CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-883

MEDICAL REVIEW

JUN 1 2000

Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Review

NDA:	20883 [N 000, BZ]
Sponsor:	Texas Biotechnology Corporation
Drug Product:	Argatroban
Date submitted:	April 20, 2000
Date Received:	April 21, 2000
Date assigned:	April 25, 2000
Review Completed:	June 1, 2000
Reviewer:	Ann T. Farrell MD

Background:

Texas Biotechnology was sent an approvable letter by the Agency on February 18, 2000 for argatroban. Argatroban is a synthetic, direct thrombin inhibitor for use as an anticoagulant in patients with heparin-induced thrombocytopenia and thrombosis. The approvable letter contained the following issues the sponsor needed to address:

1) FDA proposed labeling revision
2) requests to conduct two phase IV studies
   a) pediatric study
   b) in vitro cardiac electrophysiologic studies and animal model studies
3) need for a new trade name
4) request for a safety update

I. Label

This reviewer has reviewed the sponsor's revised label. This reviewer will highlight only those sections of the sponsor's revised label, which need additional revision.

A) CLINICAL PHARMACOLOGY

The sponsor has revised the following paragraph so it now reads:

Argatroban does not interact with heparin-induced antibodies. Evaluation of sera in 12 healthy subjects and 8 patients who received multiple doses of argatroban indicates no antibody formation to argatroban (see **ADVERSE REACTIONS**).

Reviewer's Comment: The sponsor proposes to place the information about antibody formation in the clinical studies section of the label. If so, the sponsor should replace the phrase (see ADVERSE REACTIONS) above with (see CLINICAL STUDIES).

B) PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIP

The sponsor has revised the following paragraph so it now reads:

When TRADEMARK is administered by continuous infusion, anticoagulant effects and plasma concentrations of argatroban follow similar, predictable temporal response profiles, with low intersubject variability. Immediately upon initiation of TRADEMARK infusion, anticoagulant effects are produced as plasma argatroban concentrations begin to rise. Steady-state levels of both drug and anticoagulant effect are typically attained within 1-3 hours [redacted] and are maintained until the infusion is discontinued or the dosage adjusted. Steady-state plasma argatroban concentrations increase proportionally with dose (for infusion doses up to 40 µg/kg/min in healthy subjects) and are well correlated with steady-state anticoagulant effects. For infusion doses up to 40 µg/kg/min [redacted] TRADEMARK increases in a dose-dependent fashion, the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the prothrombin time (PT) and International Normalized Ratio (INR), and the thrombin time (TT). [redacted] Representative steady-state plasma argatroban concentrations and anticoagulant effects are shown below for TRADEMARK infusion doses up to 10 µg/kg/min. (See Figure 2)

Reviewer's Comment: This reviewer recommends that sentences 5 and 6 be combined. This reviewer has also revised the phrase "patients undergoing interventional procedures such as PTCA, stent placement or atherectomy" and has replaced the phrase with "cardiac patients" because the efficacy data for patients undergoing PTCA, stent placement, and atherectomy has not been submitted for review to the Agency. The combined sentence reads as follows:

[redacted]

C) Effect on International Normalized Ratio (INR)

The sponsor has revised the paragraph under Figure 3 so it now reads:

Figure 3 demonstrates the relationship between INR for warfarin alone and INR for warfarin co-administered with argatroban. To calculate INR for warfarin alone (INR_W), based on INR for co-therapy of warfarin and argatroban (INR_{WA}), use the equation next to the appropriate curve. Example: At a dose of 2 µg/kg/min and an INR performed with Thromboplastin A, the equation 0.19 + 0.57 (INR_{WA}) = INR_W would allow a prediction of the INR on warfarin alone (INR_W) from an INR_{WA} value of 4.0 obtained on combined therapy: INR_W =0.19 +0.57 (4)=2.47 as the value for INR on warfarin alone. The error

(confidence interval) associated with a prediction is ±0.4 units. Thus, for argatroban doses of 1 or 2 μg/kg/min, INR_W can be predicted from INR_{WA}. For argatroban doses greater than 2 μg/kg/min, the error associated with predicting INR_W from INR_{WA} is ±1. Thus, INR_W cannot be reliably predicted from INR_{WA} at doses greater than 2 μg/kg/min.

Reviewer's Comment: This reviewer would separate the third sentence into two sentences for clarity as shown below:

D) CLINICAL STUDIES

1) The sponsor was requested to describe the dosing regimen for argatroban (including titration). The sponsor added the following paragraph:

The initial dose of argatroban was 2 μg/kg/min not to exceed 10 μg/kg/min

Reviewer's Comment: This reviewer recommends the statement be revised for clarity. The first sentence could read as follows:

The initial dose of argatroban was 2 μg/kg/min not to exceed 10 μg/kg/min.

The sentence after that could read as follows:

Two hours after the start of the argatroban infusion, an aPTT level was obtained and dose adjustments were made to achieve a steady state aPTT value that was 1.5 to 3.0 times the baseline value, not to exceed 100 seconds

2) **Additional Information**

The sponsor's revised label now states the following:

Reviewer's Comment: This reviewer would remove the first sentence starting with "TRADEMARK has been administered to patients...." This sentence describes the entire (HIT and non-HIT) cardiac patient population who has received the drug. If the first sentence is removed then the word "also" should be struck from the second sentence. The third sentence should be removed and replaced with the Agency's previously recommended sentence, "The safety and effectiveness of TRADEMARK for cardiac indications have not been established."

E) PRECAUTIONS

1) The sponsor has inserted the heparin statement.

Reviewer's Comment: This reviewer is not sure why it was deleted except that we are labeling this drug to be used in patients who cannot receive heparin due to a life-threatening condition. This reviewer would remove the first two sentences and revise the fourth sentence slightly.

The section would look like this instead:
Heparin: Since heparin is contraindicated in patients with heparin-induced thrombocytopenia, the co-administration of argatroban and heparin is unlikely for this indication. However, if argatroban is to be initiated after cessation of heparin therapy, allow sufficient time for heparin's effect on the aPTT to decrease prior to initiation of TRADEMARK therapy.

Reviewer's Comment: This sentence will aid physicians whose patients have heparin-induced thrombocytopenia and need to be placed on another anticoagulant as soon as possible.

2) The sponsor has altered the following section:

Thrombolytic agents: . The safety and effectiveness of TRADEMARK with thrombolytic agents have not been established (see **ADVERSE REACTIONS: Intracranial Bleeding**).

3) The sponsor has reinserted the Erythromycin paragraph. This paragraph will be reviewed by FDA Office of Biopharmaceutics for the proposed revision and accuracy.

F) ADVERSE REACTIONS

The sponsor has revised the adverse reactions section. The following table is the sponsor's revised Table 3.

Major Hemorrhagic Events*		
	Study 1 & Study 2 (All argatroban-treated patients) (n=568) %	Historical Control (n=193) %
Gastrointestinal	2.3	1.6
Genitourinary and hematuria	0.9	0.5
Decrease hemoglobin/ hematocrit	0.7	0
Multisystem hemorrhage and DIC	0.5	1
Limb and BKA stump	0.5	0
Intracranial hemorrhage	0	0.5

Minor Hemorrhagic Events*		
	Study 1 & Study 2 (All argatroban-treated patients) (n=568) %	Historical Control (n=193) %
Gastrointestinal	14.4	18.1
Genitourinary and hematuria	11.6	0.8
Decrease in hemoglobin and hematocrit	10.4	0
Groin	5.4	3.1
Hemoptysis	2.9	0.8
Brachial	2.4	0.8

*Patients may have experienced more than one event.
DIC = disseminated intravascular coagulation;
BKA = below the knee amputation.

Reviewer' s Comments: This reviewer recommends removing the following rows from the Major Hemorrhage table because there were no events for the either group of patients:

II. PHASE IV Studies Planned

a) Pediatric studies- The sponsor plans a pharmacokinetic and safety study in the pediatric population and plans to discuss and submit a protocol.
b) Cardiac studies- The sponsor plans to study the action potential in rabbit purkinjie fibers and has not yet determined the animal model.

III. Tradename

The company is considering "ACOVA". An OPDRA consult has been sent.

IV. Safety Update

Updated Safety Section did not reveal any new adverse events nor was there a significant change in the adverse events previously reported.

The Update on withdrawal/dropouts revealed no new dropouts not reported earlier.

The Summary of Worldwide Experience is unchanged.

The sponsor also provided the English translation of the Japanese label. Argatroban is approved for patients with chronic arterial occlusion, cerebral thrombosis and hemodialysis in patients with antithrombin (ATIII) deficiency. The doses approved for these indications are different in Japan than that used for HIT/HITTS patients. The Japanese label does not identify any new adverse events previously unrecognized.

Recommendations

1. The sponsor's application is approvable with minor revisions. Recommend the sponsor's labeling revised as indicated above.

2. Await OPDRA consult on proposed tradename, "ACOVA".

/S/

Ann T. Farrell MD 6-1-00

CC:
HFD-180
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HFD-180/S Aurecchia 6/1/00
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HFD-180/J Choudary
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Division of Gastrointestinal and Coagulation Drug Products

Medical Officer's Review

NDA:	20883[28.1-28.98, 17.93-17.124]
Sponsor:	Texas Biotechnology Corporation
Drug Product:	Novastan® (argatroban)
Indication:	Anticoagulant therapy in patients with heparin induced thrombocytopenia
Route of administration:	intravenous injection
Date submitted:	August 13, 1999
Date Received:	August 16, 1999
Date assigned:	August 18,1999
Review Completed:	January 13, 2000
Reviewer:	Ann T. Farrell MD

Table of Contents

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Materials Reviewed

The following materials were reviewed.

Volume number	Content
28.1	New application, Table of Contents, Labeling, Summary, Benefit/Risk statement, Patent information, Debarment statement, Field Copy certification
28.2-9	Human Pharmacokinetics, Pharmacodynamics and Bioequivalence, List of Investigators, Development History, ARG 109, ARG 112, ARG-230, 230-A, 231, SKF001, SKF002, SKF003
28.10-31	ARG-911
28.32-49	ARG-915
28.50-53	ARG-310
28.54	Other studies and information, ISE
28.55-71	ISS
28.72	Drug Overdose and Abuse, Benefit/Risk Statement, Compliance with 21 CFR 50 & 56, CRO responsibility, Monitoring Visits
28.73	Safety Update: ARG-311, ARG-915X, SKF001, SKF002, SKF003
17.74-75	ARG-911 Clinical Report
17.76-77	ARG-911 Statistical Report, ARG-911 SAS tables
17.78	ARG-915 Clinical Report
17.79	ARG-915 Statistical Report, ARG-915 SAS tables
17.80	Case Report Tabulations for SKF001
17.81	Case Report Tabulations for SKF002 and SKF003
17.82	Case Report Tabulations ARG-310
17.83-17.85	Case Report Tabulations ARG-911
17.86-17.92	Case Report Tabulations ARG-915
17.93-17.114	Case Report forms ARG-911
17.115-117	ARG-915 Deaths
17.118-119	ARG-915 Withdrawals
17.120-123	ARG-915X Deaths
17.124	ARG-915X Withdrawals

Reviewer's table

Volumes starting 2.x were submitted August 11, 1997.
Volumes starting with 17.x were submitted March 17, 1999.
Volumes starting with 28.x were submitted August 13, 1999.

Table of Abbreviations

CVA	Cerebrovascular Accident
DMSC	Data Monitoring Safety Committee
DVT	Deep vein thrombosis
HIPA	Heparin-induced platelet aggregation
HIT	Heparin-induced thrombocytopenia
HITTS	Heparin-induced thrombocytopenia and thrombosis syndrome
HPF4	Heparin-Platelet Factor 4 Complex
IMRP	Independent Medical Review Panel
ITT	Intent-to-Treat
LMWH	Low molecular weight heparin
PE	Pulmonary Embolism
SRA	^{14}C-Serotonin Release Assay
UH	Unfractionated heparin

Reviewer's table

Summary and Regulatory History

NDA 20-883 is submitted for argatroban, an antithrombin for use as an anticoagulant in patients with heparin-induced thrombocytopenia, a life-threatening condition.

Argatroban is an intravenously administered, direct thrombin inhibitor that exerts anticoagulant effects by inhibiting thrombin-mediated reactions. Argatroban is eliminated primarily though the feces with some renal excretion. Argatroban reaches steady state levels within three hours after start of infusion. The coagulation parameters normalize within four hours of stopping an infusion.

The two submitted key clinical studies, ARG-911 and ARG-915, are multicenter, open-label efficacy and safety studies involving argatroban-treated HIT and HITTS patients. The sponsor compares the efficacy outcome results from these studies with results from historical control patients.

Regulatory history

On August 11, 1997 the sponsor submitted NDA 20-883 for the approval of argatroban for the following indication: 'as anticoagulant therapy in patients with heparin-induced thrombocytopenia'. Due to significant deficiencies regarding chemistry, manufacturing and control, microbiology, and clinical issues, approval was not granted.

The sponsor addressed completely the Chemistry, Manufacturing and Controls deficiencies (see Chemistry review dated January 6, 1999), and the microbiology deficiencies (see Microbiology review dated October 20, 1998).

This submission is concerned with the previously identified clinical deficiencies. The clinical deficiencies (reproduced from the non-approval letter of May 8, 1998) are listed below:

1) *Although significant reductions in the incidence of new thrombotic events were observed for HIT and HITTS patients in both studies, the overall composite endpoint (of death, amputation, or new thrombosis) in Study ARG-911 was not statistically significant in the HIT group, and only trending in the HITTS group. When Study ARG-915 was analyzed post-hoc, there was no statistically significant difference in the overall composite endpoint in the HIT group; however, there was a statistically significant difference in the HITTS group compared to the historical control.*
2) *Your secondary analysis of deaths attributed to thrombosis or underlying disease appeared to show that argatroban reduced mortality due to thrombosis. However, when the deaths were reclassified by the medical reviewer based on data in the Case Report Forms, there was no difference in thrombotic deaths between the treatment and the historical control groups. Based on the above information, it appears that the statistically significant reduction in new thrombotic events did not result in a mortality benefit.*
3) *With respect to safety, numerical trends of greater all-cause mortality were observed in Studies ARG-911 and ARG-915 in the argatroban-treated patients. In Study ARG-911, these trends in mortality were attributed to significant imbalances in patient characteristics, with argatroban-treated patients being more compromised at baseline. However, our statistical analyses, adjusting for this imbalance, did not support this conclusion. In addition, there was a greater incidence of all-cause mortality in the argatroban-treated HIT and HITTS patients observed in Study ARG-915 where patient baseline characteristics of treatment and historical control groups were similar.*
4) *To clearly demonstrate safety and efficacy, we suggest that you either identify and analyze an appropriate historical control, or conduct an additional study comparing argatroban to a currently approved therapy for HIT/HITTS in patients who need anticoagulation.*

The Agency had a meeting with the sponsor on July 14, 1998 to discuss the action taken on NDA 20-883. The sponsor and Agency reached agreement on the following:

1) The registry of HIT and HITTS patients from Loyola Medical Center (Dr. Wallis) would serve as source of the new historical control.
2) All-cause death would be part of the primary efficacy analysis instead of death due to thromboses.

During the meeting the Agency suggested other possibilities for statistical analysis, labeling, and safety analysis.

Current submission

NDA 20-883 for argatroban for the same indication was re-submitted on August 15, 1999. The NDA re-submission includes:

1) the sponsor's new historical control group
2) a literature analysis to support the sponsor's new historical controls
3) a comparison of the results from the pivotal study ARG-911 with the new historical controls
4) a comparison of the results from the supportive study ARG-915 with the new historical controls
5) data from the completed pilot study ARG-310
6) safety information from studies ARG-915X and ARG-311
7) three drug interaction studies SKF001, SKF002, and SKF003

Clinical Background:

Heparin-induced thrombocytopenia (HIT) is a life-threatening complication of anticoagulant therapy with unfractionated heparin (UH) and low molecular weight heparin (LMWH). Two distinct subtypes of HIT have been described: Type I, a relatively benign non-immune thrombocytopenia occurring within a few days after start of heparin or LMWH administration and Type II, a more clinically severe, delayed immune-mediated thrombocytopenia that occurs 5-10 days following the start of heparin or LMWH.[1] Type II HIT is mediated by the formation of heterogeneous antibodies to the heparin-platelet factor 4 complex (HPF4).[1,2,3] The formation of antibodies and the class of antibodies formed depend on a variety of factors including specific anticoagulant used, source of anticoagulant, anticoagulant concentration, and duration of administration. The antibody-HPF4 complex binds to platelet FcγRII-A receptor. This binding leads to platelet activation, release of platelet-derived microparticles, and platelet aggregation.[1] In this review, HIT refers exclusively to HIT type II.

The antibody-HPF4 complex also binds to vascular endothelial cell surfaces causing cell injury and venous or arterial thrombosis.[3] The presence of the thrombosis defines the condition as heparin-induced thrombocytopenia with thrombosis syndrome (HITTS). Depending on the location of the thrombosis, the consequences may include deep venous thrombosis (DVT), pulmonary embolism (PE), cerebrovascular accident (CVA), occlusion of blood supply to vital organs (coronary, mesentery, etc.), limb ischemia, amputation, and death. The combined morbidity and mortality rates associated with the development of HIT may be 30% or greater.[1]

The use of laboratory tests strengthens clinical suspicion of the diagnosis. No single diagnostic test unequivocally confirms the presumptive diagnosis.[2] Two types of tests exist: functional assays and immunoassays. Functional assays measure platelet activation by heparin-dependent antibody. Functional assays include platelet aggregation, platelet aggregation with release of platelet microparticles (lumi-aggregation), and ^{14}C-serotonin release assay (SRA). Immunoassays include flow cytometry and ELISA. Although these tests support the clinical diagnosis, the sensitivity of these tests limits their value for confirmation of diagnosis.

Currently, prompt recognition of the condition, discontinuation of heparin or LMWH, and switching to other anticoagulant regimens is the standard of care. These measures, however, do not always

prevent the thrombotic and other complications that may occur. The other complications include amputation, death[1,2], skin necrosis[4,5], and venous limb gangrene syndrome[5,6]. The time course for the development of complications following heparin exposure is not well understood. Patients who develop HIT are at increased risk to develop this syndrome again with repeat heparin anticoagulation.

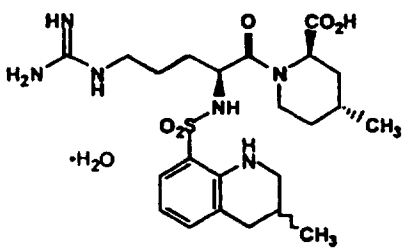
The options for anticoagulation for HIT/HITTS patients are limited. The Agency has approved lepirudin (Refludan™) for "anticoagulation in patients with heparin-induced thrombocytopenia and associated thromboembolic disease in order to prevent further thromboembolic complications". Other anticoagulants under investigation have included ancrod and the heparinoid, danaparoid. NDA 20-883 is submitted for the approval of Argatroban (Novastan®) "as anticoagulant therapy in patients with heparin-induced thrombocytopenia syndrome, who in the opinion of their attending physician, require anticoagulation."

Chemistry and Pharmacological Background of Argatroban:

Chemistry:

Argatroban is a synthetic, small-molecule (MW 526.66), direct thrombin inhibitor derived from L-arginine. The molecular formula is $C_{23}H_{36}N_6O_5S \cdot H_2O$. The chemical name for argatroban is 1-[5-[(aminoiminomethyl)amino]-1-oxo-2-[[1,2,3,4-tetrahydro-3-methyl-8-quinolinyl)sulfonyl]amino]pentyl-4-methyl-2-piperidinecarboxylic acid, monohydrate. Argatroban is a mixture of R and S stereoisomers in a 65:35 ratio. Below is the structural formula:

Figure 1



Sponsor's text volume 28.1
Argatroban is a white, odorless crystalline powder freely soluble in glacial acetic acid and slightly soluble in ethanol.

Pharmacology and Toxicology:

Argatroban is a direct thrombin inhibitor that selectively and reversibly binds to the active thrombin site. Argatroban exerts anticoagulant effects by inhibiting thrombin-mediated reactions such as conversion of fibrinogen to fibrin, activation of Factors V, VIII, and XIII, protein C, and platelet aggregation. Argatroban binds to clot bound as well as non-clot bound thrombin.

Distribution, Metabolism, and Excretion:

Following intravenous administration (IV), 54% of argatroban binds to human serum proteins (albumin 20% and α_1-acid glycoprotein 34%). Four oxidative metabolites of argatroban have been detected. Human liver microsomal P450 enzymes CYP3A4/5 catalyze the in vitro formation of these metabolites. The major route of excretion is fecal elimination presumably through biliary secretion. In healthy volunteers, infused with [^{14}C]-argatroban, approximately 65% of the radioactivity was detected over 7 days in the feces and 22% over 6 days in the urine.

Approximately 16% of the unmetabolized argatroban was detected in the urine. Plasma radioactivity was undetectable after 24 hours.

Pharmacokinetics and Pharmacodynamics:

Argatroban achieves steady state levels within 1-3 hours following the start of an infusion. These levels are maintained until the infusion is discontinued or undergoes a dosage adjustment. For infusion doses up to 40μg/kg/min., argatroban increases in a dose dependent fashion the following laboratory parameters:
. activated partial thromboplastin time (aPTT),
. activated clotting time (ACT)
. prothrombin time (PT)
. International Normalized Ratio (INR)
. thrombin time (TT)

The α and β half-lives are 7 minutes and 54 minutes respectively. Hepatic impairment results in decreased clearance.

Toxicology:

The original FDA pharmacology and toxicology review was completed on March 23, 1998. The results are summarized below:

1) the minimum lethal IV dose in single dose acute toxicity studies ranged from 124-200 mg/kg
2) continuous acute toxicity studies conducted in rats and dogs were not lethal in animals; clinical signs of toxicity in all treated dogs were peripheral vasodilation, edema, subdued behavior, dyspnea
3) in 28 day bolus and continuous IV infusion toxicity studies, no drug related toxicity was seen in any organ even at the highest dose which was 30.2 mg/kg/day
4) in the 1 month bolus toxicity study, there were few male rats who had mild cellular infiltration in the liver, however this was not dose related
5) in the 1 month bolus toxicity study, dogs demonstrated an increased frequency of vomiting and licking
6) in the 26 weeks IV toxicity study, there was noted a slight degeneration of the proximal renal tubular epithelium
7) in the 1 month continuous IV toxicity studies, local reactions were noted in the rats and dogs, additionally in dogs there were inflammatory and vascular lesions noted in the lungs that were due to experimental infusion techniques
8) in fertility testing in male and female rats, no drug related effects were seen on fertility, maternal/paternal reproductive performance, or on progression of pregnancy
9) in teratology studies in rats and rabbits, no teratogenic effects were observed
10) no mutagenic potential was demonstrated using multiple tests
11) no antigenic potential was demonstrated in testing in guinea pigs and mice
12) no hemolysis was noted for doses up to 1 mg/ml

A more detailed analysis is available in original review. The FDA pharmacology/toxicology reviewers noted no deficiencies.

Clinical Development of Argatroban

Summary of the Clinical Studies

Ccntrolled Clinical Studies:

Four clinical trials are included in the NDA database. Two clinical studies provide the primary data for the proposed indication (ARG-911 and ARG-915). Study ARG-311 is an extension of study ARG-310 for the use of argatroban for PTCA.

Clinical studies in NDA 20-883

Study #	Design	Submitted results
ARG-911 (Pivotal)	Open-label, non-randomized, multicenter, in-patient, historically controlled trial, originally study ran from 2/12/95-12/30/96. Treated patients received 2-10μg/kg/min. as an infusion based on aPTT efficacy endpoints- primary the incidence of thrombosis, amputation, and death	304 argatroban- treated patients, 193 historical controls (147 HIT, 46 HITTS). Results demonstrated a benefit for the primary composite endpoint (p=0.014) and time-to-event (p=0.022) for the HIT patients, trend towards benefit for the primary endpoint (p=0.131) and time-to-event (p=0.035) for the HITTS patients, there was no assessment of the composite thrombotic endpoint in the resubmission
ARG-915 (Supportive)	Open-label, non-randomized, multicenter, in-patient, Treated patients received 2-10μg/kg/min. as an infusion based on aPTT, no upper age limit, study conducted 11/96-10/97, Follow on efficacy and safety trial	297 total enrollment numbers, 264 argatroban-treated patients, 27 "repeat" argatroban-treated patients, results demonstrated a benefit for the primary composite endpoint (p=0.021) and time-to-event (p=0.0217) for the HIT patients, trend towards benefit for the primary endpoint (p=0.067) and a benefit for time-to-event (p=0.0124) for HITTS patients
ARG-915X	Open-label, non-randomized, multicenter, in-patient, historically controlled trial, conducted from 10/97 to 8/3/98 Treated patients received 2-10μg/kg/min. as an infusion based on aPTT, Extension safety trial	192 argatroban-treated patients, only safety information submitted in safety update
ARG-310	Open label trial to evaluate the efficacy and safety of the use of argatroban in patients with a history of HIT who required PTCA, arthrectomy, or stent implantation	30 patients with a previous documented history of HIT (24- clinical documentation only, 6-clinical diagnosis plus seropositive test, 3-seropositive test only), the investigators stated 100% of patients achieved adequate anticoagulation
ARG-311	Extension trial for 310	54 patients enrolled, Safety information submitted in the safety update section

Reviewer's table

Overall, 653 patients, including 54 repeat patients were studied in the 5 clinical trials.

Uncontrolled Phase I and II Studies:

Below is a summary table of studies with argatroban.

Phase I and II studies with argatroban

Type of Study	Subjects studied	Study numbers	Number of patients exposed[a]
ADME, Dose-ranging, PK/PD, bioavailability/bioequivalence, drug-interaction	Healthy volunteers	B0118g, B0148g, ARG-100, -101, -102,-105, -107, -108, -109, -110, -112, -113, -114, -921, -951, SKF-001, SKF-002, SKF-003, 79/1403A, plus two other published studies conducted in Japan in early 1980s	The sponsor states 128 subjects under its studies.
Special populations-dose ranging	Unstable angina, renal impairment, hepatic impairment	B0147a (Unstable angina), ARG-103 (renal impairment), ARG-106 (hepatic impairment)	The sponsor states 41 subjects under its studies.
Randomized, pilot, dose ranging, controlled	Unstable angina/PTCA, Myocardial infarction, HIT/HITTS	B0272g, ARG-210, ARG-230, ARG-231, ARG-912	The sponsor states 817 subjects under its studies.

a The sponsor is not able to give an accurate account. This drug was being developed by [redacted] for some studies and initially developed in Japan in the early 1980s.
Reviewer's table

Clinical Studies Section

The clinical studies section include 5 subsections:

1) new historical controls
2) literature analysis
3) Study ARG-911
4) Study ARG-915
5) Safety Evaluation

Each of these subsections will be addressed with comments in this review.

Selection of the New Historical Control

The historical control group consists of patients considered eligible by an Independent Medical Panel following the initial screening.
The historical control patients were enrolled from three sources:

1) eligible cases from the Loyola Medical Center (Wallis) HIT/HITTS Registry—the cases represent the core of the new historical control group and replace the historical controls originally enrolled at that site by Dr. Lewis (site 20)
2) patients from the original historical group from sites that enrolled at least one prospective patient
3) eligible cases from screening logs of patients serologically tested for HIT/HITTS provided by sites that enrolled at least three prospective patients

The selection process involves the following:

1) A case was "screened " from medical chart and hospital records for eligibility using the same inclusion/exclusion criteria previously applied to patients for inclusion in study ARG-911.
2) A case was considered a "screen failure" if it did not meet eligibility upon review of the medical charts and medical records.
3) A case was "enrolled" in the new historical control group if it was deemed by the investigator as appropriate for inclusion in the new historical control group.
4) "Enrolled" cases that were deemed "eligible" by a medical monitor or by the Independent Medical Review Panel (IMRP) were "evaluable" and comprise the appropriate new historical control group.

The Historical Control consisted of patients selected by the IMRP from the following three sources:

1) Wallis Registry

The Wallis registry includes 116 eligible consecutive patients with a serological positive test for HIT/HITTS diagnosed between January 1991 and December 1993. The reasons for screening failure are shown below:

Reasons for Screening Failure for the Wallis Registry

Reasons	Number of Cases (% of 116 registry cases)
Medical Chart Not Available	7 (6%)
Investigative Antithrombin Agent Used	3 (2.6%)
Patient < 18 years of age	1 (0.9%)
Total (all reasons)	11 (9.5%)

Reviewer's table

The following tables 5-7 provide information about cases screened or not screened and why.

2) Historical Controls from Centers Enrolling More than 1 Prospective Patient

A total of 32 patients who had also been included in the initial historical control were excluded from the new historical control because of selection bias as being "healthier" than expected controls.

3) Historical Controls Solicited from Sites that Enrolled > 3 Prospective Patients
Investigators from 42 sites were requested to provide a screening log of patients who were serologically tested for HIT/HITTS between 1991 and 1995. Seven sites provided screening logs of patients serologically tested for HIT/HITTS. Thirty-two sites failed to provide logs for the following reasons:

Table 5 Reasons that Sites that Enrolled ≥3 Prospective Patients Were Unable to Provide a Screening Log or Perform Screening Evaluations

Reason that Site Was Unable to Provide a Screening Log or Perform Screening Evaluations	Number of Sites (Of 42 sites that enrolled ≥3 prospective patients)
Unable to provide screening log	
Testing list unavailable at site for time period requested	18
Historical data review disallowed by medical records or IRB	2
Investigator no longer at site; unable to establish new contact	2
No response from investigator	1
No response from laboratory	1
	Subtotal: 24
Provided a log but did not perform screening evaluations	
Unable to resolve IRB issues	4
Unable to obtain charts	4
Previously utilized a log on which no patients were excluded for vague or unspecified reasons	2
Historical data collection disallowed by IRB	1
	Subtotal: 11
Any reason	Total: 35

Reference Documentation: Appendix 16.2.1.4

Sponsor's table volume 28.10

The results of screening at the seven sites that provided screen logs are shown below:

Table 6 Screening Results from Sites that Enrolled ≥3 Prospective Patients and Were Able to Provide a Screening Log and Perform Screening Evaluations

	Number of Cases		
	Not Previously Screened	Previously Screened	Total
Listed on logs for serological testing of HIT/HITTS	167[a]	97	264
Not screened[b]			
Reasons that cases were not screened			
Specified, valid reason for previous screen failure	NA	55	55
Tested/ admitted during prospective enrollment period	50	0	50
Reached allowable no. of historical controls from site	40	0	40
Previously enrolled in original historical control group	1	24	25
Unable to obtain medical record/chart	5	0	5
Inadvertently overlooked	0	1	1
Total	*96*	*80*	*176*
Screened[b]	71	17	88
Failed screening evaluation			
Reasons that cases failed screening evaluation			
Not heparin-induced thrombocytopenia	14	11	25
Insufficient data available	7	0	7
Terminal or uncontrolled disease	3	0	3
Less than 18 years of age	3	0	3
Hemorrhagic stroke or hemorrhage	2	0	2
Bleeding diathesis or thrombolytic therapy	2	0	2
Excluded per investigator	2	0	2
Screen failure for active arm of study	0	1	1
Total	*33*	*12*	*45*
Enrolled	38	5	43

[a] Includes 3 cases from a previously utilized screening log but for whom screening was not originally performed.
[b] During the solicitation process for new historical controls only; does not refer to screening that may have been previously performed.
Reference Documentation: Appendix 16.2.1.5

Sponsor's table volume 28.10

Table 7 displays the results of the 17 cases that had previously failed screening and were rescreened.

Table 7 Reasons for *Original* Screen Failures for 17 Cases That Were Re-screened, and Results of the Re-screening

Original Screen Failure Reason (No. of Cases)	*Reason for Re-screening*	*Results of Re-screening (No. of cases)*
Did not meet criteria (6)	Unclear what criteria were not met	Enrolled (1) Not HIT (5)
Gastrointestinal bleed (3)	Vague reason for exclusion (unclear temporal relationship to HIT/HITTS diagnosis)	Enrolled (2) Not HIT (1)
Renal failure (2)	Vague reason for exclusion	Not HIT (2)
Recent cerebrovascular accident (1)	Vague reason for exclusion (unclear temporal relationship to HIT/HITTS diagnosis)	Not HIT (1)
Multisystem events (1)	Vague reason for exclusion	Enrolled (1)
AIDS (1)	Vague reason for exclusion	Not HIT (1)
Patient critical condition (1)	Vague reason for exclusion	Failed for active arm (1)
Age, 81 year old (1)	Age criteria was relaxed (with sponsor's approval) for prospective patients	Not HIT (1)
Suspicion of HIT, but no thrombosis (1)	Thrombosis was not a criterion for inclusion	Enrolled (1)

Reference Documentation: Appendix 16.2.1

Sponsor's table volume 28.10

Five (5) additional eligible cases were added to the new historical control group from sites that enrolled ≥ 3 prospective patients.

Medical summaries and case report tabulations were generated for the 215 patients eligible for the new historical control group. This group included 115 cases from the Wallis Registry, 67 cases from the original historical control group, and 43 cases from centers enrolling > 3 prospective patients. A medical monitor reviewed the medical summary and the case report tabulations to determine eligibility, classification with respect to HIT or HITTS, and whether or not the patient developed a new thrombosis. There was agreement between the medical monitor and the investigator in 73 cases. The remaining 142 cases were reviewed by an Independent Medical Review Panel (IMRP) for further resolution.

The IMRP was comprised of three board-certified medical experts. None of these members had participated in any trial for argatroban nor had they had any previous relationship with a sponsoring company.

Expert	Specialty	Affiliation
J. Hinson Jr. MD	Critical Care	University of Missouri, Panel Chair
B. Khanderia MD	Cardiology	Mayo Clinic
R. Pruthi MD	Hematology	Mayo Clinic

Reviewer's table

The panel reclassified 27 cases and rejected 22 cases.

Reason for ineligibility	Number of cases
Thrombocytopenia due to another cause	8
Recent thrombotic stroke, head trauma, or hemorrhagic stroke	6
Lack of thrombocytopenia	4
Pre-existing thrombocytopenia	2
Recent gastrointestinal bleed	1
Increased Prothrombin time at baseline	1

Reviewer's table

The total number of patients included in the new historical control was 193. The breakdown of these patients was as follows: 93 patients from Wallis Registry, 61 patients from the original historical control group, and 39 patients from the sites that enrolled greater than 3 prospective patients. Appendix 1 contains a listing by investigator/site for the new historical control.

These patients represent the new historical control used as a comparator for the argatroban-treated patients in studies ARG-911 and ARG-915.

Literature Analysis

For this NDA re-submission, the efficacy and safety results of argatroban in HIT and HITTS populations are to be compared to an appropriate, new historical control provided by the sponsor. The validity of such historical control was checked with a literature overview of available published reports of HIT and HITTS. The literature overview was prepared by Dr. Kelton, an expert consultant for the sponsor. The literature data were also examined by this reviewer. Differences in interpretation of the Literature Analysis by the sponsor and this reviewer will be addressed in this review of the literature.

Analysis of the Literature by the sponsor's consultant

Dr. Kelton performed a series of Medline searches for English language human subjects articles:

1) articles containing the words "heparin" and "study"
2) articles containing "heparin-induced thrombocytopenia" and "study"
3) articles containing "heparin-induced thrombocytopenia" or "heparin-associated thrombocytopenia"

The following inclusion and exclusion criteria were applied to each article.

The inclusion criteria were:

1) original studies or case series with — 10 patients
2) patients with a diagnosis of HIT or HITTS
3) clinical outcome measures of thromboembolic complication, amputation, or death reported

The exclusion criteria were:

1) treatment intervention studies where all patients were given a specific drug
2) studies which included literature reviews of previously published case reports or case series

The search resulted in 10 articles fulfilling the inclusion and exclusion criteria. The articles used for the overview are listed in Appendix 2. The table below presents a brief summary of the articles.

Articles from Kelton's literature analysis

Article	Design	Population	Inclusion /Exclusion	Outcome	Reviewer's comments if any
Silver, D. et. al. Heparin-induced Thrombocytopenia, Thrombosis, and Hemorrhage. Ann. Surg. 1983, 198:301-306.	Retrospective, single site (same as Laster article although different time), HIPA tested, patients seen prior to 1983	62 patients, 28 W, 35 M, 19 to 93 years of age, 59 patients over 40, 38 on heparin for thrombosis, 24 on heparin for DVT prophylaxis	-platelet count < 100K on heparin -increased resistance to heparin -thrombo-hemorrhagic complications (initially, cause for recognition; later thrombocytopenia)	-20 deaths overall, 14 deaths due to heparin -38 pts had 52 thromboembolic complications -22 surgical procedures due to complications -5 pts had amputations	HIT and HITTS patients- events not separately reported
Makhoul R.G. Heparin-associated Thrombocytopenia and Thrombosis. J. Vasc. Surg. 1986 4:522-528.	Retrospective, single site (Duke), patients seen from 1983 to 1985	25 patients, 13 M, 12 W, the majority underwent catheterization, arteriography, or IABP, 5 had no vascular instrumentation	-thrombocytopenia (< 100K or > 50% decrease from admission value) -thrombosis -platelet aggregation	-25 HITTS -9 deaths overall, 1 death due to heparin -47 thrombo-embolic complications -43 vascular procedures including 16 amputations	HITTS patients only
Laster, J. The Heparin-Induced Thrombocytopenia Syndrome: An Update. Surgery 1987 102:763-770.	Retrospective, single site (same site as Silver above), from 1983 to 1986	169 patients, 97 M, 72 W, 2 to 94 years of age,	-platelet count < 100K -increased resistance to heparin -thromboembolic or hemorrhagic complications -positive platelet aggregation	-131 HIT, 38 HITTS -41 thromboembolic/ hemorrhagic events (24 nonpulmonary thrombosis, 6 PE, 8 hemorrhage) -21 deaths due to heparin (no distinction made between overall and HIT/HITTS related mortality) -17 thrombectomies -4 pts had amputations	No distinct made between HIT and HITTS patients

AbuRahma, A. F. Diagnostic and Therapeutic Strategies of White Clot Syndrome. Amer. J. Surg. 1991 162:175-179.	Retrospective, single site, over a 36 month period	12 pts, 7 W, 5 M, 44 to 74 years of age	-platelet count < 100K or a > 50% from admission platelet count -normalization of platelet count after stopping heparin -exclusion of other causes of thrombocytopenia -presence of thrombosis -positive HIPA test and/or -detection of white clots on pathologic examination	-12 HITTS pts (-11 pts had arterial occlusion -9 pts had DVT -4 pts had PE -8 pts combined arterial and venous thrombosis) -3 died -6 pts had amputations	HITTS only patients, new TEC not determined
Walls, J.T. Heparin-Induced Thrombocytopenia in Open-Heart surgical patients. Ann. Thor. Surg. 1992: 53:787-791.	Retrospective study on patients undergoing cardiac operations between May 1981 and April 1991	82 pts, 35 W, 47 M, age range 2 years to 87 years, reported in terms of pre-op antibody and post-op antibody	-HIPA positive -those diagnosed post-operatively had to have antibody positive post-op	- 82 HIT patients -31 pts thromboembolic events, -23 deaths overall -2 pts had amputations	Could be an overlap in patients with other Walls article
Walls, J.T. Heparin-Induced Thrombocytopenia in patients undergoing intra-aortic balloon pumping after open heart surgery. ASAIO J. 1992 M574-576 (poster)	Retrospective medical record review of patients placed on IABP after cardiac surgery	35 pts, 17 M, 18 W, 41 to 87 years of age	-HIPA positive	-35 HIT patients 14/33 died had hemorrhagic complications and died -10/17 had thromboembolic complications and died -17 had thromboembolic complications -15 pts died in hospital	Could be an overlap in patients with other Walls article
Singer, R. L. Complications from Heparin-Induced Thrombocytopenia in patients undergoing cardiopulmonary bypass. Chest 1993 104:1436-1440.	Retrospective study of patients undergoing cardiopulmonary bypass from August 1987 to December 1991, single site, post-operatively identified	11 pts, 5 M, 6 W	-decreased platelet count	-2 deaths -17 complications including 9 pts had TEC, 6 limb amputations, 2 MIs, 2 PE, 1 phlegmasia cerulea dolens -3 pts had amputations	HITTS patients only
DeMasi, R. Heparin-induced thrombocytopenia. Amer. Surg. 1994 60:26-29.	Retrospective review of all pts referred to a lab for HIPA testing from May 1986 to March 1991	10 pts	Positive HIPA	-3 deaths -5 pts had amputations -8 pts had thromboembolic events	
Warkentin T. E. A 14-year study of heparin-induced thrombocytope	Retrospective, single region study (5 hospitals) of 127 patients with	62 HIT pts, 65 HITTS pts	-platelet count < 150K -positive ^{14}C serotonin release assay	-For the HIT pts thirty day risk of thrombosis was 52.8%, - HIT pts 13 deaths during hospitalization,	Article has problems 1) ratio of HIT/HITTS is inverted compared to the ratio (HIT>

nia. Amer. J. Med. 1996 101:502-507.	serologically documented heparin-induced thrombocytopenia over a 14 year period (dates of 14 year period not given)			32 pts had thromboses, no information on amputation -HITTS pts, 13 deaths during the hospitalization, - 63 new TEC, - no information on amputation	HITTS) generally accepted and reported in the literature 2) no information collected on amputation
Nand, S. Heparin-induced thrombocytopenia with thrombosis: incidence, analysis of risk factors, and clinical outcomes in 108 consecutive patients treated at a single institution Amer. J. Hematol. 1997: 56:12-16.	Retrospective review of pts treated at Loyola from January 1991 through December 1994 who had thrombocytopenia and positive HIPA	108 pts, 76 HIT, 56 W, 52 M, median age 68 years	-thrombocytopenia (plt < 150K) -positive HIPA	information on outcome supplied only for the 32 pts who developed HITT, -5 deaths -3 amputations -32 patients developed thromboembolic complications; 14 DVTs ± PE, 6 PE alone, 8 arterial thromboses (2 CVAs, 1 MI, 4 arterial and venous)	

Reviewer's table

Composite Outcome (death, amputation, and new thrombosis)

Dr. Kelton's table for the composite outcome is shown below. The table below reflects only those articles with enough information to calculate the frequency of the composite endpoint. Only seven articles out of the ten had enough information to warrant their inclusion. The composite outcome results for the literature analysis are based on 64% of the patients in the articles. Since the articles usually reported the results for HIT and HITTS patients together, the composite outcome frequency is labeled for the HIT and HITTS population. The frequency of events for the combined population of HIT and HITTS was 41.5% with a 95% confidence interval of 36.7% to 46.3%. For the HITTS population, the frequency of events is 63.6% with a 95% confidence interval of 35.2% to 92.1%. However, Kelton used only one study of exclusively HITTS population (Singer) with eleven patients. The large confidence interval for the HITTS population is due to the small number of patients available for separate analysis.

Composite Outcome (death, amputation, and new thrombosis)

Study	Total Sample Size	Number of Patients	Percentage	95% CI
Silver *	62	56	90.3	83.0 to 97.7
Laster *	169	38	22.5	16.2 to 28.8
Abu Rahma *	12	6	50.0	21.7 to 78.3
Walls *	35	22	62.9	46.8 to 78.9
Singer *	11	7	63.6	35.2 to 92.1
DeMasi *	10	8	80.0	55.2 to 104.8
Nand *	108	32	29.6	21.0 to 38.2
Overall Estimate (HIT and HITTS)	407	169	41.5	36.7 to 46.3

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Death

All articles had some information on death rates. The tables below show the number and percentage death of deaths with the calculated confidence intervals. The frequency of death for the combined HIT and HITTS population is 17.8% (95% CI 14.5 to 21.1). The frequency of death for the HITTS population is 23.9% (95% CI 16 to 31.8).

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Outcome: Death

	Study	N	#Deaths	%	95% CI
1	Silver 1983	62	14	22.6	12.2 to 33.0
2	Makhoul 1986	25	9	36	17.2 to 54.8
3	Laster 1987	169	21	12	7.1 to 16.9
4	AbuRahma	12	3	25	0.5 to 49.5
5	Walls 1992 (Ann Thor Surg)	82	23	28	18.3 to 37.7
6	Walls 1992 ASA10 Journal	35	15	43	26.6 to 59.4
7	Singer 1993	11	2	18.2	-4.6 to 41
8	DeMasi 1994	10	3	30	1.6 to 58.4
9	Warkentin 1996 (Overall)	127	26	20.4	13.4 to 27.4
	Warkentin 1996 Group 1	65	13	20	10.3 to 29.7
	Warkentin 1996 Group 2	62	13	21	10.8 to 31.2
10	Nand 1997	108	5	4.6	0.7 to 8.6

* 13 patients were treated on 2 occasions

Overall Outcome Estimate:

Overall estimates have been provided for all remaining studies (Group A); studies including just HITT patients (Group B), and studies including a combination of HIT and HITTS (Group C).

Group	Studies Included	Total N	Number of Deaths (%)	95% of CI
A	1-8, 9 (Overall 10)	641	121 (18.9)	15.9 to 21.9
B	2, 4, 7, 9 (Group 1)	113	27 (23.9)	16.0 to 31.8
C	1, 3, 5, 6, 8, 9 (Group 2), 10	528	94 (17.8)	14.5 to 21.1

Table 6: Point estimate and 95% CI for the outcome of death.

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New Thromboses

Thromboembolic complications are reported for some but not all patients. Kelton's tables below outline how individual articles contribute to the thromboembolic rate. The tables below include 98% of the patients in the articles. The tables below demonstrate the higher event rate for thromboembolic events in the HITTS population compared to the combined HIT and HITTS population. The frequency of thromboembolic complications in the HIT and HITTS population is 35.8% (95% CI 31.7 to 39.9). The frequency of thromboembolic complications in the HITTS population is 96% (95% CI 92.2 to 99.8).

Outcome: TEC

	Study	N	#TECs	%	95% CI
1	Silver 1983	62	38	61.3	49.2 to 73.4
2	Makhoul 1986 **	25	25	100	
3	Laster 1987	169	30	17.8	12 to 23.6
4	AbuRahma 1991**	12	TEC needed for entry		
5	Walls 1992 (Ann Thor Surg)	82	31	37.8	27.3 to 48.3
6	Walls 1992 (ASAIO Journal)	35	17	48.5	31.9 to 65.1
7	Singer 1993	11	9	81.8	79.7 to 81.8
8	DeMasi 1994	10	8	80	55.2 to 104.8
9	Warkentin 1996 (Overall)	127	96	75.6	68 to 83
	Warkentin Group 1**	65	63	96.9	93.9 to 99.9
	Warkentin 1996 Group 2'	62	33	52.8	40.4 to 65.2
10	Nand 1997	108	32	29	20.4 to 37.6

* 159/243 TECs but only 88/243 related to HIT episode. Also, 13 patients were treated on 2 occasions.
' Group 2 consisted of patients with HIT (no TECs at diagnosis)
** HITT patients only (Group 1)

Overall Outcome Estimate:

Overall, estimates have been provided for all studies (Group A); studies including just HITT patients (Group B); and, studies including a combination of HIT and HITTS (Group C).

Group	Studies Included	Total N	Number of TECs	95% of CI
A	1-3, 5-8, 9(Overall), 10	629	286 (45.5)	41.6 to 49.4
B	2, 7, 9 (Group 1)	101	97 (96)	92.2 to 99.8
C	1, 3, 5, 6, 8, 9 (Group 2),10	528	189 (35.8)	31.7 to 39.9

tc: Study #4 was not included as TEC was required for eligibility and new or recurring TECs were not reported.

Table 4: Point estimate and 95% CI for the outcome of thromboembolic complications (TEC).

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Amputation

Kelton's tables below demonstrate how individual articles contributed to the calculation of rates for the endpoint of amputation. Not all articles reported an event rate for amputation. Only 62% of patients contributed to the table below. The tables demonstrate that the amputation rate for HITTS patients compared to HIT and HITTS population is much higher. The frequency of amputation is 52.1% (95% CI 38 to 66.2) for the HITTS patients. The frequency of amputation for the HIT and HITTS population is 4.9% (95% CI 2.6 to 7.2).

Outcome : Amputation

	Study	N	#Amp	%Amp	95% CI
1	Silver 1983	62	5	8.1	1.3 to 14.9
2	Makhoul 1986	25	16	64	45.2 to 82.8
3	Laster 1987	169	4	2.4	0.1 to 4.7
4	AbuRahma	12	6	50	21.7 to 78.3
5	Walls 1992 (Ann Thor Surg)	82	Not Reported		
6	Walls 1992 ASAID Journal	35	Not Reported		
7	Singer 1993	11	3	27.3	1.0 to 53.6
8	DeMasi 1994	10	5	50	19 to 80.9
9	Warkentin 1996	127	Not Reported		
10	Nand 1997	108	3	2.8	-0.3 to 5.9

* 13 patients were treated on 2 occasions

Overall Outcome Estimate:
Overall estimates have been provided for all studies (Group A); studies including just HITT patients (Group B), and studies including a combination of HIT and HITTS (Group C).

Group	Studies Included	Total N	Number of Amputations (%)	95% of CI
A	1-4, 7, 8, 10	397	42 (10.6)	7.6 to 13.6
B	2, 4, 7	48	25 (52.1)	38 to 66.2
C	1, 3, 8, 10	349	17 (4.9)	2.6 to 7.2

Note: Studies 5, 6 and 9 have not been included as no data on amputations was provided.

Table 5: Point estimate and 95% CI for the outcome of amputation.

Sponsor's text volume 28.16a

Medical Reviewer's Analysis of the Literature

A major difficulty with literature overview arises from the limitations of the articles selected for inclusion. Dr. Kelton's literature search was limited to reports published in English language literature from 1983 to 1997 and to articles containing 10 or more adult patients. There may have been some publication bias.
In general, the articles selected were not uniform in several aspects:

1) inclusion and exclusion criteria
2) endpoints reported
3) use of additional anticoagulant medication after the diagnosis of HIT/HITTS which would affect the endpoints

4) definitions of HIT and HITTS
5) the definitions of the endpoints are not the same as the NDA submission
6) the time criteria of the 37 days for the endpoint was not part of any study

All these variables may affect the validity of the literature overview.

This reviewer performed Medline searches using the same criteria used by Dr. Kelton. Only one additional article was found. Silver et. al. published Heparin-Induced Thrombocytopenia in the Newborn.[7] This article described heparin-induced thrombocytopenia in the newborn (preterm and term infants). Fourteen infants had heparin-induced antibodies. The article described the development of thromboses and death in these infants.

Kelton's literature analysis contains several deficiencies that make the use of the frequency of events difficult to use and compare with the new historical controls:

1) The majority of the articles report deaths due to heparin not deaths overall. The NDA definition is death rate overall. Thus the literature analysis death rate reflects a lower death rate than if deaths overall were included.
2) Kelton does not always use the same definition of death. For example, the Silver article reports the death rate overall as well as the death rate due to heparin. In his literature analysis, Kelton uses death rate due to heparin for the Silver's study. For the Makhoul article, he uses overall death rates, rather that Makhoul's death rate due to heparin.
3) The literature reports do not provide sufficient information on duration of observation for the events such as new thromboses, amputation, and death.
4) The Silver article is not concurrent with the NDA historical control database.
5) The composite endpoint for the Silver article is taken from a table, which includes CVA hemorrhage, and wound hematomas, which are not part of the composite endpoint.
6) The Makhoul article described patients with HITTS only. Although the article described thromboembolic complications, no details were provided to determine the rates of new TEC occurring after the original thrombosis. This reviewer would not have included this article in the literature analysis because it did not contain sufficient information for all three endpoints.
7) The Laster article does not make a distinction between the event rates for HIT and HITTS population. This article reports the death rate due to heparin only.
8) The AbuRahama article described patients with the "White Clot Syndrome". These patients are clearly HITTS patients evaluated for the endpoints of death and amputation. No information was collected on new TEC events. Kelton used this article to calculate the composite event rate for HIT/HITTS and the amputation and death rate for HITTS. This article did not contain sufficient information for all three component endpoints.
9) The Walls article (Ann Thor Surg 1992) reports at least 2 patients with amputations, however, these events were not included in the calculation of the amputation rate.
10) Some patients may have been included in both Walls article (Ann Thor Surg 1992) and Walls article (ASAIO 1992). No disclaimer was made in either article about double reporting of patients. This reviewer would not have included both articles in this literature review unless it was specified that there was no overlap.
11) The Walls article (ASAIO 1992) does not provide information on amputation.
12) The Warkentin article is a retrospective review of patients with serologically documented heparin-induced thrombocytopenia from a single region in Canada. The article does not report any information on amputation.
13) The Nand article only reports events on the 32 patients who developed thromboembolic complications out of the 108 patients who had HIT. Thus the death rate reported reflects the HITTS population. The death rate is actually 5/32 or 15.6% for the HITTS population. A separate reporting of the death rate for HIT patients is not done.

14) The patients in the Nand article are part of a retrospective survey of all patients with thrombocytopenia and a positive heparin-induced platelet aggregation seen at Loyola from January 1991 to December 1994. It must be noted that the new historical control population included in this NDA was derived from Loyola patients with seropositive HIT/HITTS diagnosed between January 1991 and December 1993. Patients overlap is likely between this literature review and the NDA historical control database.

Table 32 from Kelton's article represents the comparison of the new historical control group used for this NDA submission and the results from the literature overview. The death rate is lower in the literature analysis compared to the NDA historical controls. There are several reasons for this apparent discrepancy:

1) The mortality rate reported in most of the articles included only death due to heparin.
2) The mortality rate reported in the NDA historical controls includes death due to all causes.
3) The Nand article has an extremely low mortality rate.
4) The death rate in the literature analysis is a composite of the death rates for HIT/HITTS population from articles where this information was not clearly presented.

Table 32 Comparison Between the Historical Control Group and a Literature Analysis of Published Reports of HIT/HITTS for the Incidence of All-Cause Death and the Composite of All-Cause Death, All-Cause Amputation or Development of New Thrombosis

	HIT (%)		HITTS (%)	
	Literature Analysis[a]	Historical Control	Literature Analysis[b]	Historical Control
Death	17.8	21.8	23.9	28.3
(95%CI)	(14.5-21.1)		(16.0-31.8)	
Composite	41.5	38.8	63.3	56.5
(95%CI)	(36.7-46.3)		(35.2-92.1)	

[a] From 7 studies (death) and 8 studies (composite) with HIT and HITTS patients.
[b] From 4 studies (death) and 1 study (composite) with HITTS patients.
Reference Documentation Appendix 16.2.20

Sponsor's table volume 28.16a

Due to the variability of the endpoints described in the literature reports, the composite outcome rates are less reliable.

The frequency of deaths is the most accurate event rate for the literature review. This reviewer will not assess death rates separately for the HIT and HITTS populations since few of the articles reported death for the HIT and HITTS populations separately. Therefore, death rates from the literature and from the historical controls were compared using the endpoint of all deaths whenever this information was available. The results are shown in the following table:

Deaths reported in the literature review and historical controls for combined HIT/HITTS populations

	Literature overview	HIT/HITTS historical control
Total patients (N=)	641	193
Deaths	127*	45
Percent	19.8%	23.3%

*This number tries to reflect the all cause death rate and is similar to the NDA death definition. In the article by Silver, the death rate is reported as 14 due to HIT/HITTS and 20 due to all causes. This reviewer added those six patients in the total deaths for the literature overview.
Reviewer's table

The rate of all deaths from the literature overview remained lower than from the historical controls. Confounding factors for death rate include the findings reported in the Nand and Walls articles. First, the death rate for the Nand article is 4.6%, which is considerably different from the rate reported by all the other articles. The Nand article may also overlap with the NDA historical control database. For these reasons this reviewer has excluded these patients from the literature death rate analysis. Second, the Walls articles may contain patients who overlap with the historical control, therefore this reviewer has excluded the death rates from the Walls articles from the analysis below.

Death Reanalysis for literature review and historical controls for the combined HIT/HITTS population excluding the death rate in the Nand article and the Walls articles

	Literature overview	HIT/HITTS new historical control
Total patients (N=)	416	193
Deaths	84*	45
Percent	20.2%	23.3%

* This number tries to reflect the all cause death rate and is similar to the NDA death definition. In the article by Silver, the death rate is reported as 14 due to HIT/HITTS and 20 due to all causes. This reviewer added those six patients in the total deaths for the literature overview.
Reviewer's table

The death rates are similar for the combined population of HIT/HITTS after the Nand article and Walls articles are excluded. If all the articles included in the literature overview had reported all-cause mortality rather than that due to heparin alone, the death rate would have been higher.

Conclusion

The literature overview supports the data obtained for the historical controls submitted in the NDA.

CLINICAL TRIALS

Study ARG-911

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

Description of Protocol:
This study was an open-label, multicenter, historically controlled, prospective study of patients with HIT or HITTS treated with argatroban at dose of 2-10 μg/kg/min. The goals of the study were to evaluate the adequacy of argatroban as a prophylactic anticoagulant for the prevention of

thrombosis in patients with HIT, and to evaluate the adequacy of argatroban as an anticoagulant in the treatment of patients with HITTS.

The sponsor defined adequate argatroban treatment as either:
a) dosing needed to achieve a target APTT of 1.5 to 3 times baseline
b) dosing until appropriate anticoagulation was achieved with other agents (oral anticoagulants)
c) dosing until treatment was continued up to 14 days

The efficacy endpoints for this submission were the combined endpoint (death, amputation, and new thrombosis), all-cause death, all-cause amputation, and new thrombosis.

Amendments:

There were a total of six amendments to study protocol ARG-911. All amendments were made after the study was initiated.

Amendments for Study ARG-911

Date of Amendment	Synopsis of Amendment
March 28, 1995	Increase in number of patients from 100 with HIT/HITTS to 300 patients with 150 patients constituting a treatment arm and 150 patients constituting a "prophylactic arm" Additional pre-treatment chemistry and urine tests aPTT testing to be done centrally and locally. Historical control population with patients collected from centers participating in the study as well as other centers Typographical errors
May 1, 1995	Patients could be enrolled in absence of a heparin challenge or thrombocytopenia if a documented history of a positive heparin-induced platelet aggregation exists within the past 12 months All aPTTs performed at a central lab Hemostasis and Thrombosis Research Laboratories of Loyola University Medical Center served as Core laboratory Study Chairman-Bruce Lewis MD at Loyola Change in blood work sampling
September 15, 1995	Historical control population redefined to screen patients after January 1, 1993, inclusion/exclusion criteria used for screening better defined
September 22, 1995	Inclusion criteria removed most references to heparin-induced platelet aggregation Clarification of collection of information on concomitant clinical conditions Clarification of some radiologic tests (timing) Thirty day follow up studies
July 19,1996	Extended maximum amount of time a patient may be treated from 7 days to 14 days
December 30, 1996	Expanded historical controls to include patients with a positive SRA to match argatroban treated patients with a positive SRA

Reviewer's table

Description of Patients:

The historical control and the argatroban-treated patients are described below.

Argatroban-treated Patients

All patients who received at least one dose of the drug were included in this study. These patients constituted the argatroban arm of the intention-to-treat analysis. Appendix 1 contains a complete listing of number of patients by investigator/site.

Inclusion criteria were:

1) Males or non-pregnant females ≥ 18 and ≤ 80 years of age
2) Those with documented HITTS or HIT in the absence of thrombosis or history of a positive heparin-induced platelet aggregation test
    a) HITTS was defined by
        i) a fall in platelet count to less than 100,000/μL or a 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation other than HITTS
        ii) presence of an arterial or venous thrombosis documented by appropriate imaging technique (duplex Doppler or angiography) or supported by clinical evidence such as a myocardial infarction, stroke, pulmonary embolism, or other clinical indications of vascular occlusion (absence of pulse, cold , cyanotic extremities, etc.)
    b) HIT was defined by
        i) a fall in platelet count to less than 100,000μ/L or a 50% decrease in platelets after the initiation of heparin therapy with no apparent explanation other than HIT
        ii) the absence of clinical arterial or venous thrombosis
    c) patients could be enrolled in the absence of heparin challenge or thrombocytopenia if they had a documented history of a positive laboratory test for HIT/HITTS (e.g. heparin-induced platelet aggregation test, SRA, etc.)
3) patients willing and able to give informed consent

Exclusion criteria were:

1) any condition which in the investigator's opinion, contraindicated the use of argatroban or endangered the patient if he or she participated in this trial
2) clinically significant or uncontrolled endocrine, hepatic, renal, pulmonary, gastrointestinal, or psychiatric disorder of sufficient severity that the investigator deemed antithrombotic therapy with argatroban to be contraindicated
3) unexplained aPTT > 200% of control at baseline
4) documented coagulation disorder or unexplained bleeding diathesis unrelated to HITTS
5) lumbar puncture within the past 7 days
6) history of previous aneurysm, hemorrhagic stroke, or recent thrombotic stroke (within the past 6 months) unrelated to HITTS
7) prothrombin time greater than 16 seconds at screen in the absence of Coumadin®
8) known clinical site of bleeding. Patients with a known site of clinical bleeding could be enrolled if the investigator deemed the risk of continued thrombosis outweighed the potential bleeding risk.
9) females of known or suspected pregnancy
10) breast feeding females
11) participation in other clinical drug trials within the past 30 days
12) history of hypersensitivity to argatroban
13) concomitant use of cimetidine
14) previous participation in this trial

The following tables list the breakdown of treated and control patients by subcategory. All three categories were permitted by study design and constitute the clinical population of HIT/HITTS. Nineteen percent of HIT patients in the argatroban-treated group and 5% of HIT patients in the historical control did not have thrombocytopenia at the time of inclusion in the study. Reviewer comment: These patients represent HIT patients needing prophylactic anticoagulation.

Argatroban-treated Patients for ARG-911 (Intention-to-Treat Analysis)

Subcategory	Number of Patients
HIT	160
New diagnosis	129 (129/160=81%)
Previous diagnosis (HIT OR HITTS) in absence of current thrombocytopenia	31 (31/160=19%)
HITTS - New diagnosis	144

Reviewer's table

Historical Control for ARG-911 ("Intention-to Treat" Analysis)

Subcategory	Number of Patients
HIT	147
New diagnosis	139 (139/147=95%)
Previous diagnosis (HIT OR HITTS) in absence of current thrombocytopenia	8 (8/147=5%)
HITTS (new diagnosis)	46

Reviewer's table

Results:

Two hundred and fifty-four of 304 (83%) patients completed the study. Completion of the study was defined as:

1) until clinical resolution of the underlying condition
2) until appropriate anticoagulation was provided with other agents
3) until treatment was completed (up to 14 days)

Patient Disposition

The study protocol planned analysis was on the intent-to-treat population. The evaluable population are those patients the DMSC considered to have HIT/HITTS. Tested positive is the population of patients who had a positive HIPA or SRA test.

Patient Disposition for ARG-911

Population	HIT/ Historical Control N (%)	HIT/ Argatroban-Treated N (%)	HITTS/ Historical Control N (%)	HITTS/ Argatroban-Treated N (%)	Total Historical Control N (%)	Total Argatroban-Treated N (%)
Intent-to-Treat	147	160	46	144	193	304
Evaluable[a]	147	146 (91%)	46	134 (93%)	193	280 (92%)
Repeat Patients	0	2	0	1	0	3
Tested Positive[b]	119 (81%)	80 (50%)	30 (65%)	94 (65%)	149 (77%)	174 (57%)
Safety Analysis	147	160	46	144	193	304

Reviewer's table

a Evaluable patients were all those patients who in the opinion of the DMSC continued to meet the protocol inclusion criteria for HIT or HITTS. Twenty-four patients were excluded for the following reasons: no thrombocytopenia (12 patients), severe sepsis causing 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). See Appendix 1 for further details. Included in the evaluable population are three patients who were repeat patients.

b Tested positive means these patients had either a positive heparin-induced platelet aggregation or serotonin release assay at any time during the study.

Completion of Infusion or Premature Discontinuation of Argatroban

Patients completing argatroban infusion and withdrawals due to adverse events are listed below. Patients could withdraw from the study due to an adverse event but still be counted as having completed the infusion. The protocol permitted the infusion to be interrupted for safety reasons (adverse event, sensitivity, severely decreased platelet count, etc.) for up to 24 hours. If the infusion was interrupted for more than 24 consecutive hours, the patient was discontinued from the study. The infusion could also be discontinued at least 30 minutes before any surgical procedure. The infusion was reinstituted post operatively as soon as hemostatic control was achieved. Patients were withdrawn if they were to undergo percutaneous transluminal coronary angioplasty or any surgical procedure on argatroban. Other reasons for withdrawal included non-compliance and investigator or patient request.

Argatroban Therapy for ARG-911

Patient Disposition	HIT N	HIT %	HITTS N	HITTS %
Total number patients	160	100%	144	100%
Total number evaluable patients	147	91%	134	93%
Total number completed[a] (ITT)	139	87%	135	94%
Completed[b]				
Withdrawn - due to Adverse Event- bleed	5	3.1%	12	8.3%
Withdrawn - due to Adverse Event- other (2 hepatic failure)	7	4.4%	0	
Withdrawn – no information available	12	7.5%	17	11.8%
Withdrawn - endpoint reached (thrombosis, death)	3[e]	1.9%	6	4.2%
Up to Maximum Time Allowable[b] (ITT)	20	13%	34	24%
Resolution of Underlying Condition (ITT)[b]	18	11%	10	7%
Transferred to Warfarin (ITT)[b]	100	63%	102	77%
Transferred to Other Anticoagulant (ITT) - not known (assumed)	1	1%	5	3%
Did not complete (discontinued early)	21	13%	9	6 %
Surgery	4	2.5%	2	1.4%
Procedure	3	1.9%	0	
Patient/Family request	2	1.3%	2	1.4%
Physician request[c]	2	1.3%	2	1.4%
Switched to another argatroban trial	3	1.9%	0	
Elevated coagulation parameters	2	1.3%	2	1.4%
DNR/ life support withdrawn	1	.6%	1	.7%
Switched to another LMWH	1	.6%	0	
Catheter problem	1	.6%	0	
Transferred to another hospital	1	.6%	0	
Inability to give medication	1	.6%	0	

a Includes patients withdrawn due to Adverse events
b Patients may be in more than one group
c One patient discontinued as a result of advice by cardiology.
e One patient had an arrhthymia (bradycardiac arrest).
Reviewer's table

Protocol Deviations
Twenty-four patients failed to meet the inclusion/exclusion criteria according to DMSC. Three patients were repeat patients. These patients were considered to be protocol violations. See Appendix 3 for details.

Demographics
The demographic characteristics of the groups were well matched except for characteristics listed in the table below. The new historical controls were on average 4.5 years older than the argatroban-treated patients were. No current evidence exists that these demographic characteristics (age or sex) are important for development or outcome from HIT/HITTS.

Statistically Significant Different in Demographic Characteristics

Parameter	HIT/ Historical Control Patients	HIT/ Argatroban-treated Patients	P-value	HITT/ Historical Control Patients	HITT/ Argatroban-treated Patients	P-value
Age (years)- Mean±SD	66.1±12.3	61.3±13.5	0.001	65.7±10.9	61.5±12.7	0.045
SEX – M/F	82/64	68/92	0.022	27/18	72/72	0.305
Test Positive	119 (81%)	80 (50%)	0.0001	30 (65%)	94 (65%)	1.000

Reviewer's table

The table below demonstrates the racial composition of the study. No further conclusions can be drawn because the non-Caucasian population is small.

Racial Demographics for Study ARG-911

Race	HIT/ Historical Control Patients	HIT/ Argatroban-treated Patients	HITT/ Historical Control Patients	HITT/ Argatroban-treated Patients
Caucasian	122 (83%)	142 (89%)	38 (83%)	123 (85%)
Black	10 (7%)	10 (6%)	6 (13%)	14 (10%)
Other	15 (10%)	8 (5%)	2 (4%)	7 (5%)

Reviewer's table

Platelet Counts and Heparin Exposure between groups

The table below shows the differences between baseline platelet counts and prior heparin use within the prior 6 weeks for the groups. The baseline platelet counts were lower for the argatroban-treated patients in both HIT and HITTS groups. The differences in baseline platelet count between the two groups do not have clinical significance.[1,2,5,6] The definition of HIT/HITTS for the majority of the patients in both the argatroban-treated and historical control groups depended on the percent drop in platelet counts. The definition of prior heparin exposure was within the past six weeks. These patients consisted of those who were serologically positive but did not have thrombocytopenia at the start of the study.

Table 14 Baseline Diagnostic Characteristics of Argatroban and Appropriate New Historical Control Patients: Intent-to-Treat Patient Population

	HIT		HITTS	
Parameter	Historical Control (N =147)	Argatroban (N =160)	Historical Control (N =46)	Argatroban (N =144)
Baseline Platelet Count (x10^3/µL)				
N	129	138	39	132
Median	111.0	82.0	94.0	66.5
Interquartile Range				
Prior[a] Heparin Exposure, N (%)				
Yes	145 (99)	139 (87)	46 (100)	140 (97)
No	2 (1)	21 (13)	0 (0)	4 (3)

[a] Within six weeks prior to baseline.
Reference Documentation Appendix 16.2.6

Sponsor's table volume 28.10

Pre-existing Medical Conditions

The argatroban-treated patients had more underlying medical conditions at baseline than the historical controls. There were statistically significant differences between the historical controls and the HIT and HITTS groups. There may be under-reporting of the medical conditions in the historical controls because the information collected on these patients was retrospective while the information collected on the argatroban-treated patients was prospective.

Pre-existing Medical Conditions for ARG-911

Table 16 Summary of Baseline Medical/Surgical/Invasive Procedure Conditions of Patients: Intent-to-Treat Patient Population. Number (%) of Patients with Each Diagnosis, Ongoing Procedure or Previous Surgery (From ICD-9 Coded Terms), by Body System

	HIT					HITTS				
	Historical Control		Argatroban			Historical Control		Argatroban		
Baseline Condition[a]	N	(%)	N	(%)	P-value	N	(%)	N	(%)	P-value
Total Number of Patients	147		160			46		144		
Infectious Disease (001.0 - 139.8)	10	(7)	[illegible]	[illegible]	0.0001	4	(9)	[illegible]	(21)	0.077
Neoplasms/Oncology & Hematology (140.0 - 239.9)	[illegible]	(23)	[illegible]	[illegible]	[illegible]	4	(9)	[illegible]	(21)	0.077
Endocrine, Nutritional & Metabolic (240.0 - 279.9)	73	(50)	[illegible]	[illegible]	0.004	25	(54)	103	(72)	0.046
Blood & Blood-forming Organs (280.0 - 289.9)	22	(15)	107	(67)	<0.0001	9	(20)	98	(68)	<0.0001
Mental Disorders (290.0 - 319)	23	(16)	65	(41)	<0.0001	11	(24)	[illegible]	(33)	0.274
Nervous System (320.0 - 389.9)	19	(13)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	(34)	0.041
Circulatory System (390 - 459.9)	126	(86)	160	(100)	<0.0001	43	(94)	[illegible]	(96)	0.154
Respiratory System (460 - 519.9)	[illegible]	[illegible]	[illegible]	[illegible]	<0.0001	10	(22)	[illegible]	(61)	<0.0001
Digestive System (520.0 - 579.9)	[illegible]	[illegible]	95	(59)	<0.0001	15	(33)	71	(49)	0.061
Genitourinary System (580.0 - 629.9)	[illegible]	[illegible]	[illegible]	[illegible]	<0.0001	9	(20)	[illegible]	(47)	<0.0001
Skin and Subcutaneous Tissue (680.0 - 709.9)	5	(3)	[illegible]	(19)	<0.0001	3	(7)	[illegible]	(13)	0.417
Musculoskeletal System (710.0 - 739.9)	26	(18)	52	(33)	0.004	8	(17)	[illegible]	(42)	0.003
Congenital Anomalies (740.0 - 759.9)	0	(0)	[illegible]	[illegible]	0.007	0	(0)	7	(5)	0.198
Injury/Poisoning (800.0 - 999.9)	[illegible]	(27)	[illegible]	[illegible]	0.004	13	(28)	78	(54)	0.002

[a] Coded using ICD 9.
A patient is counted once per category.
Statistical comparisons made with Fisher's Exact Test.
Reference Documentation Appendix 16.1.9 (Tables A5 and B5).

Sponsor's table volume 28.10

Prior Medication Use

The table below shows prior medication use. Prior medication usage was higher within most drug categories for the argatroban-treated group. The differences observed between groups may partially be due to the retrospective reporting bias for the historical control.

Table 17 Number and Percentage of Patients Who Received Prior Medications (Other Than Heparin) by Anatomical/Therapeutic/Chemical (ATC) Classification; Most Frequently Prescribed: Intent-to-Treat Patient Population

	HIT				HITTS			
	Historical Control		Argatroban		Historical Control		Argatroban	
ATC Classification	N	(%)	N	(%)	N	(%)	N	(%)
Total Number of Patients	147		160		46		144	
Any Medication	60	(40.8)	148	(92.5)	26	(56.5)	135	(93.8)
Cardiac Therapy	26	(17.7)	81	(50.6)	14	(30.4)	86	(59.7)
Analgesics	24	(16.3)	74	(46.3)	12	(26.1)	94	(65.3)
Diuretics	8	(5.4)	74	(46.3)	8	(17.4)	75	(52.1)
Antibacterials for Systemic Use	27	(18.4)	68	(42.5)	17	(37.0)	85	(59.0)
Antithrombotic Agents	10	(6.8)	66	(41.3)	8	(17.4)	68	(47.2)
Plasma Substitutes and Perfusion Solutions	13	(8.8)	65	(40.6)	7	(15.2)	71	(49.3)
Psycholeptics	19	(12.9)	58	(36.3)	14	(30.4)	71	(49.3)
Antacids, Drugs for Treatment of Peptic Ulcer and Flatulence	12	(8.2)	48	(30.0)	15	(32.6)	47	(32.6)
Antihistamines for Systemic Use	11	(7.5)	41	(25.6)	6	(13.0)	47	(32.6)
Mineral Supplements	7	(4.8)	38	(23.8)	7	(15.2)	37	(25.7)
Laxatives	13	(8.8)	34	(21.3)	5	(10.9)	41	(28.5)
Beta Blocking Agents	8	(5.4)	28	(17.5)	6	(13.0)	39	(27.1)
Anesthetics	10	(6.8)	25	(15.6)	4	(8.7)	38	(26.4)
Calcium Channel Blockers	9	(6.1)	22	(13.8)	7	(15.2)	35	(24.3)
Agents Acting on the Renin-Angiotensin System	6	(4.1)	21	(13.1)	6	(13.0)	22	(15.3)
Antispasmodic and Anticholinergic Agents and Propulsive	4	(2.7)	19	(11.9)	3	(6.5)	14	(9.7)
Antihypertensives	9	(6.1)	18	(11.3)	3	(6.5)	14	(9.7)
Drugs Used In Diabetes	5	(3.4)	16	(10.0)	3	(6.5)	32	(22.2)
Muscle Relaxants	8	(5.4)	13	(8.1)	0	(0)	13	(9.0)

Prior medications are medications taken two weeks prior to study enrollment.
Reference Documentation Appendix 16.2.9 and Appendix 16.4.6

continued

Table 17 Number and Percentage of Patients Who Received Prior Medications (Other Than Heparin) by Anatomical/Therapeutic/Chemical (ATC) Classification; Most Frequently Prescribed: Intent- to-Treat Patient Population (Continued)

	HIT				HITTS			
	Historical Control		Argatroban		Historical Control		Argatroban	
ATC Classification	N	(%)	N	(%)	N	(%)	N	(%)
Antihemorrhagics	2	(1.4)	13	(8.1)	2	(4.4)	11	(7.6)
Antiinflammatory and Antirheumatic Products	4	(2.7)	12	(7.5)	5	(10.9)	12	(8.3)
Vitamins	1	(0.7)	12	(7.5)	1	(2.2)	9	(6.3)
Corticosteroids for Systemic Use	6	(4.1)	11	(6.9)	1	(2.2)	19	(13.2)
Anti-asthmatics	4	(2.7)	11	(6.9)	4	(8.7)	15	(10.4)
All Other Therapeutic Products	3	(2.0)	11	(6.9)	3	(6.5)	9	(6.3)
Antianemic Preparations	0	(0)	7	(4.4)	2	(4.4)	12	(8.3)
Ophthalmologicals	2	(1.4)	2	(1.3)	1	(2.2)	13	(9.0)

Prior medications are medications taken two weeks prior to study enrollment.
Reference Documentation Appendix 16.2.9 and Appendix 16.4.6

Sponsor's table volume 28.1 0

Concomitant Medications

The table below shows concomitant medication usage within groups. Differences of greater than 5% between the treatment groups (with a higher percentage for the historical control) include the following categories: cardiac therapy, antacids, drugs for the treatment of peptic ulcer disease

and flatulence, diuretics, mineral supplements, diabetes medication, calcium channel blockers, angiotensin inhibitors, and antihemorrhagics.

Table 18 Number and Percentage of Patients Who Received Concomitant Medication by Anatomical /Therapeutic/Chemical (ATC) Classification; Most Frequently Prescribed: Intent-to-Treat Patient Population

	HIT				HITTS			
	Historical Control[a]		Argatroban		Historical Control[a]		Argatroban	
ATC Classification	N	(%)	N	(%)	N	(%)	N	(%)
Total Number of Patients	147		160		46		144	
Any Medication	145	(98.6)	160	(100)	46	(100)	144	(100)
Cardiac Therapy	110	(74.8)	101	(63.1)	31	(67.4)	88	(61.1)
Analgesics	54	(36.7)	98	(61.3)	32	(69.6)	107	(74.3)
Unable to be Classified	78	(53.1)	98	(61.3)	28	(60.9)	100	(69.4)
Antibacterials for Systemic Use	80	(54.4)	86	(53.8)	29	(63.0)	97	(67.4)
Psycholeptics	48	(32.7)	86	(53.8)	19	(41.3)	74	(51.4)
Antacids, Drugs for Treatment of Peptic Ulcer and Flatulence	70	(47.6)	84	(52.5)	30	(65.2)	66	(45.8)
Diuretics	93	(63.3)	83	(51.9)	19	(41.3)	84	(58.3)
Antithrombotic Agents	36	(24.5)	71	(44.4)	17	(37.0)	64	(44.4)
Laxatives	33	(22.4)	63	(39.4)	12	(26.1)	69	(47.9)
Plasma Substitutes and Perfusion Solutions	55	(37.4)	61	(38.1)	16	(34.8)	71	(49.3)
Mineral Supplements	29	(19.7)	41	(25.6)	13	(28.3)	22	(15.3)
Antihistamines for Systemic Use	15	(10.2)	36	(22.5)	13	(28.3)	35	(24.3)
Beta Blocking Agents	34	(23.1)	35	(21.9)	11	(23.9)	45	(31.3)
Antianemic Medications	15	(10.2)	35	(21.9)	5	(10.9)	23	(16.0)
Anesthetics	19	(12.9)	33	(20.6)	6	(13.0)	37	(25.7)
Drugs Used in Diabetes	37	(25.2)	32	(20.0)	17	(37.0)	56	(38.9)
Calcium Channel Blockers	47	(32.0)	32	(20.0)	14	(30.4)	36	(25.0)
Anti-asthmatics	28	(19.0)	27	(16.9)	16	(34.8)	35	(24.3)
Agents Acting on the Renin-Angiotensin System	49	(33.3)	26	(16.3)	7	(15.2)	30	(20.8)

[a] Medications received while hospitalized
Reference Documentation Appendix 16.2.10 and Appendix 16.4.6

Continued

Table 18 Number and Percentage of Patients Who Received Concomitant Medication by Anatomical /Therapeutic/Chemical (ATC) Classification; Most Frequently Prescribed: Intent-to-Treat Population (*Continued*)

	HIT				HITTS			
	Historical Control[a]		Argatroban		Historical Control[a]		Argatroban	
ATC Classification	N (147)	(%)	N (160)	(%)	N (46)	(%)	N (144)	(%)
Vitamins	13	(8.8)	22	(13.8)	5	(10.9)	16	(11.1)
Antispasmodic and Anticholinergic Agents and Propulsive	13	(8.8)	20	(12.5)	3	(6.5)	14	(9.7)
Corticosteroids for Systemic Use	16	(10.9)	18	(11.3)	5	(10.9)	17	(11.8)
Antihypertensives	14	(9.5)	12	(7.5)	1	(2.2)	15	(10.4)
Muscle Relaxants	11	(7.5)	12	(7.5)	4	(8.7)	15	(10.4)
Antimycotics for Systemic Use	7	(4.8)	12	(7.5)	4	(8.7)	11	(7.6)
Psychoanaleptics	6	(4.1)	12	(7.5)	4	(8.7)	9	(6.3)
Antidiarrheal, Intestinal Antiinfectives	3	(2.0)	11	(6.9)	1	(2.2)	8	(5.6)
Cough and Cold Preparations	2	(1.4)	10	(6.3)	1	(2.2)	5	(3.5)
Thyroid Therapy	12	(8.2)	9	(5.6)	0	(0.0)	2	(1.4)
Antifungals for Dermatologic Use	14	(9.5)	8	(5.0)	5	(10.9)	13	(9.0)
All other Therapeutic Products	4	(2.7)	8	(5.0)	0	(0)	8	(5.6)
Antiepileptics	4	(2.7)	8	(5.0)	1	(2.2)	6	(4.2)
Antiinflammatory and Antirheumatic Products	7	(4.8)	8	(5.0)	3	(6.5)	4	(2.8)
Antihemorrhagics	11	(7.5)	4	(2.5)	1	(2.2)	9	(6.3)

[a] Medications received while hospitalized
Reference Documentation Appendix 16.2.10 and Appendix 16.4.6

Sponsor's table volume 28.10

Sponsor's Efficacy Analyses

Categorical and Time-To-Event Analyses
The sponsor presents both analyses because of the variability in the follow-up period. Sixty-two historical control and 74 argatroban-treated patients had follow-up periods less than 37 days. The minimum follow-up period for the historical control was 5 days while the minimum period of follow-up time for the argatroban-treated patients was 19 days.

Categorical analysis

Listed below are the efficacy results for Study ARG-911. The patients are listed once by the most severe endpoint. A few patients did achieve multiple endpoints.

For the HIT population, this study demonstrated that use of argatroban resulted in a statistically significant reduction in the composite endpoint of new thrombosis, death, and amputation and the thrombosis endpoint. A lower percentage of argatroban-treated patients in the HIT group died during the 37-day period. No treatment benefit was demonstrated for the HIT population for the endpoint of amputation.

For the HITT population, a lower percentage of patients experienced new thrombosis or death compared to the historical controls. No benefit was seen for amputation.

Efficacy Results for ARG-911 (37-day period)

Parameter	HIT / Historical control	HIT/ argatroban-treated	P-value	HITTS/ Historical control	HITTS/ argatroban-treated	P-value
Total number	147	160		46	144	
Reached composite endpoint (ITT)	57/147 (38.8%)	41/160 (25.6%)	0.014[a]	26/46 (56.5%)	63/144 (43.8%)	0.131[a]
Reached Composite endpoint (evaluable population)	57/147 (38.8%)	37/146 (25.3%)	0.006[c]	26/46 (56.6%)	62/134 (46.3%)	0.039[c]
Reached Composite endpoint (seropositive population)	45/119 (37.8%)	16/80 (20%)	0.004[c]	19/30 (63.3%)	43/94 (45.7%)	0.018[c]
Death (all causes) (ITT)	32 (21.8%)	27 (16.9%)	0.311[b]	13 (28.3%)	26 (18.1%)	0.146[b]
Amputation (all causes)	3 (2%)	3 (1.9%)	1[b]	4 (8.7%)	16 (11.1%)	0.787[b]
New thrombosis	22 (15%)	11 (6.9%)	0.027[b]	9 (19.6%)	21 (14.6%)	0.486[b]

[a]Chi-squared test
[b]Fisher's test
[c]Kaplan-Meier Log rank test
Reviewer's table

Repeat Patients

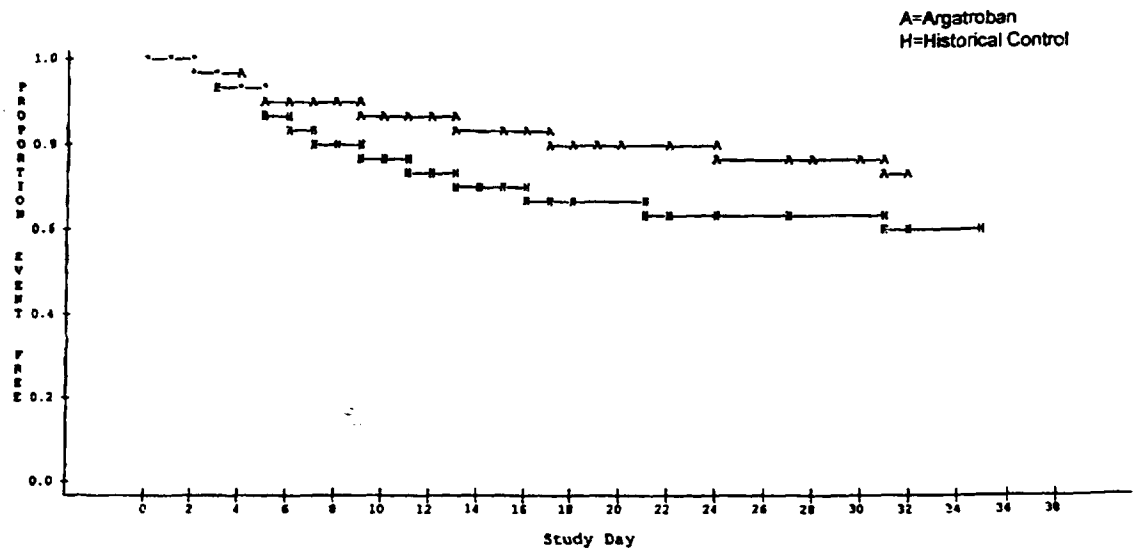
No repeat patients developed thromboses or had amputations. Of the 3 repeat patients, only patient 081-004 reached an endpoint (death). Patient 081-001 completed the study, but reentered as 081-004 and died during the re-entry study follow-up period. The sponsor did not include this patient in the analysis of 30-day deaths because she was a major protocol violator having entered the study twice, however the sponsor did include this patient as patient 081-001 as a death occurring after 37 days.

Kaplan-Meier Time-to-Event Analyses

Kaplan-Meier Time-to-Event for HIT (ITT) for the Composite Endpoint

The graph below demonstrates the statistically significant benefit seen for the HIT arm in the time to event analysis.

Arg-911, HIT Arm, Time to First Event for the Composite Efficacy Endpoint



Summary

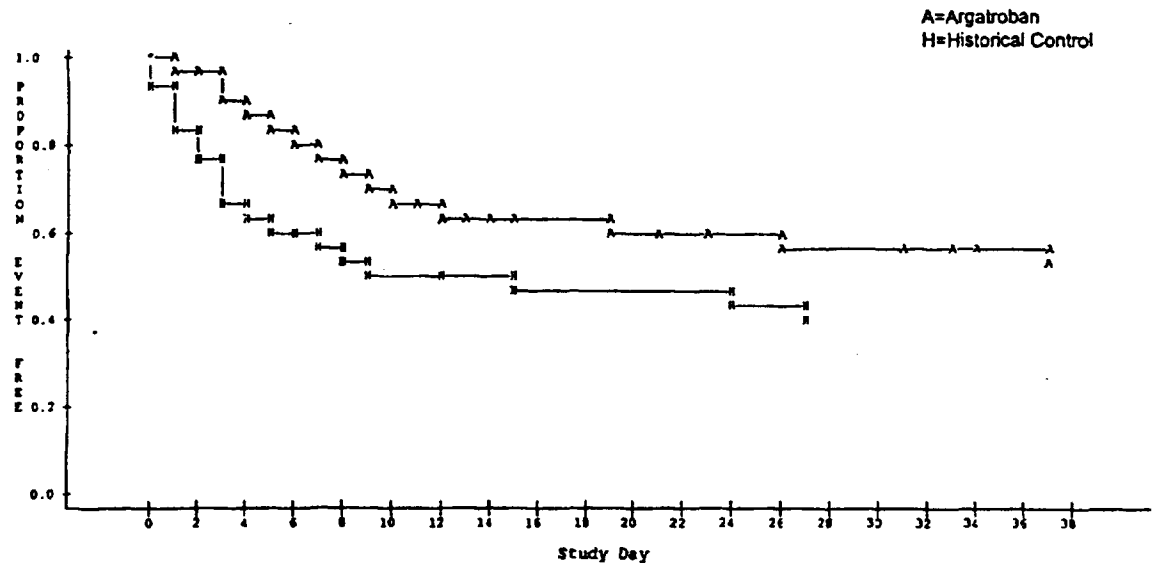
TRT	Total	No. Events	Median Time (Days)	Uncensored range(Days)	Log Rank Chi Sq. 1df	p-value	Hazard Ratio	95% CI
ARG	160	41	.	0 - 32	7.361	0.0067	0.425	0.234-0.772
HC	147	57	.	1 - 35				

Sponsor's graph volume 28.10

Kaplan-Meier Time-to-Event for HITTS (ITT)

The graph demonstrates the statistically significant (p=0.018) result for the HITTS population over the historical control.

ARG-911, HITTS Arm, Time to First Event for the Composite Efficacy Endpoint



Summary

TRT	Total	No. Events	Median Time (Days)	Uncensored range(Days)	Log Rank Chi Sq. 1df	p-value	Hazard Ratio	95% CI
ARG	144	63	.	1 - 37	[illegible]	[illegible]	[illegible]	[illegible]
HC	46	26	12	0 - 27				

Sponsor's graph volume 28.10

Additional Analyses

Evaluable Population

Evaluable patients were all those patients who in the opinion of the DMSC continued to meet the protocol inclusion criteria for HIT or HITTS. Twenty-four patients were excluded for the following reasons: no thrombocytopenia (12 patients), severe sepsis causing 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).

The results shown below support the conclusion reached in the intent-to-treat analysis. Using hazard ratios for the HIT arm, the historical controls have a 77% excess risk of thrombosis, amputation, or death compared to the argatroban treated population. For the HITTS arm, the historical controls have a 60% excess risk of thrombosis, amputation, or death compared to the argatroban treated population.

Table 24 Between-Group Comparison of the Composite Endpoint (Death, Amputation, or New Thrombosis within 37 Days): Evaluable Patient Population

	HIT						HITTS					
	Historical Control		Argatroban			Hazard Ratio	Historical Control		Argatroban			Hazard Ratio
Parameter	N	(%)	N	(%)	P-value[a]	(95% CI)	N	(%)	N	(%)	P-value[a]	(95% CI)
Total Number of Patients	147		146				46		134			
Composite Endpoint[a]	57	(39)	37	(25)	0.006	1.77 (1.17 - 2.68)	26	(57)	62	(46)	0.039	1.60 (1.01 - 2.53)

[a] Based on the Kaplan-Meier log rank test for the composite endpoint.
Reference Documentation Appendix 16.1.9 (Tables A12b and B12b).

Sponsor's table volume 28.10

Test Positive Population

This population included patients who either had a positive HIPA or SRA. The table below illustrates the results of the efficacy analysis in this patient population. The results support those seen in the intent to treat population analysis. The degree of statistical significance in favor of argatroban is greatest in the test positive population.

Table 25 Between-Group Comparison of the Composite Endpoint (Death, Amputation, or New Thrombosis within 37 Days): Test Positive Patient Population

	HIT						HITTS					
	Historical Control		Argatroban			Hazard Ratio	Historical Control		Argatroban			Hazard Ratio
Parameter	N	(%)	N	(%)	P-value[a]	(95% CI)	N	(%)	N	(%)	P-value[a]	(95% CI)
Total Number of Patients	119		80				30		94			
Composite Endpoint	45	(38)	16	(20)	0.004	2.25 (1.27 - 3.99)	19	(63)	43	(46)	0.018	1.88 (1.10 - 3.24)

[a] Based on the Kaplan-Meier log rank test for the composite endpoint.
Reference Documentation Appendix 16.1.9 (Table A12a and B12a)

Sponsor's table volume 28.10

Pooled Centers

Three pooled centers were created for the historical control group based on enrollment. These were not prespecified in the protocol. Imbalance in contributions to either treatment group in the HIT or HITTS arm arise from the use of Dr. Wallis' registry.
The Centers were:

1) Center A (site 020) – Loyola Dr. Wallis' HIT/HITTS registry
2) Center B – centers other than site 020 that provided more than 10 historical controls (3 sites 002, 060, and 113)
3) Center C – 20 sites that provided at least one historical control and 68 sites that provided no controls

Distribution of patients among pooled centers
The sponsor performed pooled center analysis to support the above categorical and time-to-event analyses. The greatest percentage of historical controls are from the Center A while the greatest percentage of argatroban-treated patients are from centers which contributed 0-10 historical controls. The table below shows the distribution of patients in the pooled center analysis.

Table 11 Distribution by Study Arm and Pooled Center

	HIT				HITTS			
	Historical Control		Argatroban		Historical Control		Argatroban	
Pooled Center	N=147	(%)	N=160	(%)	N=46	(%)	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[a]	0.001				0.001			

[a] Chi square test with df=2.
Reference Documentation Appendix 16.1.9
Sponsor's table volume 28.10

Efficacy Results for Pooled Center Analysis

In general, the hazard ratio was in the direction of greater risk for an endpoint to occur in the historical control group than in the argatroban-treated population. These results were not consistent across all pooled centers. No increased risk was observed in the historical controls in the HIT arm of Center B.

Table 21 Time to First Event Analysis By Pooled Centers: Intent-to-Treat Population

	HIT						HITTS					
	Historical Control		Argatroban		Hazard		Historical Control		Argatroban		Hazard	
Pooled Center	#Event/N	(%)	#Event/N	(%)	Ratio	95% CI	#Event/N	(%)	#Event/N	(%)	Ratio	95% CI
Center A	35/77	(45)	2/21	(10)	[redacted]	[redacted]	12/16	(75)	8/21	(38)	2.76	1.12, 6.78
Center B	11/44	(25)	5/14	(36)	[redacted]	[redacted]	6/13	(46)	4/10	(40)	1.62	0.45, 5.80
Center C	11/26	(42)	34/125	(27)	[redacted]	[redacted]	8/17	(47)	51/113	(45)	1.17	0.55, 2.46

Reference Documentation Appendix 16.1.9 [redacted]
Sponsor's table volume 28.10

Co-variate Analyses

The sponsor investigated the role of treatment and baseline characteristics on time to an event. The antibody test result was analyzed for a potential interaction with treatment by proportional hazards regression analysis. There was no suggestion from the results that having a baseline positive antibody test resulted in an increased likelihood of response to treatment with argatroban.

The sponsor also investigated the role of baseline characteristics that significantly impacted the time to first event. In the HIT group, disease of the circulatory system and infectious disease remained statistically significant predictors of the time to first outcome. In the HITTS group, baseline conditions of skin and subcutaneous tissue remained statistically significant predictors of the time to first outcome.

In the HIT group, after adjusting for potential patient baseline effects on treatment, the historical control had more than a two fold greater risk of first event per unit time than patients treated with argatroban. In the HITTS group, after adjusting for potential patient baseline effects on treatment, the historical control had a 69% greater risk of first event per unit time than patients treated with argatroban.

Time-to-Event Analyses on a Cumulative Duration Adjusted for Duration Bias

The table below demonstrates the statistical significance over the time intervals using both the log rank and Wilcoxon test. The generalized Wilcoxon test emphasizes earlier versus later differences while the log rank test equally weighs differences across all time periods. Significant differences between group differences were detected in favor of argatroban for all intervals but the first 7 days in the HIT group. In the HITTS arm, the degree of statistical significance by the Wilcoxon test was consistently greater suggesting that the significant treatment effect may be due to the incidence of early events, primarily new thrombosis, in the historical control group.

Table 23 Cumulative Summary of Categorical and Time to First Event Analysis for the Composite Endpoint, By Study Day Intervals: Intent-to-Treat Patient Population

	HIT					HITTS				
Interval (Study Days)	Historical Control (N=147) N Events (%)	Argatroban (N=160) N Events (%)	Log Rank, P-value	Wilcoxon, P-value		Historical Control (N=46) N Events (%)	Argatroban (N=144) N Events (%)	Log Rank, P-value	Wilcoxon, P-value	
0 - 7	27 (18)	17 (11)	0.056	0.066		20 (43)	36 (25)	0.004	0.001	
0 - 14	43 (29)	26 (16)	0.006	0.007		23 (50)	54 (38)	0.022	0.005	
0 - 21	51 (35)	33 (21)	0.004	0.005		24 (52)	58 (40)	0.025	0.005	
0 - 28	54 (37)	38 (24)	0.007	0.007		26 (57)	60 (42)	0.011	0.003	
0 - 37	57 (39)	41 (26)	0.007	0.007		26 (57)	63 (44)	0.018	0.003	

Reference Documentation Appendix 16.1.9 (Tables A11 and B11).

Sponsor's table volume 28.10

An average of three days elapsed between the discontinuation of heparin and the institution of argatroban. There were three event-free days for the argatroban-treated population compared to the historical controls. The sponsor reanalyzed the data by reassigning study day 3 as the new study day 0 for the historical controls. After adjustment of patients who developed a thrombosis during those three days, the reanalysis demonstrated that the new historical controls with HIT and HITTS had an increased risk of event per unit time over argatroban patients of 67% and 74% respectively. These results are consistent with those obtained with the unadjusted time to event analysis where the increased risk for the historical controls was approximately 70%. Thus no suggestion of a duration bias was found.

Resolution of Thrombocytopenia

The median platelet counts for the HIT and HITTS treatment groups increased relative to the new historical controls. The table below illustrates this effect. The argatroban-treated patients in the HIT arm experienced a mean increase in the platelet count while the historical controls experienced a mean decrease in platelet counts.

Reviewer comment: This discrepancy may arise from the following considerations. The argatroban-treated patients have their heparin stopped (which reduces the function of immune complexes[1,2,5,6]) and are started on a medication to prevent further propagation of a thrombus. The historical control patients had only their heparin stopped. Published literature suggests a procoagulant effect may exist after heparin is discontinued.[8]

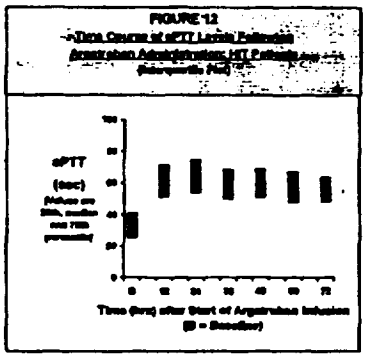
Similar results were seen in the HITTS arm of this trial.

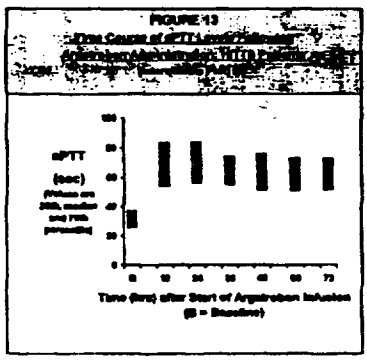
Day of Platelet count	HIT/argatroban treated (median platelet count)	P-value	HITTS/argatroban treated (median platelet count)	P-value
Baseline	81,000/μl		66,400/μl	
Day 3	131,500/μl	<0.001	120,000/μl	<0.001
Conclusion of treatment	185,000/μ	<0.001	198,000/μl	<0.001

Reviewer's table

Anticoagulant Effect

The sustained anticoagulant effect of argatroban after the start of an infusion is shown below..





Sponsor's tables volume 28.10

The table below shows the number and percentage of argatroban-treated patients achieving an adequate anticoagulant effect.

Table 27 Numbers and Percentages of Argatroban-Treated Patients Achieving An Anticoagulant Effect (aPTT ≥1.5X Baseline)

	HIT		HITTS	
Anticoagulant Effect Achieved[a]	# Achieved/ N	(%)	# Achieved/ N	(%)
During Study	133/160	(83)	135/144	(94)
By First Assessment[b]	106/139	(76)	104/129	(81)

[a] Attain an aPTT ≥1.5X patient's baseline aPTT value.
[b] For patients whose starting dose of argatroban was 2 µg/kg/min and for whom data was available.
At first assessment, mean aPTT = 64.1 s for HIT; 70.3 s for HITTS.
Mean time to first assessment for those with anticoagulant success = 4.6 h for HIT; 3.9 h for HITTS.
95% CI for success rate: 68 - 83% for HIT; 73 - 87% for HITTS.
Reference Documentation Appendix 16.2.27 and Appendix 16.1.9

Sponsor's table volume 28.10

The anticoagulant effect was achieved rapidly with the mean time being 4.6 hours for the HIT arm and 3.9 hours for the HITTS arm.

The anticoagulant effect was achieved rapidly with the mean time being 4.6 hours for the HIT arm and 3.9 hours for the HITTS arm.

Assessment of the Efficacy Components

Thromboembolic Complications

The table below shows the frequency and types of thromboembolic events. For the HIT arm, thirteen thromboembolic events occurred in ten patients. For the HITTS arm, thirty-eight thromboembolic events occurred in twenty-seven patients.

Table 28 Number and Percentage of Patients with Anatomical Sites of Thromboembolic Complications (TECs): Intent -to-Treat Population (Argatroban group)

	HIT		HITTS	
	N	(%)	N	(%)
Total Number of Patients	160		144	
Number of Patients with TEC	10	(6)	27	(19)
Number of TECs[a]	13	(8)	38	(26)
Venous	12	(8)	32	(22)
Venous Thrombosis	10	(6)	23	(16)
Pulmonary Embolism	2	(1)	9	(6)
Arterial	1	(1)	6	(4)
Limb Artery Thrombosis	1	(1)	1	(1)
Thrombotic Stroke/CVA	0	(0)	1	(1)
Myocardial Infarction	0	(0)	1	(1)
Other	0	(0)	3	(2)

[a] Patients could have more than one TEC.
Reference Documentation Appendix 16.4.9 and 16.2.11A, 16.2.11B

Sponsor's table volume 28.10

Limb Amputation

Twenty-three operations were performed in twenty-two argatroban treated patients within the 30-day period. This group included 3 patients with HIT and 19 patients with HITTS.

The table below shows information on these amputations and other medical conditions.

Table 30 Amputation Procedures Performed On Argatroban-treated HIT and HITTS Patients

Patient Number	Cause[a]	Site of Amputation[b]	Days from Initiation of Argatroban to Procedure	Significant Medical History[d]
HIT PATIENTS				
002-008	O	R-Forearm	8	—
014-001	I	R-AKA	4	PVD
032-002	O	L-Big Toe	38	Alcoholism, Narcotics Abuse
081-007	O	R-AKA	22	Diabetes, PVD
HITTS PATIENTS				
002-004	O	L-Foot	33	Warfarin Skin Necrosis, CAD
003-001	I	R-BKA	10	Colon Cancer, CHF
011-001	I	L-Forearm	13	Angina, CVA
011-002	I	L-AKA	5	Diabetes, PVD, CHF
017-003	O	L-BKA	6	Diabetes, PVD
020-029	I	L-Foot	3	—
020-029	O	L-BKA	21	—
020-103	I	R-AKA	23	Diabetes, PVD, CHF
034-001[c]	I	L-AKA; R-Foot	2; 16	PVD
037-005	I	R-Foot + L-BKA	8	Diabetes, CAD, UA
037-007	I	R-BKA + L-AKA	4	CAD, CHF
060-002[c]	I	L-BKA; R-Foot	7; 10	Diabetes, CAD, CHF
067-003	I	R-Hand	33	Diabetes, Colon Cancer
079-001[c]	I	R-AKA + L-BKA; Fingers	3; 26	CAD, Raynaud's Syndrome, CHF
080-001	I	Bilateral-BKA	10	Diabetes, PVD
082-001	I	Bilateral-BKA	10	Diabetes, CAD, CHF
085-001	O	R-BKA	14	Diabetes, CAD
091-003	I	R-BKA + L-AKA	1	Diabetes, PVD, CAD
138-001	I	R-BKA	6	CAD

[a] I = due to ischemic complications of HIT/HITTS; O = due to other reasons.
[b] AKA = above the knee amputation; BKA = below the knee amputation; L = left; R = right.
[c] Patient 034-001 underwent the L-AKA procedure on day 2 and the R-Foot procedure on day 16. Patient 060-002 underwent the L-BKA procedure on day 7 and the R-Foot procedure on day 10. Patient 079-001 underwent the R-AKA + L-BKA on day 3 and the fingers procedure on day 26.
[d] CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; PVD = peripheral vascular disease; UA = unstable angina.
Reference Documentation Appendices 16.4.9, and 16.4.17
Sponsor's table volume 28.10

Analysis of All-known Death

A between-group comparison was performed of all deaths including those that occurred beyond the 37-day period. Within both study arms, the incidence of death was numerically lower for the drug treatment groups than for the historical controls although statistical significance was not achieved.

Table 29 Between-Group Analysis of All-Known Death: Intent-to-Treat Population

	HIT					HITTS				
	Historical Control		Argatroban			Historical Control		Argatroban		
Parameter	N	(%)	N	(%)	P-value[a]	N	(%)	N	(%)	P-value[a]
Total Number of Patients	147		160			46		144		
All-known Death	34	(23.1)	30	(18.8)	0.399	14	(30.4)	28	(19.4)	0.152

[a] Based on Fisher's Exact test.
Reference Documentation Appendices 16.1.9 (Tables A9b and B9b) and 16.2.11A
Sponsor's table volume 28.10

Drug-Dose, Drug Concentration, and Relationships to Response

No clear-cut dose response relationship was observed during the trial. This result was expected since the dose of argatroban must be adjusted according to the aPTT. Within 24 hours of cessation of argatroban infusion, the aPTT values had decreased to below the therapeutic range.

Drug-Drug and Drug-Disease Interactions

Patients used concomitant medications during the study . No formal hypothesis testing was undertaken with other drugs. Concomitant use of warfarin resulted in prolongation of the prothrombin time (PT).
Covariate analysis, as outlined above, suggested that for the HIT arm, baseline conditions or diseases involving infection and the circulatory system were independent predictors of time to first outcome. For the HITTS group, diseases involving the skin and subcutaneous tissue were independent predictors of time to first outcome.

Conclusions

The efficacy results from this trial indicates that argatroban is active as an anticoagulant and significantly reduces the combined risk of new thrombosis, amputation and death for the HIT population. The efficacy results seen in the HITTS population are trending towards a statistically significant reduction in the argatroban-treated group compared to the historical control. The fact that statistically significant differences between treated group and historical control are not seen for the HITTS population may reflect the more severe pathophysiologic process and the irreversibility of the thrombotic complications, particularly for the endpoint of amputation. The efficacy of the intent-to-treat analyses is supported by the statistically significant results seen for the evaluable and the seropositive populations.

Study ARG-915

In the initial NDA submission, study ARG-915 included 174 total argatroban-treated patients, 85 HIT patients and 89 HITTS patients. In this re-submission, a total of 264 argatroban-treated patients were entered in the study: 125 HIT patients and 139 HITTS patients. The repeat patients were 27: 20 HIT patients and 7 HITTS patients. The same historical control group that was used as comparator for Study ARG-911 was used for Study ARG-915.

Protocol Summary:

Title: An Open-Label Clinical Study of Novastan® (brand of argatroban) in Patients with Heparin-Induced Thrombocytopenia(HIT)/Heparin-Induced Thrombocytopenia and Thrombosis (HITTS)

The inclusion and exclusion criteria were the same as for Study ARG-911 except for the following:
The following exclusion criteria were deleted:

1) history of sensitivity to cimetidine
2) previous participation in this trial

The following exclusion criteria were added:

1) terminally ill patients with a life expectancy of < 2 weeks
2) anticipated long term (more than 2 weeks) use of a thrombin inhibitor

Patient Disposition for ARG-915

Population	HIT/ Historical Control N (%)	HIT/ Argatroban -Treated N (%)	HITTS/ Historical Control N (%)	HITTS/ Argatroban -Treated N (%)	Total Historical Control N (%)	Total Argatroban -Treated N (%)
Intent-to-Treat[a]	147	125	46	139	193	264
Repeat Patients[a]	0	20	0	7	0	27
Safety Analysis	147	125	46	139	193	264

a Repeat patients were not included in the intent to treat analysis.
Reviewer's table

Seventy-nine percent of HIT patients and 78 % of HITTS patients completed treatment. The table below shows the discontinuation rates. Those patients achieving an endpoint accounted for less than 9% of patients.

Reviewer's Adjudication of Patient Disposition for ARG-915

Patient Disposition	HIT N	HIT %	HITTS N	HITTS %
Total number patients	125	100	139	100
Total number completed (ITT)[a]	99	79.2%	109	78.4%
Completed[b]				
Up to Maximum Time Allowable (ITT)[b]	5	4%	13	9.4%
Resolution of Underlying Condition (ITT)[b]	15	12%	11	7.9%
Transferred to Warfarin (ITT) or other anticoagulant[b]	79	63.2%	85	61.2%
Did not complete (discontinued early)	26	20.8%	30	21.6%
Adverse Event- Endpoint Reached (Amputation, Death, or New Thrombosis)	7	5.6%	9	6.5%
Adverse Event- Bleeding	2	1.6%	2	1.4%
Adverse Event- decreased platelet count/DIC	2	1.6%	2	1.4%
Adverse Event - MSOF	0		2	1.4%
Hypercoagulable state	1	.8%	0	
Protocol Violation	1	.8%	0	
Surgery/ Anticipated Surgery	2	1.6%	3	2.2%
Patient/Family request	1	.8%	1	.7%
Switched to another argatroban trial	4	3.2%	2	1.4%
Elevated coagulation parameters	0		3	2.2%
Elevated liver function tests	0		2	1.4%
DNR/ life support withdrawn	4	3.2%	4	2.9%
Unclear/Other	2	1.6%	0	

a Includes patients withdrawn due to adverse events. See sponsor's table following this one for those patients considered completers who withdrew to adverse events.
b Patients may be in more than one group
Reviewer's table

The table below shows the adverse events that led to withdrawal. The sponsor included these patients among those completing treatment with argatroban.

Table 19 Adverse Events Leading to Withdrawal of HIT and HITTS Patients

	HIT			HITTS			TOTAL		
	Number of			Number of			Number of		
	AEs	Patients[a]	(%)	AEs	Patients[a]	(%)	AEs	Patients[a]	(%)
Total Number of Patients	125			139			264		
Total Number of Patients Who Withdrew	7	6	(4.8)	15	14	(10.1)	22	20	(7.8)
Anemia	1	1	(0.8)	0	0	(0.0)	1	1	(0.4)
Arrythmia	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Bilirubinemia	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Cardiac Arrest	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Coagulation Time Increased	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Death	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Disseminated Intravascular Coagulation	1	1	(0.8)	1	1	(0.7)	2	2	(0.8)
GI Haemorrhage	1	1	(0.8)	2	2	(1.4)	3	3	(1.1)
Haematemesis	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Hypertension Intracranial	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Hypotension	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Necrosis Ischaemic	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Oral Haemorrhage	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Peripheral Gangrene	0	0	(0.0)	1	1	(0.7)	1	1	(0.4)
Purpura	2	1	(0.8)	0	0	(0.0)	2	1	(0.4)
Thrombocytopenia	1	1	(0.8)	1	1	(0.7)	2	2	(0.8)
Uncoded	1	1	(0.8)	0	0	(0.0)	1	1	(0.4)

[a] Patient counted once per event
Patients who discontinued study drug due to an adverse event were counted as completers.
Reference Documentation Appendix 16.2.13.1

Sponsor's table volume 28.32

The table below shows the completion rate for those repeat patients.

Reviewer's Adjudication of Repeat Patient Disposition for ARG-915

Patient Disposition	HIT N	HIT %	HITTS N	HITTS %
Total number patients	20	100	7	100
Total number completed (ITT)	19	95%	6	85.7%
Completed				
Up to Maximum Time Allowable (ITT)	1	5%	0	
Resolution of Underlying Condition (ITT)	2	10%	1	14.3%
Transferred to Warfarin (ITT) or other anticoagulant	16	80%	5	71.4%
Did not complete (discontinued early)	1	5%	1	14.3%
Adverse Event- Endpoint Reached (Amputation, Death, or New Thrombosis)	1	5%	1	14.3%

Reviewer's table

Protocol Deviations

One patient (020-017) was discontinued from the study when both the SRA and HIPA were determined to be negative. Patient 039-002 had pre-existing DIC and was removed from the study. Patient 036-006 was removed from the study after the baseline aPTT was found to be elevated. These patients were not removed from the ITT and safety analyses.

Demographics
There was no significant difference in demographics between the 193 historical controls and the 264 argatroban treated patients. The average patient was Caucasian and mid-60's in age.

Below is a table comparing certain demographics for the historical controls and the argatroban treated patients for Study ARG-915.

Demographic Characteristics for Study ARG-915

Parameter	HIT/ New Appropriate Historical Control	HIT/ Argatroban-treated Patients	HITT/ New Appropriate Historical Control	HITT/ Argatroban-treated Patients
Race				
Caucasian	122 (83%)	110 (88%)	38 (83%)	124 (89%)
Black	10 (7%)	8 (6%)	6 (13%)	8 (6%)
Other	15 (10%)	7 (6%)	2 (4%)	7 (5%)
Gender				
Female	64 (44%)	63 (50%)	18 (39%)	60 (43%)
Male	82 (56%)	62 (50%)	27 (59%)	79 (57%)

Reviewer's table

Baseline Platelet counts for argatroban-treated patients
The median platelet counts for the argatroban-treated are similar to those of the historical controls. Prior heparin exposure is similar to that seen in Study ARG-911 and reflects the study design.

PROTOCOL 915

BASELINE DIAGNOSTIC CHARACTERISTICS	PATIENTS	
	[illegible]	[illegible]
TOTAL NUMBER OF PATIENTS	125	139
BASELINE PLATELET COUNT (X 10^3/mm cu)		
N	124	137
MEDIAN	110.50	96.00
INTERQUARTILE RANGE	63.5 - 1,173.50	54.0 - 21,000.00
PRIOR HEPARIN EXPOSURE, N (%)		
YES	106 (85%)	130 (94%)
NO	19 (15%)	9 (6%)

Sponsor's table volume 28.42

Pre-existing Medical Conditions

The sponsor's table for the argatroban-treated patients is shown below. The percentages of the various pre-existing medical conditions are similar to those seen with the argatroban-treated groups in Study ARG-911.

Prior Medication Use

The table below shows prior medication use for argatroban-treated patients. This table is similar to that for the argatroban-treated patients in Study ARG-911. The percentages of patients for the prior medication use categories are similar to those seen with the argatroban-treated groups in Study ARG-911.