

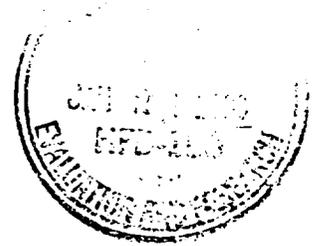
**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-883

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION



Date: Jan. 18, 2000

NDA: 20-883

APPLICANT: Texas Biotechnology Corporation.

NAME OF DRUG: Novastan[®] (Argatroban) Injection.

INDICATIONS: Prevention of thrombosis in patients with (i) heparin-induced thrombocytopenia (HIT) and (ii) heparin-induced thrombocytopenia and thrombosis syndrome (HITTS).

USER FEE DUE DATE: 2/15/2000.

DRUG CLASSIFICATION: 1P.

DOCUMENTS REVIEWED: NDA Volumes 17.1, 17.6 - 17.72, 17.4 - 17.79, Dated 3/19/1999 and 28.1, 6.74, 6.76, 6.77, 6.77a, 6.78, 6.79, Dated 8/16/99.

MEDICAL REVIEWER: Dr. Ann Farrel (HFD-180).

STATISTICAL REVIEWER: Wen-Jen Chen, Ph.D.

KEYWORDS/PHRASE: Clinical studies; NDA review; composite endpoint; confidence intervals; historical control; interim analysis; open-label.

1.0 INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a relatively common adverse effect of heparin therapy, occurring in approximately 5% to 10% of patients who receive heparin. Furthermore, the development of vascular thrombosis is considered the most devastating complication of heparin therapy. Patients who develop the syndrome of heparin-induced thrombosis carry a very high mortality risk.

Clinical observations associated with the syndrome include heparin-induced immune complexes which unpredictably cause vascular thrombosis that is worsened by continuation of heparin therapy and results in diffuse uncontrolled clotting, limb ischemia, organ infarction, cerebral vascular accidents, and death. This sequence of events is referred to as the heparin-induced thrombocytopenia-thrombosis syndrome (HITTS).

This submission consists of a single primary study, Study ARG-911, and a supportive study, Study ARG-915. Both studies were previously reviewed and a non-approval letter was issued on 5/8/98.

Following suggestions contained in the non-approval letter, the sponsor identified a new historical control group. The criteria for selecting the control group were set forth in a meeting with Dr. Talarico and several reviewers from the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) on 7/14/98 (see minutes for details).

One problem identified previously with the previous control was a single investigator (Dr. Warkentin) provided 45% of historical control patients (30% HIT and 60% HITTS) from 3 study centers in Canada. However, no argatroban-treated patients were enrolled from these three sites. In addition, the incidence of the overall composite endpoint was 75% in HIT patients and 46% in HITTS patients compared to a much lower rate in other centers that enrolled HIT patients (9-26%) and a higher rate in other centers which enrolled HITTS patients (64-69%). Thus, the historical control patients provided from these three Canadian sites resulted in a disproportionately higher overall composite event rate in the historical HIT (but not HITTS) patients.

2.0 STUDY# ARG-911

2.1 Background Information

Objectives: The objective of this study was to evaluate the use of argatroban as

1. a prophylactic anticoagulant for the prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT), and
2. a therapeutic anticoagulant in the treatment of patients with heparin-induced thrombocytopenia and thrombosis syndrome (HITTS).

Study Design: This was a multicenter, in-patient, non-randomized, open-label, historical controlled study. Each patient underwent a pre-treatment period (within 1-week before initiating treatment), treatment period (up to 14 day infusion), and follow-up period (30 ± 7 days which includes the treatment period). All argatroban patients were to be started on an argatroban infusion of 2 µg/kg/min.

Based upon discussions with FDA, the new historical control group selected by the sponsor was to consist of:

- Eligible cases from the Loyola (Wallis) registry of patients with HIT/HITTS – these cases were to serve as the core of the new historical control group and to replace the historical controls originally enrolled at that site (site 20) by Dr. Lewis;
- Historical controls from the original historical control group who were enrolled from sites

that enrolled at least one prospective patient;

- Additional eligible cases solicited from investigative sites that enrolled at least three prospective patients.

Based on this reviewer's analysis, the number of argatroban-treated and new historical control patients for each site met the above three rules. However, one investigator, Dr. Lerner (Code 113), enrolled 4 argatroban and 14 new historical control patients, violating the rule that for each prospective patient enrolled at a given site, no more than 3 new historical controls will be acceptable.

The sponsor indicated that clinical data for the new historical controls were collected retrospectively while those of argatroban-treated patients were collected prospectively. In addition, the new historical controls were enrolled between 1991 and 1995 while the argatroban-treated patients were enrolled from 2/12/95 to 12/30/96. Because patients from these two populations were not enrolled at the same time and not randomized from one homogenous population, the demographics variables and baseline medical conditions between these two populations were examined for possible confounding variables. The investigation of confounding variables will be discussed in section 2.2.1.

Sample Size Determination: The sponsor indicated that when the FDA suggested an appropriate new historical control group be identified for the comparison with the argatroban group, the sample size (304 patients) of the argatroban group was known, as well as the 37-day incidence (35%) of the occurrence of death, amputation, or new thrombosis. Given an anticipated 37-day incidence among the historical controls with a diagnosis of HIT/HITTS equal to 50%, it was estimated that 200 historical controls would provide a two-sided test with 90% power to detect a significant treatment effect (i.e., a greater than 30% relative reduction in the risk, amputation, or new thrombosis) using a significance level of 0.05.

Dosing Schedule and Measurements: Patients were administered an infusion of argatroban at a starting dose of 2 µg/kg/min and an aPTT was to be evaluated approximately 2 hours after initiating the infusion. Novastan[®] dosing was to be adjusted as clinically indicated (aPPT not exceeding 3 times control) and was not to exceed a maximum rate of 10 µg/kg/min. The aPPT was checked approximately 2 hours after each dose change until the aPPT was in the desired therapeutic range (1.5-3x baseline). Once a therapeutic aPPT was achieved, patients remained on this infusion until clinical resolution of their underlying condition, or appropriate anticoagulation was provided with other agents, or until treatment was continued for up to fourteen days.

Study Population: The inclusion criteria for the patient population included

- Males and non-pregnant females age ≥ 18 and ≤ 80 years;
- Those with documented heparin-induced thrombocytopenia and thrombosis syndrome or heparin-induced thrombocytopenia in the absence of thrombosis or history of a positive heparin-induced platelet aggregation test; etc.

The exclusion criteria for the patient population included

- Any condition which, in the investigator's opinion, contraindicated the use of argatroban or endangered the patient if he/she participated in this trial;
- Clinical 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;
- Unexplained aPTT > 200% of control at baseline;
- Documented coagulation disorder or bleeding diathesis unrelated to HITTS; etc.

The sponsor declared that the inclusion and exclusion criteria were applied equally to select the new historical controls and argatroban-treated patients, evaluated by the investigator and/or a clinical monitor (page 47 in sponsor's Volume 74).

Clinical Evaluations and Follow-up: In the pre-treatment period, patient evaluations were to include medical history, physical examinations, vital signs, CBC w/platelet count, urinalysis, urine HCG, heparin-induced platelet aggregation (HIPA) test, signs and symptoms of clinical ischemic syndromes, aPPT, a 12-lead electrocardiogram (prior to initiation of infusion), concomitant medication, and adverse events.

Treatment and post-treatment patient evaluations were to include vital signs, arterial and venous duplex doppler (performed as appropriate for those patients who develop thrombosis while receiving argatroban infusion), V/Q scan (V/Q scan was to be performed on for those patients who develop new pulmonary embolism while receiving argatroban infusion), aPPT (at least once daily, and 2 hours after each dose), HIPA test, and adverse events as clinically warranted.

Argatroban patients were to be followed both during treatment and 30 days (\pm 7 days) following the initiation of therapy for the occurrence of one (or more) of the following efficacy outcomes: death (all causes), amputation (all causes), and development of new thrombosis. Patients in the new historical control were to be followed for 37 days after their baseline date.

Primary and Secondary Efficacy Variables: As discussed in the meeting minutes from July 14, 1998, the primary efficacy endpoint was the composite of all-cause mortality, all-cause amputation, and development of a new thrombosis within 37 days from the baseline date. It was agreed that the primary analysis would be based upon a simple comparison of event rates for the composite endpoint. Time to the first occurrence of all-cause death, all-cause amputation, or development of a new thrombosis would also be analyzed as a secondary endpoint.

The baseline date for the argatroban group was the date that argatroban was initiated. However, for the new historical control group, the baseline date was the date on which heparin was discontinued after the platelet count met inclusion criteria or the date on which the platelet count met inclusion criteria after heparin was initiated. As will be noted later in this review, this may have led to an imbalance between the treatment and control arms with respect to the proportion of subjects with a reported use of heparin six weeks prior to baseline.

Sponsor's efficacy analysis plan

The statistical analyses were conducted separately for the HIT and HITTS groups and no interim analyses were to be performed.

The efficacy endpoints were analyzed for the following three sets of patients:

- Intent-to-treat (ITT) population (primary analysis population) - all patients who received argatroban treatment and all historical controls in the new historical control group.
- Evaluable population – all patients receiving argatroban and determined by the data safety and monitoring committee (DSMC) to have the clinical diagnosis of HIT or HITTS as specified in the inclusion criteria, and all historical controls in the new historical control group.
- Test-positive population – all patients and the new historical controls who had a positive laboratory test for heparin-induced thrombocytopenia (specifically, either the heparin-induced platelet aggregation or the serotonin release assay) at any time during the study.

The primary efficacy endpoint was analyzed using categorical data methods while time to the first event (the secondary endpoint) were analyzed using a Log-rank test. In addition, the hazard ratio and its 95% confidence interval were estimated by applying the proportional hazard regression analysis with only treatment in the model.

A Log-rank test was also applied to compare the time to the first event between sub-groups formed for each baseline medical condition (YES or NO) using the ITT population. The baseline medical conditions analyzed by the sponsor included circulatory system, blood & blood forming organ, respiratory system, congenital anomalies, digestive system, endocrine & nutritional & metabolic disease, infectious disease, genitourinary system, musculoskeletal system, neoplasms/oncology & hematology, nervous system, skin & subcutaneous tissue, injury/poisoning, and mental disorders.

Disposition of Patients: A total of 497 patients were in the study, including 304 patients (160 with HIT and 144 with HITTS) in the argatroban group, and 193 patients (147 with HIT and 46 with HITTS) in the new historical control group. Table 2.1.1 summarizes the patient disposition between groups (HIT and HITTS) for the ITT, evaluable, and test-positive populations.

Table 2.1.1 (sponsor's) Patient Disposition

	ARGATROBAN			HISTORICAL		
	HIT	HITTS	TOTAL	HIT	HITTS	TOTAL
Intent-To-Treat	160	144	304	147	46	193
Evaluable	146	134	280	147	46	193
Test-Positive	80	94	174	119	30	149

Source: sponsor's Table 8 in Volume 74.

Table 2.1.1 shows that 280 of the 304 patients (92%) in the argatroban group were considered evaluable for HIT or HITTS. Twenty-four patients were excluded for the following reasons: no thrombocytopenia (12 patients), severe sepsis explaining the thrombocytopenia (5 patients), thrombocytopenia due to systemic lupus erythematosus with antiphospholipid syndrome (3 patients), chronic thrombocytopenia due to other cause without any change related to heparin exposure (3 patients), and thrombocytopenia not due to heparin as per investigator (1 patient). All 193 patients in the new historical control group were deemed to have heparin-induced disease.

The test-positive population represented 57% (174/304) and 77% (149/193) of the intent-to-treat population for the argatroban and new historical control group.

Premature Discontinuations: A total of 21 (13%) and 9 (6%) for the HIT and HITTS patients, respectively, prematurely discontinued argatroban infusion due to surgery or patient request for withdrawal. The proportion discontinuing argatroban due to "other reasons" was 15 (9%), and 6 (4%) for the HIT and HITTS groups, respectively.

Distribution by Pooled Centers: Three pooled centers were created based on the enrollment into the new historical control group. Centers were as follows: center A, site 20; center B, centers other than site 20 that provided more than 10 historical controls (3 centers - sites 002, 060, and 113); and center C, all other centers (88 centers). Table 2.1.2 summarized the distribution of patients by study arms and pooled center.

Table 2.1.2 Distribution (Sponsor's) by Study Arm and Pooled Center

Pooled Center	HIT		HITTS	
	Historical Control N=147 (%)	Argatroban N=160 (%)	Historical Control N=46 (%)	Argatroban N=144 (%)
Center A	77 (52)	21 (13)	16 (35)	21 (15)
Center B	44 (30)	14 (9)	13 (28)	10 (7)
Center C	26 (18)	125 (78)	17 (37)	113 (78)
P-value*	0.001*		0.001*	

Source: sponsor's Table 11 in Volume 74; *: Chi-square test with df=2;

*: Significant utilizing significance level of .05.

Table 2.1.2 shows that a statistically significant difference exists in patient distribution among centers between argatroban and the historical control for both HIT and HITTS (p=0.001 for both

groups). For center C, which was made up of 88 small centers, the argatroban arm had 60% (78% - 18%) and 41% (78% - 37%) more patients than the historical control arm, respectively for HIT and HITTS.

2.2 Sponsor's Statistical Analysis and Results

2.2.1 Baseline Characteristics Comparisons

Tables 2.2.1.1 and 2.2.1.2 summarize the results of baseline characteristics and pre-treatment medical history of the ITT patients.

Table 2.2.1.1 (Sponsor's) Comparison of Baseline Characteristics for ITT Population

Parameter	HIT		HITTS	
	Historical (N=147)	Argatroban (N=160)	Historical (N=46)	Argatroban (N=144)
Age (Yrs): Mean \pm SE	66.1 \pm 12.3	61.3 \pm 13.5	65.7 \pm 10.9	61.5 \pm 12.7
	2-sided p*=0.001		2-sided p*=0.045	
Gender (M/F %)	56/44	43/57	59/39	50/50
	2-sided p*=0.022		2-sided p=0.305	
Race (Caucasian)	83%	89%	83%	85%
Weight	80.0 \pm 22.8	78.9 \pm 18.6	83.8 \pm 24.7	83.0 \pm 20.5
Mean Dose (μ g/kg/min)	-	2.0 \pm 0.1	-	1.9 \pm 0.1
Infusion Duration (Days)	-	5.3 \pm 0.3	-	5.9 \pm 0.2
Time From Heparin Discontinuation To Initial Infusion or Follow-up (days)	-	1.0 (1.7)	-	3.1 (4.6)
Median Platelet Count ($\times 10^3/\mu$ L): Baseline	111.0	82.0	94.0	66.5
Prior Heparin Exposure [#] , N (%)	145 (99%)	139 (87%)	46 (100%)	140 (97%)

Source: Sponsor's Table 12, 14 and 19 in Volume 74; *: significant difference at 0.05 level.

#: Within 6 weeks prior to Infusion.

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Table 2.2.1.2 Comparison (Sponsor's) of Pre-Treatment Medical History from ICD-9 Coded Terms for the ITT population

Baseline Condition	HIT		HITTS	
	Historical	Argatroban	Historical	Argatroban
Infectious Disease	7%	23% (2p [*] =0.0001) [*]	9%	21% (2p=0.077)
Neoplasms/Oncology & Hematol	23%	24% (2p=0.788)	9%	21% (2p=0.077)
Endocrine Nutrition & Metabolic	50%	66% (2p=0.004) [*]	54%	72% (2p=0.046) [*]
Blood & Blood-forming organs	15%	67% (2p<0.0001) [*]	20%	68% (2p<0.0001) [*]
Mental Disorders	16%	41% (2p<0.0001) [*]	24%	33% (2p=0.274)
Nervous System	13%	24% (2p=0.013) [*]	17%	34% (2p=0.041) [*]
Circulatory System	86%	100% (2p<0.0001) [*]	94%	98% (2p=0.154)
Respiratory System	24%	58% (2p<0.0001) [*]	22%	61% (2p<0.0001) [*]
Digestive System	21%	59% (2p<0.0001) [*]	33%	49% (2p<0.061)
Genitourinary System	21%	53% (2p<0.0001) [*]	20%	47% (2p<0.0001) [*]
Skin and Subcutaneous Tissue	3%	19% (2p<0.0001) [*]	7%	13% (2p=0.417)
Musculoskeletal System	18%	33% (2p=0.004) [*]	17%	42% (2p=0.003) [*]
Congenital Anomalies	0%	5% (2p=0.007) [*]	0%	5% (2p=0.198)
Injury/Poisoning	27%	43% (2p=0.004) [*]	28%	54% (2p<0.002) [*]

Source: Sponsor's Table 16 in Volume 74; #: Fisher's 2-sided p-value;

*: Significant utilizing significance level of .05.

Table 2.2.1.1 indicated the following:

- the argatroban group and historical controls are comparable with respect to race and weight;
- the patients of the historical control group are significantly older than those of the argatroban group (2-sided p=0.001 and 0.045 for the HIT and HITTS groups, respectively);
- for the HIT group, the historical control group has significantly more male patients than the argatroban group (2-sided p=0.022);
- platelet counts in the argatroban group are lower than those in the historical control group for both the HIT and HITTS groups;
- for the HIT group, the historical control and the argatroban arm, do not appear comparable with respect to exposure to heparin in the previous six weeks (99% versus 87%, respectively).

Table 2.2.1.2 shows that statistically significant differences between two treatment groups were detected in most categories with the exceptions of Neoplasms/Oncology & Hematology in the HIT and HITTS groups, and infectious disease, mental disorders, circulatory system, digestive system, skin and subcutaneous tissue, and congenital anomalies in the HITTS group.

2.2.2 Summary of Sponsor's Efficacy Analysis Results

Categorical Analysis for the Primary Efficacy Endpoint

Table 2.2.2.1 reports the results of categorical data analyses on the numbers and percentages of HIT and HITTS patients separately for death (all causes), amputation (all causes), or development of new thrombosis, and the composite endpoint during the 37-day study period

using the ITT patient population. Events were reported based on the following severity ranking: death>amputation>new thrombosis. Note that in a telephone conference held at 2:00 p.m., December 10, 1999, the sponsor declared that there were no missing data need to be handled in the event analyses.

Table 2.2.2.1 (Sponsor's) Categorical Analysis Results on the Composite Endpoint and Its Individual Component Using ITT Patient Population

Parameter	HIT				HITTS				
	Historical Control		Argatroban		Odds Ratio (95% CI)	Historical Control		Argatroban	
	N (%)	N (%)	N (%)	N (%)		P-value	P-value	Odds Ratio (95% CI)	
Total Patients	147	160				46	144		
Death (All Causes) ^b	32 (21.8)	27 (16.9)	0.311			13 (28.3)	26 (18.1)	0.146	
Amputation (all causes) ^b	3 (2.0)	3 (1.9)	1.00			4 (8.7)	16 (11.1)	0.787	
New Thrombosis ^b	22 (15.0)	11 (6.9)	0.027*			9 (19.6)	21 (14.6)	0.486	
Composite Endpoint	57 (38.8)	41 (25.6)	0.014*	1.84 (1.13, 2.99)		26 (56.5)	63 (43.8)	0.131	1.67 (0.86, 3.26)

Source: Sponsor's Table 20 in volume 74; *: Significant utilizing significance level of 0.05;

a: Based on the 2-sided Fisher's exact test for the individual components and on the Chi-square test for the composite endpoint;

b: Reported only if it was the most severe outcome (severity ranking: death>amputation>new thrombosis).

Table 2.2.2.1 shows that among patients with HIT, the incidence of the composite endpoint for the argatroban arm 25.6% (41/160) was significantly smaller than the 38.8% (57/147) incidence observed for the historical control arm ($p=0.014$). On the basis of the estimated odds ratio (1.84), patients in the new historical control arm have an 84% excess in the odds of death, amputation, or new development of thrombosis than patients in the argatroban arm. However, among the patients with HITTS, the difference between the two treatment arms was not significant.

As for the individual components of the composite endpoint, except new thrombosis for patients with HIT, the incidence for each of the three components (death, amputation, or new thrombosis) was not significantly different between argatroban and the new historical control arms for both the HIT and HITTS groups.

Log-Rank Test For the Secondary Efficacy Endpoint - time to the first composite event

Table 2.2.2.2 summarizes the results of survival analyses on the time-to-first-event for the composite endpoint for both the HIT and HITTS groups using the ITT population.

Table 2.2.2.2 Log-rank tests for the composite endpoint using ITT population

Parameter	HIT				HITTS			
	NO. of Patients		Logrank	Hazard Ratio	NO. of Patients		Logrank	Hazard Ratio
	Arga. ¹	HC. ²	P-value	(95% CI)	Arga. ¹	HC. ²	P-value	(95% CI)
Argatroban vs. Historical	160	147	0.007*	1.725 (1.15-2.58)	144	46	0.018*	1.71 (1.08-2.70)

1: argatroban; 2: Historical Control; *: significant utilizing significance level of 0.05.

Table 2.2.2.2 indicates that a statistically significant difference was detected in favor of argatroban treatment for both HIT and HITTS groups ($p=0.007$ and 0.018 , respectively). Based on the hazard ratios estimated for both the HIT (1.725; 95% CI, 1.15 – 2.58) and HITTS groups (1.71; 95% CI, 1.08 – 2.70), the patients in the historical control group have approximately 1.725 and 1.71 times the risk (for one of the three diseases: death, amputation, or thrombosis) as do the argatroban-treated patients for HIT and HITTS groups, respectively.

Similar to the results for the ITT patients, among the evaluable patients, a statistically significant between-group difference in favor of argatroban treated patients was detected on the time to the first event of the composite endpoint for both the HIT and HITTS groups ($p=0.006$ and 0.039 , respectively).

Results for Center Analyses

Table 2.2.2.3 presents the results of the composite endpoint (all-cause death, all-cause amputation, and the development of a new thrombosis within 37 days from baseline) analysis by pooled centers using the ITT patient population.

Table 2.2.2.3 (Sponsor's) Results of the first event analysis using the ITT population

Pooled Center	HIT				HITTS			
	Historical		H-A	2-pvl ²	Historical		H-A	2-pvl
	Control (H)	Arga. ¹ (A)			Control (H)	Arga. (A)		
Center A	35/77 (45%)	2/21 (10%)	35%	0.002*	12/16 (75%)	8/21 (38%)	37%	0.045*
Center B	11/44 (25%)	5/14 (36%)	-11%	0.5	6/13 (46%)	4/10 (40%)	6%	1.00
Center C	11/26 (42%)	34/125 (27%)	15%	0.16	8/17 (47%)	51/113 (45%)	2%	1.00

Source: Sponsor's Table 21 in Volume 74; Arga.: Argatroban; *: Significance at 0.05 level; 2-pvl: P-value from two sided Fisher's exact test performed by this reviewer.

Table 2.2.2.3 indicates that except for center A, the differences between the Argatroban and historical controls are not significantly different for both the HIT and HITTS groups. The numerical results suggest that the overall result may be originating entirely from patients enrolled in Center A. The characteristics of patients in center A are explored in a following section.

Analysis for the Effect of Baseline Medical Conditions

Table 2.2.2.4 reports the results of Logrank tests for the effects of the baseline medical

conditions on the time to first event for both HIT and HITTS groups using the ITT patient population.

As indicated in the Sponsor's efficacy analysis plan, the Log-rank test was used to compare the time to event curves between sub-groups formed for each baseline medical condition (YES or NO) using the ITT population (note, treatment was ignored for this analysis).

Table 2.2.2.4 (Sponsor's) Results of the effects for the patient baseline conditions on the time to first event using ITT population

Medical Condition (ICD9 Code)	Logrank Test P-Value	
	HIT	HITTS
Infectious Disease	0.038*	0.739
Neoplasms Oncology & Hematology	0.727	0.891
Endocrine, Nutritional & metabolic	0.412	0.348
Blood & Blood-forming Organs	0.623	0.454
Mental Disorders	0.630	0.885
Nervous System	0.498	0.506
Circulatory System	0.026*	0.461
Respiratory System	0.517	0.990
Digestive System	0.269	0.871
Genitourinary System	0.916	0.827
Skin & Subcutaneous Tissues	0.210	0.065
Musculoskeletal System	0.419	0.194
Congenital Anomalies	0.260	0.788
Injury/Poisoning	0.796	0.417

Source: Sponsor's Table 22B in Volume 74; *: Significance declared at the level of 0.10.

Table 2.2.2.4 indicates that except for infectious disease ($p=0.038$) and the circulatory system ($p=0.026$) in the HIT group, no other baseline characteristics show significant effects on the time to event.

2.2.3 Summary of Adverse Events

Bleeding and other adverse events were reported during the study course. A bleed was defined as major if it was overt and (1) was associated with a decrease in hemoglobin of ≥ 2 g/dL, and led to transfusion of ≥ 2 units, or (2) was intracranial, retroperitoneal, or occurred into a major prosthetic joint. Bleeds that were reported but did not require more than 2 units of blood were considered as minor. Bleeding and other most frequent adverse events (AE) experienced by $\geq 5\%$ of patients are summarized in Table 2.2.3.1. The sponsor described the majority of these bleeding events as minor.

Table 2.2.3.1 (Sponsor's) Summary of bleeding and other adverse events for the entire study period HIT Arm

Events		Historical Control	Argatroban	2-Sided Fisher Exact P-Value ^a
Bleeds:	All bleeds	72/147 (49%)	69/160 (43%)	
	Major bleeds	12/147 (8.2%)	5/160 (3.1%)	0.078
	Minor bleeds	60/147 (40.8%)	64/160 (40%)	0.91
AEs on ≥ 5% of Patients	Total Body System	105/147 (71.4%)	125/160 (78%)	0.19
	Gastro-Intestinal system disorders	3/147 (2%)	17/160 (11%)	0.002*
	Respiratory system disorders	13/147 (9%)	12/160 (8%)	0.68
	Cardiovascular Disorders, General	5/147 (3%)	11/160 (7%)	0.2
	Resistance Mechanism Disorders	20/147 (14%)	10/160 (6%)	0.035*
	Respiratory System Disorders	8/147 (5%)	9/160 (6%)	1.0
	Heart Rate and Rhythm Disorders (Atrial)	21/147 (14%)	7/160 (4%)	0.003*
	Vascular Disorders	17/147 (12%)	6/160 (4%)	<0.001*

HITTS Arm

Events		Historical Control	Argatroban	2-Sided Fisher Exact P-Value ^a
Bleeds:	All bleeds	20/46 (44%)	75/144 (52%)	
	Major bleeds	1/46 (2.2%)	15/144 (10.4%)	0.12
	Minor bleeds	19/46 (41.3%)	60/144 (41.7%)	1.00
AEs on ≥ 5% of Patients	Total Body System	40/46 (87%)	123/144 (85%)	1.00
	Body as Whole – General Disorders (Pain)	2/46 (4%)	13/144 (9%)	0.53
	Gastro-Intestinal Sys. Disorders (Constipation)	1/46 (2%)	12/144 (8%)	0.19
	Urinary System Disorders	2/46 (4%)	11/144 (8%)	0.74
	Cardiovascular Disorders, General	0/46 (0%)	13/144 (9%)	0.04*
	Resistance Mechanism Disorders	2/46 (4%)	10/144 (7%)	0.73
	Platelet, Bleeding & Clotting Disorders	6/46 (13%)	10/144 (7%)	0.22
	Vascular Disorders (Thrombophlebitis)	1/46 (2%)	10/144 (7%)	0.30
	Vascular Disorders (Thrombophlebitis Deep)	7/46 (15%)	8/144 (6%)	0.055

Source: Sponsor's Table 41, 42 & Table 47; #: 2-sided Fisher Exact tests were performed by this reviewer;

* Significant utilizing significance level of 0.05.

Table 2.2.3.1 indicates that overall, no significant differences in the incidence of bleeding (major, or minor bleed) between argatroban and new historical control arms were found for both the HIT and HITTS groups, at the .05 level of significance.

The percentage of patients experiencing at least one adverse event for argatroban was not significantly different from those of the historical control arm for both the HIT and HITTS groups ($p=0.19$ and 1.00 , respectively). However, the percentages for the argatroban HIT patients were significantly different from those of the historical control HIT patients on gastro-intestinal system disorders ($p=0.002$), resistance mechanism disorders ($p=0.035$), heart rate and rhythm disorders ($p=0.003$), and vascular disorders ($p<0.001$). In addition, for the HITTS group, a significantly higher percentage of patients in the argatroban arm than in the historical control arm experienced general cardiovascular disorders ($p=0.04$). Of the 125 HIT and 123 HITTS patients with at least one AE, 29 (23%) HIT and 39 (32%) HITTS were identified as possibly, probably, or definitely drug-related.

2.3 Reviewer's Analyses and Comments

In the following, a number of analyses are reported which were conducted for this review. These analyses have been based upon a data set submitted by the applicant on 8/10/1999. This data set replaced an earlier data set in which 39 argatroban patients were erroneously censored prior to the full follow-up time.

Comparison of the Chi-square and Log-Rank Test Results

During a meeting with the sponsor (7/14/98), it was agreed that the primary endpoint would be evaluated based upon the simple event rates for the follow-up period. FDA also requested at that time that a log-rank test also be provided. For the HIT subgroup, the p-value was .014 for the chi-square test and .007 for the Log-rank test. For the HITTS subgroup, the p-values were .131 and .018, respectively. There was a corresponding difference in the risk reductions between the two approaches with the risk reduction from the time to event analysis being larger than the risk reduction based upon the simple rates. Based upon an examination of the time to event curves provided by the applicant (Table A7 and Table B7 in sponsor's Volume 76, submitted on August, 1999), the difference between the two approaches appears to be originating from a fairly transient difference between the treatments during the first week or two of follow-up. That is, there is a more pronounced treatment effect favoring the experimental arm during weeks 1-2 followed by a somewhat higher event rate during the remaining period of follow-up for the experimental arm. The net effect is to produce a relatively smaller effect over the full period of observation than for the first two weeks of follow-up. This effect is seen for both HIT and HITTS patients, but is much more pronounced for HITTS patients.

Investigation of Potential Confounding Variables

Because the sponsor's analysis is based upon a historical control, it is necessary to determine if differences in patient characteristics between the groups used for comparison may be accounting for the observed treatment effects. In order to investigate the effect of potentially confounding variables, this reviewer performed the following three analyses using the ITT database: I.) Analysis for the effect of baseline variables on treatment efficacy, II.) Center consistency analysis, and III.) Subgroup analysis to assess internal consistency.

I. Analysis for the effect of baseline variables on the treatment efficacy

It has been observed that the baseline variables including reported disease at entry, age, gender, test-positive status (TESTP), heparin exposure within 6 weeks prior to infusion (HEPEP) and baseline platelet count (BPLATC) differed between the argatroban and historical control patients. In order to investigate whether the observed treatment effects may be attributed to these imbalances a number of statistical analyses were conducted. These analyses were conducted for both the HIT and HITTS groups.

Prior to examining these variables, it is noted that it is possible that the observed differences could be the result of differential recording techniques due to different starting dates between the new historical controls and argatroban-treated patients. Differential recording of information would call into question the quality of the information for the new historical control group. On the other hand, if the data have been recorded correctly, this would call into question the comparability of the two groups.

The first series of analyses were designed to determine if the treatment effect observed was consistent over the values of the base line variables (i.e., test for interaction). The particular method was determined by the scale of measurement for the baseline variate. For the analysis of event rates, the Breslow-Day (B-D) method was used for dichotomous baseline variables (i.e., baseline disease, gender, HEPEP, and TESTP) and logistic regression was used for continuous baseline variables (i.e., age and BPLATC). For the time to event analyses (i.e., Log-rank), Cox regression was used to investigate the effect of for both the dichotomous and continuous baseline variables.

In the test for interaction, a p-value of .2 was used for evaluation. The second series of analyses were driven by the results of this test. If the interaction was below .2, the treatment effect was presented separately for each level of the baseline variate. If the p-value was above .2, a model was fit which incorporated a "main effect" for the covariate for testing the treatment effect.

The baseline diseases investigated in these analyses included: circulatory system (CIRC), blood & blood forming organ (BBFO), respiratory system (RESP), congenital anomalies (CONG), digestive system (DIG), endocrine & nutritional & metabolic disease (ENM), infectious disease (INFD), musculoskeletal system (MUSC), nervous system (NERV), skin & subcutaneous tissue (SST), injury/poisoning (INJP), and mental disorders (MENT). The results for the tests of interaction between treatment group and baseline variables are summarized in Table 2.3.2.1.

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Table 2.3.2.1 Results of the interaction analysis (p-values) between treatment group and each of the analyzed baseline variables for both the HIT and HITT groups.

Dichotomous baseline variables

BAELINE VARIABLE	HIT		HITTS	
	B-D ¹	COX ²	B-D	COX
BBFO (Yes/No)	0.91	0.77	0.113	0.106
RESP (Yes/No)	0.36	0.33	0.42	0.49
DIG (Yes/No)	0.70	0.81	0.31	0.11
ENM (Yes/No)	0.20*	0.27	0.048*	0.022*
GEN (Yes/No)	0.634	0.56	0.20*	0.13*
INFD (Yes/No)	0.90	0.99	0.59	0.46
MUSC (Yes/No)	0.78	0.83	0.076*	0.006*
NERV (Yes/No)	0.43	0.36	0.11*	0.13*
SST (Yes/No)	0.67	0.69	0.80	0.78
INJP (Yes/No)	0.25	0.44	0.975	0.94
MENT (Yes/No)	0.83	0.99	0.089*	0.094*
HEPEP (Yes/No)	0.007*	0.025*	NA	NA
TESTP (Yes/No)	0.49	0.49	0.44	0.55
GENDER (Female/Male)	0.78	0.34	0.34	0.17*

Continuous baseline variables

BAELINE VARIABLE	HIT		HITTS	
	LOGIST. ³	COX P.	LOGIST.	COX P.
BPLATC	0.48	0.46	0.002*	0.01*
AGE	0.72	0.62	0.44	0.76

¹: P-value from Brewslow-Day test; ²: P-value from Cox regression model;

³: P-value from logistic regression; *: Significant utilizing significance level of 0.20;

NA: Not applicable due to all patients in new historical control group being prior heparin exposures.

For the HIT group, Table 2.3.2.1 indicates that the treatment effect may be different for baseline disease ENM and time of heparin use (HEPEP). For the HITTS group, treatment effect may depend upon the following: gender, BPLATC, and baseline diseases ENM, GEN, MUSC, NERV, and MENT.

For those baseline variables with a suspected interaction, the event rates and tests of significance were calculated for each level of the baseline variable. Table 2.3.2.3 provides the results of these analyses.

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Table 2.3.2.3 (Reviewer's) Treatment effect comparisons by baseline variable with possible interaction.

HIT group

BASELINE VARIABLE	ARGA.* (A.)	HIST.* (H.)	A. - H.	FISH-P¹	LOGRNK-P²
ENM (With Disease)	22.6% (24/106)	41.1% (30/73)	-18.5%	0.013*	0.007*
ENM (Without Disease)	31.5% (17/54)	36.5% (27/74)	-5.0%	0.58	0.35
HEPEP (With Prior Exposure)	29.5% (41/139)	38.6% (56/145)	-9.1%	0.13	0.063
HEPEP (Without prior Exposure)	0.0% (0/21)	50% (1/2)	-50%	0.087	0.0012*

HITTS group

BASELINE VARIABLE	ARGA.* (A.)	HIST.* (H.)	A. - H.	FISH-P¹	LOGRNK-P²
ENM (With Disease)	43.7% (45/103)	72% (18/25)	-28.3%	0.014*	0.0001*
ENM (Without Disease)	43.9% (18/41)	38.1% (8/21)	5.8%	0.79	0.81
GEN (With Disease)	44.1% (30/68)	77.8% (7/9)	-33.7%	0.08	0.003*
GEN (Without Disease)	43.4% (33/76)	51.4% (19/37)	-8.0%	0.55	0.17
MUSC (With Disease)	35% (21/60)	75% (6/8)	-40%	0.051	0.0001*
MUSC (Without Disease)	50% (42/84)	52.6% (20/38)	-2.6%	0.85	0.44
NERV (With Disease)	46.9% (23/49)	87.5% (7/8)	-40.6%	0.054	0.002*
NERV (Without Disease)	42.1% (40/95)	50% (19/38)	-7.9%	0.44	0.16
MENT (With Disease)	47.9% (23/48)	36.4% (4/11)	11.5%	0.53	0.69
MENT (Without Disease)	41.7% (40/96)	62.9% (22/35)	-21.2%	0.047*	0.002*
Gender (Female)	50% (36/72)	55.6% (10/18)	-5.6%	0.79	0.43
Gender (Male)	37.5% (27/72)	59.3% (16/27)	-21.8%	0.069	0.005*

*: Argatroban treatment group; #: Historical control group; ¹: P-value from 2-sided Fisher Exact test;

²: P-value from Log-rank test; †: Significant under significance level of 0.05.

For the HIT group, Table 2.3.2.3 suggests that the overall treatment effect associated with argatroban may be originating only for patients with ENM disease (FISH-P=0.013 and LOGRNK-P=0.007). We also notice that for argatroban the lack of exposure to heparin in the previous six weeks has a dramatic effect on the event rate and treatment comparison (FISH-P=0.087 for subjects lacking exposure to heparin for the previous six weeks). This result is difficult to interpret since it is the result of 21 subjects receiving argatroban and only 2 subjects from the historical control. However, the argatroban effect for the 87% (139/160) of argatroban patients with prior heparin exposures is not significantly better than that of new historical control (FISH-P=0.13). This suggests that the overall treatment effect may be explained by an imbalance with respect to prior heparin use. Subjects with no heparin use in the prior six weeks are at a much-reduced risk for events, with virtually all of these subjects receiving argatroban.

For the HITTS patient population, argatroban is significantly better than the historical control for patients with ENM disease (FISH-P=0.014 and LOGRNK-P < 0.001) and without MENT disease (FISH-P=0.047 and LOGRNK-P = 0.002).

The baseline variables without significant treatment by variable interaction are shown below in Table 2.3.2.4.

Table 2.3.2.4 (Reviewer's) Results for the treatment effect comparisons using Cochran Mantel Haenszel test, Logistic Regression, and Cox regression model

BAELINE VARIABLE	HIT		HITTS	
	MTLC-P A.VS.H ¹	COX-P A.VS.H ²	MTLC-P A.VS.H	COX-P A.VS.H
BBO (Yes/No)	0.007*	0.004*	0.17	0.03*
RESP (Yes/No)	0.004*	0.002*	0.11	0.016*
DIG (Yes/No)	0.020*	0.015*	0.132	0.017*
ENM (Yes/No)	NA	NA	NA	NA
GEN (Yes/No)	0.007*	0.004*	NA	NA
INFD (Yes/No)	0.003*	0.001*	0.12	0.019*
MUSC (Yes/No)	0.018*	0.01*	NA	NA
NERV (Yes/No)	0.018*	0.01*	NA	NA
SST (Yes/No)	0.026*	0.016*	0.102	0.014*
INJP (Yes/No)	0.013*	0.008*	0.17	0.031*
MENT (Yes/No)	0.007*	0.004*	NA	NA
HEPEP (Yes/No)	NA	NA	----	----
TESTP (Yes/No)	0.005*	0.002*	0.131	0.02*
GENDER (Female/Male)	0.011*	0.008*	NA	NA
BPLATC	0.013*	0.01*	NA	NA
AGE	0.02*	0.008*	0.24	0.045*

¹: P-value from Cochran Mantel Haenszel test using dichotomous baseline variable as a stratum factor or Logistic regression using continuous baseline variable as a covariate to compare the treatment effects of argatroban vs. new historical control;

²: P-value from Cox regression model to compare the treatment effects of argatroban vs. new historical control using baseline variable as a covariate; * : Significant utilizing significance level of 0.05;

NA: Not Applicable due to significant interaction between baseline variable and treatment effect;

----: Not performed due to all patients in new historical control group were prior heparin exposures.

For the HIT group, Table 2.3.2.4 indicates that the treatment effect of argatroban is significantly better than that of the new historical control after adjustment for each of the baseline variables. This suggests that the imbalances at baseline for these variables are not greatly effecting the treatment comparisons.

For the HITTS group, Table 2.3.2.4 shows that the risk of a composite event for the new historical control patients is comparable to the unadjusted analysis. That is, the Mantel-Haenszel and logistic regression analyses are not significant, while the log-rank test results reach the .05 level. As for the HIT group, this suggests that the imbalances at baseline for these variables are not greatly effecting the treatment comparisons.

II. Center consistency analysis

Since a statistically significant difference in patient distribution among centers between

argatroban and the new historical control was found for both the HIT and HITTS groups, further analyses have been conducted for this review. Specifically, the homogeneity of treatment effect by center has been investigated using the Breslow-Day test. Table 2.3.3.1 displays the results for these analyses.

Table 2.3.3.1 (Reviewer's) Results (p-value) for testing the interaction between treatment group and center using ITT patient database

	HIT ARM	HITTS ARM
	B-D. ¹	B-D
INT. BET. TRT. & CENT. ²	0.027*	0.223

¹: P-value from Breslow-Day test; ²: Interaction between treatment and center;

*: Significant under significance level of 0.05;

Table 2.3.3.1 indicates that the interaction between treatment group and center is significant at the .05 level ($p=.027$) for HIT patients. In order to further explore the interaction effect, the event rates for the composite endpoint are presented in Table 2.3.3.2.

Table 2.3.3.2 (Reviewer's) First event rates of the composite endpoint for HIT group

	ARGATROBAN (A) % (EVENTS/N)	HISTORICAL (H) % (EVENTS/N)	% DIFF. H - A
Center A	9.5% (2/21)	45.5% (35/77)	36%
Center B	35.7% (5/14)	25% (11/44)	-10.7%
Center C	27.2% (34/125)	42.3% (11/26)	15.1%

Table 2.3.3.2 shows that the overall treatment effect is coming almost completely from center A with little overall difference between the arms for the remaining subjects. It appears that the historical control is fairly constant for each center, but that the rates for argatroban are quite low for center A. Table 2.3.3.4 contains p-values for the treatment comparison by center.

Table 2.3.3.4 (Reviewer's) Results for the treatment effect comparisons by center group for HIT group, using ITT database

	CENTER A FIH-P ¹	CENTER B FIH-P	CENTER C FIH-P
Argatroban vs. Historical Control	0.002*	0.50	0.16

¹: P-value from 2-sided Fisher Exact test; *: significant utilizing significance level of 0.05.

Table 2.3.3.4 shows that only for center A, patients in argatroban group have significantly lower first event rate (FIH-P=0.002) than that in the new historical control group for the composite endpoint of death, amputation, or thrombosis. It should be noted that center A only enrolled 13% of argatroban-treated patients, yet appears to account for virtually the entire treatment effect.

In order to explore the patient characteristics associated with center A, this reviewer has performed the following two analyses i.) efficacy analysis using demographics variables as a stratification factors and ii.) analysis of odds using center group as a stratification factor.

i.) Efficacy analysis

One of the approaches used to investigate the effect of center was to simultaneously examine the effect of age and gender by center. As first step, we define the following two variables: CNTGRP and AGE. CNTGRP consists of two center groups: Center A - patients from center A and Non-Center A – patients from center B and center C; AGE also consists of two subgroups: Non-Senior – patients with age ≤ 65 and Senior – patients with age > 65 . Table 2.3.3 displays the results by gender and age categories

Table 2.3.3.5 (Reviewer's) Treatment comparisons on the primary composite endpoint (ITT population) by gender and age group

GENDER	AGE GROUP	HIT GROUP			
		ARG. ¹ (A) Events/N (%)	HIST. ² (H) Events/N (%)	A – H (%)	P-VALUE ³
MALE	NONSENIOR	7/37 (18.9%)	18/40 (45.0%)	-26.1%	0.017*
MALE	SENIOR	8/31 (25.8%)	15/42 (35.7%)	-9.9%	0.45
FEMALE	NONSENIOR	11/53 (20.8%)	7/16 (43.8%)	-23%	0.10
FEMALE	SENIOR	15/39 (38.5%)	17/48 (35.4%)	3.1%	0.83

¹: Argatroban treatment group; ²: New historical control group;

³: P-value from two-sided Fisher Exact test; *: significant utilizing significance level of 0.05.

Note: Breslow-Day test for the heterogeneity of odds ratios for argatroban vs. new historical control across the strata formed by gender and age group has a p-value of .173

It can be seen in Table 2.3.3.5 that treatment effects favor argatroban for all but senior females. For this one group there is apparent difference between the treatment arms. Of course, the sample sizes are too small to make definitive statements regarding this particular group of subjects.

Since senior females have no apparent treatment effect, the number of subjects in this category for Center A was examined. The results of this investigation are displayed in Table 2.3.3.6.

Table 2.3.3.6 (Reviewer's) Odds in enrolling female patients with age > 65 between Center A and Non-Center A for Argatroban patients in HIT group

CNTGRP\GENAGC	SENIOR FEMALES (N0)	OTHERS (N1)	ODDS (N0/N1)
Center A	4	17	0.24
Non-Center A	35	104	0.34

It can be seen in this table that Center A has a slightly decreased proportion of subjects in the group with the lowest treatment effect. Though this may have favored argatroban for Center A, the relationship is not large enough to explain the overall favorable result for argatroban.

ii.) Analysis of odds of prior heparin use by center

Recall the results displayed Table 2.3.2.3 show that effect of argatroban is highly related to prior heparin exposure. The present analysis, shown in Table 2.3.3.7 compares the odds of argatroban-treated patients having prior heparin exposure between Center A and Non-Center A.

Table 2.3.3.7 (Reviewer's) Odds in enrolling patients with prior heparin exposure between Center A and Non-Center A for Argatroban patients in HIT group

CNTGRP\HEPEP	YES (N0)	NO (N1)	ODDS (N0/N1)
Center A	16	5	3.2
Non-Center A	123	16	7.7

Table 2.3.3.7 shows that the odds of having heparin exposure in the past six weeks is lower in Center A than for the remainder of subjects receiving argatroban (3.2 versus 7.7). Therefore, the reduced rate of prior heparin exposure may be at least partially responsible for the lower event rate in Center A for patients receiving argatroban. Since virtually all of the subjects from the historical control received heparin in the previous 6 weeks, it is impossible to statistically establish whether or not the reduced rate is due to argatroban or the lack of heparin use.

III. Subgroup Analysis

To assess the consistency of results across subgroups, this reviewer also applies two-sided Fisher's Exact tests to perform subgroup analyses for gender, race and age.

Gender

Table A.1.1 in Appendix I presents this reviewer's gender (Female and Male) analysis results for the comparisons of treatment effects for both the HIT and HITTS groups.

The results are briefly summarized below:

- The effect of argatroban is found superior to or borderline significantly better than that of the new historical control for males in HIT ($p=0.022$) and HITTS ($p=0.069$) arms, respectively.
- In general, the subgroup results indicate at least a positive trend in the male and female in favor of argatroban.
- The sample size is insufficient to determine if females respond to a lesser degree than males.

Race

Table A.1.2 in Appendix I presents this reviewer's race group analysis (Caucasian and non-Caucasian) results for the comparisons of treatment effects. In general, the subgroup results indicate at least a positive trend in the Caucasian and non-Caucasian in favor of argatroban. The sample size is insufficient to determine if there are statistically significant differences among the

race groups.

Age

Table A.1.3 in Appendix I presents this reviewer's age group analysis (≤ 65 and > 65) results for the comparisons of treatment effects.

The results are briefly summarized below:

- The effects of argatroban are found superior to those of new historical control for patients younger than 65 years old for both HIT ($p=0.0028$) and HITTS ($p=0.045$) arms;
- In general, the subgroup results indicate at least a positive trend for the two age groups, age ≤ 65 and age > 65 , in favor of argatroban.

2.4 Comments/Conclusions of treatment effects

~ For HIT group ~

- ◆ Overall, argatroban was found to be associated with a reduction in the rate of events for the composite endpoint of death, amputation and new thrombosis. The p-value for the overall comparison is .014 based upon a chi-square test. From a statistical perspective, this is not a very robust level of evidence when compared to the "usual" standard of replicated trial results with 2 or more trials at the .05 level.
- ◆ In addition to the above concern regarding the p-value for the overall result, it is important to consider that the statistical analysis is based upon an historical control which was selected after an initially selected control failed to establish a treatment effect.
- ◆ This trial, like all historically controlled studies, is subject to biases that are not present in a randomized clinical trial. That is, it is possible that inherent differences in the groups being compared may account for an observed difference rather than any difference in the treatments. For the HIT group, we observed many differences in baseline characteristics between the argatroban group and the historical control. Statistical analysis suggests that the observed treatment effect for argatroban is not originating from the differences in the baseline disease and demographic variables. However, there was an important difference discovered with respect to prior heparin in the previous six weeks. Approximately, 13% of the argatroban were reported as not having such heparin exposure while only 1% of the historical controls was in this group. Since none of the patients receiving argatroban who did not have heparin exposure in the previous assessed six weeks had a clinical event, this imbalance (13% vs. 1%) is quite serious. When subjects lacking prior heparin exposure in the previous weeks are deleted from the analysis (an analysis adjusted for prior heparin use is not possible due to the lack of historical controls), there is no longer a significant difference between the treatment arms ($p=.13$). Therefore, it must be concluded statistically that the treatment effect of argatroban is confounded with prior heparin use.
- ◆ The statistical analysis indicates that there is both an imbalance in sample size and an

interaction between the applicant's grouped centers and the effect of argatroban. In center A, 21 patients received argatroban while 77 historical control patients were from this center. Additionally, the rate of events was 36% lower (absolute) for argatroban in center A while there was essentially no difference in the event rate for the remaining 91 centers (the vast majority of the argatroban patients came from the smallest centers. The statistical analysis suggests that the argatroban patients in the highest identified risk groups, prior heparin in the previous six weeks and senior females, were disproportionately lower for center A.

~ For HITTS arm ~

- ◆ The effect of the treatment argatroban is not superior to that of the new historical control by sponsor's Chi-square test on the primary endpoint: the first occurrences of death, amputation, and the new development of thrombosis.
- ◆ The effect of argatroban superior to that of new historical control is not established by Cochran Mantel Haenszel test or logistic regression using baseline variable as a stratum factor or covariate, respectively, on the primary endpoint.
- ◆ The Log-rank analysis on time to the first event indicates that risk of the new historical control patients is significantly higher than that of the argatroban-treated patients in receiving one of the three diseases: death, amputation, or thrombosis. An examination of the time to event distribution suggests that the Log-rank test is reflecting an early transient effect that dissipates by week 4.

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3.0 SUPPORTIVE STUDY (STUDY# ARG-915)

3.1 Background Information

Objectives: The objective of this study was to evaluate the safety and efficacy of argatroban in patients with HIT/HITTS currently requiring anticoagulation with a non-heparin thrombin inhibitor.

Study Design: The same historical control group of patients used in study ARG-911 was used in this supportive study to compare the efficacy between the new historical control and argatroban groups. The study design was similar to that used in ARG-911 (see section 2.1).

Sample Size Determination: The sponsor indicated that no sample size was predefined since the main objective was to continue to offer argatroban to patients requiring the drug during the regulatory review process.

Study Population: The inclusion criteria for the patient population included

- Males and non-pregnant females at least 18 years of age;
- Those with documented heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) or history of a positive heparin-induced platelet aggregation test; etc.

The sponsor indicated that patients who were previously enrolled in ARG-911 were also eligible for enrollment in this study. In addition, patients enrolled in ARG-915 were allowed to be re-enrolled if necessary

The exclusion criteria for the patient population included

- Any condition which, in the investigator's opinion, contraindicated the use of argatroban or endangered the patient if he/she participated in this trial;
- Clinical 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;
- Unexplained aPTT > 200% of control at baseline;
- Documented coagulation disorder or bleeding diathesis unrelated to HITTS; etc.

For detail, refer to the section of inclusion/exclusion criteria in volume 32 submitted by the sponsor.

Clinical Evaluations and Follow-up: Refer to the sub-section for Clinical Evaluations and Follow-up in section 2.1 of Study ARG-911.

Primary Efficacy Variables: Refer to sub-section for Primary Efficacy Variables in section 2.1 of Study ARG-911.

Sponsor's efficacy analysis plan: The statistical analyses were conducted separately for the HIT and HITTS groups of the study and no interim analyses were to be performed. All efficacy and safety analyses were based on intent-to-treat population for both the HIT and HITTS study groups.

Disposition of Patients: A total of 457 patients were enrolled in this study, including 264 patients (125 with HIT and 139 with HITTS) in the argatroban group, and 193 patients (147 with HIT and 46 with HITTS) in the historical control group. Table 3.1.1 summarizes patient disposition between groups (HIT and HITTS) for ITT populations.

Table 3.1.1 (sponsor's) Patient Disposition

	ARGATROBAN			HISTYORICAL		
	HIT	HITTS	TOTAL	HIT	HITTS	TOTAL
Intent-To-Treat	125	139	264	147	46	193

Source: sponsor's Table 2 in Volume 32.

Premature Discontinuations: In this study, 21% (26/125) and 22% (30/139) of the HIT and HITTS patients, respectively, prematurely discontinued argatroban infusion. The most common reason for discontinuation was adverse events: 9% and 13% of the HIT and HITTS groups, respectively.

Distribution by Pooled Centers: Unlike Study ARG-911, the sponsor did not create center groups for analysis.

3.2 Sponsor's Statistical Analysis and Results

3.2.1 Baseline Characteristics Comparisons

The sponsor did not perform any statistical tests to compare baseline characteristics between the study arms. Tables 3.2.1.1 and 3.2.1.2 summarize baseline characteristics and pre-treatment medical history.

Table 3.2.1.1 (Sponsor's) Comparison of Baseline Characteristics for ITT Population

Parameter	HIT		HITTS	
	Historical (N=147)	Argatroban (N=125)	Historical (N=46)	Argatroban (N=139)
Age (Yrs): Mean ± SE	66.1±12.3	63.6±14.0	65.7 ± 10.9	64.6 ± 13.5
Gender (M/F %)	56%/44%	50%/50%	59%/39%	57/43%
Race (Caucasian)	83%	88%	83%	89%
Weight	80.0±22.8	74.0±17.5	83.8±24.7	84.8±20.7
Mean Dose (µg/kg/min)	-	1.8 ± 0.1	-	1.9 ± 0.1
Infusion Duration (Days)	-	5.1 ± 0.4	-	7.2 ± 0.6
Days Since Heparin discontinuation	-	1.4 ± 0.2	-	2.2 ± 0.3

Source: Sponsor's Table 5 and 7 in Volume 32.

Table 3.2.1.2 (Sponsor's) Medical History By ICD-9 Coded Terms For ITT population

Baseline Condition	HIT		HITTS	
	Argatroban (N=125)		Argatroban (N=139)	
	N	(%)	N	(%)
Cancer	13	(10.4)	17	(12.2)
Diabetes	30	(24.0)	55	(39.6)
Hepatic Impairment	8	(6.4)	15	(10.8)
Lupus Erythematosus	4	(3.2)	3	(2.2)
Renal Impairment	35	(28.0)	33	(23.7)
ARDS	16	(12.8)	17	(12.2)
Sepsis	25	(20)	23	(16.5)
On Circulatory Assist Device	20	(16.0)	23	(16.5)
Hemodialysis	14	(11.2)	25	(18.0)
Ventilation	5	(4.0)	8	(5.8)
Previous CABG	42	(33.6)	80	(57.7)

Source: Sponsor's Table 6 in Volume 32.

Table 3.2.1.1 indicated that there were no major discrepancies between argatroban and historical control patients on age, gender, race, and weight.

For medical historical data, the sponsor emphasized that it is difficult to perform direct comparisons between the argatroban and historical control patients. Table 3.2.1.2 therefore, did not present the information with regard to the historical control group.

3.2.2 Summary of Sponsor's Efficacy Analysis Results

Primary Efficacy Analysis Results

Table 3.2.2.1 displays the results of analyses on the numbers and percentages of HIT and HITTS patients separately for death (all causes), amputation (all causes), development of new thrombosis, and the composite endpoint during the 37-day study period for the ITT patient population. Events were reported separately for death, amputation, and new thrombosis using the following priority: death>amputation>new thrombosis.

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Table 3.2.2.1 (Sponsor's) Categorical Analysis Results on the Composite Endpoint and Its Individual Component Using ITT Patient Population

Parameter	HIT				HITTS			
	Historical Control		Argatroban	Odds Ratio (95% CI)	Historical Control		Argatroban	Odds Ratio (95% CI)
	N (%)	N (%)			N (%)	N (%)		
Total Patients	147	125			46	139		
Death (All Causes) ^b	32 (21.8)	21 (16.8)	0.357		13 (28.3)	35 (25.2)	0.700	
Amputation (all causes) ^b	3 (2.0)	6 (4.8)	0.309		4 (8.7)	16 (11.5)	0.786	
New Thrombosis ^b	22 (15.0)	5 (4.0)	0.004*		9 (19.6)	6 (4.3)	0.003*	
Composite Endpoint	57 (38.8)	32 (25.6)	0.021*	1.84 (1.09, 3.099)	26 (56.5)	57 (41.0)	0.067	1.87 (0.95, 3.67)

Source: Sponsor's Table 8 in Volume 78. *: Significant under significance level of 0.05;

a: Based on the 2-sided Fisher's exact test for the individual components and on the Chi-square test for the composite endpoint.

b: Reported only if most severe outcome (severity ranking: death>amputation>new thrombosis).

Table 3.2.2.1 shows that among patients with HIT, the composite endpoint was recorded in the argatroban group for 25.6% (32/125) of subjects which was significantly less than the 39% (57/147) observed for the historical control group (p=0.021). However, among patients with HITTS, the composite failed to reach the .05 level of significance (p=0.067).

As for the individual components of the composite endpoint, except new thrombosis for patients with HIT (p=0.004) or HITTS (p=0.003), the incidences for other two components, death and amputation, were not significantly different between argatroban and the historical control group for both HIT and HITTS groups.

Table 3.2.2.2 summarized the results of the time to event analysis for the composite endpoint for both the HIT and HITTS groups using the ITT population.

Table 3.2.2.2 (Sponsor's) Results of Logrank tests on the time-to-first-event for the composite endpoint using ITT population

Parameter	HIT				HITTS			
	NO. of Patients		Logrank P-value	Hazard Ratio (95% CI)	NO. of Patients		Logrank P-value	Hazard Ratio (95% CI)
	Arga. ¹	HC. ²			Arga. ¹	HC. ²		
Argatroban vs. Historical	125	147	0.0217*	1.646 (1.07-2.54)	139	46	0.0124*	1.78 (1.12-2.83)

1: argatroban; 2: Historical Control; *: significant utilizing significance level of 0.05.

Table 3.2.2.2 indicates that a statistically significant difference was detected in favor of argatroban treatment for both the HIT and HITTS groups (p=0.0217 and 0.0124, respectively). Based on the hazard ratio estimated for both the HIT arm (1.646; 95% CI, 1.07 – 2.54) and HITTS group (1.78; 95% CI, 1.12 – 2.83), the patients in the historical control group have approximately 1.65 and 1.78 times the risk relative to the argatroban-treated patients for the HIT and HITTS groups, respectively.

3.2.3 Summary Of Adverse Events

A total of 56 argatroban-treated patients (21 HIT and 35 HITTS) died during the study period. Eight additional patients (3 HIT, 3 HITTS, and 2 unknown) died outside of the study period for a total of 62 deaths in the argatroban-treated patients. A total of 45 historical controls (32 HIT and 13 HITTS) died during time interval equivalent to the study period (37 days). An additional three historical controls (2 HIT and 1 HITTS) died outside of the study period for a total of 48 deaths in the historical-control patients.

Table 3.2.3.1 summarized the incidence for major and minor bleeds (Refer to sub-section 2.2.3 for definitions of major and minor bleedings).

Table 3.2.3.1 (Sponsor's) Summary of major and minor bleedings

HIT Group

		Historical Control	Argatroban	2-Sided Fisher Exact P-Value [#]
Bleeds:	All bleeds	72/147 (49%)	41/125 (33%)	
	Major bleeds	12/147 (8.2%)	4/125 (3.2%)	0.119
	Minor bleeds	60/147 (40.8%)	37/125 (30%)	0.058

HITTS Group

		Historical Control	Argatroban	2-Sided Fisher Exact P-Value [#]
Bleeds:	All bleeds	20/46 (43.5%)	66/139 (47.5%)	
	Major bleeds	1/46 (2.2%)	6/139 (4.3%)	0.683
	Minor bleeds	19/46 (41.3%)	60/139 (43.5%)	0.865

Source: Sponsor's Table 41, 42 & Table 47; #: 2-sided Fisher Exact tests were performed by this reviewer.

Table 2.2.3.1 indicated that overall, no apparent difference in the incidence of bleeding (major or minor bleeds) between argatroban and the historical control group both the HIT and HITTS.

3.3 Reviewer's Analyses and Comments

For this supportive study, this reviewer performed subgroup analysis to assess internal consistency, using the ITT database.

The sponsor on 8/10/1999 submitted the data used in this analysis. This data set replaced a previous data set in which five (5) argatroban patients (3 in HIT and 2 in HITTS) were mistakenly reported as having no primary event.

Subgroup Analysis

To assess the consistency of efficacy results across subgroups, this reviewer applies two-sided Fisher Exact tests for the subgroups listed below.

Gender

Table A.2.1 in Appendix II presents this reviewer's gender (Female and Male) analysis results for the comparisons of treatment effects for both the HIT and HITTS groups. In general, the subgroup results indicate a positive trend in the male and female in favor of argatroban.

Race

Table A.2.2 in Appendix II presents this reviewer's race group analysis (Caucasian and non-Caucasian) results for the comparisons of treatment effects. In general, the subgroup results indicate a positive trend in the Caucasian and non-Caucasian in favor of argatroban.

Age

Table A.2.3 in Appendix II presents this reviewer's age group analysis (≤ 65 and > 65) results for the comparisons of treatment effects. In general, the subgroup results indicate a positive trend for the two age groups, age ≤ 65 and age > 65 , in favor of argatroban.

3.4 Comments/Conclusions of treatment effects

For both the HIT and HITTS groups, the results for study ARG-915 favored argatroban over the historical control. The result for the HITTS group approached but did not reach the .05 level of significance.

This study has been appropriately described as supportive. It is difficult to determine statistically if the advantage seen for the argatroban treated patients is due to argatroban or the manner of selecting subjects. For example, subjects were allowed to enroll repeatedly to receive argatroban. It seems very unlikely that subjects previously failing argatroban would have been enrolled in this follow-up study.

For these reasons, the extensive statistical analyses conducted for study ARG-911 to identify potential confounding variables have not been conducted. For a statistical standpoint, study ARG-915 is generally supportive of study ARG-911 but should be viewed as descriptive in nature.

4.0 Overall Conclusions of treatment effects

~ For HIT patients ~

For patients in ARG-911 and ARG-915 receiving argatroban, there were fewer events seen in comparison to the common historical control. Due to methodological concerns the applicant has classified study ARG-915 as supportive of the results from study ARG-911. As such, ARG-911 forms the primary basis of the applicant's conclusion that argatroban is significantly better than

the historical control. When the statistical data from study ARG-911 was examined, a number of statistical issues were identified. Two of these issues are of greatest potential impact. The first is the observation that the treatment effect was limited to only a single center. The second is that there was an imbalance in the number of subjects with prior heparin use in the previous six weeks. The argatroban group enrolled virtually all of the subjects lacking prior heparin use in the previous 6 weeks. When this relatively small group of subjects is deleted, there is no apparent treatment effect. Taken together, these two issues undermine the applicant's claim that a statistically significant difference has been achieved.

~ For HITTS group ~

A statistically significant difference was not established in study ARG-911 using the agreed upon primary analysis of a simple comparison of event rates. The apparent statistical significance based upon the secondary Log-rank analysis appears to be reflecting a transient effect during the second week of follow-up. Otherwise, these two analyses, event rate analysis for the primary endpoint and Log-rank analysis for the secondary endpoint, are in reasonable agreement.

/S/
U

Wen-Jen Chen Ph.D.,
Mathematical Statistician

Concur: Dr. Flyer

/S/ 1/18/00

Dr. Nevius

1/18/00

cc: Archival NDA# 20-883

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