APPENDIX I

Table A.1.1 (Reviewer's) P-values for treatment comparisons on the first event rates of the composite endpoint by Gender for ITT patient population

	HIT GROUP				HITTS GROUP			
GENDER	ARG.[1] (A) Events/N (%)	HIST.[2] (H) Events/N (%)	A – H (%)	FIH-P[3]	ARG. (A) Events/N (%)	HIST. (H) Events/N (%)	A – H (%)	FIH-P
FEMALE	26/92 (28.3%)	24/64 (37.5%)	-9.2%	0.23	36/72 (50%)	10/18 (55.6%)	-5.6%	0.79
MALE	15/68 (22.1%)	33/82 (40.2%)	-18.1%	0.022*	27/72 (37.5%)	16/27 (59.3%)	-21.8%	0.069

[1]: Argatroban treatment group; [2]: New historical control group;
[3]: P-value from two-sided Fisher Exact test; *: significant under significance level of 0.05.

Table A.1.2 (Reviewer's) P-values for treatment comparisons on the first event rates of the composite endpoint by Race for ITT patient population

	HIT GROUP				HITTS GROUP			
RACE	ARG.[1] (A) Events/N (%)	HIST.[2] (H) Events/N (%)	A – H (%)	FIH-P[3]	ARG. (A) Events/N (%)	HIST. (H) Events/N (%)	A – H (%)	FIH-P
CAUCASIAN	35/142 (24.7%)	44/122 (36.1%)	-11.4%	0.059	51/123 (41.2%)	18/38 (47.4%)	-6.2%	0.58
NON-CAUCASIAN	6/18 (33.3%)	13/25 (52%)	-18.7%	0.351	12/21 (57.1%)	8/8 (100%)	-42.9%	0.033*

[1]: Argatroban treatment group; [2]: New historical control group;
[3]: P-value from two-sided Fisher Exact test; *: significant under significance level of 0.05

APPENDIX I

Table A.1.3 (Reviewer's) P-values for treatment comparisons on the first event rates of the composite endpoint by Age group for ITT patient population

	HIT GROUP				HITTS GROUP			
AGE GROUP	ARG.[1] (A) Events/N (%)	HIST.[2] (H) Events/N (%)	A – H (%)	FIH-P[3]	ARG. (A) Events/N (%)	HIST. (H) Events/N (%)	A – H (%)	FIH-P
AGE ≤ 65	18/90 (20%)	25/57 (43.9%)	-23.9%	0.0028*	30/77 (39%)	13/20 (65%)	-26%	0.045*
AGE > 65	23/70 (32.9%)	32/90 (35.6%)	-2.7%	0.74	33/67 (49.3%)	13/26 (50%)	-0.7%	1.00

[1]: Argatroban treatment group; [2]: New historical control group;
[3]: P-value from two-sided Fisher Exact test; *: significant under significance level of 0.05.

APPENDIX II

Table A.2.1 (Reviewer's) P-values for treatment comparisons on the first event rates of the composite endpoint by Gender for ITT patient population

	HIT GROUP				HITTS GROUP			
GENDER	ARG.[1] (A) Events/N (%)	HIST.[2] (H) Events/N (%)	A – H (%)	FIH-P[3]	ARG. (A) Events/N (%)	HIST. (H) Events/N (%)	A – H (%)	FIH-P
FEMALE	16/63 (25.4%)	24/65 (36.9%)	-11.5%	0.19	27/60 (45%)	10/19 (52.6%)	-7.6%	0.61
MALE	16/62 (25.8%)	33/82 (40.2%)	-14.4%	0.078	30/79 (38%)	16/27 (59.3%)	-21.3%	0.072

[1]: Argatroban treatment group; [2]: New historical control group;
[3]: P-value from two-sided Fisher Exact test;

Table A.2.2 (Reviewer's) P-values for treatment comparisons on the first event rates of the composite endpoint by Race for ITT patient population

	HIT GROUP				HITTS GROUP			
RACE	ARG.[1] (A) Events/N (%)	HIST.[2] (H) Events/N (%)	A – H (%)	FIH-P[3]	ARG. (A) Events/N (%)	HIST. (H) Events/N (%)	A – H (%)	FIH-P
CAUCASIAN	27/110 (24.6%)	44/122 (36.1%)	-11.5%	0.064	51/124 (41%)	18/38 (47.4%)	-6.4%	0.58
NON-CAUCASIAN	5/15 (33.3%)	13/25 (52%)	-18.7%	0.33	6/15 (40%)	8/8 (100%)	-60%	0.007*

[1]: Argatroban treatment group; [2]: New historical control group;
[3]: P-value from two-sided Fisher Exact test; *: significant under significance level of 0.05

APPENDIX II

Table A.2.3 (Reviewer's) P-values for treatment comparisons on the first event rates of the composite endpoint by Age group for ITT patient population

	HIT GROUP				HITTS GROUP			
AGE GROUP	ARG.[1] (A) Events/N (%)	HIST.[2] (H) Events/N (%)	A – H (%)	FIH-P[3]	ARG. (A) Events/N (%)	HIST. (H) Events/N (%)	A – H (%)	FIH-P
AGE ≤ 65	13/61 (21.3%)	25/57 (43.9%)	-22.6%	0.011*	25/62 (40.3%)	13/20 (65%)	-24.7%	0.072
AGE > 65	19/64 (29.7%)	32/90 (35.6%)	-5.9%	0.49	32/77 (41.6%)	13/26 (50%)	-8.4%	0.50

[1]: Argatroban treatment group; [2]: New historical control group;
[3]: P-value from two-sided Fisher Exact test; *: significant under significance level of 0.05.

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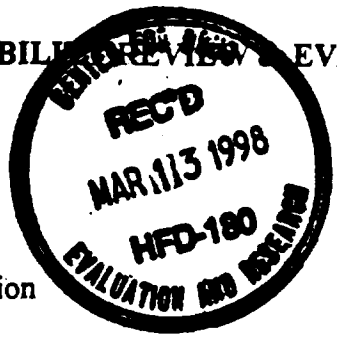
STATISTICAL STABILITY REVIEW AND EVALUATIONS



MAR 12 1998

NDA # 20-883

Applicant: Texas Biotechnology Corporation

Drug Names: Novastan® (Argatroban) Injection

Drug Classification: 1P

Indication: Treatment of Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS), and prevention of thrombosis in patients with HIT

Statistical Reviewer: A. J. Sankoh, Ph.D.

Medical/Chemistry Reviewer: K. Sizer, M.D./A. Al-Hakim, Ph.D.

Date of Document: 06/27/97, 11/17/97; **Date received by reviewer:** 9/3/97, 11/18/97.

45-Day Meeting and Filing Date: 10/02/97. **User Fee Date:** 2/15/98; **Extension:** 5/15/98.

Volumes Reviewed: 3 & 4, 6/27/97; 1 & 2, 11/17/97; 1, 1/27/98.

I. Introduction

The sponsor has submitted analysis results of the stability data for five lots (of Novastan® 100 mg/mL in amber vials currently undergoing testing) tested after 12 months of storage. Three of the five lots have closures with [redacted] and two have closures with the [redacted] The five lots represent three batches of Novastan® bulk solution. The statistical analysis was performed on the potency data for the five lots to predict lifetime. The sponsor indicated that because the amounts of related substances were less than 0.1% in the 12 months of 25°C [redacted] storage (both upright and inverted conditions), no related substances analysis was performed.

II. *Sample Identification*

Name: Novastan®

[redacted]

Statistical Analysis Methods

Statistical analysis was performed in accordance with FDA/Division of Biometrics Drug Formulation Stability Program using the parameters label claim with an upper bound of 110%, lower bound of 90%, α=.05, and 2-sided confidence interval estimates displayed in months. Because this is a liquid product and has the possibility of evaporation, a 2-sided test is used.

The data were analyzed to test for the poolability across all lots, storage orientation, stopper material and manufacturing batch. Equality of zero-time intercepts (or batch effect) and time-by-batch interaction effects across lots tests were performed using the standard statistical procedures described in the FDA "Guidelines for submitting Documentation for Stability of Human Drugs and Biologics". The level of significance used for each test is .25. A significance level of $p>0.25$ for both the main effect (batch) and interaction effect (time-by-batch) for all lots would suggest the use of a linear regression model based on the pooled slope and zero-time intercept. If $p<0.25$ for batch but $p>0.25$ for time-by-batch interaction effect, then a linear regression model was to be run using the pooled slopes for all of these lots and the zero-time-intercept of the individual lots. If both significance levels for batch and slopes for each lot failed this minimum criterion test (i.e., $p<0.25$), separate linear regression models were to be run. The general linear regression model in either case is $y=ax+b$, where y is the novastan potency, x is the time in months, a is the slop of the regression line and b is the intercept of the regression line.

III. Summary of Results : Sponsor's Analysis Results/Reviewer's Comments

Based on the analysis methods described above, and using the stability SAS data sets submitted by the sponsor (summarized in **Table 1** below), this reviewer's analysis results (which are consistent with those by the sponsor) are summarized in **Tables 2 & 3** below.

Sponsor's analysis results indicate linear regression models with separate intercepts but common slope for each storage position per batch. This reviewer's analyses of the submitted stability SAS data sets did not contradict these findings (see **Tables 2 & 3** below). The fitted lines and the predicted expiry periods for each position summarized in B below are also consistent with those by the sponsor. The corresponding graphical displays, as per this reviewer's analyses of the submitted stability SAS data sets, are provided as attachments. All of these findings are also consistent between stopper material and production.

Table 1/Individual Batch Potency Assay Data at 25° C/60% RH (Lots M020PJ, M021PJ, M295PK, M245PF and M246PF)

TIME	M020PJ_I	M020PJ_U	M021PJ_I	M021PJ_U	M245PF_I	M245PF_U	M246PF_I	M246PF_U	M295PK_I	M295PK_U
0	101.9	101.9	101.6	101.6	99.0	99.0	99.2	99.2	94.2	94.2
0	101.4	101.4	101.3	101.3	98.9	98.9	99.5	99.5	94.7	94.7
0	.	.	.	.	.	.	.	.	95.0	95.0
0	.	.	.	.	.	.	.	.	95.0	95.0
1	100.0	101.4	103.8	99.6	98.9	98.9	97.1	99.5	94.9	94.9
1	100.2	99.9	101.0	99.9	99.3	98.1	99.8	99.7	94.9	94.5
2	100.2	100.8	100.7	101.5	99.6	98.8	99.0	97.2	94.0	94.1
2	100.5	100.8	100.8	100.4	97.2	99.5	99.3	99.6	94.0	93.8
3	100.9	101.0	100.7	101.0	99.8	99.4	98.9	99.8	94.4	95.1
3	101.1	101.1	101.1	101.2	100.2	99.8	98.8	98.7	94.7	94.8
3	.	.	.	.	.	.	99.1	98.4	.	.
3	.	.	.	.	.	.	99.3	99.4	.	.
6	100.8	101.4	101.4	101.1	98.9	99.6	99.1	99.4	94.8	94.9
6	100.9	100.9	101.3	101.0	99.3	99.0	98.8	99.3	94.6	95.1
9	101.9	101.6	101.6	101.8	98.7	97.7	99.4	98.9	95.3	95.3
9	101.7	102.1	101.6	101.5	99.0	99.4	97.3	99.3	95.3	95.1
12	101.3	101.1	100.0	101.3	99.9	98.9	99.8	99.8	94.8	95.1
12	101.3	101.5	101.3	101.3	99.2	99.8	99.5	99.6	96.6	94.8

I=inverted, U=upright (storage position)

Table 2/ Diagnostic Regression Analysis Results

SOURCE	SS	DF	MS	F	P
A	817.08	18	45.39	110.367	0.00000
B	814.07	9	90.45	219.921	0.00000
C	3.01	9	0.33	0.813	0.60497
D	52.65	128	0.41		
E	1449633.61	20	72481.68		

Table 3/Fitted Models and Predicted Dating Period

Batch	Fitted Line: $y=\beta_0 + \beta_1 * x$ β_0 (intercept)	β_1(slope)	Estimated Dating Period (Based on Separate Intercepts, Common Slope)
M020PJ-I	100.847	0.034	48 Months
M020PJ-u	101.047	0.034	48 ✓
M021PJ-I	101.140	0.034	48 ✓
M021PJ-u	100.876	0.034	48 ✓
M245PF-I	98.976	0.034	48 ✓
M245PF-u	98.897	0.034	48 ✓
M246PF-I	98.841	0.034	48 ✓
M246PF-u	99.054	0.034	48 ✓
M295PK-I	94.685	0.034	48 ✓
M295PK-u	94.635	0.034	48 ✓

I=inverted, U=upright (storage position)

Conclusion

Sponsor's analysis results (see Tables 2 and 3 above and attached Figures) indicate a 48-month expiry date. This reviewer's analyses of the submitted SAS data set did not contradict these findings. In this reviewer's assessment, therefore, the stability data submitted by the sponsor support at least a 12-month expiry period.

A. J. Sankoh, Ph. D.
/S/ 3/4/98
Mathematical Statistician

Concur:
Dr. Welch /S/ 3/4/98

cc: Archival NDA # 20-883
HFD - 180
HFD - 180/Drs. Talarico, Sizer, Al-Hakim/Ms DuBeau
HFD - 344/Dr. Barton
HFD - 720/Drs. Welch/Sankoh
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STATISTICAL REVIEW & EVALUATION

Date MAR 10 1998

NDA# 20-883

Applicant: Texas Biotechnology Corporation

Drug Name: Novastan® (Argatroban)

Indication: (i) Treatment of heparin-induced thrombocytopenia and thrombosis syndrome (HITTS)
(ii) Prevention of thrombosis in heparin-induced thrombocytopenia (HIT).

Drug Classification: 1P

Statistical Reviewer: A. J. Sankoh, Ph.D.

Clinical Reviewer: The statistical issues addressed in this review have been discussed with the medical reviewer, K. Sizer, M.D.

Date of Document: August 15, 1997; **Date Received by Reviewer:** September 10, 1997

Filing Date: October 02, 1997; **User Fee Due Date:** February 15, 1998

Volumes Reviewed: 1.1, 2.10, 1.152-1.154, 1.154a, 1.154b: August 15, 1997.

Keywords/Phrases: Baseline imbalance; composite endpoint; confidence intervals; historical control; interim analysis; open-label.

Major Issues/Concerns (see Reviewer's Comments on pages 17-19)

1. The disproportionately higher number of historical control events, 24/36=67% of the total HIT (and 30/59=51% of the total HITTS) patient population from centers that enrolled only 30% of HIT (60% HITTS) historical control patients and no argatroban patients in pivotal study ARG-911.

2. Inconsistency and/or lack of robustness of model-based and/or subgroup analysis (ARG-911) results adjusted for baseline covariate imbalances/ death-predictive factors for the HIT patient population in both the pivotal study ARG-911 and supportive study ARG-915.

3. The high number of reported argatroban deaths from (the interim results of) study ARG-915 (already 26% HITTS in study ARG-915 as of September 1997, 18% HITTS in the completed pivotal study ARG-911, compare to 15% historical control; see Table 13).

I. BACKGROUND

Experiments demonstrating that heparin treatment unexpectedly decreased platelet counts in animals were first reported in the 1940s. Since then, clinical observations have revealed that heparin induced thrombocytopenia (HIT) is a relatively common adverse effect of heparin therapy, occurring in approximately 5-10% of patients who receive this drug. HIT has been reported after administration of all types of unfractionated heparin and low molecular weight heparin (LMWH). However, higher incidences of thrombocytopenia with bovine heparin have been reported compared to porcine heparin. Heparin-dependent antiplatelet antibodies have also been reported in patients undergoing open heart surgery. 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 frequently, death. This sequence of events is referred to as the heparin-induced thrombocytopenia-thrombosis syndrome (HITTS).

Minus the cessation of heparin therapy, removal of the immunoglobulin and immune complexes, or substitution of available alternative anticoagulants, no treatment is currently approved for patients suffering from HITTS; LMWH, [redacted]) and several other drugs ([redacted] have been used with varying success.

[redacted]

This submission consists of a single pivotal study (protocol #ARG-911 submitted to IND [redacted] in support of the safety and efficacy of [redacted] in the treatment of patients with heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), and the prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT). Additional information in the form of historical control is provided for comparison purpose.

II. STUDY DESIGN (ARG 911; conducted from 2/95 to 10/96)

This is an open-label, multi center study, comparing 304 non-randomly assigned Novastan® (144 HITTS and 160 HIT diagnosed) patients to 217 (109 HITTS and 108 HIT diagnosed) historical control patients, respectively, for the safety and effectiveness of Novastan® in the

treatment/prevention of HITTS/HIT.

Patients generally qualified for this study if they were between 18 and 80 years of age and were suspected of having heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), or heparin-induced thrombocytopenia (HIT) with a positive heparin-induced platelet aggregation (HIPA) test in the absence of thrombosis or a history of positive HIPA or serotonin release assay (SRA) laboratory test for HIT or HITTS.

HITTS was defined as:

a. a fall in platelet count to less than 100,000 or 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation other than HITTS, and

b. presence of an arterial or venous thrombosis documented by appropriate imaging technique (duplex doppler ultrasound or angiography) or supported by clinical evidence such as acute myocardial infarction, stroke, pulmonary embolism, or other clinical indications of vascular occlusion (absence of pulse, cold, cyanotic extremities, etc.).

HIT in the absence of thrombosis was defined as:

a. a fall in platelet count to less than 100,000 or 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation other than HITTS, and

b. the absence of clinical arterial or venous thrombosis.

Patients could be enrolled in the absence of a heparin challenge or thrombocytopenia if they had a documented history of a positive laboratory test for HIT/HITTS.

Drug infusion was to be started with a Novastan® infusion of 2 mμ g/min, and an aPTT was to be evaluated 2 hours after the beginning of the infusion. Novastan® dosing was to be adjusted as clinically indicated (aPTT not exceeding 3 times control) and was not to exceed 10 mμ g/min. Patients were to remain in their therapeutic aPTT infusion dose until clinical resolution of their underlying condition, or appropriate anticoagulation was provided with other agents, or treatment had been continued for seven days.

Patient evaluations were to include pre-treatment medical history, physical examinations, lab tests (hematology, chemistry, urinalysis, urine or serum HCG, aPTT, etc.), a 12-lead electrocardiogram (prior to initiation of infusion), HIPA test, arterial and venous duplex doppler of the upper and lower extremities, and V/Q scan (V/Q scan was to be performed on all patients). Evaluations of signs and symptoms of clinical ischemic syndromes were to include

A limb ischemia to determine presence or absence of pain, palpable pulse, pallor, and

neurological function in the affected limb;

B pulmonary embolism to determine presence or absence of shortness of breath, chest X-ray changes, and chest pain;

C venous thrombosis to determine presence or absence of pain, heat in the affected limb, and compare the diameters of the affected and unaffected limbs;

and to determine the presence or absence of acute myocardial infarction, stroke secondary to HITTS, and other arterial thrombosis.

Treatment and post-treatment patient evaluations were to include vital signs, aPTT (at least once daily and 2 hours after each dose), arterial and/or venous duplex doppler, and/or V/Q scans as clinically warranted. A 30-day (±7 days) follow-up visit was also scheduled to assess all thrombi occurring after hospital discharge.

III. SPONSOR'S PLANNED ANALYSES & ANALYSIS METHODS

Study Objectives and Efficacy Endpoints

The primary objectives of the study were to determine the safety and efficacy of Novastan® as:

(i) an anticoagulant in the treatment of HITTS patients,
(ii) a prophylactic anticoagulant for the prevention of thrombosis in patients with HIT.

To insure that at least 300 (150 HIT and 150 HITTS diagnosed) patients received up to seven days of Novastan® infusion, a sufficient number of patients was to be enrolled. All patients with a documented history of positive laboratory test for HIT/HITTS were to be included.

As per protocol sample size estimation, the primary efficacy endpoint for the treatment of HITTS is a composite endpoint defined as the *first occurrence of the incidence of death or amputation due to ischemia*. For the prevention of thrombosis in HIT patients, the primary efficacy endpoint is a composite endpoint defined as the *first occurrence of the incidence of new thrombosis, death or amputation due to ischemia*. Components of the composite endpoints (death, amputation, and the development of new thrombosis occurring during treatment with Novastan®) are specified as secondary endpoints.

Calculations for sample size determinations for both the HIT and HITTS populations (see below) appeared to be based on these two protocol-defined primary-endpoints. However, the study summary report contained in volume 152, page 65, seemed to suggest that the primary analyses for both the HIT and HITTS patient populations were based on the following primary composite endpoints:

(1) *first occurrence of the incidence of all-cause mortality, all-cause amputation, and the*

development of a new thrombosis,

(2) *the first occurrence of the development of new thrombosis, mortality due to thrombosis, and amputation due to ischemia.*

In response to this reviewer's request for clarification on whether there was a protocol amendment that led to the above indicated changes/modifications in the primary endpoint, the sponsor (on 12/16/97) responded that both the overall composite and the thrombotic composite endpoints were compiled in the same manner. This reviewer's understanding of the sponsor's response is that the two are essentially the same because each is comprised of the same components of ischemic death, amputation and new thrombosis; efficacy assessment in this review will therefore be limited to the broader primary composite endpointm of the *first occurrence of the incidence of all-cause mortality, all-cause amputation, and the development of a new thrombosis.*

Sample Size Determination

To detect a treatment difference of magnitude 30% to 40% in the incidence of death or amputation for the treatment of HITTS, and death, amputation, or the development of a new thrombosis for the prevention of HIT with a two-sided 90% powered test, a sample size of at least 150 Novastan and 50 historical control patients were to be enrolled.

Sponsor's Analysis Methods

The prospective study data were to be compared to an historical control group collected from centers participating in the study. Data from patients diagnosed with HITTS or HIT after January 1, 1993 (later amended to January 1985 due to relative scarcity of HITTS patients) were to be screened using the inclusion/exclusion criteria of the prospective study. Pediatric (due to minimum age requirement) and oncology (because of anticipated high likelihood of thrombocytopenia due to underlying conditions or concomitant chemotherapy) patients were generally not to be included in the historical control group.

It should, however, be noted that sponsor's Table 10, page 95 of Vol. 152 indicates that a total of 108 (44 HIT and 64 HITTS) patients with a medical history of oncology/hematology were included in the historical control group (see Table 3 below). It should further be noted that even though the protocol indicated that no more than 25% of the total number of historical control cases were to come from any one site, Dr. Warkentin, whose site enrolled no Novastan patient contributed about 45% of the historical control patient population.

The impact of these historical control patients on the observed overall efficacy results will be addressed in the comments section of this review.

The protocol indicated that the primary comparisons between the treated and control groups were to be based on the differences between the two groups using a *one-sample normal approximation for differences in proportions*. Logistic regression models were also to be used to adjust for any known baseline covariate imbalances or imbalance for predictive risk factors

such as age, gender, use of intravenous heparin administration, etc. The protocol also stipulated that only patients with documented positive heparin-induced platelet aggregation (HIPA) test by the central HIPA testing laboratory, or patients entered into the study with a documentation of a positive HIPA test by history (within the last 12 months) were to be included in the efficacy analyses for both the HIT and HITTS patient populations respectively.

For the evaluation of incidence rate for the composite endpoint over the entire study period (≤ 14 infusion days + 30 follow-up days), age, sex, mean argatroban dose over the length of infusion, renal impairment, hepatic impairment, usage of the 3 most commonly taken concomitant medications, medical history, body weight, use of cardiac assist, need for dialysis, ventilation and previous CABG (see **Tables 2-4** below) were to be used (if so indicated) as covariates in the regression model. The one-sample normalization test and model based analyses were to be done separately for each endpoint for the HIT and HITTS patient populations.

The incidences of death, amputation and new thrombosis during therapy were to be assessed and compared with a historical control group; treatment effectiveness was to be declared if the observed treatment difference in favor of Novastan® attained a statistical significance of .05 or less.

Baseline Characteristics Comparisons

Table 1 below summarizes patient disposition between the two groups for the ITT, evaluable and SRA positive data sets. The sponsor's analysis results summarized in **Table 2** below indicate the two groups (i.e., AG-911 and historical control) were comparable with respect to weight, gender, race, and time to initial infusion. However, the historical control group of patients were significantly older than those for argatroban (2-sided p-value=.025 for the HIT and .053 for the HITTS).

Table 1/Patient Disposition Per Disease & Data Set Category

	Argatroban			HISTORICAL		
	HIT	HITTS	Total	HIT	HITTS	Total
Enrolled/ITT	160	144	304	108	109	217
Evaluable	146	134	280	108	109	217
SRA Positive	70	86	156	35	72	107

A comparison of prior medication use (by anatomical/ therapeutic/ chemical (ACT) classification) within two weeks of study admission by this reviewer also indicates significant differences (all against argatroban) at least for the medications or class of medications listed in **Table 3** below.

Prior heparin exposure was comparable between the two groups (99% in the historical control versus 87% in the argatroban group for the HIT, and 100% in the historical control versus 97 in the argatroban group for the HITTS patient population, respectively).

Table 2/Comparison of Baseline Characteristics For ITT Patient Population* (From Sponsor Tables 5,6 & 8, Vol 152)

ITT Data Set/ Treatment	HIT		HITTS	
	Historical	Argatroban	Historical	Argatroban
Age (Yrs): Mean±SE	65±11	61±14	65±10	62±13
	2-sided p=.025 against Historical		2-sided p=.053 against Historical	
Gender (M/F %)	50/50	43/57	51/49	50/50
Race (Caucasian)	92%	89%	94%	85%
Weight: Mean±SE	79±24	79±19	84±20	83±21
Mean Dose (μg/kg/min)	-	2.0±0.1	-	1.9±0.1
Infusion Duration (Days)	-	5.3±0.3	-	5.9±0.2
Time From Heparin Discontinuation To Initial Infusion or Follow-up (days)	1.0 (3.7)	1.0 (1.7)	0.5 (1.9)	3.1 (4.6)
Median Platelet Count ($\times 10^3$): Baseline	84.00	82.00	72.00	65.50
% of Prior Heparin Exposure#	99%	87%	100%	97%

*: Significant differences at the .05 level are indicated by p-values; #: 6 Weeks Prior to Infusion.

Table 3/ Some Prior Medication Use With Significant Imbalance Between Groups For ITT Population *[Data From sponsor Table 12 Vol 152]*

	HIT		HITTS	
ATC Classification	Historical	Argatroban	Historical	Argatroban
1. Antithrombotic Agents	28%	58% (Fisher's 2p<.0001)	23%	60% (2p<.0001)
2. Psycholeptic	54%	56%	49%	57% (2p=.0003)
3. Cardiac Therapy	51%	54%	33%	60% (2p<.0001)
4. Diuretics	30%	46% (2p=.008)	27%	53% (2p<.0001)

2p=2-sided p-value.

Table 4/Comparison of Pre-treatment Medical History From ICD-Coded Term

	HIT		HITTS	
Medical History	Historical	Argatroban	Historical	Argatroban
1. Cardiovascular	94%	100% (Fisher's 2p=.007)	99%	99% (2p=1.00)
2. Oncology/Hematol	41%	75% (2p<.001)	64%	74% (2p=.010)
3. Diabetes/Endocrine	48%	68% (2p=.002)	49%	72% (2p<.001)
4. Genito-Urinary	57%	71% (2p=.026)	45%	64% (2p=.003)
5. Respiratory	57%	66% (2p=.156)	50%	70% (2p=.001)
6. Injury/Poisoning	43%	44% (2p=.900)	34%	54% (2p=.001)
7. Dermatology	19%	30% (2p=.045)	11%	22% (2p=.029)
8. Miscellaneous	77%	88% (2p=.030)	80%	83% (2p=.512)
9. Cancer*	9%	18% (2p=.052)	16%	17% (2p=.736)
10. Renal Impairment*	11%	29% (2p=.003)	6%	26% (2p<.001)
11. Hepatic Impairment	5%	9% (2p=.164)	1%	10% (2p=.001)
12. Sepsis*	6%	12% (2p=.090)	3%	12% (2p=.009)
13. Previous CABG	36%	29% (2p=.229)	24%	49% (2p<.001)
Ongoing Procedures With Significant Imbalance				
15. Hemodialysis*	4%	14% (2p=.006)	1%	7% (2p=.026)
16. CAD*	7%	12% (2p=.206)	2%	13% (2p=.001)
17. Ventilation*	12%	6% (2p=.071)	8%	8% (2p=1.00)

CAD=Circulatory Assist Device. Information extracted from sponsor's Tables 10 & 11 Vol 152; Hematol=Hematology; *: indicates covariates in regression/Cox proportional hazard models (see Table 7 below); 2p=2-sided p-value..

Furthermore, sponsor's analysis results also indicate statistically significant baseline characteristics imbalance for the medical/surgical/invasive procedures summarized in **Table 4** above (all p-values indicate imbalance against argatroban).

The protocol specified that patients were to remain on argatroban infusion until clinical resolution of their underlying condition, or appropriate anticoagulation was provided from other agents, or until treatment was continued for up to 14 days (maximum infusion time). According to sponsor's Table 3 of Vol. 152, 87% (139/160) of HIT and 94% (135/144) of HITTS argatroban treated patients were in compliance with one or more of these criteria:

	Maximum Infusion Time	Clinical Resolution	Transferred To Warfarin
HIT	20 (13%)	18 (11%)	100 (63%)
HITTS	34 (24%)	10 (7%)	102 (71%)

About 21 (13%) HIT and 9 (6%) HITTS argatroban patients were classified as premature discontinuation.

Note that baseline characteristic patterns in the sponsor defined and analyzed evaluable and SRA data sets are similar to those in the ITT data set discussed above. This review will not therefore repeat these descriptions for the evaluable and SRA data sets.

Interim Analyses

Interim analyses were planned at approximately 33%, 66% and 100% of the expected patient enrollment. To ensure an overall type I error rate of .05 (2-sided), symmetric O'Brien-Fleming type group sequential boundaries generated by the Lan-DeMets alpha spending function for normal approximation test at critical levels of ± 3.50 ($\alpha = .0004$), ± 2.53 ($\alpha = .011$) and ± 1.99 ($\alpha = .047$) for the first, second and third interim analyses were specified.

The NDA report on page 79 of volume 152 indicates that the Data Safety Monitoring Committee (DSMC) met on three occasions (12/95, 3/96 and 9/96) and efficacy and safety interim results were presented and discussed at all three meetings. Even though Interim analysis results were presented and discussed on all three occasions, the report indicates *no formal hypothesis testings were actually carried out*. Furthermore, the report indicates that historical control data were not available for the first two meetings. It should also be pointed out that SAS outputs contained in volume 153 suggest that the final analyses were performed on July 24, 1997, about 12 months after the last DSMC meeting.

In response to this reviewer's request for further clarification on the number and nature of any interim analyses conducted on the accumulating efficacy data, the sponsor reiterated (12/16/97) that while the data were examined on three different occasions (for safety monitoring only) by the DSMC, *no formal hypothesis testing were carried out at any of these occasions*; that the July 24, 1997 statistical analyses were the only formal comparative analyses of the efficacy data.

It should be noted that both the original NDA and the 12/16/97 submissions did not include the outputs of these *informal interim looks*, and/or the minutes DSMC deliberations. This reviewer cannot, therefore, ascertain the informal/formal nature of these interim looks.

IV. SUMMARY OF SPONSOR'S EFFICACY ANALYSIS RESULTS

Primary Efficacy Analysis Results

Tables 5a below summarizes the sponsor's primary efficacy analysis results for the entire study period, infusion (i.e., ≤ 14 days) and 30-Day follow-up period for the primary composite endpoint; 95% CI estimates are by the one-sample exact binomial for within treatment group proportions, and by asymptotic normality for differences in proportions (N-H)/odds ratios.

Table 5a/ Analysis Results of the Composite Endpoint: Incidence of Death/Amputation/Thrombosis *(Data from sponsor Tables 15/16, Vol 152)*

Treatment Period/ Treatment Group	HIT Patient Population			HITTS Patient Population		
	Novastan (N)	Historical (H)	N-H [OR]; 2p-val	Novastan (N)	Historical (H)	N-H [OR]; 2p-val
Entire Study Period	43/160 (27%)	36/108 (33%)	-6%; [.74]; .260	62/144 (43%)	59/109 (54%)	-11%; [.64]; .080
95% CI:	(20, 34)*	(25, 43)*	(-18, 5);[.43, 1.3]	(35, 52)*	(44, 64)*	(-23,13);[.39,1.06]
Infusion: ≤14 Days	8/160 (5%)	28/108 (26%)	-21%; [.15]; <.001	30/144 (21%)	47/109 (43%)	-22% ;[.34]; <.001
95% CI:	(2, 10)*	(18, 35)*	(-30 -12); [.07,.35]	(15, 28)*	(34, 53)*	(-34, -11);[.20,.60]
>14 Days Period	35/160 (22%)	8/108 (7%)	15%; [3.5]; =.003ª	38/144 (26%)	12/109 (11%)	15%; [2.9]; =.003ª
95% CI:	(16, 29)*	(3, 14)*	(6, 23); [1.6, 7.9]	(19, 34)*	(6, 18)*	(6, 25); [.14, 5.9]

Note: OR < 1 or -ve (N-H)% favors Novastan; a: indicates strength of evidence in favor of historical control; *: 95% CI based on exact 1-sample binomial test (by this reviewer)..

Table 5b below summaries sponsor's primary analysis results for the secondary efficacy endpoints for the infusion (≤14 days) and for the entire study period (infusion+30-Day). Note that 95% CI estimates for within treatment group proportions are by the one-sample exact method, while those for differences in proportions (N-H), and/or odds ratios (OR) are by asymptotic normality of the difference in proportions/ORs.

Table 5b/ Analysis Results For Components of the Composite Endpoint [Death, Amputation, and new thrombi]

Endpoints/ Treatment Group	HIT Patient Population			HITTS Patient Population		
	Novastan (N)	Historical (H)	N-H [OR]; 2p-val	Novastan (N)	Historical (H)	N-H [OR]; 2p-val
Infusion: ≤14 Days						
New Thrombi	3/160 (2%)	21/108 (19%)	-18%; [.08]; <.001	16/144 (11%)	41/109 (38%)	-27%; [.21]; <001
95% CI:	(0, 5)*	(12, 28)*	(-25, -10);[.02, .27]	(6, 17)*	(29, 47)*	(-37,-16);[.11,.40]
Any Amputation	1/160 (.6%)	4/108 (4%)	-3%; [.16]; =.109	8/144 (6%)	9/109 (8%)	-3%; [.65];= .406
95% CI:	(0, 3)*	(1, 9)*	(-7, 0);[.02, 1.48]	(2, 11)*	(4, 15)*	(-9, 4);[.24, 1.8]
Any Death	4/160 (3%)	8/108 (7%)	-5%; [.32]; =.080	7/144 (5%)	12/109 (11%)	-6%; [.41];=.078
95% CI:	(0, 6)*	(3, 14)*	(-10, .01);[.09, 1.1]	(2, 10)*	(6, 18)*	(-13,.01);[.16,1.1]
Entire Study Period						
New Thrombi	10/160 (6%)	25/108 (23%)	-17%; [.22]; <.001	27/144 (19%)	45/109 (41%)	-23%; [.33]; <.001
95% CI:	(3, 11)*	(16, 32)*	(-26,-8);[.10, .48]	(13, 26)*	(32, 51)*	(-34, -11);[.19,.58]
Any Amputation	4/160 (3%)	4/108 (4%)	-1%; [.67]; .584	18/144 (13%)	13/109 (12%)	1%; [1.06]; .890
95% CI:	(0, 6)*	(1, 9)*	(-9, 5);[.12, 3.7]	(8, 20)*	(7, 20)*	(-8, 9);[.49, 2.26]
Any Death	29/160 (18%)	12/108 (11%)	7%; [1.8]; .102	26/144 (18%)	16/109 (15%)	3%; [1.28]; .496
95% CI:	(12, 25)*	(6, 19)*	(-1, 15);[.86, 3.6]	(12, 25)*	(9, 23)*	(-6, 13);[.7, 2.53]

Data from sponsor Tables 15 &16, pages 107 & 108 of Volume 152; *: 95% CI based on exact 1-sample binomial test (by this reviewer).

Secondary/Supportive Efficacy Analysis Results

To investigate the impact of the observed significant baseline characteristic imbalances (indicated in **Tables 3** and **4** above) on the composite endpoint in general, and the 'all-cause mortality' component of the composite endpoint in particular, the influence of protocol-specified covariates was evaluated by the sponsor using logistic regression and Cox proportional hazard models. Except for *diabetes, lupus erythematosus* and *previous CABG surgery* baseline characteristic factors, sponsor's analysis results summarized in **Table 6** below indicate significant influence on the all-cause mortality endpoint by all baseline characteristic/ risk factors investigated.

Table 6/ Logistic Regression & Cox Proportional Hazards Model Results: Baseline Effect On 'All-Cause Death'

	Logistic Model			Cox Proportional Model		
Medical History	P-value	OR	95% CI	P-value	OR	95% CI
1. Cancer	0.029	1.90	(1.05, 3.32)	0.031	1.74	(1.05, 2.89)
2. Renal Impairment	<0.001	4.56	(2.68, 7.75)	<0.001	3.90	(2.46, 6.16)
3. Hepatic Impairment	0.082	2.00	(0.88, 4.26)	0.102	1.75	(0.90, 3.43)
4. Diabetes	0.664	1.12	(0.66, 1.85))	0.661	1.11	(0.70, 1.77)
5. Sepsis	0.028	2.20	(1.06, 4.36)	0.026	1.99	(1.09, 3.63)
6. Lupus Erythematosus	0.966	1.03	(0.23, 3.27)	0.995	1.00	(0.32, 3.20)
7. Respiratory Distress	<0.001	3.09	(1.80, 5.23)	<0.001	2.71	(1.72, 4.28)
8. Receiving Hemodialysis	0.001	3.54	(1.67, 7.32)	<0.001	3.00	(1.65, 5.45)
9. Cardiac Assist Device	0.043	2.50	(0.99, 4.04)	0.023	2.01	(1.01, 3.67)
10. Undergoing Ventilation	0.005	1.02	(0.29, 1.72)	0.003	2.44	(1.34, 4.43)
11. Previous CABG	0.945	1.02	(0.62, 1.66)	0.924	1.02	(0.65, 1.61)

Information extracted from sponsor Table 14, Vol 152.

In an attempt to adjust observed treatment effect on all cause-mortality for any imbalance that is due to the above observed significant baseline characteristics/risk factors, sponsor's (covariate secondary) efficacy analyses for the 'all-cause mortality' and 'overall composite endpoint' were carried out with adjustment for differences between the argatroban and historical control groups for the seven covariates with p-values$\leq$.05 in **Table 6** above. **Table 7** below summaries sponsor's logistic regression and Cox hazard model analysis results (for the ITT population) adjusted for these seven covariates (model|7), and for three of these seven covariates identified (by a step-wise regression model) as the most influential predictors of all-cause death and/or the overall composite endpoint.

Note that for the HIT patient population, while the results for the overall composite endpoint suggest robust covariates effects (*the logistic regression and Cox proportional hazard model results indicate similar argatroban effectiveness strength direction-wise, even though the logistic regression results are at best borderline*), the results for the all-cause mortality endpoint are somewhat inconsistent. For the HITTS patient population, however, the covariate analysis results show a significant consistent covariate effect for the overall composite endpoint, and a robust positive (even though not significant) effect on the all-cause mortality endpoint.

Table 7/ Sponsor's Logistic Regression/Cox Proportional Hazard Model Analysis Results

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

Data from sponsor Appendix 16.1.9.3.4 of Volumes 154 & 154a; |None: indicates model results unadjusted for covariate imbalance;
|3: model results adjusted for cancer, renal impairment (Renal) & respiratory distress syndrome (RDS) ;
|7: model results adjusted for imbalances in cancer, renal, RDS, sepsis, Cardiac assist device, ventilation, and dialysis (see Table 6 above).

Other Primary Efficacy Analysis Results

Table 8 below summarizes the sponsor's other analysis results based on the thrombotic composite endpoint (first occurrence of death, amputation due to ischemia, and new thrombi) for the entire study period, and for the infusion period. Note that for the HIT patient population, the protocol specified primary endpoint was the overall composite endpoint. [That is, sample size calculations for the trial for the HIT patient population was based on the overall composite endpoint.]

Table 8/ Analysis Results For the Thrombotic Composite Endpoint *[Data from sponsor Tables 15/16, Vol 152]*

Study Period/ Treatment Group	HIT Patient Population			HITTS Patient Population		
	Novastan (N)	Historical (H)	N-H [OR]; 2p-val	Novastan (N)	Historical (H)	N-H [OR]; 2p-val
Entire Study Period 95% CI:	11/160 (7%) (3, 12)*	28/108 (26%) (18, 35)*	-19%; [.21]; <.001 (-28,-10);[.10, .45]	40/144 (28%) (21, 36)*	54/109 (50%) (40, 59)*	-22%; [.39]; =.004 (-34,-10);[.23,.66]
Infusion Period 95% CI:	4/160 (3%) (2, 10)*	24/108 (22%) (15, 31)*	-20%; [.09]; <.001 (-28 -12); [.03,.27]	24/144 (17%) (11, 24)*	50/109 (46%) (36, 56)*	-29% ;[.24]; <.001 (-40, -18);[.13,.42]

*: 95% CI based on exact 1-sample binomial test (by this reviewer).

Tables 9a-9c below summarize efficacy analysis results (by this reviewer) for some selected subgroups for the overall composite endpoint (**Table 9a & 9b**) and for the all-cause mortality endpoint (**Table 9c**). Note that since the majority of centers/investigators enrolled less than three patients, a by center summary of the results is not meaningful. Instead, the review is focused on the comparison of event rates in the 4 largest centers [*(# 020, 059, 060, and 113)*, out of a total of 103 centers] that enrolled a total of 10 or more patients versus event rates in the 3 centers *(# 200, 201 and 202)* that enrolled no argatroban patients, versus event rates in the remaining 96 sites that enrolled a total three or fewer patients (see **Table 9a** below).

Table 9a/Comparison of Results Between Seven Sites Vs Rest For Composite Endpoint (Data From Submitted SAS Data Set, Disk #7)

# of Sites; Patients Per Site	HIT Patient Population			HITTS Patient Population		
	Novastan (N)	Historical (H)	N-H; 2p; 95% CI	Novastan (N)	Historical (H)	N-H; 2p; 95% CI
3 Sites; 0 Novas Pt	0/0 (0%)	24/32 (75%)	-75%	0/0 (0%)	30/65 (46%)	-46%
4 Sites; >10/Site	5/36 (14%)	4/45 (9%)	+5%;.485;(-9, 19)	9/33 (27%)	11/16 (69%)	-42%; .003;(-69,-14)
96 Sites; <10/Site	38/124 (31%)	8/31 (26%)	5%; .586;(-13,22)	53/111 (48%)	18/28 (64%)	-16%; .106 (-37, 3)

Table 9b/Comparison of Results Across Selected Subgroups For Composite Endpoint (Data From Submitted SAS Data Set, Disk #7)

Subgroup/ Treatment Group		HIT Patient Population			HITTS Patient Population		
		Novas (N)	Histo (H)	N-H; 2p-val; 95% CI	Novas (N)	Histo (H)	N-H; 2p-val; 95% CI
Sex:	Male	16/68 (24%)	15/54 (28%)	-4%; .594; (-20, 11)	27/72 (38%)	31/56 (55%)	-18%; .041; (-35, -.01)
	Femal	27/92 (29%)	21/54 (39%)	-10%;.242; (-26, 6)	35/72 (49%)	28/53 (53%)	-4%; .641; (-22, 14)
Age:	≤65yrs	21/81 (26%)	16/43 (37%)	-11%; .202; (-29, 6)	27/74 (36%)	26/44 (59%)	-23%; .015; (-41, -4)
	>65✓	22/79 (28%)	20/65 (31%)	-3%; .702; (-18,.12]	35/70 (50%)	33/65 (51%)	-1%; .929; (-18, 16)
Cancer:	NO	34/131 (26%)	30/98 (31%)	-5%; .440; (-16, 7)	49/119 (41%)	51/92 (55%)	-14%; .038; (-28,-.01)
	Yes	9/29 (31%)	6/10 (60%)	-29%; .102; (-64, 6)	13/25 (52%)	8/17 (47%)	+5%; .753; (-26, 36)
RDS:	NO	29/131 (22%)	24/89 (27%)	-5%; .416; (-16, 7)	47/115 (41%)	53/97 (54%)	-14%; .044; (-27, -.01)
	Yes	14/29 (48%)	12/19 (63%)	-15%; .303; (-43, 13)	15/29 (52%)	6/12 (50%)	+2%; .920; (-32, 35)
Renal:	NO	24/114 (21%)	32/94 (34%)	-13%; .036;(-25,-.01)	43/107 (40%)	53/103 (51%)	-11%; .099; (-25, 2)
	Yes	19/46 (41%)	4/14 (29%)	+13%; .366;(-15, 40)	19/37 (51%)	6/6 (100%)	-49%; .027; (-75, -6)
CAD:	NO	38/141 (27%)	33/101 (33%)	-6%; .338;(-17, 6)	50/125 (40%)	58/107 (54%)	-14%; .029; (-27, -1)
	Yes	5/19 (26%)	3/7 (43%)	-16; .437; (-58, 25)	12/19 (63%)	½ (50%)	+13%; .723; (-59, 86)
CABG:	NO	38/114 (33%)	29/69 (42%)	-9%; .240; (-23, 6)	33/73 (45%)	45/83 (54%)	-9%; .259; (-25, 7)
	Yes	10/46 (22%)	7/39 (18%)	+4%; .661; (-13, 21)	29/71 (41%)	14/26 (54%)	-13%; .254; (-35, 9)
Ventila:	NO	40/151 (26%)	27/95 (28%)	-2%; .742; (-13, 10)	55/133 (41%)	55/100 (55%)	-14%; .037;(-27, -.01)
	Yes	3/9 (33%)	9/13 (69%)	-34%; .116; (-74, 9)	7/11 (64%)	4/9 (44%)	+19%; .457; (-27, 65)

Note: +ve (N-H) difference indicates at least an historical control group numerical advantage; CAD=Cardiac Assist Device; RDS= Respiratory Distress Syndrome; ventila=ventilation.

Table 9c/Comparison of Results Across Selected Subgroups For All-Cause Mortality *(Data From Submitted SAS Data Set, Disk #7)*

Subgroup/ Treatment Group		HIT Patient Population			HITTS Patient Population		
		Novas (N)	Histo (H)	N-H; 2p-val; 95% CI	Novas (N)	Histo (H)	N-H; 2p-val; 95% CI
Sex:	Male	11/68 (16%)	5/54 (9%)	+7%; .246; (-5, 19)	14/72 (19%)	11/56 (20%)	-00%; .978; (-14, 14)
	Femal	18/92 (20%)	7/54 (13%)	+7%;.284; (-5, 19)	12/72 (17%)	5/53 (9%)	+7%; .2241; (-4, 19)
Age:	≤65yrs	12/81 (15%)	5/43 (12%)	+3%; .612; (-9, 16)	10/74 (14%)	4/44 (9%)	+4%; .452; (-7, 16)
	>65✓	17/79 (22%)	7/65 (11%)	+10%; .074;(-1,.23)	16/70 (23%)	12/65 (18%)	+4%; .527; (-9, 18)
Cancer:	NO	22/131 (17%)	8/98 (8%)	+9%; .044; (0, 17)	19/119 (16%)	14/92 (15%)	+7%; .882; (-9, -11)
	Yes	7/29 (24%)	4/10 (40%)	-16%; .362; (-50, 18)	7/25 (18%)	2/17 (12%)	+6%; .319; (-15, 47)
RDS:	NO	18/131 (14%)	7/89 (8%)	+6%; .156; (-2, 14	18/115 (16%)	12/97 (12%)	+3%; .472; (-6, 13)
	Yes	11/29 (38%)	5/19 (26%)	+12%; .432; (-17,43)	8/29 (28%)	4/12 (33%)	-6%; .759; (-45, 27)
Renal:	NO	13/114 (11%)	10/94 (11%)	+.8%; .861;(-78, 9)	12/107 (11%)	11/103 (11%)	+.5%; .901; (-8, 9)
	Yes	16/46 (35%)	2/14 (14%)	+21%; .188;(-10, 47)	14/37 (38%)	5/6 (83%)	-46%; .047; (-83, -.01)
CAD:	NO	24/141 (17%)	11/101 (11%)	+6%; .116; (-3, 15)	19/125 (15%)	16/107 (15%)	+.2%; .958; (-9, -9)
	Yes	5/19 (26%)	1/7 (14%)	+12%; .632; (-32,53)	7/19 (37%)	0/2 (0%)	+37%; .508; (-44, 74)
CABG:	NO	21/114 (18%)	9/69 (13%)	+5%; .323; (-5, 16)	11/73 (15%)	12/83 (15%)	+.6%; .915; (-11, 12)
	Yes	8/46 (17%)	3/39 (8%)	+10%; .344; (-9, 30)	15/71 (21%)	4/26 (15%)	+6%; .600; (-16, 26)
Ventila:	NO	26/151 (17%)	9/95 (9%)	+8%; .072; (-.7, 11)	21/133 (16%)	14/100 (14%)	+2%; .703; (-7, 11)
	Yes	3/9 (33%)	3/13 (23%)	+10%; .662;(-31.5 9)	5/11 (45%)	2/9 (22%)	+23%; .327 (-22, 68)

Note: +ve (N-H) difference indicates at least an historical control group numerical advantage; CAD=Cardiac Assist Device; RDS= Respiratory Distress Syndrome.

To further investigate the impact of the imbalance in pre-existing conditions on treatment effect, **Table 9b** and **9c** above summarize this reviewer's subgroup analysis results for some selected subgroups (identified as predictive of death by sponsor's analyses; see **Table 6** above)

for the overall composite endpoint (**Table 9b**) and the all-cause mortality (**Table 9c**) endpoint. The results of these subgroup analyses failed to unequivocally confirm the sponsor's suspicion that argatroban's unimpressive performance (especially for the HIT patient population) was due to the presence of more of these pre-existing conditions in the argatroban group.

SUMMARY OF SAFETY EVENTS

Bleeding and other adverse events were reported during the study course. A Bleed was described as major if it was overt and (1) was associated with a decrease in hemoglobin of ≥2 g/dL, and (2) led to a transfusion of ≥ 2 units, or (3) was intracranial, retroperitoneal, or occurred into a major prosthetic joint. Bleeds that did not required more than 2 units of blood were described as minor. Bleeding and other adverse events experienced by ≥5% of patients are summarized in **Table 10** below.

Overall, there were significantly more bleeding incidences in the argatroban than in the historical control group for both the HIT and HITTS patient populations (Fisher's exact 2-sided p-value <.001). The majority of these bleeding incidences were described as minor; there was no significant difference in major bleeding events between argatroban and the historical control group (see top rows in Table 10 below). A total of 125/160 (78%) argatroban vs 49/108 (45%) historical control HIT patients experienced at least one adverse event [AEs, (Fisher's 2-sided p-value <.001)]. For the HITTS patient population, a total of 123/144 (85%) argatroban vs 72/109 historical control patients reported at least one AE (2-sided Fisher's exact p-value <.001). Of the 125 HIT and 123 HITTS patients with at least one AE, 29 (23%) HIT and 39 (32%) HITTS described their AEs as possibly, or probably or definitely drug related.

Table 10/ Summary of Bleeding and Other Adverse Events For The Entire Study Period [*Data From Sponsor Tables 41-43, 47, Vol 152*]

	Centers	HIT			HITTS		
		Novas	Hist	Fisher Exact 2p	Novas	Hist	Fisher's Exact 2p
Bleeds:	All Bleeds	69/160 (43%)	20/108 (19%)	<.001	75/144 (52%)	28/109 (26%)	<.001
	Minor Bleeds	64/160 (40%)	13/108 (12%)	<.001	60/144 (42%)	18/109 (17%)	<.001
	Major Bleeds	5/160 (3%)	7/108 (7%)	.234	15/144 (10%)	10/109 (9%)	.833
AEs on ≥5% of Patients	Total Body System	125/160 (78%)	49/108 (45%	<.001	123/144 (85%)	72/109 (66%)	<.001
	GISD	7/160 (4%)	2/108 (2%)*		8/144 (6%)	4/109 (4%)	
	VED	3/160 (2%)	7/108 (6%)		9/144 (6%)	2/109 (2%)	
	PBCD	12/160 (8%)	4/108 (4%)		9/144 (6)	7/109 (6%)	

GISD=Gastro-Intestinal System Disorders; VED=Vascular Extra cardiac Disorders PBCD=Platelet, Bleeding & Clotting Disorders.
*: Includes GISD events related to vomiting only.

A total of 3 (2 HIT and 1 HITTS) drug related deaths were reported (as per database EffDATA.SD2 submitted by the sponsor).

V. SUMMARY of ADDITIONAL SAFETY & EFFICACY RESULTS (Submitted 2/6/98)

This section summarizes interim analysis efficacy information (from study #ARG-915) submitted by the sponsor (2/6/98) in support of the safety and efficacy results of pivotal study ARG-911. As in study ARG-911, study ARG-915 was designed as an open-label, non-randomized, multi-center, historical control study in the treatment of HITTS and prevention of thrombosis in HIT. The same historical control set of patients used in study ARG-911 (108 HIT and 109 HITTS) is used to compare and contrast the performance of argatroban in the

treatment of HITTS (89 patients) and in the prevention of thrombosis in HIT (85 patients) in this current supportive study. These interim analysis results are based on 174 (about 69%) of the proposed patient enrollment.

The primary and secondary objectives, endpoints and protocol specified analyses for this study (ARG-915) are the same as described for study ARG-911. This reviewer will, therefore, not reproduce these descriptions.

To facilitate between studies comparative assessment, side-by-side summaries of both studies' analysis results will be provided where possible. **Tables 10 & 11** below provide a comparative summary of patient disposition and baseline characteristics of the argatroban treated patients in the prospective studies, ARG-911 and ARG-915 (as per interim analysis results based on 174 of planned patient enrollment), and the historical control group of patients. Sponsor's interim patient baseline characteristic information for study ARG-915, summarized in **Table 11** below, indicate no significant imbalance between argatroban treated patients and the historical control group of patients regarding race, age, gender, and weight.

Table 10/ ITT Patient Disposition Per Disease & Data Set Category

Treatment/ Study	ARG-911			ARG-915			Pooled: ARG-911 + 915		
	HIT	HITTS	Total	HIT	HITTS	Total	HIT	HITTS	Total
Argatroban	160	144	304	85	89	174	245	233	478
Historical	108	109	217	108	109	217	108	109	217

Table 11/Comparison of Baseline Characteristics For ITT Patient Population*

ITT Data Set/ Treatment		ARG-911		ARG-915	
		HIT	HITTS	HIT	HITTS
Age (Yrs): Mean±SD:	Novastan	61±14	62±13	64±13	65±14
	Historical	65±11	65±10	65±11	65±10
	2-Sided p-value	0.025	0.053	0.441	0.896
Gender (M/F %):	Novastan	43/57	50/50	51/49	46/54
	Historical	50/50	51/49	50/50	51/49
Race (Caucasian):	Novastan	89%	85%	91%	90%
	Historical	92%	94%	92%	94%
Weight: Mean±SD:	Novastan	79±19	83±21	75±18	83±22
	Historical	79±24	84±20	79±24	84±20
Mean (±SE) Dose (μg/kg/min):	Novastan	2.0±0.1	1.9±0.1	1.9±0.1	2.5±0.7
Infusion Duration (Days)	Novastan	5.3±0.3	5.9±0.2	4.9±0.4	7.3±0.8
Time From Heparin D/C to first:	Novastan	1.0±1.7	3.1±4.6	0.5 (1.9)	2.4±0.5
Novastan Infusion/ Follow-up (days):	Historical	1.0±3.7	0.5±1.9	1.0±3.7	0.5±1.9
Median Platelet Count ($\times 10^3$), Baseline:	Novastan	82.00	65.50	-	
	Historical	84.00	72.00		
% of Prior Heparin Exposure#	Novastan	87%	97%		
	Historical	99%	100%		

*: Significant differences at the .05 level are indicated by p-values; #: 6 Weeks Prior to Infusion;
(Data extracted from sponsor Tables 5,6 & 8, Vol 152 (study ARG-911, Tables 4, 5, Vol 4.10a)

A comparison of baseline characteristics regarding medical/surgical/invasive procedures also indicate that, compared with study ARG-911, the patient population (as per interim patient

information) in study ARG-915 are more evenly matched with the historical control group (see **Table 4** above for the different medical history cases).

Table 12/Comparison of Pre-treatment Medical History From ICD-Coded Term ***(From Sponsor Tables 6 & 8 for ARG-915)***

Medical History	ARG-911						ARG-915					
	HIT		HITTS		2-Sided p-val		HIT		HITTS		2-Sided p-val	
	Novas	Hist	Novas	Histo	HIT	HITTS	Novas	Histo	Novas	Histo	HIT	HITTS
Cardiovascular	100%	94%	99%	99%	.007	1.000	100%	94%	98%	99%	.035	.587
Diabetes/Endocrin	68%	48%	72%	49%	.002	<.001	59%	48%	72%	49%	.149	.001
Injury/Poisoning	44%	43%	54%	34%	.900	.001	26%	43%	32%	34%	.022	.763
Cancer*	18%	9%	17%	16%	.052	.736	9%	9%	3%	16%	1.00	.004
Renal Impairment*	29%	11%	26%	6%	.003	<.001	26%	13%	17%	6%	.026	.011
Hepatic Impairme	9%	5%	10%	1%	.164	.001	2%	5%	7%	1%	.468	.047
Ongoing Procedures												
CAD*	12%	7%	13%	2%	.206	.001	15%	7%	17%	2%	.058	<.001
Ventilation*	6%	12%	8%	8%	.071	1.000	0%	12%	2%	8%	<.001	.116
Previous CAB	29%	36%	49%	24%	.229	<.001	32%	36%	51%	24%	.545	<.001

CAD=Circulatory assist device; *: indicates covariates in regression/Cox proportional hazard Model (see Table 7).
Note: All p-values are by Fisher's exact.

Table 12 above summaries the cases for which the interim information indicate significant imbalances between the historical control group and the argatroban treated patients. That is, unlike study ARG-911 where there are significantly more patients in the argatroban group with pre-existing conditions at baseline than in the historical control group, there appears to be (at least numerically) more patients in the historical control group with pre-existing conditions at baseline than in the argatroban group (see **Table 12** above).

Summary of Sponsor's Primary Efficacy Analysis Results

Table 13 below presents a comparative summary of sponsor's primary efficacy analysis results for the two studies (ARG-911 and ARG-915). Note that the results for ARG-915 are as observed and not adjusted for the reported interim analysis.

Table 13/Summary of Primary Efficacy Results For Overall Composite Endpoint & Its Components For Entire Study Period

Treatment/ Study	ARG-911		ARG-915 (Interim Results)		ARG-911+915 (By Reviewer)	
	HIT	HITTS	HIT	HITTS	HIT	HITTS
Overall: Novas	43/160 (27%)	62/144 (43%)	21/85 (25%)	33 /89 (37%)	64/245 (26%)	95/233 (41%)
Histor	36/108 (33%)	59/109 (54%)	36/108 (33%)	59/109 (54%)	36/108 (33%)	59/109 (54%)
Difference (N-H)	-6%	-11%	-9%	-17%	-7%	-13%
95% CI; P-value	(-18,-5); .260	(-23, 13); .080	(-21, 4); .186	(-31, -3); .015	(-18, 3); .176	(-25, -2); .020
All Death: Novas	29/160 (18%)	26/144 (18%)	16/85 (19%)#	23/89 (26%)#	45/245 (18%)	49/233 (21%)
Histor	12/108 (11%)	16/109 (15%)	12/108 (11%)	16/109 (15%)	12/108 (11%)	16/109 (15%)
Difference (N-H)	+7%	+3%	+8%;	+11%	+7%	+6%
95% CI; P-value	(-1, 15); .102	(-6, 13); .496	(-2, 17); .137	(-0, 15); .052	(-0, 15); .063	(-2, 15); .141
Amputation: Novas	4/160 (3%)	18/144 (13%)	6/85 (7%)#	13/89 (15%)#	10/245 (4%)	31/233 (13%)
Histor	4/108 (4%)	13/109 (12%)	4/108 (4%)	13/109 (12%)	4/108 (4%)	13/109 (12%)
Difference (N-H)	-1%	+1%	+3%;	+3%	0%	+1%
95% CI; P-value	(-9, 5); .584	(-8, 9); .890	(-6, 14); .501	(-7,12); .582	(-7, 6); .907	(-6, 9); .718
Thrombosis: Novas	10/160 (6%)	27/144 (19%)	3/85 (4%)#	8/89 (9%)#	13/245 (5%)	35/233 (15%)
Histor	25/108 (23%)	45/109 (41%)	25/108 (23%)	45/109 (41%)	25/108 (23%)	45/109 (41%)
Difference (N-H)	-17%	-23%	-19%;	-32%	-18%	-26%
95% CI; P-value	(-26, -8); <.001	(-34, -11); <.001	(-31, -8); .002	(-43,-21); <.001	(-26,-9); <.001	(-37,-16); <.001

#: Includes 5 HITTS and 1 HIT deaths not included in sponsor's (Table 11, Vol 4.10a) but listed on page 7 297 of Vol 4.10g.

Sponsor's model based analysis (logistic regression and Cox proportional hazard) results with adjustment for the all cause-mortality component of the overall composite endpoint are summarized in **Table 14** below.

Table 14/ Sponsor's Logistic Regression/Cox Proportional Hazard Model Analysis Results For All-Cause Death

Analysis Models for All-Cause Death	ARG-911 HIT	ARG-911 HITTS	ARG-915 (Interim Results)* HIT	ARG-915 (Interim Results)* HITTS
Logistic Model	OR/RR; 95% CI; P-value	OR/RR; 95% CI; P-value	OR/RR; 95% CI; P-value	OR/RR; 95% CI; P-value
No Covariates	1.77; (.88, 3.77); .121	1.28; (.66,2.57); .48	1.71; (.76, 3.96); .197	1.47; (70, 3.12); .305
3 Covariates (Stepwise)	1.34; (.62, 3.02); .459	0.65; (.29, 1.44); .29	1.87; (.76, 4.52); .163	1.18; (.53, 2.62); .685
7 Covariates@	1.24; (.56, 2.89); .610	0.51; (.21, 1.19); .13	1.88; (.75, 4.96); .185	-
Hazard Model				
No Covariates	1.62; (.82, 3.18); .166	1.27; (.68,2.36); .46	1.65; (.76, 3.57); .202	1.49; (76, 2.92); .250
3 Covariates (Stepwise)	1.25; (.62, 2.55); .535	0.61; (.30, 1.26); .19	1.71; (.77, 3.78); .189	1.12; (.55, 2.29); .762
7 Covariates@	1.16; (.55, 2.43); .694	0.54; (.25, 1.13); .10	1.83; (.76, 4.37); .175	1.22; (.58, 2.69); .600

Data from sponsor Appendix 16.1.9.3.4 of Vol 154 & 154a for ARG-911 & Table 13 Vol 39 for ARG-915;
*: Excludes 5 HITTS & 1 HIT patients listed on page 7 297 of Vol 4.10g.
|None: indicates model results unadjusted for covariate imbalance;
|3: model results adjusted for cancer, renal impairment (Renal) & respiratory distress syndrome (RDS) ;
|7: model results adjusted for imbalances in cancer, renal, RDS, sepsis, Cardiac assist device, ventilation, and dialysis (see Table 6 above).
@: For study ARG-915, 5 covariates (renal, sepsis, RDS, hemodialysis and ventilation) were used in the multivariate model.

VI. SUMMARY OF EFFICACY RESULTS & REVIEWER'S COMMENTS

Summary of Efficacy Results

The sponsor's analysis results for the primary overall composite endpoint (all-cause mortality, all-cause amputation, or the development of new thrombotic events) summarized in **Tables 5-8, 13 & 14** above suggest that

(i) For the infusion period (≤ 14 days) for study ARG-911, argatroban is superior to the historical control group for both the treatment of HITTS and the prophylactic prevention of thrombosis in HIT patients respectively; the corresponding 2-sided p-values for the absolute differences in proportions (22% for HITTS and 21% for HIT) favoring argatroban are both ≤.001, and the associated 95% confidence interval estimates of (-34, -11) for HITTS and (-30, -12) for HIT are both entirely negative (see **Tables 5a** above for study ARG-911 only).

(ii) For the follow-up period (>14 days) for study ARG-911, however, argatroban is inferior to the historical control group for both the treatment of HITTS and prophylactic prevention of thrombosis in HIT patients respectively; the corresponding 2-sided p-values for the absolute difference in proportions (of 15% for both HITTS and HIT) in favor of the historical control group are respectively ≈.003, and the associated 95% confidence interval estimate of (6, 25) for both HITTS and HIT is entirely positive (see **Tables 5a** above for study ARG-911 only).

(iii) For the entire study period (infusion+follow-up) for study ARG-911, argatroban holds a slight numerical advantage over the historical control group; the corresponding 2-sided p-values for the absolute difference in proportions (of 11% for HITTS and 6% for HIT) favoring argatroban are respectively .080 and .260, and the associated 95% confidence interval estimates of (-23, 13) for HITTS and (-18, 5) for HIT contain zero (see **Table 5a** above for study ARG-911 only).

Similar trends are observed from the interim analysis results of study ARG-915; argatroban is shown effective for the HITTS patient population but only numerically better for the HIT patient population (see **Table 13** above for both studies).

(iv) As per the analysis results for the components of the composite primary endpoints (see **Table 5b** for study ARG-911 only), the above observed argatroban advantage during the infusion period, and for the entire study period (see **Table 13** for both studies) is shown to have derived primarily from the development of new thrombotic events. For both death and amputation, the argatroban treated patients faired at least numerically worse than the historical control group of patients.

(v) The model based results (logistic regression and Cox proportional hazard, with adjustment for risk factors identified as having significant impact on death) results (see **Table 7** for study ARG-911 only, and **Table 14** for both studies), do not convey a discernable picture to conclusively attribute argatroban's poor performance regarding deaths (in particular) to the presence of any imbalance in pre-existing conditions. At least for study ARG-915, the results seem to indicate a diminishing treatment benefit as more and more covariates are entered into the models (see **Table 14** above).

REVIEWER'S COMMENTS

Disposition of Historical Control Patients and & Events

(i) It should be noted that of the 217 (108 HIT and 109 HITTS) historical control patients enrolled in study ARG-911, 158 (73% overall, (71%) HIT and 81 (74%) HITTS) were contributed by 7 (7%) of the 103 participating centers. Furthermore, 3 of these 7 centers contributing 97 [45% overall, (30%) HIT and (60%) HITTS] patients, enrolled no argatroban patients.

Distribution of Historical Control Events For Composite Endpoint Events For The Entire Study Period[R]

Centers	HIT (Historical)	Rates Comparability (Fisher's Exact)	HITTS (Historical)	Rates Comparability (Fisher's Exact)	Total (Historical)
3 Sites W/No Novas Patients.	24/32 (75%)	vs	30/65 (46%)	vs	54 (56%)
4 Largest Sites W/≥10 Pts/Site	4/45 (9%)	<.001	11/16 (69%)	.162	15/61 (25%)
(Other) 96 Sites W<3 Pts/Site	8/31 (26%)	<.001	18/28 (64%)	.120	26/59 (44%)

*: 4 centers enrolling a total of ≥10 pts/site; #: Sum>100 due to rounding up; R=Analysis Results by this reviewer.

The summary results in the table above clearly indicate that, at least for the *HIT patient population*, the event rate from Dr. Warkentin's three sites is significantly disproportionately higher than the rates from any other group of sites (Fisher's exact 2-sided p-value for comparability of rates between Dr. Warkentin's sites and the other groups <.001).

In addition, the table below (see **Table 9a** also) indicate that 67% (24/36) of the total number of HIT events in the historical control group came from Dr. Warkentin's 3 sites, even though these 3 sites combined, enrolled less than 30% (32/108) of the total HIT historical control patient populations.

Comparison of Distribution of Composite Endpoint Events For The Entire Study Period

Centers	HIT			HITTS		
	Novas	Hist	Fisher Exact 2p	Novas	Hist	Fisher's Exact 2p
All Events	43 (100%)	36 (100%)	-	62 (100%)	59 (100%)	-
3 W/No Novas Pts.	0 (0%)	24 (67%)	<.001	0 (0%)	30 (51%)#	<.001
4 Largest*	5 (12%)	4 (11%)	1.000	9 (15%)	11 (19%)#	0.628
(Other) 96 Sites	38 (88%)	8 (22%)	<.001	53 (85%)	18 (31%)#	<.001

*: 4 centers enrolling a total of ≥10 pts/site; #: Sum > 100 due to rounding up.

Note that no efficacy data sets for study ARG-915 were provided on diskette and no display of patient or events disposition by center is provided by the sponsor. The above comments therefore are limited to study ARG-911.

Impact of Pre-existing Conditions on Argatroban Performance

(ii) *HIT Patient Population*. This reviewer's subgroup analysis results do not support sponsor's model based analysis results which seem to suggest that argatroban's poor performance is primarily due to the presence of more patients with pre-existing conditions in the argatroban treatment arm. This reviewer's subgroup analysis results [for subgroups of patients classified as presenting with and without *cancer, respiratory distress syndrome (RDS), renal impairment (Renal), cardiac assist device (CAD), CABG, and ventilation*] for study ARG-911 indicate that, except for renal impairment and CABG subgroups for which the historical control group is shown to have a slight numerical advantage, argatroban holds a numerical advantage over the historical control group for all subgroups of patients classified as presenting with these pre-existing conditions (as measured by the overall composite endpoint). Similarly, except for the subgroup of patients without renal impairment condition for which argatroban is shown to be statistically superior to the historical control group at the .05 level of significance, argatroban only holds a slight numerical edge over the historical control group for the subgroups of patients classified as not presenting with either of these pre-existing conditions (see **Table 9b** above).

For the all-cause mortality endpoint, argatroban is shown to be consistently numerically inferior to the historical control group, both for the subgroups of patients classified as presenting and not presenting with these pre-existing conditions (see **Table 9c** above). Gender and age subgroup analysis results consistently show numerical trends in favor of argatroban (see top of **Table 9b & 9c** above).

(iii) *HITTS Patient Population*. For the HITTS patient population, this reviewer's subgroup analysis results [for subgroups of patients classified as presenting with and without *cancer, respiratory distress syndrome (RDS), renal impairment (Renal), cardiac assist device (CAD), CABG, and ventilation*] for study ARG-911 seem to support sponsor's claim that argatroban is disadvantaged by the presence of more patients presenting with these pre-existing conditions at baseline. For renal impairment and CABG subgroups for which argatroban is shown to have a slight numerical advantage over the historical control group for the subgroup of patients presenting with these pre-existing conditions (as measured by the overall composite endpoint). On the other hand, argatroban is shown to be statistically superior to the historical control group at the .05 level of significance for the subgroups of patients classified as not presenting with either of these pre-existing conditions, except for the subgroup of patients without renal

impairment and CABG conditions for which argatroban is only numerically better than the historical control group (see **Table 9b** above).

For the all-cause mortality endpoint however, except for the subgroup of patients with renal impairment condition for which argatroban is shown to be superior to the historical control group at the .05 level of significance, argatroban is shown to be consistently numerically inferior to the historical group for both subgroups of patients presenting with and without these pre-existing conditions at baseline (see **Table 9c** above). Gender and age subgroup analysis results consistently show numerical trends in favor of argatroban (see top of **Table 9b & 9c** above).

Note that the sponsor has not provided the interim efficacy data for study ARG-915 to this reviewer. The above comments on the impact of pre-existing conditions/risk factors are with reference to study ARG-911 only. However, sponsor's model based results summarized in **Table 14** seem to indicate that the presence of such conditions in study ARG-915, if any, has no negative impact on the performance of argatroban regarding all-cause mortality. This is indicated by the diminishing argatroban advantage over the historical control group as more covariates (in addition to treatment) are added to the models.

It should also be noted that in addition to the 39 (22%) argatroban vs 28 (13%) historical control deaths (Fisher's exact 2-sided p-value=.015 against argatroban) documented in the interim report of study ARG-911 (as of September 1997), additional 26 argatroban deaths have also been reported among the remaining patients. This brings the total argatroban number of deaths to 65 (26%), as of December 1997 (Fisher's exact 2-sided p-value=.0005 against argatroban). In either case, this indicates a significantly higher number of deaths among the argatroban treated patients.

CONCLUSIONS

1. In this reviewer's assessment, the efficacy data in this submission do not provide adequate support for the efficacy of argatroban as an anticoagulant in the treatment of heparin-induced thrombocytopenia and thrombosis syndrome (HITTS), or in the prevention of thrombosis in patients with heparin-induced thrombocytopenia (HIT) for the following reasons:

(i) even though argatroban appears to be effective during the infusion period (≤ 14 days, not specified as the primary time point in the protocol) for the overall composite primary endpoint (for study ARG-911), 67% of the HIT and 51% of the HITTS events in the historical control group came from an investigator who enrolled no argatroban patients; thus providing no basis for event-by-treatment comparison for this investigator,

(ii) the analysis results for the entire study period (the protocol specified primary time point) for the overall composite primary endpoint indicate only a slight numerical edge for the historical control over the argatroban group for both studies for the HIT patient population; for the HITTS patient population, study ARG-911 again indicate a numerical trend in favor of argatroban. While the interim analysis results of study ARG-915 indicate a significant advantage for argatroban, this significant advantage becomes insignificant upon adjustment for interim analysis (note that in order to maintain an overall type I error rate of .05 for a planned

sample size of, say, 122 HITTS patients, the required p-value for rejection of the null hypothesis of no treatment difference with 89 available interim patient information is .0116, by

(iii) the analysis results for the all-cause mortality endpoint indicate argatroban is significantly inferior to the historical control group,

(iv) the model-based analysis results for the overall composite endpoint for study ARG-911 (and the all-cause mortality endpoint for both studies), adjusted for risk and baseline characteristic factors determined to impact death, and/or subgroup analysis results, indicate weak, inconsistent and non-robust support for the efficacy of argatroban for the HIT patient population.

(v) the overall number of deaths, to date, is significantly higher in the argatroban treated group.

2. In this reviewer's assessment, there were significantly more (overall) bleeding and adverse events in the argatroban than in the historical control group. Most of these events are, however, classified as minor bleeds and not major bleeds or serious adverse events by the sponsor.

3. The entry age to this study is 18 years or older. The pediatric implication of this drug is therefore not clear to this reviewer.

A. J. Sankoh, Ph. D.
/S/ 3/09/98
Mathematical Statistician

Concur: /S/ 3/9/98
Dr. Welch

cc: Archival NDA # 20-883
HFD - 180
HFD - 180/Drs. Talarico/Sizer/Ms DuBeau
HFD - 720/Drs. Welch/Sankoh
HFD - 344/Dr. Barton
HFD - 720 File Copy