shown on the following two pages.

The majority of primary outcome events for patients in the historical control group occurred in the first 14 days following heparin discontinuation. Specifically, 81% of new thromboses, 100% of amputations, 67% of all-deaths, and 76% of overall composite endpoint events occurred in the first 14 days following the discontinuation of heparin in HIT patients. For HITTS patients, 89% of new thromboses, 69% of amputations, 75% of all deaths, and 81% of overall composite endpoint events occurred in the first 14 days following the discontinuation of heparin (Vol. 4.1, pp. 191-2).

The occurrence of primary efficacy parameters during the argatroban infusion period, and during the 30-day post-infusion followup periods for the intention-to-treat HIT and HITTS populations treated with argatroban are shown below (adapted from Tables 3S - 6S, vol. 105, pp. 107-10).

**Primary Efficacy Outcomes for HIT Patients
DURING ARGATROBAN INFUSION**

Parameter	Argatroban ^a	
	N	% (95% CI)
Total Number of Patients	160	100 -
New Thrombosis	3	2 (0,4)
Amputation:		
All cause amputation	1	1 (-1,2)
Due to ischemic complication ^b	1	1 (-1,2)
Due to other reasons	0	0 (0,0)
Death:		
Due to thrombosis	0	0 (0,0)
Treatment-Emergent	1	1 (-1,2)
Due to Pre-existing Conditions	3	2 (0,4)
Thrombosis Composite Outcome ^c	4	3 (0,5)
Composite Outcome ^d	8	5 (2,8)

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

**Primary Efficacy Outcomes for HIT Patients
DURING 30-DAY POST-INFUSION FOLLOWUP PERIOD**

Parameter	Argatroban ^b		
	N	%	(95% CI)
Total Number of Patients	155	100	-
New Thrombosis	7	5	(1,8)
Amputation:			
All cause amputation	3	2	(0,4)
Due to ischemic complication ^c	0	0	(0,0)
Due to other reasons	3	2	(0,4)
Death:			
Due to thrombosis	0	0	(0,0)
Treatment-Emergent	1	1	(-1,2)
Due to Pre-existing Conditions	24	15	(10,21)
Thrombosis Composite Outcome ^f	7	5	(1,8)
Composite Outcome ^g	35	23	(16,29)

^a Study period was -37 days.

^b Infusion period was 1 to 14 days.

^c Based on the Z-statistic from the 1-sample Normalization Test.

^d 2-sample test based on logistic regression, modeling for the effect treatment.

^e Secondary to HIT/HITTS.

^f Any occurrence of new thrombosis, amputation due to HIT/HITTS, or death due to thrombosis.

^g Any occurrence of new thrombosis, amputation or death.

**Primary Efficacy Outcomes for HITTS Patients
DURING ARGATROBAN INFUSION**

Parameter	Argatroban ^b		
	N	%	(95% CI)
Total Number of Patients	144	100	-
New Thrombosis	16	11	(1,16)
Amputation:			
All cause amputation	8	6	(2,9)
Due to ischemic complication ^c	8	6	(2,9)
Due to other reasons	0	0	(0,0)
Death:			
Due to thrombosis	1	1	(-1,2)
Treatment-Emergent	0	0	(0,0)
Due to Pre-existing Conditions	6	4	(1,7)
Thrombosis Composite Outcome ^f	24	17	(11,23)
Composite Outcome ^g	30	21	(14,27)

^a Study period was -37 days.

^b Infusion period was 1 to 14 days.

^c Based on the Z-statistic from the 1-sample Normalization Test.

^d 2-sample test based on logistic regression, modeling for the effect treatment.

^e Secondary to HIT/HITTS.

^f Any occurrence of new thrombosis, amputation due to HIT/HITTS, or death due to thrombosis.

^g Any occurrence of new thrombosis, amputation or death.

**Primary Efficacy Outcomes for HITTS Patients
DURING 30-DAY POST-INFUSION FOLLOWUP PERIOD**

Parameter	Argatroban ^a	
	N	% (95% CI)
Total Number of Patients	137	100 -
New Thrombosis	12	9 (4,13)
Amputation:		
All cause amputation	12	9 (4,13)
Due to ischemic complication ^b	8	6 (2,10)
Due to other reasons	4	3 (0,6)
Death:		
Due to thrombosis	0	0 (0,0)
Treatment-Emergent	1	1 (-1,2)
Due to Pre-existing Conditions	18	13 (7,19)
Thrombosis Composite Outcome ^c	20	15 (9,21)
Composite Outcome ^d	38	28 (20,35)

^a Study period was ~37 days.

^b Infusion period was 1 to 14 days.

^c Based on the Z-statistic from the 1-sample Normalization Test.

^d 2-sample test based on logistic regression, modeling for the effect treatment.

^e Secondary to HIT/HITTS.

^f Any occurrence of new thrombosis, amputation due to HIT/HITTS, or death due to thrombosis.

^g Any occurrence of new thrombosis, amputation or death.

Primary Efficacy Outcome Results

Evaluable population

Evaluable patients were defined as all patients who 1) received argatroban or were in the historical control population, and 2) were determined by the DSMC to have a clinical diagnosis of HIT or HITTS. Ninety-two percent of argatroban-treated patients were evaluable. Primary efficacy outcome results were comparable for the evaluable and intention-to-treat populations.

SRA Positive population

The SRA Positive population consisted of argatroban-treated patients who were positive for HIT by an SRA, and the historical control population patients who had a baseline SRA test performed and were positive. The SRA positive population represented approximately 50% of the intention-to-treat population "with the SRA being either negative or indeterminate in the remainder of the patients." Primary efficacy outcome results for the SRA positive HIT and HITTS populations are summarized below (Tables 26 and 27, vol. 105, pp. 154-5).

Development of New Thrombosis, Amputation, Death, and Composite Outcome Endpoint for HIT Patients

Parameter	Historical Control ^a		Argatroban ^b		HIT		Treatment Odds Ratio (95% CI)		P-value ^d
	N	% (95% CI)	N	% (95% CI)	P-value ^c	Ratio	(95% CI)		
Total Number of Patients	35	100	70	100	-	-	-	-	-
New Thrombosis	21	60 (44,78)	3	4 (0,9)	<0.001	0.03	(0.01, 0.10)	<0.001	
Amputation:									
Due to ischemic complications ^e	0	0 (0,0)	1	1 (-1,4)	-	-	-	-	-
Due to other reasons	0	0 (0,0)	3	4 (0,9)	-	-	-	-	-
Death:									
Due to thrombosis	3	9 (-1,18)	0	0 (0,0)	0.010	-	-	-	-
Treatment-emergent	0	0 (0,0)	0	0 (0,0)	-	-	-	-	-
Due to pre-existing conditions	2	6 (-2,13)	7	10 (3,17)	0.122	1.8	(0.4, 12.8)	0.465	
Thrombotic Composite Outcome ^f	22	63 (47,79)	4	6 (0,11)	<0.001	0.04	(0.01, 0.11)	<0.001	
Overall Composite Outcome ^g	24	69 (53,84)	14	20 (11,29)	<0.001	0.1	(0.0, 0.3)	<0.001	

^a Overall study period was -37 days.

^b Infusion period was 1 to 14 days; overall study period was -37 days.

^c Based on the Z-statistic from the 1-sample Normalization Test.

^d 2-sample test based on logistic regression, modeling for the effect treatment.

^e Secondary to HIT/HITTS.

^f The number (%) of patients who experienced one or more of: new thrombosis, amputation due to ischemic complications of HIT/HITTS, or death due to thrombosis.

^g The number (%) of patients who experienced one or more of: new thrombosis, all-cause amputation, or all-cause death.

P<0.050 indicating statistical significance.

Development of New Thrombosis, Amputation, Death, and Composite Outcome Endpoint for HITTS Patients

Parameter	Historical Control ^a		Argatroban ^b		HITTS		Treatment Odds Ratio (95% CI)		P-value ^d
	N	% (95% CI)	N	% (95% CI)	P-value ^c	Ratio	(95% CI)		
Total Number of Patients	72	100	86	100	-	-	-	-	-
New Thrombosis	30	42 (30,53)	19	22 (13,31)	<0.001	0.4	(0.2, 0.8)	0.009	
Amputation:									
Due to ischemic complication ^e	5	7 (1,13)	9	10 (4,17)	0.199	1.6	(0.5, 5.3)	0.441	
Due to other reasons	0	0 (0,0)	2	2 (-1,6)	-	-	-	-	
Death:									
Due to thrombosis	3	4 (0,9)	1	1 (-1,3)	0.163	0.3	(0.0, 2.2)	0.262	
Treatment-emergent	0	0 (0,0)	1	1 (-1,1)	-	-	-	-	
Due to pre-existing conditions	4	6 (0,11)	13	15 (8,23)	<0.001	3.0	(1.0,11.1)	0.063	
Thrombotic Composite Outcome ^f	32	44 (33,56)	26	30 (21,40)	0.008	0.5	(0.3, 1.0)	0.066	
Overall Composite Outcome ^g	34	47 (36,59)	38	44 (34,55)	0.573	0.9	(0.5, 1.7)	0.703	

^a Overall study period was -37 days.

^b Infusion period was 1 to 14 days; overall study period was -37 days.

^c Based on the Z-statistic from the 1-sample Normalization Test.

^d 2-sample test based on logistic regression, modeling for the effect treatment.

^e Secondary to HIT/HITTS.

^f The number (%) of patients who experienced one or more of: new thrombosis, amputation due to ischemic complications of HIT/HITTS, or death due to thrombosis.

^g The number (%) of patients who experienced one or more of: new thrombosis, all-cause amputation, or all-cause death.

P<0.050 indicating statistical significance.

A total of 32% of historical control and 44% of argatroban-treated HIT patients, and 66% of historical control and 60% of argatroban-treated HITTS patients were SRA-positive. Note however, that 68% of argatroban-treated HIT patients were positive for a HIPA, SRA, or H-PF4 ELISA for the HIT antibody (13% were negative, and 19% were not tested); 67% of argatroban-treated HITTS patients were positive for a HIPA, SRA, or H-PF4 ELISA for the HIT antibody (5% were negative, and 28% were not tested). Similarly, 78% of historical control HIT patients were positive for a HIPA or SRA for the HIT antibody (22% were negative); 96% of historical control HITTS patients were positive for a HIPA or SRA for the HIT antibody (4% were negative).

A summary of primary efficacy outcomes for the SRA Positive population is shown below.

**Efficacy Outcomes for the SRA Positive Population
in Study ARG-911**

Efficacy Outcomes	HIT			HITTS		
	Hist Ctrl 35	Argatro 70	P-value*	Hist Ctrl 72	Argatro 86	P-value*
New Thromboses	21(60%)	3(4%)	<0.0001	30(42%)	19(22%)	0.010
Amputation	0(0%)	4(6%)	0.299	5(7%)	11(13%)	0.293
All-cause Death	5(14%)	7(10%)	0.529	7(10%)	15(17%)	0.176
Overall Composite	24(69%)	14(20%)	<0.0001	34(47%)	38(44%)	0.750

* two-sided Fisher's Exact Test

Adapted from Sponsor's Tables 26 and 27, vol. 105, pp. 154-5

Statistically significant reductions in new thromboses for argatroban-treated HIT and HITTS patients were seen. For HIT patients, 3(4%) patients in the argatroban group compared to 21(60%) patients in the historical control group experienced a new thrombosis ($p = <0.0001^*$). For HITTS patients, 19(22%) patients in the argatroban group compared to 30(42%) patients in the historical control group experienced a new thrombosis ($p = 0.010^*$).

Numerically greater amputations were seen for argatroban-treated HIT and HITTS patients. Numerically greater all-cause deaths were also seen for argatroban-treated HITTS patients. For HIT patients, 7(10%) patients in the argatroban group compared to 5(14%) patients in the historical control group died ($p = 0.528^*$). For HITTS patients, 15(17%) in the argatroban group compared to 7(10%) patients in the historical control group died ($p = 0.176^*$).

The incidence of the overall composite endpoint was significantly reduced for argatroban-treated HIT patients, and not significantly different between treatment groups for HITTS patients (due to the numerical trend toward greater amputation and all-cause death in HITTS patients).

* two-sided Fisher's Exact Test

Population with a HISTORY OF A POSITIVE LABORATORY TEST FOR HIT/HITTS

Included in the 160 patients with HIT in the argatroban group were 31 patients with a documented history of a positive laboratory test for HIT/HITTS who required anticoagulation. These patients were considered as part of the HIT patient population in subsequent analyses. Two such patients were also included in the HIT historical control group.

At the FDA request, a separate analysis was performed for this group of patients (Vol. 4.1, pp. 333-352). These patients were of mean age 61 years and mean weight 83 kg in the argatroban group, and mean age 70 years and mean weight 68 kg in the historical control group. Sexes were equally distributed in both groups. The mean number of days study medication was begun following discontinuation of heparin was 1.2 days in the argatroban-treated group and 0.0 days in the historical control group. The mean argatroban dose was 2.2 µg/kg/min for a mean duration of 5.2 days (median 4.4 days). A summary of the primary efficacy outcome results is shown below (Vol. 4.1, pg. 335).

Primary Outcome Results of Patients with a HISTORY OF a Positive Laboratory Test for HIT/HITTS

	HISTORICAL CONTROL		ARGATROBAN-TREATED	
	ACTIVE†	NON-ACTIVE††	ACTIVE†	NON-ACTIVE††
Total Number of Patients	106	2	129	31
NEW THROMBOSIS	25 (24%)	0 (0%)	8 (6%)	2 (6%)
ALL-AMPUTATION	3 (3%)	1 (50%)	3 (2%)	1 (3%)
ALL-CAUSE DEATH	12 (11%)	0 (0%)	29 (22%)	0 (0%)
OVERALL COMPOSITE OUTCOME	35 (33%)	1 (50%)	40 (31%)	3 (10%)

† ACTIVE refers to patients with a diagnosis of HIT on study entry.
†† NON-ACTIVE refers to patients with a HISTORY of a positive laboratory test for HIT/HITTS on entry into the study.