

Additional Efficacy Analyses: PTT change from baseline at ICU arrival was 11.9 seconds in the HD group and 7.6 seconds in the LD group compared to 2.2 seconds in the PLA group. (P-values equal to 0.000 and 0.046 compared to placebo, respectively).

There were no significant differences from placebo in days spent in ICU or in the hospital. The HD group received significantly less study medication than the PLA group (559 ml versus 573 ml, respectively; p-value = 0.003).

Significantly fewer HD and LD patients than PLA patients used desmopressin to control bleeding. Significantly more PLA than either HD, LD or PPO patients used epsilon aminocaproic acid: HD 3%, LD 3%, PPO 6%, PLA 15% (p<0.01). No patients received tranexamic acid.

The HD group exhibited significantly shorter times than the PLA group for all surgical variables reported (bypass time, cross clamp time, surgery duration, time under anesthesia and closing time).

For the population of patients valid for safety, significantly fewer HD (1%, 1/173) and LD (1%, 1/180) patients than PLA (4%, 7/178) patients required a reoperation because of a surgical bleed. For the population of patients valid for efficacy, no HD or LD patients required a reoperation because of diffuse bleeding, whereas 3% (5/157) of PLA patients required such surgery (P-values= 0.016 and 0.024 compared to placebo, respectively).

Treatment by Center Interactions: Interactions seen for units of blood product or its constituents might be due to the small number of patients, making consistency across centers less likely. Interactions detected for the thoracic drainage variables were of a quantitative, not qualitative nature. In nearly all centers for each variable, drainage was greater in the placebo group than in each of the active treatment groups.

Placebo minus high dose differences varied greatly across centers for total bypass and cross clamp times with HD worse than PLA at 5 and 6 centers respectively. However, these variables are highly correlated and similar interactions would be expected.

Cardioplegia volume exhibited a high degree of variability both within and across centers. Body temperature maintained during bypass varied very little within centers. There was no indication of any overall treatment differences.

SAFETY RESULTS

Evaluation of All Adverse Events (AE): Incidence rates of adverse events for each body system are tabulated here. Significantly fewer HD and LD than PLA patients experienced a cardiovascular event.

System	Incidence (n(%)) of Adverse Events For Each Body System		APPEARS THIS WAY ON ORIGINAL	
	High Dose (N=173)	Low Dose (N=180)	Pump Prime (N=173)	Placebo (N=178)
Any Body System	137 (79)*	144 (80)*	140 (81)*	158 (89)
Body as a Whole	61 (35)	62 (34)	60 (35)	42 (24)
Cardiovascular	107 (62)*	111 (62)*	122 (71)	131 (74)
Digestive	46 (27)	42 (23)	33 (19)	49 (28)
Endocrine	2 (1)	3 (2)	0 (0)	0 (0)
Hemic and Lymphatic	7 (4)*	12 (7)*	15 (9)*	33 (19)
Metabolic & Nutritional	16 (9)	27 (15)	13 (8)	22 (12)
Musculoskeletal	2 (1)	4 (2)	3 (2)	6 (3)
Nervous	23 (13)	23 (13)	22 (13)	26 (15)
Respiratory	54 (31)	66 (37)	60 (35)	64 (36)
Skin and Appendages	9 (5)	10 (6)	9 (5)	10 (6)
Special Senses	0 (0)	4 (2)	2 (1)	1 (1)
Urogenital	17 (10)	17 (9)	13 (8)*	27 (15)

* P-value \leq 0.05, compared to placebo

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Individual events for which either an active treatment group rate was not within 5% of the placebo rate, or for which a statistically significant comparison to placebo exists are shown in the following table. Contrary to prior studies, the event "myocardial infarction" did not meet the selection criteria for the above table.

Incidence (n(%)) of Selected Adverse Events

Event	High Dose	Low Dose	Pump Prime	Placebo
Fever	35 (20)	31 (17)	36 (21)	42 (24)
Atrial Fibrillation	52 (30)	43 (24)*	47 (27)	61 (34)
Hemorrhage	2 (1)*	5 (3)*	4 (2)*	14 (8)
Coagulation Disorder	2 (1)*	2 (1)*	2 (1)*	14 (8)
Hyperglycemia	5 (3)*	4 (2)	0 (0)	0 (0)
Confusion	4 (2)*	10 (6)	2 (1)*	13 (7)

* P-value ≤ 0.05, compared to placebo

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Incidence rates of drug-related adverse events for each body system and for those individual events with active treatment statistically or numerically (by >5%), different from placebo are shown next.

Incidence (n(%)) Drug-Related Adverse Events
For Each Body System and Selected Events

System or Event	High Dose	Low Dose	Pump Prime	Placebo
Any Body System	42 (24)	46 (26)	51 (29)	52 (29)
Body as a Whole	7 (4)	5 (3)	10 (6)	8 (4)
Cardiovascular	28 (16)	30 (17)	38 (22)	36 (20)
Myocardial Infarction	4 (2)	2 (1)	9 (5)*	2 (1)
Digestive	9 (5)	9 (5)	5 (3)	6 (3)
Hemic and Lymphatic	2 (1)*	1 (1)*	2 (1)*	10 (6)
Coagulation Disorder	2 (1)	0 (0)*	1 (1)	6 (3)
Metabolic and Nutritional	1 (1)	8 (4)	0 (0)	3 (2)
Musculoskeletal	0 (0)	1 (1)	1 (1)	0 (0)
Nervous	2 (1)	4 (2)	6 (3)	2 (1)
Respiratory	5 (3)	3 (2)	8 (5)	5 (3)
Skin and Appendages	3 (2)	3 (2)	2 (1)	2 (1)
Special Senses	0 (0)	0 (0)	0 (0)	1 (1)
Urogenital	7 (4)	6 (3)	6 (3)	6 (3)

*P-value ≤ 0.05, compared to placebo

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The PPO group had significantly higher incidence of MI than the PLA group.

Deaths and Dropouts due to Adverse Events and Serious Adverse Events

There were three deaths in the HD group, four in the LD group, five in the PPO group, and three in the PLA group.

Serious adverse events (including those leading to death) occurred in 13% (23 of 173) of HD patients, 15% (27 of 180) of LD patients, 16% (27 of 173) of PPO patients and 17% (31 of 178) of PLA patients. One patient in the HD group, three patients in the PPO group and three patients in the PLA group recorded an adverse event for which the outcome was discontinuation of study drug administration.

Clinical Laboratory Evaluation: Those tests for which at least one active dose group rate was statistically different from, or not within 5% of the placebo rate are shown here.

Incidence of Laboratory Abnormalities

	High Dose %	Low Dose %	Pump Prime %	Placebo %
<u>High</u>				
BUN	38	24	33	31
Chloride	35	42	38	43
Bicarbonate	17	11	9*	17
Phosphorus	28*	19	15	13
Uric Acid	10	5*	12	11
LDH	85	84	89	91
SGOT	75	85*	81	81
Monocytes	29	18	24	23
Basophils	14	9	7	7
Platelets	21	16	15*	24
Prothrombin Time	76	81	78	83
PTT	93*	78*	65	53
<u>Low</u>				
Sodium	48	43	47	41
Total Protein	64	69	73	72
Albumin	58	62	60	64
Phosphorus	6*	14	9	12
Calcium	37	47	42	35
Uric Acid	1	6*	4	1
CPK	6	16	7	12
Eosinophils	8	9	4	10
PTT	1*	2	1	5
<u>Abnormal</u>				
Protein (urine)	8	0*	0*	3

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*P-value ≤ 0.05, compared to placebo

The analyses of baseline and change from baseline for the chemistry, hematology and coagulation tests are summarized in the following table.

**Mean Change from Baseline in Laboratory Values
Approximately 7 Days Post Surgery**

<u>Variable (Units)</u>	<u>High Dose</u>	<u>Low Dose</u>	<u>Pump Prime</u>	<u>Placebo</u>
RBC (x10 ⁶ /mm ³)	-0.89*	-0.98*	-1.10	-1.11
WBC (x10 ³ /mm ³)	1.99	1.39	1.43	2.09
HGB (g/dl)	-2.98*	-3.27*	-3.54	-3.63
HCT(%)	-7.81*	-8.59*	-9.60	-9.72
Neutrophils (%)	4.35	4.38	5.15	5.31
Lymphocytes (%)	-7.13	-7.08	-7.32	-7.89
Monocytes (%)	0.89	1.13	0.57	0.56
Eosinophils (%)	0.22	0.53	0.59	0.64
Basophils (%)	-0.13	-0.06	-0.08	-0.13
Glucose (mg/dl)	1.05	10.12	10.16	2.89
Sodium (meq/dl)	-1.64	-1.21	-1.66	-1.09
Potassium (meq/dl)	0.15	0.05	0.10*	-0.02
Chloride (meq/dl)	-2.41	-1.55	-2.35	-2.02
Bicarbonate (meq/dl)	1.25	1.11	1.32	1.57
SGPT (U/L)	19.42	16.15	16.35	18.62
Platelet Count (x10 ⁶ /mm ³)	97.16	82.27	92.73	89.82
Creatinine (mg/dl)	0.10	-0.02	-0.02	-0.03
BUN (mg/dl)	3.80	2.92	2.43	3.66
LDH (U/L)	61.70	41.64*	63.90	71.82
SGOT (U/L)	5.93*	6.49*	6.02*	11.89
Total Protein (g/dl)	-0.78	-0.50	-0.90	-0.91
Albumin (g/dl)	-0.69	-0.69	-0.70	-0.71
Phosphorus (mg/dl)	0.54*	0.31*	0.23	0.11
Calcium (mg/dl)	-0.41	-0.14	-0.44	-0.42
Uric Acid (mg/dl)	-0.06	-0.23	-0.22	-0.01
Total Bilirubin (mg/dl)	0.10*	0.03*	0.14*	0.34
Alkaline Phosphate (U/L)	24.02	20.67	14.11	15.17
Prothrombin Time (sec)+	0.91*	0.81*	1.01*	1.35
PTT (sec)+	-2.05*	-5.26	-5.06	-6.05
CPK (U/L)	33.00	47.67	170.44*	39.18

+ : Final measurement; Day 7 measurement not required

Changes from baseline in creatinine (mg/dl) were negligible, ranging between -0.01 and 0.01 over the four treatment groups. Although by Day 7, SGPT had risen from baseline by about 18 U/L in each treatment group, at follow-up all treatments groups exhibited negative changes from baseline. To further examine the effect of treatment on these two variables, treatment emergent incidence rates of varying levels of creatinine and SGPT abnormalities were examined. There were no significant differences from placebo, and no indication of a lasting effect of treatment on creatinine or SGPT.

Other Safety Parameters: Patients were asked to fill out an angina questionnaire prior to surgery and at 4-6 weeks follow-up. There were no notable differences from placebo for incidence rates of change.

The blinded assessment of perioperative MI by the Core ECG laboratory (CEL) showed the following results:

	High Dose	Low Dose	Pump Prime	Placebo
% Definite MI: ECG Data	6%	6%	5%	4%
% Definite or Probable	8%	10%	13%	10%
% Definite, Probable, Possible	11%	13%	16%	10%
% No MI	89%	87%	84%*	91%

*p-value < 0.05, compared to placebo

Significantly fewer patients in the PPO group than in the PLA group were categorized as having had no myocardial infarction. For most characteristics examined, the PPO group was consistently worse than the PLA group. Results by strata are summarized here.

	Incidence of No MI by Strata			
	High dose	Low Dose	Pump Prime	Placebo
Low Risk/MI	72/77 (94%)	64/70 (91%)	69/75 (92%)	64/71 (90%)
High Risk/MI	75/88 (85%)	83/99 (84%)	71/91 (78%)	90/99 (91%)
High Risk/Bleed.	109/123 (89%)	109/129 (84%)	108/129 (84%)	113/128 (88%)
Low Risk/Bleed.	38/42 (90%)	38/40 (95%)	32/37 (86%)	41/42 (98%)

Trends in favor of placebo over active treatment existed for the subset of patients at high risk for MI, but not for the subset of patients at low risk for MI. Also, the PLA versus PPO difference

is seen largely in the low risk for bleeding stratum as compared to the high risk for bleeding stratum.

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CONCLUSIONS:

This study confirms the efficacy of HD, LD and PPO aprotinin regimens over placebo in patients undergoing primary CABG in terms of the following parameters:

- Percentage of patients requiring donor blood (HD:33%; LD:35%; PPO:33%; PLA:52%)
- Median (Range) number of units of donor blood transfused (HD:0.0 ; LD:0.0 ; PPO:0.0 PLA:1.0 units)
- Mean total volume of post-operative thoracic drainage (HD:78S; LD:811; PPO:899; PLA:1286 mL)

Females appeared to have a greater chance of requiring donor blood than males. There were no consistent, obvious differences by other demographic characteristics.

In four centers (1,8,10, and 19) PLA was superior to HD and LD aprotinin. This treatment by center interaction was probably due to a better than average placebo response.

Approximately 75% of patients were considered to be at high risk of bleeding mostly as a result of aspirin ingestion. This stratum also demonstrated the efficacy of HD, LD and PPO aprotinin regimens over placebo in primary CABG, whereas in the stratum of patients at low risk of bleeding, statistically significant efficacy was only demonstrated in the LD group with respect to units (and volume) of blood required. However, more than 25% of patients at low risk of bleeding were enrolled at one center (#14) which demonstrated a larger treatment effect than all other centers combined. The small number of patients in each treatment group in this substratum limit the value of these data.

Significantly fewer HD, LD, and PPO patients used any donor blood product compared with PLA.

All active treatment groups were superior to PLA for reduction in thoracic drainage analyzed at 6 hours post-op., as total volume and as mL/hr for the first 6 hours for the population as a whole and in the high risk for bleeding stratum. In the low risk of bleeding

stratum, the PPO group was not significantly different from the PLA group.

As expected, the post-op PTT was more prolonged with aprotinin than with placebo.

There were no significant differences in the three treatment groups from PLA in days spent in the ICU or hospital. The HD group had significantly shorter times than the PLA group for all surgery-time variables, however, treatment by center interactions were observed. More important, for the population of patients valid for efficacy no HD or LD patients required reoperation because of diffuse bleeding whereas 3% of PLA patients did. DDAVP and EACA were used more often in the PLA than the HD or LD groups to control bleeding.

Fewer HD, LD, or PPO patients experienced a treatment emergent event compared with PLA patients (HD: 79%; LD: 80%; PPO: 81%; PLA:89%). There were no statistically significant differences with respect to deaths across any of the treatment groups.

The investigator-reported rates for MI were not statistically different: HD: 5%; LD:3%; PPO:5%; PLA:2%. However, the prospective blinded MI analysis performed by the Core ECG laboratory demonstrated a statistical significance ($p=0.045$) in the percentage of patients who had no MI in the PPO group (84%) compared with the placebo group (91%).

Graft Occlusion was assessed from other terms reported by the investigators (such as coronary occlusion, thrombosis) and was as follows: HD: 1%; LD: 1%; PPO: 1%; PLA: 0%.

Any renal dysfunction observed was of a transient nature and not clinically significant. There was no difference among the various treatment groups for liver dysfunction, based on SGPT levels. Significantly fewer patients had elevated SGOT levels in the LD group compared with PLA. The mean change of CPK from baseline at day 7 post-surgery was significantly higher in the PPO group compared with PLA.

REVIEW OF STUDY D91-007

Title of the study: "a Single-center, Randomized, double-blind, Placebo-controlled, Group comparison Pilot study of Aprotinin effect on Heparin Usage and Platelet dysfunction during cardiopulmonary bypass.

Objectives of the Study: The objectives of the study were:
1) to evaluate the interaction of aprotinin with heparin in order to determine whether aprotinin was a "heparin sparing" agent. This analysis was prompted by the observation that the celite ACT in heparinized patients treated with aprotinin is prolonged beyond that expected by the heparin administration,
2) to evaluate the effect of aprotinin on platelet function, and,
3) to evaluate the efficacy parameters of reduction in bleeding and transfusion requirement.

Background Information: The excessive bleeding caused by CPB is associated with both platelet activation and transient platelet dysfunction. The bleeding time increases progressively during CPB concomitantly with increase in plasma levels of platelet factor 4 (PF4) and beta-thromboglobulin (beta TG). The bleeding time and the levels of the platelet alpha granules proteins return to normal after discontinuation of CPB. Failure of the bleeding time to return to normal results in excessive post-operative bleeding.

The platelet functional abnormality associated with CPB has been attributed to a post-activation refractory state secondary to protease-dependent activation during the CPB. The mechanism by which aprotinin reduces blood loss in patients undergoing cardiac surgery with CPB is unclear, but it may be related to preservation of platelet function postoperatively by inhibition of activation by coagulation-dependent serine-proteases.

It has been demonstrated that activated platelets express neoantigens (activation epitopes) on the membrane surface that can be detected by immunofluorescent flow cytometry using murine antibodies directed against the activation epitopes.

One aspect of the study was to assess the activating effect of CPB on platelets and the inhibitory effect of aprotinin. The following parameters of platelet activation, thrombin

production, and plasmin formation were compared between the aprotinin and placebo groups at various times during and after CPB:

- Bleeding Time (BT)
- Platelet Activation Epitopes
- Platelet Aggregation by ADP and Collagen-
- Beta-TG and PF4
- Fibrinopeptide a (FPA), Thrombin:Antithrombin Complex (T:AT), and D-dimer levels.

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The results of this part of the study are not available at present and will be submitted at a later date.

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Effect of Aprotinin on Heparin Usage:

Background: The rationale for assessing the interaction of aprotinin and heparin was based on the observation that the administration of heparin during cardiac surgery to patients receiving Aprotinin resulted in a prolongation of the ACT in excess to that expected for the amount of heparin administered. This effect of aprotinin was initially interpreted as a "heparin sparing" effect and lead to the use of reduced heparin dosage. It is now clear that the aprotinin effect on ACT is an artifact of the interaction of aprotinin with the celite used as activator.

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Summary of the Investigational Plan: a total of 99 patients (56 males and 43 females) requiring elective open-heart surgery were enrolled in the study and were randomized to aprotinin high-dose regimen (n=35), aprotinin low-dose regimen (n=34), and to placebo (n=30).

The patient randomization was stratified to primary or repeat cardiac surgery; the patients in each stratum were substratified according to use of normothermic or moderately hypothermic CPB.

Anesthesia and surgery were performed as routinely practiced at Emory Univ. Hospital.

Heparin was administered in a loading dose of 400 IU/kg prior to cannulation. Activated Clotting Time (ACT) and heparin-protamine titration (HPT) were performed using the Hepcon HMS system.

While on CPB, ACT and HPT were performed at 30, 60 and 90 minutes of bypass. Additional heparin was administered based on HPT to maintain the heparin level at 300 IU/kg.

After discontinuation of CPB, heparin was neutralized with protamine sulfate at a dose determine by the HPT.

Blood conservation techniques were those conventionally employed at the study center. Blood was transfused if the Hct was lower than 18% intraoperatively or less than 22% post-operatively or whenever clinically indicated.

Study drug was administered blindly, the aprotinin regimens used were the high-dose or full-dose, and the low-dose or half-dose.

Patients with aprotinin allergy, with bleeding diathesis, comorbid conditions, patients treated with heparin or antiplatelet drugs (ASA or NSAID) prior to surgery and patients unable to receive blood transfusion were excluded.

To assess the effect of aprotinin on heparin requirement, the total amount of heparin given to maintain a level of 300 IU/kg up 90 minutes after CPB was compared in the three groups.

To assess the effect of aprotinin on anesthetic requirement during open heart surgery, the regimen was standardized and the total amount of each drug given to aprotinin patients was compared to that administered to placebo patient.

Statistical Analysis: The primary efficacy variable was the amount of heparin administered through 90' of CPB and the primary comparison was between high-dose group and placebo. All test were two-tailed at alpha level of 0.05.

The sample size was determined on an estimated requirement of heparin for the first 90' of CPB of 10,845 IU with a difference of 10.000 IU between high-dose and placebo being clinically meaningful. Patients with CPB duration of less than 90' and patients requiring maintenance of appropriate heparin level after the 90' HPT determination were not considered valid for analysis

Subject Groups: The patients valid for analyses are summarized below:

<u>Patients valid for:</u>	High-dose n=35(%)	Low-dose n=34(%)	placebo n=30(%)
Analysis of safety	35(100)	34(100)	30(100)
Analysis of heparin Usage	21(60)	23(68)	23(77)
Analysis of Platelet Function	26(74)	28(82)	24(80)
All other efficacy Analyses (transfusion, blood loss)	31(69)	32(94)	29(97)

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No patients discontinued after randomization. Of the patients valid for analysis of efficacy, 66% were stratified to primary sternotomy, 39% had normothermic CPB, 76% had valve surgery and 24% had CABG surgery.

The treatment groups were similar for demographic and baseline cardiac characteristics. All patients took at least one medication in addition to study drug.

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EFFICACY RESULTS

Heparin Usage: The results of the heparin analysis are summarized in the following table:

Heparin Analysis (Excluding heparin in pump).
Patients valid for efficacy analysis of heparin usage.

	High-dose n=21	Low-dose n=23	Placebo n=23
Heparin (up to 105 min)			
Mean IU	41239	41139	43043
Mean IU/kg	555	540*	584
Heparin (End of Surgery)			
Mean IU	42371	42313	45239
Mean IU/kg	570	558**	609

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* p >0.10 compared to placebo
**p <0.05, compared to placebo

The observed difference was less than 2000 IU. Similar results were obtained in the patient population valid for safety analysis.

The results indicate that aprotinin is not "heparin sparing" and that patients require similar amounts of heparin regardless of

aprotinin administration. The lack of treatment effect was seen across all subgroup examined.

Blood Donor Requirement through Day 12: The results of the data for patients valid for efficacy are summarized in the following table:

Donor blood requirement through day 12. Patients valid for efficacy

Variable	High-dose n=31	Low-dose n=31	Placebo n=29
% requiring blood	74*	88	97
Median (range)			
Units required	2	2	5
mL required	500	500	1250

*p-value <0.05, compared to placebo.

The results indicate that the high-dose regimen was superior to placebo for number of patients requiring blood and for amount of blood transfused; the low-dose group was better than placebo for the amount of blood required.

These results were consistent across demographic, stratification, and type of surgery subgroups.

The donor blood requirement through day 12 by type of surgery for patients valid for efficacy are summarized in the following table:

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Donor Blood Requirement Through Day 12
By Type of Surgery
Patients Valid for Efficacy

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	High Dose	Low Dose	Placebo
CABG done			
n	12	11	12
% Requiring Blood	75	91	92
Median Units required	3	2	4.5
Median milliliters required	750	500	1275
CABG not done			
n	19	18	17
% Requiring Blood	74	86	100
Median Units Required	2	2	5
Median Milliliters Required	500	500	1250

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The median number of units in the high-dose group (3) and low-dose group (2) were less than that required in the placebo group. The results of the analysis by intent-to-treat were similar to those for the efficacy population.

Donor blood products requirement: Two of 31 patients in the high-dose group (6%), 3 of 32 patients in the low-dose group (9%), and 14 of 29 patients in the placebo group (48%) required donor blood products.

Thoracic Drainage: The thoracic drainage rate in mL/hr over the first 6 hours was significantly lower for the high- and low-dose aprotinin groups compared to placebo. The data are summarized in the following table:

APPEARS THIS WAY ON ORIGINAL		Thoracic Drainage Patients Valid for Efficacy		
		High Dose	Low Dose	Placebo
Thoracic Drainage	N	31	32	28
Rate: 0-6 hours post surgery (ml/hr)	Mean	50*	55*	157
	SE	17	17	18
Thoracic Drainage	N	31	32	27
Volume: 6 hours post surgery (ml)	Mean	302*	331*	792
	SE	62	61	67
Thoracic Drainage	N	31	31	27
Volume: Total post surgery (ml)	Mean	1200*	1039*	2313
	SE	183	183	196

*: Significantly different from placebo, $p < 0.05$

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Additional Efficacy Analyses: The mean number of days in ICU was 2.8 for the high-dose, 2.6 for the low-dose and 3.6 for the placebo group ($p=0.041$). Closure time was significantly less in the high- and in the low-dose groups (63') compared to placebo (80').

Two patients, 1 in the low-dose and 1 in the placebo group required re-operation.

Anesthesia Interaction: No difference from placebo were noted in the aprotinin groups for amount of anesthetic agents used.

SAFETY RESULTS

None of the adverse events were considered to be treatment-related. The incidence rates of treatment-emergent AE are summarized in the following table:

APPEARS THIS WAY ON ORIGINAL	INCIDENCE OF TREATMENT EMERGENT EVENTS BY BODY SYSTEM						Overall p-value
	High Dose n(%) (N=35)		Patients Valid for Safety Low Dose n(%) (N=34)		Placebo n(%) (N=30)		
Any Body System	35	(100)	34	(100)	30	(100)	1.000
Body as a Whole	18	(51)	22	(65)	16	(53)	0.492
Cardiovascular	32	(91)	30	(88)	28	(93)	0.829
Digestive	17	(49)	12	(35)	13	(43)	0.533
Hemic & Lymphatic	7	(20)	8	(24)	11	(37)	0.284
Metabolic & Nutritional	12	(34)	9	(26)	9	(30)	0.779
Musculoskeletal	2	(6)	1	(3)	2	(7)	0.860
Nervous	14	(40)	10	(29)	14	(47)	0.356
Respiratory	31	(89)	29	(85)	29	(97)	0.311
Skin & Appendages	3	(9)	1	(3)	1	(3)	0.618
Special Senses	3	(9)	2	(6)	1	(3)	0.870
Urogenital	9	(26)	2	(6)	6	(20)	0.082

Events which were not within 15% of the placebo rate or for which a statistically significant difference was observed are listed in the following table:

Event	Incidence (n(%) of Selected Adverse Events					
	High Dose		Low Dose		Placebo	
Ventricular Tachycardia	5	(14%)	6	(18%)*	0	(0%)
Hypotension	1	(3%)	0	(0%)*	4	(13%)
Asthma	9	(26%)	4	(12%)*	11	(37%)
Atrial Flutter	8	(23%)	7	(21%)	2	(7%)
Arrhythmia	7	(20%)	5	(15%)	1	(3%)
Lung Disorder	27	(77%)	23	(68%)	25	(93%)
Pleural Effusion	7	(20%)	10	(29%)	11	(37%)

*: Statistically different from placebo, $p \leq 0.05$

Ventricular tachycardia occurred only in the aprotinin groups. The overall incidence of MI's was not increased in the aprotinin groups: 23% (8/35) in the high-dose group, 15% (5/34) in the low-dose group, and 20% (6/30) in the placebo group.

For the subset of patients undergoing CABG, 3/13 (23%) in the high-dose group, 3/11 (27%) in the low-dose group, and 4/13 (31%) in the placebo group experienced MI.

The incidence of MI for patients undergoing valve replacement was 5/22 (23%) in the high-dose group, 2/22 (9%) in the low-dose group, and 2/17 (12%) in the placebo group.

There were no deaths or drop-outs due to AE in the study.

Clinical Laboratory Evaluation: No clinically relevant laboratory abnormalities were observed.

The changes from baseline for laboratory tests performed at the scheduled time from surgery are summarized in the following table:

Variable (Units)	Mean Change from Baseline in Laboratory Values Approximately 7 Days Post-Surgery		APPEARS THIS WAY ON ORIGINAL Placebo
	High Dose	Low Dose	
RBC (x10 ⁶ /mm ³)	-0.94	-0.95	-0.94
WBC (x10 ³ /mm ³)	1.08	1.30	3.06
HGB (g/dl)	-2.89	-2.91	-2.72
HCT (%)	-8.63	-8.55	-8.20
Glucose (mg/dl)	-13.97	-8.96	-3.23
Sodium (meq/dl)	-1.69	-1.81	-1.92
Potassium (meq/dl)	0.23*	0.07	-0.18
Chloride (meq/dl)	-1.50	-0.96	-1.42
Bicarbonate (meq/dl)	-1.00	-0.62	0.85
SGPT (U/L)	44.50	7.96	-17.12
Platelet Count (x10 ⁶ /mm ³)	61.97*	46.24	-6.43
Creatinine (mg/dl)	0.00*	-0.01*	-0.17
BUN (mg/dl)	1.36	-0.46	-1.08
LDH (U/L)	86.47	72.14	122.24
SGOT (U/L)	15.57	4.74	1.64
Total Protein (g/dl)	-1.03*	-1.09	-1.52
Albumin (g/dl)	-0.88	-0.97	-1.06
Phosphorus (mg/dl)	0.51	1.05*	-0.25
Calcium (mg/dl)	-0.54	-0.72	-0.82
Uric Acid (mg/dl)	-0.12	-0.55	-0.60
Total Bilirubin (mg/dl)	0.11	-0.11*	0.39
Alkaline Phosphate (U/L)	8.37	27.65	10.24
Prothrombin Time (sec)+	1.51	1.96	1.49
PTT (sec)+	7.12	3.36	4.17
CPK (U/L)+	319.36	283.64	311.25

+ : Final measurement; Day 7 measurement not required

* : P-value ≤ 0.05, compared to placebo

There were no significant differences from placebo and no persistent effect of aprotinin on creatinine and LFTs. Clinically significant changes from pre-op ECG (HD 51%, LD 71% and placebo 47%) and age-indetermined MI (HD 14%, LD 24% and placebo 7%) were most frequent in the low-dose group. These MI occurred prior to 4-6 weeks follow-up in the aprotinin patients and at follow-up for the placebo patients.

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CONCLUSIONS:

The analysis of the interaction of heparin with aprotinin indicates that aprotinin has no "heparin sparing" effect and that patients on CPB treated with aprotinin should receive heparin at the recommended fixed dose or based on the results of HPT or ACT performed with reagents not affected by aprotinin.

No data are available on the effect of aprotinin on platelet function.

High-dose aprotinin significantly reduced the percentage of patients receiving blood and blood products transfusion as well as the amount of blood required for transfusion and the volume of thoracic drainage. Low-dose aprotinin significantly reduced the amount of blood transfused and the volume of thoracic drainage, but not the number of patients transfused.

In contrast to a prior study (D89-005) which had shown no efficacy of aprotinin in valve replacement surgery, a post-hoc analysis showed a benefit from aprotinin therapy in valve patients in the present study.

Ventricular tachycardia (VT) occurred in 11 patients all in the aprotinin groups. The VT was severe in three patients. The incidence of MI was similar among treatment groups, however, the highest incidence of clinically significant changes from pre-operative ECG and a greater incidence of age-indeterminate MI occurred in the low-dose aprotinin group. In the subset of patients undergoing valve surgery, the incidence of MI was higher in the high-dose aprotinin group compared to placebo.

PH 25504: RETROSPECTIVE STUDY OF ANAPHYLAXIS ON RE-EXPOSURE

This retrospective analysis was performed to investigate the frequency of anaphylactic reactions after a second administration of Trasylol. Data were obtained from the medical records of all patients undergoing cardiac surgery at the German Heart Centre Berlin from 1989 to 1995, at the German Heart Centre Munich from 1988 to 1995, and at the Benedikt Kreutz Centre Bad Krozingen from 1986 to 1991.

A total 387 patients were identified for a total of 421 reexposures (31 patients had a third intervention, of these 3 had a third redo surgery). Six patients were reexposed within less than 2 days, therefore 381 patients were included in the analysis.

The average age of all of the 387 patients was 35 years (11 days-82 years), 66.1% were males. The study population consisted of 135 children (average 3 years) and 252 adults (older than 12 years, average age 52 years).

The average Trasylol dosage at the first operation was 0.55 M KIU in children and 4.0 M KIU in adults. The average time between the first and the second operation was 1 year 2 months for children and 1 year 10 months for adults.

Of the 240 patients with information, 44 (11.4%) had history of allergy. Of the 302 patients with information, 204 (52.7%) had a concomitant disease.

The average time interval between two consecutive operations was 644 days for adults and 454 days for children. a total of 231 intervals between exposures were 6 months or longer.

The average interval between the two consecutive Trasylol exposures of all these 11 patients was 169 days (22-1106 days, median of 52 days). The overall average dosage was 3.89 M KIU (0.9-6.0 M KIU) at the preceding surgery (74,600 KIU for all patients). The average children's dosage per kg body weight was 60,300 KIU, corresponding to that of 77,000 KIU per kg body weight in adults.

Of the 265 re-exposed patients with information, 121 (31.3 %) received corticosteroids, 250 (64.6 %) of 387 patients with information received H1/H2-blockers. Most of the children (64%) received corticosteroids, most of the adults (77%) did not. The H1/H2-blockers were given to most of the adults and the children. Three of the reacting patients had a test dose.

An allergic/anaphylactic reaction was reported in 9 cases, in two further cases a doubtful allergic/anaphylactic reaction was reported. Six patients had a confirmed drop in blood pressure, for one patient a drop in peripheral vascular resistance was reported and for two further patient a circulatory failure was reported. One had no vascular reaction, only flush and was judged as doubtful, for an other an anaphylactic shock was reported.

Eight of the 9 patients received H1/H2-blockers and three received corticosteroids.

Two of the 9 patients with unquestionable reaction died.

The frequency of reactions was 2.8%, 95% CI 1.4-5.0 (11 of 387 reexposed valid patients). Omitting the 6 patients having less than 2 days between first and second operation, the incidence becomes 2.9% (95% CI 1.5-5.1). Taking only into account the 9 patients with unquestionable reactions gives a frequency of 2.4 % (95% CI 1.1-4.4).

For 9 of the 11 reactions, the time between the two consecutive operations was less than half a year, for one patient the time interval was 1106 days. There were 173 patients with an reexposure interval documented greater than 1 day and less than 6 months. Therefore, the overall frequency of reaction in this subgroup is 9/173 or 5.2% (95 % CI 2.4-9.6), or 8 unquestionable reactions in 173 patients or 4.6% (95% CI 2.0-8.9).

Among the 221 patients with at least one reexposure interval documented as being greater or equal to 6 months, there were 2 reactions giving a frequency of 0.91% (95% CI 0.11-3.2). One of the 2 reactions was unquestionable, equal to a frequency of 1/221 patients or 0.45% (95% CI 0.011-2.5).

There were 381 valid patients from 421 reexpositions in total. Of these, 412 occurred with an interval greater than 1 day.

The following frequencies were calculated from all the data:

	<u>Frequency</u>	<u>95 % CI</u>
All reactions from all reexposures >1 day (11 from 412)	2.7%	1.3-4.7
All unquestionable reactions from all re-exposures >1 day (9 from 412)	2.2%	1.0-4.1
All reactions from all reexposures \geq 6 months, only patients with information (2 from 231)	0.87%	0.11-3.1
All unquestionable reactions from all re-exposures >6 months (1 from 231)	0.43%	0.01-2.4
All reactions from all reexposures >1 day, <6 months (9 from 179)	5.0%	2.3-9.3
All unquestionable reactions from all re-exposures >1 day <6 months (8 from 179)	4.5%	1.9-8.6

The frequency of all reactions by age and gender for the valid patient population are summarized in the following table:

	<u>Frequency</u>	<u>95 % CI</u>
All valid adults (9/248)	3.6 %	1.7-6.8
All valid children (2/133)	1.5 %	0.18-5.3
All valid male patients (6/254)	2.4 %	0.87-5.1
All valid female patients (5/126)	4.0 %	1.3-9.0
All male adults (5/178)	2.8 %	0.92-6.4
All female adults (4/70)	5.7 %	1.6-14.0

The data suggest that the risk of an anaphylactic/allergic reaction is much higher within the first 6 months after an exposition to Trasylol, than at later times. Anaphylaxis occurred more frequently in adults than in children and in women than in men.

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OVERALL CONCLUSIONS OF TRASYLOL EFFICACY AND SAFETY

Since the approval of the current labeling for Trasylol on October 12, 1994, several additional placebo-controlled trials have been completed in the United States. These trials have increased the size of the Trasylol safety database, in CABG surgery, by 986 patients.

At the time of the original NDA submission the efficacy and safety data on Trasylol-treated patients undergoing primary CABG surgery in U.S. trials was limited to a subset of patients in one study which included both primary and repeat CABG patients. Since then two large, controlled trials in primary CABG surgery have been completed and are included in this submission. In total, six placebo-controlled, double-blinded, randomized clinical trials which included patients undergoing either primary or repeat CABG surgery have been conducted under

The studies are summarized in the following table:

U. S Studies in CABG Surgery

<u>Study No.</u>	<u>Indication(s)</u>	<u>Design</u>	<u>Dosage Regimens</u>
D89-004	Repeat CABG	DB,R,PC,parallel	High-Dose Low-DoseB Placebo
D92-008	RepeatCABG	DB,R,PC,parallel	High Dose Low DoseB Pump prime only Placebo
D89-006	Primary and repeat CABG	DB,R,PC,parallel	High Dose Placebo
D91-007	Primary and Repeat CABG and/or valve	DB,R,PC,parallel	High Dose Low DoseB Placebo
D92-016	Primary CABG	DB,R,PC,parallel	High Dose Low Dose Pump Prime Placebo
D92-048	Primary CABG	DB,R,PC,parallel	High Dose Placebo

Overview of Efficacy: An overview of the efficacy data for all patients evaluated in placebo-controlled studies pooled by indication (repeat CABG or primary CABG) and by dose regimen (high dose, low dose, pump prime only or placebo) is summarized in the following two tables.

Efficacy Variables: Repeat CABG Patients in U. S. Studies

Mean (S.D.) or % of Patients

VARIABLE	PLACEBO	PUMP PRIME	Low-Dose	High-Dose
	REGIMEN N=156	REGIMEN+ N=68	Trasylol Regimen B N=113	Trasylol Regimen A N=143
% OF REPEAT CABG PATIENTS WHO REQUIRED DONOR BLOOD	76.3%	72.1%	48.7%*	46.9%*
UNITS OF DONOR BLOOD TRANSFUSED	3.7(4.4)	2.5(2.4)	2.2(5.0)*	1.6(2.9)*
mL OF DONOR BLOOD TRANSFUSED	1132(1443)	756(807)	723(1779)*	515(999)*
PLATELETS TRANSFUSED (Donor Units)	5.0 (10.0)	2.1(4.6)*	1.3(4.6)*	0.9(4.3)*
CRYOPRECIPITATE TRANSFUSED (Donor Units)	0.9 (3.5)	0.0(0.0)*	0.5(4.0)	0.1(0.8)*
FRESH FROZEN PLASMA TRANSFUSED (Donor Units)	1.3 (2.5)	0.5(1.4)*	0.3(1.1)*	0.2(0.9)*
THORACIC DRAINAGE RATE (mL/hr)	89 (77)	73(69)	66(244)*	40(36)*
TOTAL THORACIC DRAINAGE VOLUME (mL)	1659(1226)	1561(1370)	1103(2001)	960(849)*
REOPERATION FOR DIFFUSE BLEEDING	1.9%	2.9%	0%	0%

* Significantly different from placebo, $p < 0.05$

Efficacy Variables: Primary CABG Patients in U. S. Studies
Mean (S.D.) or % of Patients

VARIABLE	PLACEBO	PUMP PRIME	Low-Dose	High-Dose
	REGIMEN	REGIMEN+	Trasylol	Trasylol
	N=624	N=159	REGIMEN B N=175	REGIMEN A N=641
% OF PRIMARY CABG PATIENTS WHO REQUIRED DONOR BLOOD	53.5%	32.7%*	37.1%*	36.8%*
UNITS OF DONOR BLOOD TRANSFUSED	1.7(2.4)	0.9(1.6)*	1.0(1.6)*	0.9(1.4)*
mL OF DONOR BLOOD TRANSFUSED	584(840)	286(518)*	313(505)*	295(503)*
PLATELETS TRANSFUSED (Donor Units)	1.3(3.7)	0.5(2.4)*	0.3(1.6)*	0.3(1.5)*
CRYOPRECIPITATE TRANSFUSED (Donor Units)	0.5(2.2)	0.0(0.0)*	0.1(0.8)*	0.0(0.0)*
FRESH FROZEN PLASMA TRANSFUSED (Donor Units)	1.6(1.7)	0.2(1.7)*	0.2(0.8)*	0.2(0.9)*
THORACIC DRAINAGE RATE (mL/hr)	87677)	51(36)*	45(31)*	39(32)*
TOTAL THORACIC DRAINAGE VOLUME (mL)	1232(711)	852(653)*	792(465)*	705(493)*
REOPERATION FOR DIFFUSE BLEEDING	1.4%	0.6%	0%	0%*

* Significantly different from placebo, $p < 0.05$

Both High Dose and Low Dose Trasylol Regimen, but not the Pump Prime Regimen, were superior to placebo in reducing perioperative blood loss and the need for blood transfusions in patients undergoing repeat CABG surgery.

All Trasylol Regimens were superior to placebo in reducing perioperative blood loss and the need for donor blood transfusions when administered prophylactically to patients undergoing primary CABG

surgery. However, in the stratum of patients at low risk of bleeding, statistically significant efficacy was demonstrated only in the low-dose group with respect to units of blood.

The efficacy results with the Pump Prime Regimen have been inconsistent with evidence for efficacy in primary but not in repeat CABG surgery.

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Overview of Safety: The total CABG safety pool includes 1424 Trasyolol-treated patients (all doses) and 861 placebo patients.

Overall, there was little difference between the Trasyolol and placebo treatment groups in the incidence of treatment-emergent adverse events. Mortality rates difference was not significant: 2.7% and 3.4% in the placebo and Trasyolol groups respectively.

Safety issues which have been specifically addressed include incidence of MI, graft patency, allergy/anaphylaxis on re-exposure to Trasyolol, and post-operative renal and hepatic dysfunction.

Myocardial Infarction: The incidence of investigator-reported myocardial infarction was 8% in the Trasyolol group compared to 6% in the placebo group, a non-significant difference.

Because of the variability of the clinical criteria for the diagnosis of myocardial infarction among investigators, a prospective, blind assessment of MI was performed in three later studies (D92-016, D92-008, and D92-048) of patients undergoing either repeat or primary CABG surgery. In these studies, ECGs, cardiac enzymes, and other data were analyzed by a blinded consultant employing an algorithm for the diagnosis of definite, probable, or possible MI. When analyzed in this manner, the incidence of definite MI across all three studies was 5.9% and 4.7% in the Trasyolol-treated and placebo patients, respectively, a non-significant difference.

Graft Patency: Six earlier studies have assessed the effect of aprotinin on graft patency. The studies are summarized in the following table:

Graft patency after CABG surgery in by-patient and by-graft analyses.
All studies were randomized and placebo-controlled

Study	Procedure	High-Dose Aprotinin	Low-Dose Aprotinin	Control
Bistrup	MRI Scan			
Per-Patient		88% (n=43)	APPEARS THIS WAY ON ORIGINAL	92% (n=47)
Per-Graft		96% (n=131)		97% (n=138)
Lemmer	Cine CT			
Per-Patient		84% (n=83)		91% (n=81)
Per-Graft		92% (n=176)		95% (n=163)
Havel	Angio			
Per-Graft		94% (n=39)	95% (n=42)	93% (n=40)
Kalangos	Angio			
Per-Graft		99% (n=142)	100% (n=128)	99% (n=139)
Laub	Cine CT			
Per-Patient		69% (n=16)		100% (n=16)
Per-Graft		88% (n=43)	APPEARS THIS WAY ON ORIGINAL	100% (n=38)
Reichart	Angio			
Per-Patient		73% (n=37)		81% (n=32)
Per-Graft		85% (n=88)		92% (n=84)

Five studies failed to show any statistically significant difference in graft closure rates between aprotinin and placebo groups. The study by Laub et al. showed a statistically significant difference between the two groups in the per-patient analysis (p-value=0.04) and borderline significance in the by-graft analysis (p-value=0.057).

Subsequently, the multi-center, multi-national, large study (D92-048) was designed and sized specifically to address the issue of graft patency by means of post-operative angiography. Of the 13 study sites, 10 were in the United States and three were non-US centers (one in Denmark, two in Israel).

The results are presented in the following table.

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Incidence of Graft Closure, Myocardial Infarction and Death by Treatment Group

	Overall % Closure Rates*		% MIs**	% Deaths***
	All Centers n=703	US Centers n=381	All Centers n=831	All Centers n=870
Trasylol	14.4	9.4	2.8	1.4
Placebo	10.9	9.5	3.8	1.6
CI for the difference	1.3 - 9.6)+	-3.8 - 5.9+	-3.3 - 1.5'	-1.9 - 1.4'

* Population: all patients with assessable saphenous vein grafts

** Population: all patients assessable by blinded consultant

***All patients

+ 90%; per protocol

' 95%; not specified in protocol

" (Drug-Placebo)

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The results showed a significantly increased overall risk of graft closure for Trasylol-treated as compared to placebo patients (p=0.035). However, further analysis showed a significant treatment-by site interaction for one of the non-US sites (sites #3) versus the U.S. centers. When graft closures were analyzed for U.S. centers only, there was no difference between treatment groups. The results were similar when analyzed as the percentage of patients with at least one SVG closure postoperatively or as the percentage of SVGs closed. There were no differences between groups in the incidence of myocardial infarction (2.9% Trasylol vs 3.8% placebo) or of death (1.4% Trasylol vs 1.6% placebo).

Hypersensitivity/Anaphylaxis: The incidence of hypersensitivity-type reactions and anaphylaxis, rare in patients exposed to Trasylol for the first time, increases on repeat exposure to Trasylol. In the controlled clinical trials in CABG surgery performed in US and Europe patients with a known history of prior exposure to Trasylol were excluded from participation, therefore, any available data on patients re-exposed to Trasylol has come from spontaneous reports. The best available data are provided by a recent retrospective review of the records of 387 patients with documented re-exposure to Trasylol in Germany revealed an incidence of hypersensitivity/anaphylactic reactions to be 2.7%. Two patients who

experienced these reactions subsequently died. The data from this report also suggest that the incidence of hypersensitivity/anaphylactic reaction is considerably higher (5%) when re-exposure occurs within 6 months of the initial exposure than when re-exposure occurs beyond 6 months after initial exposure (0.9%).

Postoperative Renal Dysfunction: The incidence of serum creatinine elevations > 0.5 mg/dL above pre-treatment levels was 9% in Trasylol-treated as compared to 8% in placebo patients (p=0.248). The incidence of the more clinically significant elevations of > 2.0 mg/dL above baseline was only 1 % in each treatment group (p=0.883). The effect of Trasylol on postoperative renal function in CABG patients was transient and not clinically significant.

Postoperative Hepatic Dysfunction: The pooled data from all CABG patients in the U.S. placebo-controlled trials shows no evidence of increased postoperative hepatic dysfunction in Trasylol-treated patients. The incidence of treatment-emergent increases in ALT (SGPT) > 1.8 times the upper limit of normal was 14% in both Trasylol-treated and placebo patients (p=0.687), while the incidence of increases > 3 times the upper limit of normal was 5% in both groups (p=0.847). There was no increase in the incidence of treatment-emergent elevations in AST (SGOT), LDH, or alkaline phosphatase in Trasylol-treated as compared to placebo patients.

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PROPOSED REVISIONS IN THE TRASYLOL PACKAGE INSERT and RECOMMENDATIONS

A copy of the annotated revised labeling and a copy of the Draft Revised Text are appended to this review.

The following major labeling revisions have been submitted by the sponsor:

- 1) Indication for use no longer to be limited to patients undergoing repeat CABG surgery or to those patients undergoing primary CABG surgery where the risk of bleeding is especially high or when transfusion is unacceptable or unavailable. Instead, all patients undergoing CABG surgery would be considered eligible for Trasylol therapy. This revision is reflected in the INDICATION AND USAGE and in the DOSAGE AND ADMINISTRATION Sections (page 9 and 28, respectively) of

the annotated revised labeling.

Recommendations: For patients undergoing primary CABG, the indication for use of Trasylol should remain limited to patients at high risk of bleeding because of inconsistent results of efficacy of Trasylol in patients at low risk of bleeding (Study D92-016). The DOSAGE AND ADMINISTRATION section of the revised labeling should not be changed.

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2) Presentation of the updated efficacy data from clinical trials summarized by patients grouped according to indication (repeat CABG, primary CABG) and by treatment regimen (Regimen A or High-Dose, Regimen B or Low-Dose, Pump Prime Only, Placebo), on pages 3 and 7, respectively, of the annotated revised labeling.

Combined presentation of the primary efficacy variables (percentage of patients who required any donor blood or the number of units of donor blood transfused) and the secondary efficacy variables (reductions in the requirements for donor blood products, thoracic drainage, reduction in the need for reoperation for diffuse bleeding), in one table each for primary and for repeat CABG data (pages 6 and 8, respectively, of the annotated revised labeling).

Recommendations: The changes are acceptable.

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3) Deletion of references to the cardiac valve study from the efficacy results in the CLINICAL TRIALS Section (page 9 of the annotated labeling) because there was no evidence of efficacy in that study and because the indication of Trasylol for valve surgery has not been approved for marketing.

Recommendations: The reference of cardiac valve surgery can be deleted from the efficacy results, however, the information of lack of efficacy of Trasylol in valve surgery (which is deleted on page 9 of the annotated labeling) should be included in the WARNINGS section.

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4) Revised tabulation of adverse reactions by body system

reported from all CABG patients (n=1424) and placebo patients (n=861) in all placebo-controlled U.S. studies (pages 19 and 20 of revised annotated labeling) and exclusion of the patients undergoing valve surgery from the safety pool.

Recommendations: The safety data for patients undergoing valve surgery should not be excluded from the tabulation of adverse events because the Trasyolol regimens used were the same as those used for CABG surgery and because the adverse events experienced may be independent of the underlying surgical procedure (i.e. allergic reactions, MI).

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5) Expansion of the WARNING and of the PRECAUTIONS section of the insert to include recent data on the incidence of hypersensitivity/anaphylaxis reactions on reexposure to Trasyolol (pages 10, 11, 12, 13 and 29 of the revised annotated labeling).

Recommendations: The proposed revision of the WARNING section, as well as the revision of the PRECAUTIONS section concerning the risks of allergic reactions are acceptable.

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6) Revision of the Laboratory Monitoring of Anticoagulation during Cardiopulmonary Bypass and Other Laboratory Findings sections (pages 15, 16 and 27 of the revised annotated labeling) to reflect the methods that are currently most widely employed in the U.S. and Europe.

Recommendations: The revisions of the above sections are acceptable.

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7) Addition of sub-sections dealing with myocardial infarction and graft patency under the ADVERSE REACTIONS section (pages 21 and 22, respectively, of the annotated revised labeling).

Recommendations: The revisions are acceptable. The table included with the sub-section of Myocardial Infarction in the annotated labeling is incorrect, however, a corrected table has been included in the Draft Revised Text.

8) Pooling of all safety laboratory findings for patients undergoing CABG surgery in U.S. placebo-controlled trials, excluding cardiac valve surgery patients. The Laboratory Findings section has been updated and revised to reflect the much larger experience with Trasylol and the recent information concerning effects of Trasylol on renal and hepatic function (pages 25 and 26, respectively, of the annotated revised labeling).

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Recommendations: The safety laboratory findings for cardiac valve surgery patients should not be excluded. The changes are otherwise acceptable.

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Lilia Talarico, M.D.

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