FDA BRIEFING DOCUMENT:

ANTI-INFECTIVE ADVISORY COMMITTEE

DROTRECOGIN ALFA (ACTIVATED)

[RECOMBINANT HUMAN ACTIVATED PROTEIN C (rhAPC)]

XIGRIS™

BLA # 125029/0

SEPTEMBER 12, 2001

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Section I-Introduction

Purpose

This briefing document presents data from the clinical studies of Drotrecogin alfa (activated) as submitted in Biologics License Application (BLA) application BLA # 125029/0 from Eli Lilly and Company and an analysis of these data in order for the Anti-Infective Advisory Committee to render advice and comments on the safety and efficacy of this product.

Sponsor

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Product

Recombinant Human Activated Protein C (rhAPC).

Proposed Indication

rhAPC is indicated for the "treatment of pediatric and adult patients with sepsis associated with acute organ dysfunction (severe sepsis). Treatment with rhAPC reduces mortality in patients with severe sepsis".

Proposed Contraindications

rhAPC has the potential to increase the risk of bleeding. rhAPC is contraindicated in the following situations: active internal bleeding, recent (within 3 months) hemorrhagic stroke, recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma requiring hospitalization, trauma patients with increased risk of life-threatening bleeding, patients with an epidural catheter, and patients with intracranial neoplasm or mass lesion.

Background

Sepsis syndrome results from a generalized inflammatory and procoagulant host response to an infection. Proinflammatory cytokines (e.g. tumor necrosis factor, interleukin-1) are capable of activating coagulation and inhibiting fibrinolysis while the procoagulant thrombin is capable of stimulating multiple inflammatory pathways. Protein C is a circulating plasma zymogen that, in the presence of thrombin in complex with thrombomodulin (TM) is converted to activated Protein C (APC). APC with Protein S as a cofactor inactivates Factor Va and VIIIa and limits thrombin generation, so APC exerts an antithrombotic effect by inhibiting those factors. Some *in vitro* data indicate that APC has indirect profibrinolytic activity by its ability to inhibit plasminogen activator inhibitor-1 (PAI-1) and limiting generation of activated thrombin activatable-fibrinolysis-inhibitor. Additionally, some *in vitro* data indicate APC exerts an anti-inflammatory effect by inhibiting human tumor necrosis factor production by monocytes, by blocking leukocyte adhesion to selectins, and by limiting the inflammatory responses within the microvascular endothelium induced by thrombin generation. Drotrecogin alfa (activated) and endogenous human APC are inactivated in plasma by protease inhibitors.

Manufacturing

Drotrecogin alfa (activated) is human APC produced by recombinant DNA technology. The manufacturing process involves the secretion of the inactive Protein C zymogen into the culture medium by an established human cell line into which the complementary DNA for natural human Protein C has been inserted. Human Protein C is enzymatically activated to human APC, subsequently purified and is supplied as a sterile, lyophilized, white to practically white powder. Each vial contains 5 mg or 20 mg of drotrecogin alfa (activated). The lyophilized drug product is initially solvated in water for injection to a concentration of 2 mg/ml followed by dilution into sterile saline (0.9% sodium chloride) for intravenous infusion.

Pharmacokinetics

A variety of infusion rates and duration of infusions were investigated in phase 1 studies using nonspecific subjects at a normalized infusion rate of 24 ug/kg/hr. Plasma clearance was 28 ± 9 L/hr ($Cl_p \pm$ SD, N=190). Elimination was biphasic with a rapid initial phase ($t\frac{1}{2}\acute{a}$=13 minutes) and a slower second phase ($t\frac{1}{2}\hat{a}$=1.6 hours). The short half-life of 13 minutes accounts for approximately 80% of the area under the plasma concentration curve and governs the initial rapid attainment of plasma rhAPC concentrations towards the steady-state. Plasma rhAPC steady-state concentrations are proportional to the infusion rate over a range of infusion rates from 12 ug/kg/hr to 48 ug/kg/hr. In healthy subjects, greater than 90% of the steady-state plasma concentration is attained within 2 hours following the start of a constant-rate intravenous infusion. In the phase 2 trial, infusion from 12 ug/kg/hr to 30 ug/kg/hr rapidly produced steady-state plasma concentrations that were proportional to infusion rates. Results of phase 2 and phase 3 studies indicate that Cl_p in patients with severe sepsis is higher than that in normal healthy subjects. In the phase 3 trial, pharmacokinetics were evaluated in 342 patients

administered a 96-hour continuous infusion at 24 ug/kg/hr. Elimination half-lives were not calculated in patients with sepsis, instead the pharmacokinetic profile of rhAPC was characterized by clearance and C_{ss}. Pharmacokinetics were characterized by attainment of steady-state plasma concentration within 2 hours following the start of the infusion and in the majority of patients, measurements of rhAPC beyond 2 hours after termination of the infusion were below the quantifiable limit (<10 ng/mL), suggesting rapid elimination of drotrecogin alfa from the systemic circulation. Clearance was reported to be 42 L/hour in the phase 3 study (EVAD) with an infusion of 24 ug/kg/hr and 46 $\pm$ 38 for phase 2 studies up to 30 ug/kg/hr for 24 hours (x$\pm$SD).

Brief Description of Studies

<u>Phase 1</u>

Appendix 1 describes the phase 1 studies that were conducted assessing the pharmacokinetic and pharmacodyamic parameters and one safety trial in patients with purpura fulminans.

<u>Phase 2</u>

- **F1K-MC-EVAO Pediatric Patients, noncontrolled study**

This was an open-label, multicenter trial in pediatric patients with severe sepsis. Sixty patients, age 1 day to 17 years, at 9 centers were to be studied. The study was conducted in two parts. In part 1, rhAPC was administered at 6, 12, 24 or 36 ug/kg/hr for 6 hours once daily for a 4 day treatment in 23 patients. In part 2, 96 hour infusion at 24 ug/kg/hr (based on Part 1 results) was studied in 37 patients. See Section IV-Pediatrics.

- **F1K-MC-EVAA Placebo-controlled study**

This was a double-blind, placebo-control, dose-ranging study in adults with severe sepsis. 135 patients from 40 centers were enrolled, 131 consisted of the intent-to-treat (ITT) population, from 19 to 89 years. Study was conducted in 2 parts. Stage 1, 48 hour continuous iv infusion in 72 patients were studied. Stage 2, 96 hour continuous iv infusion of rhAPC in 59 patients were studied. rhAPC dose-ranging was 48 hour iv infusion at 12, 18, 24 or 30 ug/kg/hr or 96 hour iv infusion at 12, 18 or 24 ug/kg/hr. Placebo was sterile 0.9% sodium chloride or 5% dextrose water.

<u>Phase 3</u>

- **F1K-MC-EVAD Placebo-controlled study**

This was a randomized, double-blind, placebo-controlled, multicenter study in adults with severe sepsis. A total of 1728 subjects were enrolled, 1690 patients consisted of the ITT population at 164 centers. rhAPC was administered at a continuous iv infusion 96 ±1 hours at 24 ug/kg/hr rhAPC. Placebo was sterile 0.9% sodium chloride or 0.1% human serum albumin added to placebo. Primary endpoint of the study was 28 day all-cause mortality status.

Section II – Phase II F1K-MC-EVAA Clinical Study

Study Description

The F1K-MC-EVAA phase 2 study investigated the safety and pharmacokinetics of rhAPC. The objective of the study was to identify the effective dose range and dose duration of rhAPC in the correction of sepsis-induced intravascular coagulation and in the prevention or improvement of sepsis-induced organ failure. rhAPC or placebo was administered as a continuous intravenous (iv) infusion for 48 or 96 hours to 131 patients with severe sepsis for the proposed indication.

Study Design

Primary objectives of the study were to assess the safety of administration of rhAPC as a function of dose and dose duration, to determine the degree to which the coagulation abnormalities of severe sepsis are affected by the administration of rhAPC as a function of dose and dose duration and to determine an effective dose and dose duration of rhAPC administration based on the ability of rhAPC to alter the coagulation abnormalities of severe sepsis, for use in future studies. Secondary objectives were to determine the baseline characteristics (coagulation profile, Protein C antigen level, Protein C functional activity and Factor V Leiden) of patients with severe sepsis which may be predictive of individuals who may benefit from the use of rhAPC and the pharmacokinetics of rhAPC in patients with severe sepsis, to estimate the effect of rhAPC on organ dysfunction associated with severe sepsis, and transfusion-free, systemic inflammatory response syndrome (SIRS)-free, intensive care unit (ICU)-free days, and 28-day all-cause mortality for patients with severe sepsis. The study was conducted in two sequential steps, designated as Stage 1 and Stage 2, and both were double-blind, placebo-controlled, dose-ranging studies of rhAPC administered as a continuous iv infusion over a fixed interval of 48 hours (Stage 1) and 96 hours (Stage 2). The initial rhAPC dose used in both stages was 12 ug/kg/hr. The starting dose was chosen based on results from three Phase 1 studies. In these studies, the 12 ug/kg/hr dose was shown to be safe and tolerable. In Stage 1 and Stage 2, after the initial dose of 12 ug/kg/hr, subsequent increased doses were determined by the Data Monitoring Board convened to review the available safety, pharmacokinetic, and pharmacodynamic data. A total of 72 patients received study drug in Stage 1 and total of 59 patients in Stage 2. The study included 131 patients total, of whom 41 received placebo and 90 received rhAPC, infused at rates ranging from 12 to 30 ug/kg/hr for 48 or 96 hours.

Efficacy

Percent mortality by treatment group is shown below in Table 1. A 15% relative risk reduction in 28-day all-cause mortality was observed when comparing rhAPC-treated patients with all placebo-treated patients (29% versus 34%, chi-square test, p=0.55).

The sponsor noted that a 40% relative risk reduction was observed when comparing the high dose rhAPC-treated patients (24 and 30 ug/kg/hr) with placebo-treated patients

(21% versus 34%). However, these were retrospective analyses, and no consistent dose effects were seen in this relatively small study.

An analysis of adverse events and bleeding rates suggest the dose of 24 ug/kg/hr rhAPC yielded an improved safety profile as compared to 30 ug/kg/hr or lower doses of 12 and 18 ug/kg/hr. During the period of drug infusion for Stages 1 and 2, the percentage of patients experiencing at least one treatment-emergent adverse event was 46% in the groups given doses of 24 ug/kg/hr and 30 ug/kg/hr rhAPC versus 75% for patients given 12 and 18 ug/kg/hr; in patients given placebo, treatment-emergent adverse events occurred in 61% of the cases. Additionally, 30% (N=8) of the patients dosed at 24 ug/kg/hr rhAPC versus 50% (N=6) of those dosed at 30 ug/kg/hr experienced an elevated whole blood APTT and required reductions in dosing during the first 48 hours of infusion. When indicators of pharmacological activity such as d-dimer concentrations or interleukin (IL)-6 levels during the period of infusion were considered, they supported the dose of 24 ug/kg/hr and an infusion period of 96 hours.

Table 1. Percent mortality by treatment group

Treatment	N	Mortality N (%)
High rhAPC doses		
APC 30 ug/kg/hr 48 hour duration	12	3 (25)
APC 24 ug/kg/hr 96 hour duration	15	5 (33)
APC 24 ug/kg/hr 48 hour duration	12	0 (0)
Total	39	8 (21)
Low rhAPC doses		
APC 18 ug/kg/hr 96 hour duration	15	7 (47)
APC 18 ug/kg/hr 48 hour duration	11	3 (27)
APC 12 ug/kg/hr 96 hour duration	14	5 (36)
APC 12 ug/kg/hr 48 hour duration	11	3 (27)
Total	51	18 (35)
Total of all rhAPC patients	**90**	**26 (29)**
Placebo 48 hour duration	26	10 (39)
Placebo 96 hour duration	15	4 (27)
Total of all placebo patients	**41**	**14 (34)**
Total number of phase 2 patients	131	40 (31)

rhAPC vs. placebo p=0.545.

Section III – Phase III F1K-MC-EVAD Clinical Study

Study Description

The F1K-MC-EVAD phase 3 study was a randomized, double-blind, placebo-controlled, multicenter, study of rhAPC administered as a continuous 96-hour intravenous infusion in patients with severe sepsis. The efficacy, safety, and pharmacokinetics of a 96-hour infusion of rhAPC were evaluated using a dose of 24 ug/kg/hr. Patients were randomly assigned in a 1:1 ratio to receive either rhAPC or placebo. Approximately 2280 patients were planned to be enrolled in the study. The primary objective of the study was to demonstrate rhAPC reduces 28-day all-cause mortality in patients with severe sepsis. Secondary objectives were to show that rhAPC reduces 28-day all-cause mortality in patients with severe sepsis and Protein C deficiency at baseline, to evaluate the effects of rhAPC on organ function (cardiovascular, respiratory, renal, hematologic, and hepatic), to evaluate the health economic impact of rhAPC administration in patients with severe sepsis and to further characterize the pharmacokinetics. Clinical laboratory tests performed included hematology and clinical chemistry, platelets, activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer, Il-6 level, APC resistance, APC level, Protein C (PC) functional activity, anti-APC antibody, antithrombin functional activity and Protein S functional activity.

Study Design

There were two separate window periods prior to study drug administration to be met for study eligibility. Window I was a 24 hour time frame immediately prior to enrollment during which patients were screened for eligibility to enter the study. Patients who met all of the inclusion criteria and did not meet any of the exclusion criteria were eligible for entry in the study. Window II was a 24 hour time frame during which baseline efficacy and safety assessments were performed before the start of the study drug. Patients randomly assigned to the placebo received 0.1% human serum albumin (HSA) solution for 96 hours. The primary efficacy endpoint in this study was mortality status through the 28 days (672 hours) after the initiation of study drug infusion. All patients who received study drug for any length of time were followed to determine 28-day survival status, regardless of whether they were withdrawn from study drug.

Selection of Study Population

Appendix 2 describes in detail patients with severe sepsis with the inclusion and exclusion criteria used to select the study population.

Statistical Plan

The primary efficacy analysis was based on the Cochran-Mantel-Haenszel test stratified by pre-infusion APACHE II quartile, age class and baseline Protein C activity class for the intent-to-treat (ITT) (with pooling of under-represented strata). The relative risks and corresponding confidence interval, were calculated using the logit adjusted relative risk

method with an adjustment for pre-infusion acute physiology and chronic health evaluation (APACHE) II quartile, age class, and baseline Protein C activity class (with pooling of under-represented strata). A Data and Safety Monitoring Board (DSMB), external to the sponsor, was established to evaluate interim data and had the authority to recommend trial suspension if safety concerns arose or if the predictive probability of establishing efficacy was low and to recommend trial termination for efficacy according to pre-specified criteria.

The following subgroup analyses were performed: Protein C deficiency status (>80%, 80%); baseline Protein C activity class (unknown, >80%, >60 to 80%, >40 to 60%, and 40%); antithrombin (AT) III deficiency status; AT III quartile; APACHE II quartile; age class (<60, ≥60 years); gender; country of investigative site; investigative site; origin; instrumental Activities of Daily Living (ADL) index quartile; renal, respiratory, cardiovascular, coagulation, unexplained metabolic acidosis organ failure criteria status; number of systemic inflammatory response syndrome (SIRS) criteria met at baseline (3 or 4); number of organ failure criteria met (1, 2, 3, 4 or 5); cardiovascular, renal, coagulation, respiratory, liver organ dysfunction/failure (SOFA score); septic shock status; acute respiratory distress syndrome (ARDS) status; disseminated intravascular coagulation (DIC) status; invasive mechanical ventilation status; time from meeting Criteria A, B and C to initiation of study drug (<12 hours, 12-24 hours); time from first sepsis induced organ failure to start of study drug administration (24 hours, >24 hours); immunocompromised (yes/no); APC resistance (yes/no); actual infection confirmed by a positive culture (yes/no); and positive blood culture (yes/no).

Results of Interim Analyses

The study design included two planned interim analyses, which occurred shortly after 760 patients and 1520 patients were enrolled, received study drug, and completed the protocol. The statistical guidelines to suspend study enrollment for efficacy with respect to 28-day mortality followed the O'Brien-Fleming[1] method as implemented by Lan and DeMets[2]. The first interim analysis occurred in October 1999; the second, in June 2000 and included a review of 1520 patients who had received rhAPC or placebo. The pre-specified two-sided critical alpha levels for the first and second interim analyses were 0.0002 and 0.0118 respectively. After the second interim, the DSMB recommended that study enrollment be suspended because of a statistically significant reduction in 28-day all-cause mortality in rhAPC-treated patients compared with placebo-treated patients. Data from 1520 patients showed 192 of the 768 (25%) rhAPC-treated patients and 236 of the 752 (31%) placebo-treated patients did not survive 28 days (primary stratified analysis p=0.0071, nonstratified p=0.0057). Trial enrollment was suspended on 28 June 2000. At the time of enrollment suspension, 1728 patients already had been enrolled, 1690 patients had received the study drug for any length of time and constituted the intent-to-treat (ITT) population for the study.

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[1] Biometrics 35:549-556, 1979.
[2] Biometrika 70:659-663, 1983.

Removal of Patients from Therapy or Assessment

Patients were considered to have completed the protocol if their 28-day survival status was available. Thirty-eight patients were discontinued from the study before receiving study drug. Of these, thirty-seven patients were followed for 28-day survival status, although they were not considered to have completed the protocol. One patient was lost to follow up Patient 946-4605, who was assigned to rhAPC treatment.

Section IIIA-Baseline characteristics

The data presented in the following tables summarize the baseline characteristics and demographics found in both the rhAPC and placebo groups.

A. Gender

Below is a summary of gender in both treatment groups and in the total number of patients. For treatment effect see Table 8 and for safety Table 45.

Table 2. Baseline distribution of gender

Gender	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Female	373 (44)	353 (42)	726 (43)
Male	477 (56)	487 (58)	964 (57)

B. Age

Below is a summary of the age classes in both treatment groups and in the total number of patients. For treatment effect see Table 10 and for safety Table 46.

Table 3. Baseline distribution of age

Age Classification (years)	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
<60	375 (44)	366 (44)	741 (44)
≥60	475 (56)	474 (56)	949 (56)
<65	437 (51)	449 (54)	886 (52)
≥65	413 (49)	391 (47)	804 (48)
<75	645 (76)	659 (79)	1304 (77)
≥75	205 (24)	181 (22)	386 (23)

C. Ethnic Origin

Below is a summary of the ethnic origin of the patient in both treatment groups and in the total number of patients. For treatment effect see Table 9 and for safety Table 47.

Table 4. Baseline distribution of ethnic origin

Ethnic origin	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
African descent	70 (8)	61 (7)	131 (8)
Western Asian	5 (1)	6 (1)	11 (1)
Caucasian	695 (82)	689 (82)	1384 (82)
East/Southeast Asian	9 (1)	13 (2)	22 (1)
Hispanic	34 (4)	40 (5)	74 (4)
Other	37 (4)	31 (4)	68 (4)

The data presented above show well-balanced treatment groups with respect to gender, age and ethnic origin.

D. Disease Severity

Presented below is a summary of the conditions accompanying severe sepsis and the
APACHE II scores at baseline found in the treatment groups.

Table 5. Baseline distribution of disease severity

Variable	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Shock[1]			
No	252 (30)	238 (28)	490 (29)
Yes	598 (70)	602 (72)	1200 (71)
ARDS[2]			
No	725 (85)	706 (84)	1431 (85)
Yes	125 (15)	134 (16)	259 (15)
DIC[3]			
DIC	800 (94)	774 (92)	1574 (93)
No DIC	49 (6)	66 (8)	115 (7)
Unspecified	1	0	1
Ventilation			
No	227 (27)	188 (22)	415 (25)
Yes	623 (73)	652 (78)	1275 (75)
Immunocompromised[4]			
No	763 (90)	771 (92)	1534 (91)
Yes	87 (10)	69 (8)	156 (9)
Pre-infusion APACHE II			
Mean (range 3-53)	25	25	25
Median	24	24	24

1)   Septic shock is defined under the cardiovascular organ failure as described in Appendix 2 (arterial systolic blood pressure (SBP) of less than or equal to 90 mm Hg or mean arterial pressure (MAP) of less than or equal to 70 mm Hg) in the phase 3 inclusion criteria.

2)   Patients were defined as having acute respiratory distress syndrome (ARDS) at baseline if each of the following three criteria were present within 24 hours prior to the start of study drug infusion: chest x-ray shows bilateral infiltrates consistent with pulmonary edema on the frontal chest radiograph (these infiltrates may be patchy, diffuse, homogeneous or asymmetric but not explained by tumor, pleural effusion or simple atelectasis); at the time of the chest x-ray, the central venous pressure, pulmonary capillary wedge pressure or clinical assessment did not indicate central venous volume overload; or PaO2/FiO2 less than or equal to 200.

3)   Patients were defined as having disseminated intravascular coagulation (DIC) at baseline if they had, if any 2 of the following 4 criteria were met within 24 hours prior to initiating study drug infusion: platelet count <100,000 mm^3 or a 50% decrease from any value in the last 3 days; prothrombin time or activated partial thromboplastin time >1.2 times the upper limit of normal (ULN); evidence of procoagulant and/or fibrinolytic activation based on a D-dimer >ULN; or evidence of inhibitor consumption based on either protein C activity, protein S activity or antithrombin III activity below the lower limit of normal.

4)   Immunocompromised was defined as patients who received treatment that suppresses resistance to infection, eg. immunosuppression chemotherapy, radiation, long-term recent high-dose steroids (>0.3 ìg/kg/day of prednisone or equivalent daily for 6 months), or had a disease that was sufficiently advanced to suppress resistance to infection, such as leukemia, lymphoma, or AIDS.

The mean APACHE II scores were similar between rhAPC and placebo. The percentage
of patients requiring ventilation was higher in placebo 78% vs. 73% with rhAPC.

E. Pre-infusion SIRS and Organ Failure Status

Presented below is a summary of the number of patients that met systemic inflammatory response syndrome (SIRS) criteria and organ failures (OF) criteria at baseline within the respective treatment groups.

Table 6. Baseline distribution of pre-infusion SIRS and organ failure status

Variable	rhAPC (850)	Placebo (840)	Total N (1690)
Number of SIRS[1] criteria met			
2	3 (0)	3 (0)	6 (0)
3	341 (40)	324 (39)	665 (39)
4	506 (60)	513 (61)	1019 (60)
Number of Organ Failure (OF) met			
0	1 (0)	0	1 (0)
1	215 (25)	203 (24)	418 (25)
2	270 (32)	272 (33)	543 (32)
3	214 (25)	218 (26)	432 (26)
4	119 (14)	116 (14)	235 (14)
5	31 (4)	30 (4)	61 (4)
Cardiovascular OF met			
No	248 (29)	228 (27)	476 (28)
Yes	602 (71)	612 (73)	1214 (72)
Respiratory OF met			
No	218 (26)	200 (24)	418 (25)
Yes	632 (74)	640 (76)	1272 (75)
Hematology OF met			
No	712 (84)	710 (85)	1422 (84)
Yes	138 (16)	130 (16)	268 (16)
Renal OF met			
No	493 (58)	487 (58)	980 (58)
Yes	357 (42)	353 (42)	710 (42)
Acidosis OF Met			
No	551(65)	558 (66)	1109 (66)
Yes	299 (35)	282 (34)	581 (34)
Type of OF at study entry in patients with single OF			
Cardiovascular	66 (8)	58 (7)	124 (7)
Hematology	6 (1)	6 (1)	12 (1)
Acidosis	11 (1)	7 (1)	18 (1)
Renal	19 (2)	14 (2)	33 (2)
Respiratory	113 (13)	118 (14)	231 (14)

1) Systemic inflammatory response syndrome (SIRS)-the body's physiological response to conditions include trauma, burns, pancreatitis, and infection develops as a consequence of infection is referred to as sepsis. SIRS was defined as under the inclusion criteria for phase 3 (at least 3 of 4: temperature; heart rate-tachycardia (e.g. heart block

or beta blockers need only meet 2 of the 3 other criteria); respiratory rate or acute mechanical ventilation; or white blood cells) Appendix 2.

The data presented above show 25% of the patients had one organ failure at the time of entry criteria prior to the start of infusion. The most common single failure at entry was respiratory failure at 14%.

F. Infection data

The lung and the abdomen were the most common site of infection. Gram-negative and gram-positive data appear in Appendix 4 Table 57.

G. Central laboratory data

The total number of patients that were Protein C deficient at baseline was 82%. There were patients classified as "unknown" due to an error in the sampling collection, and therefore baseline central laboratory data were not available for all patients. Protein C activity classes were defined as 40%, 41-60%, 61-80%, >80% and unknown. Protein C deficiency and severe Protein C deficiency were defined as 80% and 65% respectively. Antithrombin deficiency is described as <80% and given as percentages. Factor V Leiden or Hong Kong/Cambridge mutation for APC resistant status was described as negative or positive. Proportion of patients with Protein C activity 40% was 39% in the rhAPC group vs. 34% in the placebo group; severely Protein C deficient 73% rhAPC vs. 67% placebo; and Protein C deficiency 83% rhAPC vs. 80% in the placebo group. Appendix 4 Table 58 presents the baseline distribution of laboratory data.

The mean platelets levels at baseline were similar with $197 \times 10^3/mm^3$ in rhAPC and $204 \times 10^3/mm^3$ (total mean $200 \times 10^3/mm^3$) in the placebo treatment group.

Section IIIB-EFFICACY

A. Primary Efficacy Analysis: 28 Day All Cause Mortality and Treatment Effect

The observed mortality in all randomized patients for the ITT population is presented in the table below. The 28 day all cause mortality in the placebo group was 31% (259/840) as compared with 25% (210/850) in the rhAPC group. This 6% reduction in mortality in rhAPC treated patients is statistically significant (p=0.0054, stratified, CMH; p=0.0049, nonstratified Chi squared). The estimate of relative risk is 0.8 [95% confidence intervals (CI): 0.7, 0.9].

Table 7. Primary 28-Day all-cause mortality in all randomized patients-ITT population

THERAPY	Alive at Day 28	Died by Day 28	Total
	N (%)	N (%)	
Placebo	581 (69)	259 (31)	840
rhAPC	640 (75)	210 (25)	850
			1690

p=0.0054 (stratified, CMH); p=0.0049 (non stratified, Chi square)

Presented below is the Kaplan-Meier survival curve for all patients in the study (n=1690, ITT).

Product-Limit Survival Fit
Survival Plot
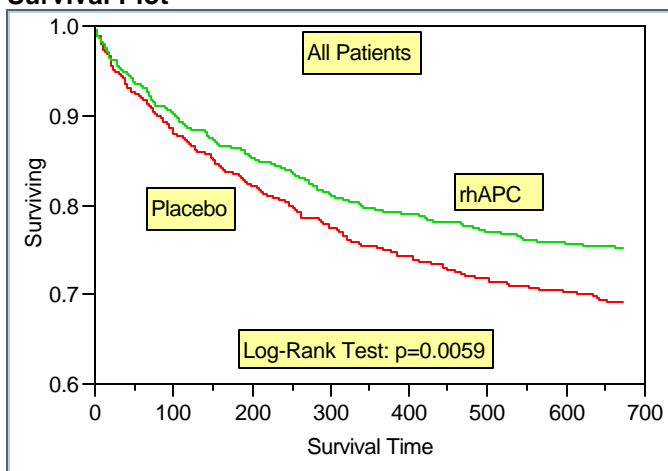
Figure 1. Kaplan-Meier survival curve

The survival curve was lower for patients in the placebo treatment group as compared to the rhAPC treatment group. The two curves separate gradually over the duration of the study. The difference between the two survival curves was statistically significant (p=0.0059, Log-Rank Test).

B. Treatment Effect and Gender

Below are data presented on mortality and gender of the patients.

Table 8. 28-Day all-cause mortality analyses stratified by gender

Gender	rhAPC (850)		Placebo (840)		Relative	95% CI
	Total N	N (%)	Total N	N (%)	Risk (RR)	for RR
Female	373	94 (25)	353	108 (31)	0.82	0.65, 1.04
Male	477	116 (24)	487	151 (31)	0.78	0.64, 0.96

CI=Confidence Interval.

The mortality rates between the gender groups and treatment arms are similar.

C. Treatment Effect and Ethnic Origin

Below are data presented on mortality and ethnic origin of the patients.

Table 9. 28-Day all-cause mortality analyses by ethnic origin

Ethnic Origin	rhAPC (850)		Placebo (840)		Relative	95% CI
	Total N	N (%)	Total N	N (%)	Risk (RR)	for RR
African descent	70	19 (27)	61	23 (38)	0.72	0.44, 1.19
Western Asian	5	0	6	1 (17)	0.39	0.02, 7.89
Caucasian	695	170 (24)	689	214 (31)	0.70	0.66, 0.94
East/South-east Asian	9	2 (22)	13	4 (31)	0.72	0.17, 3.14
Hispanic	34	7 (21)	40	8 (20)	1.03	0.42, 2.55
Other	37	12 (32)	31	9 (29)	1.12	0.54, 2.30

The mortality rates by ethnic origin do not indicate differences. The numbers are too small outside the Caucasian group to exclude differences.

D. Treatment Effect and Age Class

The below data are presented for mortality and age class.

Table 10. 28-Day all-cause mortality analyses by age class

Age Class (years)	RhAPC (850)		Placebo (840)		Relative Risk	95% CI
	Total N	N (%)	Total N	N (%)	(RR)	for RR
<60	375	59 (16)	366	75 (21)	0.77	0.56, 1.05
60	475	151 (32)	474	184 (39)	0.82	0.69, 0.97
<65	437	68 (16)	449	94 (21)	0.74	0.56, 0.99
65	413	142 (34)	391	165 (42)	0.81	0.68, 0.97
<75	645	141 (22)	659	170 (26)	0.85	0.70, 1.03
75	205	69 (34)	181	89 (49)	0.68	0.54, 0.87

There appears to be a rhAPC treatment effect regardless of age. Safety data with regard to age as described in Table 46 showed no trends with serious bleeds or serious adverse events.

FDA exploratory analyses included a further breakdown of age groups into intervals of 10 years to look more specifically at the mortality within different age intervals. The table below presents the efficacy outcome measures in these various age groups.

Table 11. Primary 28-Day all-cause mortality analyses stratified by age

STRATA	THERAPY	Alive at Day 28 N (%)	Died by Day 28 N (%)	Total
AGE >10 – 20	Placebo	7 (100)	0 (0)	7
	rhAPC	8 (89)	1 (11)	9
				16
AGE >20 – 30	Placebo	36 (86)	6 (14)	42
	rhAPC	39 (89)	5 (11)	44
				86
AGE >30 – 40	Placebo	53 (85)	9 (15)	62
	rhAPC	64 (86)	10 (14)	74
				136
AGE >40 – 50	Placebo	94 (83)	19 (17)	113
	rhAPC	90 (87)	14 (13)	104
				217
AGE >50 – 60	Placebo	101 (71)	41 (29)	142
	rhAPC	115 (80)	29 (20)	144
				286
AGE >60 – 70	Placebo	124 (69)	57 (31)	181
	rhAPC	130 (74)	45 (26)	175
				356
AGE >70 – 80	Placebo	134 (61)	86 (39)	220
	rhAPC	149 (65)	82 (36)	231
				451
AGE >80 – 90	Placebo	30 (43)	39 (57)	69
	rhAPC	41 (68)	19 (32)	60
				129
AGE >90 – 100	Placebo	2 (50)	2 (50)	4
	rhAPC	4 (44)	5 (56)	9
				13
				1690

p=0.0043 (stratified, CMH). p=0.601 (homogeneity, Breslow-Day)

A graphical representation of these data is displayed in the figure below.

Treatment Effect and Age
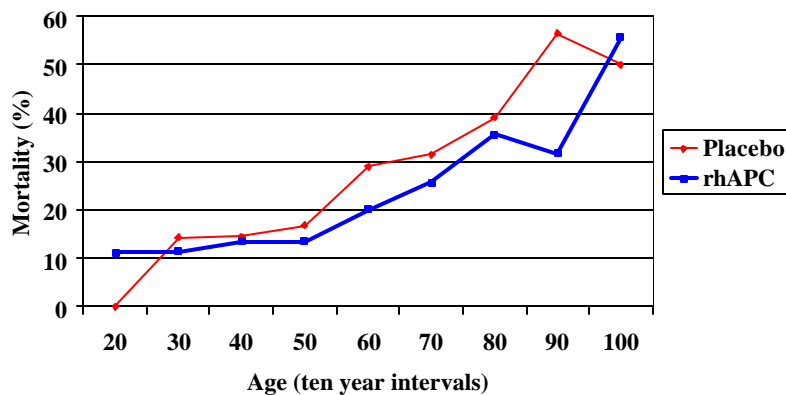
Figure 2. Mortality by age intervals of ten years

Overall, mortality tends to increase with age. The data suggest less benefit from rhAPC therapy in patients < 50 years of age.

E. Treatment Effect and Baseline APACHE II Score

The Acute Physiology and Chronic Health Evaluation (APACHE) II was used in this study. It is a classification system that assesses a patient's severity of disease based on 12 physiologic measurements, age, and previous health status. The higher the APACHE II score, the greater the severity of disease involvement. Appendix 3 contains the APACHE II scoring system. The APACHE II scores were divided into quartiles. The scores in the APACHE II quartiles ranged from 3-19, the second from 20-24, the third from 25-29 and finally the fourth from 30-53.

Presented below are data on interactions between APACHE II scores and mortality. These data show some evidence of interactions between treatment effect on mortality and APACHE II quartiles (p=0.09).

Table 12. 28-Day all-cause mortality analyses by APACHE II quartiles

APACHE II Quartile (score)	rhAPC (850)		Placebo (840)		Relative Risk (RR)	95% CI for RR
	Total N	N (%)	Total N	N (%)		
1st (3-19)	218	33 (15)	215	26 (12)	1.25	0.78, 2.02
2nd (20-24)	218	49 (22)	222	57 (26)	0.88	0.63, 1.22
3rd (25-29)	204	48 (24)	162	58 (36)	0.66	0.48, 0.91
4th (30-53)	210	80 (38)	241	118 (49)	0.78	0.65, 0.96

In contrast to the all the other quartiles, mortality for rhAPC was higher than placebo (15 vs. 12% respectively) in the first APACHE II quartile. This reverse trend in mortality is of concern, particularly due to the significant number of serious bleeds which occurred in the APACHE II first quartile. Safety data for the first APACHE II quartile is presented in Table 48. The observation that the apparent large effect was smaller in the second quartile than in the third and fourth quartiles together with the observation that it was reversed in the first quartile raises the question of whether the treatment has benefit in patients with lower APACHE II scores. Potentially the serious bleeding events may have an adverse effect on survival which overrides any benefit in the less severely ill patients.

Presented below are the Kaplan-Meier survival curves for APACHE II quartiles.

Quartile=1
Product-Limit Survival Fit
Survival Plot
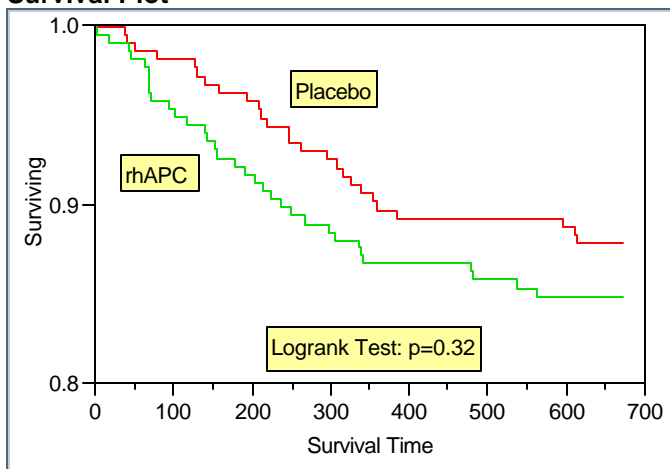
Quartile=2
Product-Limit Survival Fit
Survival Plot
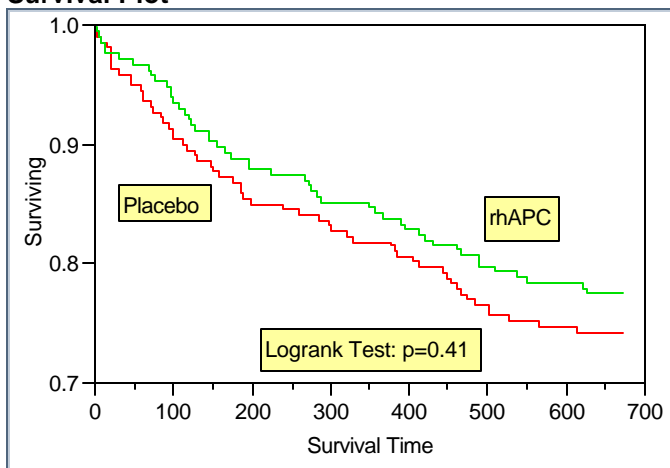
Quartile=3
Product-Limit Survival Fit
Survival Plot
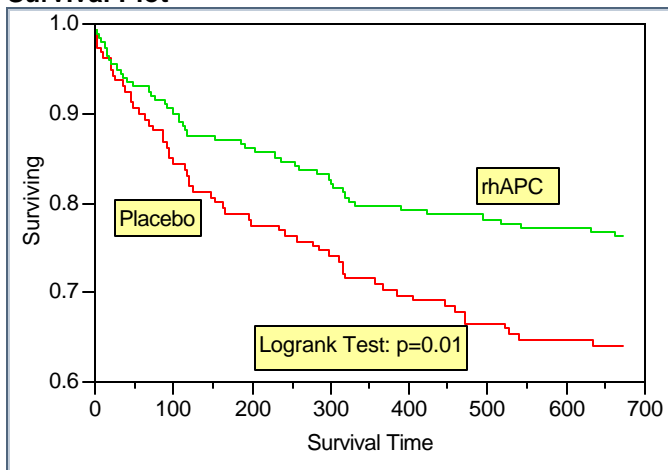
Quartile=4
Product-Limit Survival Fit
Survival Plot
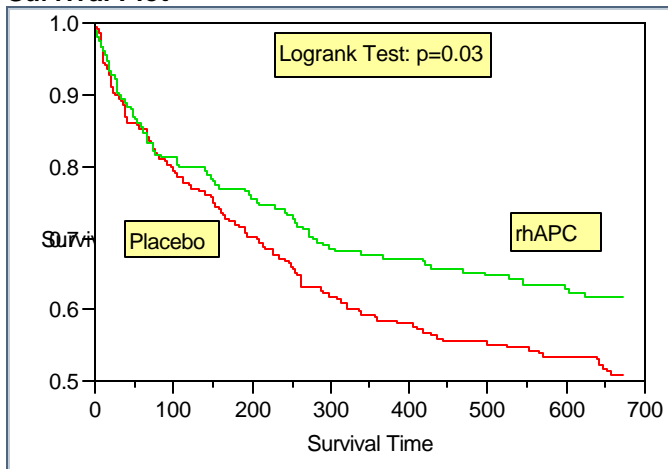
Figure 3. Kaplan-Meier survival curves by APACHE II quartiles

It is interesting to note, the fourth quartile showed onset of benefit occurring later.

These interactions between treatment and baseline APACHE II scores were further analyzed by dividing baseline APACHE II scores into intervals of 5 units. These results are presented in the table below.

Table 13. Primary 28-Day all-cause mortality analyses stratified by APACHE II score at baseline

STRATA	THERAPY	Alive at Day 28 N (%)	Died by Day 28 N (%)	Total
APACHE II Score 0-5	Placebo	1 (100)	0 (0)	1
	rhAPC	1 (100)	0 (0)	1
				2
APACHE II Score >5-10	Placebo	12 (92)	1 (8)	13
	rhAPC	11 (82)	2 (18)	11
				24
APACHE II Score >10-15	Placebo	64 (86)	10 (14)	74
	rhAPC	68 (87)	10 (13)	78
				152
APACHE II Score >15-20	Placebo	135 (83)	26 (16)	161
	rhAPC	140 (83)	29 (17)	169
				330
APACHE II Score >20 - 25	Placebo	169 (75)	55 (25)	224
	rhAPC	178 (77)	54 (23)	232
				456
APACHE II Score >25 - 30	Placebo	98 (61)	62 (39)	160
	rhAPC	142 (77)	43 (23)	185
				345
APACHE II Score >30-35	Placebo	63 (54)	54 (46)	117
	rhAPC	68 (62)	42 (38)	110
				227
APACHE II Score >35-40	Placebo	27 (42)	38 (58)	65
	rhAPC	21 (57)	16 (43)	37
				102
APACHE II Score >40-45	Placebo	10 (53)	9 (47)	19
	rhAPC	9 (50)	9 (50)	18
				37
APACHE II Score >45-50	Placebo	2 (33)	4 (67)	6
	rhAPC	3 (43)	4 (57)	7
				13
APACHE II Score >50-55	Placebo	0	0	0
	rhAPC	1	1 (50)	2
				2
				1690

p=0.0142 (stratified, CMH), p=0.403 (homogeneity, Breslow-Day)

The treatment effect occurred largely in patients with APACHE II scores > 25.

A graphical representation of these data is presented in the below figure.

Treatment Effect and APACHE II
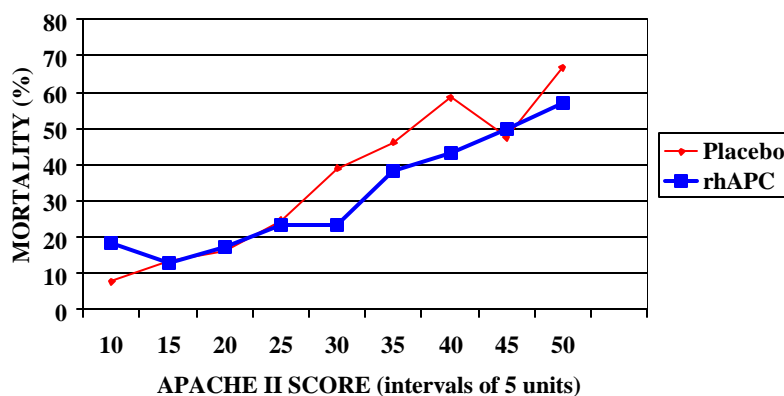
Figure 4. Mortality by APACHE II intervals of 5 units

Additional analyses were performed using APACHE II octiles and half octiles (see Appendix 5 Figure 10). These results show similar trends.

F. Treatment Effect and Organ Dysfunction

Presented below are data on treatment effect and the number of organ dysfunctions at baseline. Organ dysfunctions are defined under Appendix 2.

Table 14. 28-Day all-cause morality subgroups analyses for number of organ dysfunctions

Number of Organ Dysfunctions	RhAPC (850)		Placebo (840)		Relative Risk (RR)	95% CI for RR
	Total N	N (%)	Total N	N (%)		
1	215	42 (20)	203	43 (21)	0.92	0.63, 1.35
2	270	56 (21)	273	71 (26)	0.80	0.59, 1.08
3	214	56 (26)	218	75 (34)	0.76	0.57, 1.02
4	119	46 (39)	116	54 (47)	0.83	0.62, 1.12
5	31	10 (32)	30	16 (53)	0.60	0.33, 1.11

CI=Confidence Intervals.

A graphical representation of these data are displayed in the below figure.
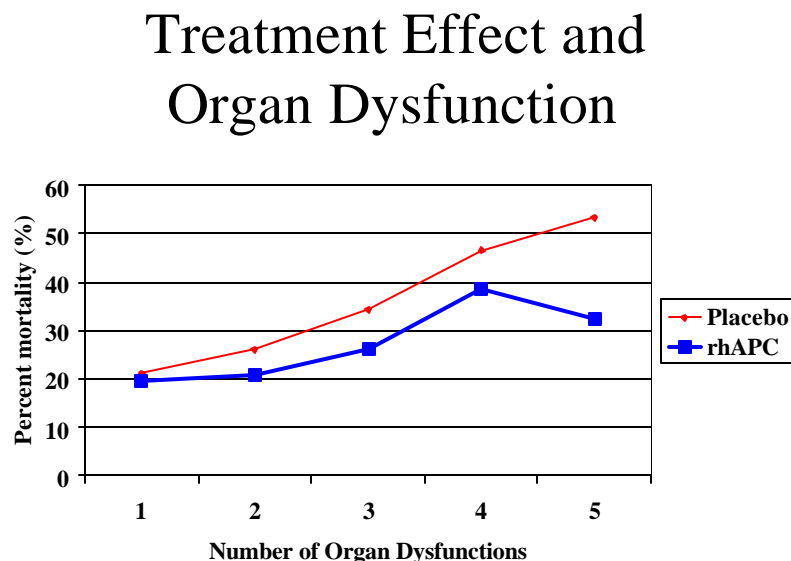
Figure 5. Mortality by number of organ dysfunctions

Patients with fewer than 2 dysfunctional organs at baseline were less likely to have a beneficial treatment effect, than were those with 2 or more dysfunctional organs. Treatment effects appeared relatively consistent regardless organ dysfunction type (i.e. cardiovascular, renal, pulmonary, hematologic and acidotic dysfunctions). See below figure and Appendix 5 Table 60.

Presented in the figure below (as depicted in the license application) is a plot of the relative risk estimates and their 95% confidence intervals (CI) across the subgroups defined by various clinical measures of disease severity. The results across the subgroups defined by biochemical measures are presented in Appendix 5 Figure 11. The point estimates of the relative risks are shown by the diamonds below and the limits of 95% CI by the horizontal lines. If the observed mortality in rhAPC and placebo groups are the same, then the relative risk estimate is equal to one. A relative risk estimate of less than 1, shows lower mortality in the rhAPC group compared to placebo, on the other hand, a relative risk estimate greater than 1, shows a higher risk of mortality in the rhAPC group relative to placebo.

	N	PLAC	TRT
Primary	1690	30.8	24.7
APACHE II			
4THQ	451	49	38.1
3RDQ	366	35.8	23.5
2NDQ	440	25.7	22.5
1STQ	433	12.1	15.1
Cardiovascular OF			
YES	1214	32	25.1
NO	476	27.6	23.8
Cardiovascular SOFA			
2 to 4	1196	32.4	27.3
0 or 1	494	26.6	19.1
Shock within 6 hrs			
YES	1200	34.2	26.3
NO	490	22.3	21
Any Shock			
YES	1362	32.5	26
NO	328	23.3	19.7
Respiratory OF			
YES	1272	31.6	25.6
NO	418	28.5	22
Respiratory SOFA			
2 to 4	1479	31.7	26.4
0 or 1	184	26.4	12.9
Ventilator			
YES	1275	33.1	27.3
NO	415	22.9	17.6
Hematologic OF			
YES	268	36.9	27.5
NO	1422	29.7	24.2
Hematologic SOFA			
2 to 4	366	40	27.7
0 or 1	1317	28.3	23.9
Renal OF			
YES	710	40.5	32.5
NO	980	23.8	19.1
Renal SOFA			
2 to 4	564	41.4	32.6
0 or 1	1122	25.7	20.4
Metabolic OF			
YES	581	41.5	29.8
NO	1109	25.4	22
Hepatic SOFA			
2 to 4	275	36.2	31.4
0 or 1	1265	30.2	22.7
Organ Failures			
5	61	53.3	32.3
4	235	46.6	38.7
3	432	34.4	26.2
2	543	26	20.7
1	418	21.2	19.5

Relative Risk of Death (95% CI)

Figure 6. 28-Day all-cause mortality across subgroups defined by clinical measures of baseline disease severity

G. Treatment Effect in Subgroups defined by organ dysfunction and APACHE II Quartiles

Presented below are data on the observed mortality in the twenty subgroups defined by organ dysfunction and APACHE II quartiles.

Table 15. Observed mortality in strata defined by APACHE II quartiles and number of organ dysfunctions at baseline

Number of Organ dysfunctions at Baseline		APACHE II Quartile							
		First		Second		Third		Fourth	
		%	N	%	N	%	N	%	N
1	Placebo	8	77	25	61	15	34	55	31
	rhAPC	7	89	22	59	29	38	41	29
2	Placebo	16	80	23	77	40	48	31	68
	rhAPC	13	75	22	81	18	61	32	53
3	Placebo	13	40	21	53	43	47	50	78
	rhAPC	31	39	23	52	20	60	32	63
4	Placebo	12	17	44	25	38	29	67	45
	rhAPC	36	14	20	20	37	35	48	50
5	Placebo	0	1	33	6	75	4	58	19
	rhAPC	0	0	33	6	10	10	47	15

The shaded strata show groups with relative risks on rhAPC less than 0.8 than on placebo.

H. Treatment Effect and Protein C Levels

Presented below are data on mortality and Protein C activity levels.

Table 16. Ordered analysis of 28-Day all-cause mortality analyses stratified by Protein C activity class

Protein C Activity Class	rhAPC		Placebo		Relative Risk	95% CI for RR
	Total N	N (%)	Total N	N (%)		
Unknown	51	14 (28)	65	16 (26)	1.12	0.60, 2.07
40%	330	91 (28)	285	119 (43)	0.66	0.53, 0.82
41-60%	240	65 (27)	227	56 (25)	1.10	0.81, 1.49
61-80%	139	26 (19)	158	40 (25)	0.74	0.48, 1.14
> 80%	90	14 (16)	105	28 (27)	0.58	0.33, 1.04

Ordered analysis p <0.00001. Unordered analysis p < 0.00001.

Mortality was greater on rhAPC in the unknown and 41-60% class. No clear trends were noted with mortality and Protein C activity. Due to a sampling error not all laboratory values were available for all patients.

Presented below are data on mortality and Protein C deficiency.

Table 17. 28-Day all-cause mortality analyses by Protein C deficiency class

Protein C Deficiency	rhAPC (850)		Placebo (840)		Relative Risk	95% CI for RR
	Total N	N (%)	Total N	N (%)		
Deficient (80%)	709	182 (26)	670	215 (32)	0.80	0.68, 0.95
Not deficient (> 80%)	90	14 (16)	105	28 (27)	0.58	0.33, 1.04
Unknown	51	14 (28)	65	16 (25)	1.12	0.60, 2.07

These data show no clear correlation between baseline protein C levels and treatment effect from rhAPC.

I. Treatment Effect and DIC

Presented below are data showing mortality in patients with DIC at baseline.

Table 18. Primary 28-Day all-cause mortality analyses stratified by the presence of DIC at baseline

DIC Status at Baseline	rhAPC		Placebo		Relative Risk	95% CI for RR
	Total N	Mortality N (%)	Total N	Mortality N (%)		
Present	800	196 (25)	774	243 (31)	0.78	0.67, 0.92
Absent	49	14 (29)	66	16 (24)	1.18	0.65, 2.16

DIC=Disseminated intravascular coagulation.

The data indicate the treatment benefit in patients with DIC present at baseline and no treatment benefit in patients not at DIC at baseline.

J. Treatment Effect and Biomarkers

Presented below are data on treatment effect and five biomarkers. There is no clear trend with respect to treatment effect on mortality in subgroups defined by these biomarkers.

Table 19. 28-Day all-cause mortality subgroup analyses for selected biomarkers

	RhAPC (850)		Placebo (840)		Relative Risk (RR)	95% CI for RR
	Total N	N (%)	Total N	N (%)		
Il-6 Baseline Quartile						
1st (<143.9 pg/ml)	191	20 (11)	217	48 (22)	0.47	0.29, 0.77
2nd (143.91-491.56 pg/ml)	220	58 (26)	189	50 (27)	1.00	0.72, 1.38
3rd (492-2570 pg/ml)	207	59 (29)	202	67 (33)	0.86	0.64, 1.15
4th (>2574 pg/ml)	209	65 (31)	200	87 (44)	0.72	0.55, 0.92
Antithrombin Baseline Deficiency						
Deficient	655	166 (25)	618	201 (33)	0.78	0.67, 0.93
Not deficient	139	28 (20)	146	39 (27)	0.75	0.49, 1.16
Antithrombin Baseline Activity Quartile						
1st (<0.44)	212	68 (32)	186	83 (45)	0.72	0.56, 0.93
2nd (0.45-0.59)	202	48 (24)	191	62 (33)	0.73	0.53, 1.01
3rd (60-0.74)	182	41 (23)	188	40 (21)	1.06	0.72, 1.56
4th (0.75)	198	37 (19)	199	55 (28)	0.68	0.47, 0.98
Factor V Leiden Mutation for APC resistance						
Negative	768	190 (25)	768	238 (31)	0.80	0.68, 0.94
Positive	33	4 (12)	32	5 (16)	0.78	0.23, 2.63
Factor V Hong Kong Mutation for APC resistance						
Negative	794	193 (24)	785	234 (30)	0.82	0.69, 0.96
Positive	1	1 (100)	2	1 (50)	2.00	0.50, 8.00

Distribution of the biomarkers at baseline in treatment groups is presented in Appendix 4 Table 58.

A number of analyses of biomarkers were performed based on the treatment arm assignment. A marker of thrombin generation D-dimer showed a decrease in levels on the rhAPC arm compared to placebo (Appendix 5 Figure 12). Platelet counts and antithrombin levels showed no differences between the treatment groups.

K. Treatment Effect and SOFA Scores

Analyses were performed with Sequential Organ Failure Assessment (SOFA) scores. The SOFA scoring system is a 0-4 scale. The higher the score, the more severe the organ (respiratory, coagulation, liver, cardiovascular, and renal) failure assessment. No conclusive differences were observed.

L. Treatment Effect and Microbiology

Presented in Appendix 5 Table 62 are data for the presumed site of infection, Gram stain class, and culture. No conclusive trends were noted.

M. Functional Status Data–Survivors

Data showing subject location at time of discharge from the hospital and at the 28-day end of the study are presented below. For subject location at baseline to hospitalization see Appendix 4 Table 59. More subjects survived in the rhAPC arm of the trial and their overall functional capacity was similar to those that survived in the placebo arm of the trial. Despite the increased survival rate in the rhAPC arm, sepsis is a devastating event with only 25% of the total enrolled subjects achieving discharge home to an un-assisted life style at day 28 compared to 80% prior to the sepsis event.

Table 20. Subject location after discharge-survivors

	rhAPC (640)		Placebo (581)		Total (1221)	
	N	(%)	N	(%)	N	(%)
Home – No Supp.	123	(19)	107	(18)	230	(18)
Home – Paid Supp.	44	(7)	39	(7)	83	(7)
Home - Unpaid Supp.	95	(15)	96	(17)	191	(16)
Not Discharged	270	(42)	234	(40)	504	(41)
Other Hospital	32	(5)	29	(5)	61	(5)
Skill Nursing Home	76	(12)	76	(13)	152	(12)

Table 21. Subject location at study Day 28-survivors

	rhAPC (640)		Placebo (581)		Total (1221)	
	N	(%)	N	(%)	N	(%)
Home – No Supp.	158	(25)	144	(25)	302	(25)
Home – Paid Supp.	38	(6)	35	(6)	73	(6)
Home - Unpaid Supp.	79	(12)	78	(13)	157	(13)
Other Hospital	23	(4)	20	(3)	43	(4)
Skill Nursing Home	61	(10)	66	(11)	127	(10)
Study Hospital	281	(44)	238	(41)	519	(43)

The number of days that were free from ventilator use, vasopressors, SIRS, ICU and hospital care are listed below. The survivors of sepsis after rhAPC treatment were comparable to the survivors in the placebo arm in that the rhAPC treated subjects were not on ventilators longer nor did they require vasopressors longer.

Table 22. Vasopressor, ventilator, SIRS, ICU and hospital free days survivors only

	rhAPC (640)	Placebo (581)
Mean		
Vasopressor	25	25
Ventilator	18	18
SIRS	12	12
ICU	16	16
Hospital	8	8
Median		
Vasopressor	27	27
Ventilator	22	22
SIRS	11	12
ICU	19	20
Hospital	7	6

Additionally, the comparison of baseline status and 28 day status for the below criteria revealed a well-balanced outcome between the placebo group and the rhAPC treated group. If patients survived the sepsis episode with rhAPC treatment they did not appear to function at a decreased level or require more support than those treated with placebo.

Table 23. Patient vasopressor, ventilator, ICU and hospitalization status (%)

		rhAPC (640) %	Placebo (581) %
Vasopressor	Baseline	59	62
	Day 28	2	2
Ventilator	Baseline	71	75
	Day 28	14	15
ICU	Baseline	100	100
	Day 28	16	14
Hospital	Baseline	100	100
	Day 28	43	41

Section IIIC- Changes to the Clinical Protocol

I. Overview

In June 1999, a protocol amendment was submitted to the agency and the inclusion and exclusion criteria were modified (see Appendix 6). The sponsor's objective for the revised amendment was to exclude patients with non-sepsis related diseases. The new inclusion and exclusion criteria were modified to reflect this objective.

In August 1999, the sponsor introduced a change in the manufacturing of the drug. The original manufactured drug was referred to as Bulk Drug Substance (BDS) BDS2 and the newly manufactured drug BDS2+. A number of extensive analyses were conducted. No differences were detected between the two manufactured products. Given the complexity of the molecule, however, one cannot exclude the possibility of undetected differences.

A significant difference in mortality was observed between the first and second half of the study as displayed below in Figure 7. The mortality rates for the 720 patients enrolled under the original protocol were 30% for placebo and 28% for rhAPC. Under the revised protocol, the mortality rates for the 970 enrolled patients were 31% for placebo and 22% for rhAPC (Table 25). The mortality rates for rhAPC the original and newly manufactured product were 29% compared to 19%. The implementation of this manufacturing change occurred in about half way through the study, at about the same time as the changes in the protocol.

Overall, an analysis of the two protocol versions showed that under the amended version of the protocol there were fewer patients: with malignancies, experiencing non-sepsis deaths, with chronic APACHE II health points, who had with life support withdrawn, who were immunocompromised (including patient on chemotherapy and radiotherapy), at nursing facility prior to entry, and with disabilities and more patients were at home prior to the onset of sepsis.

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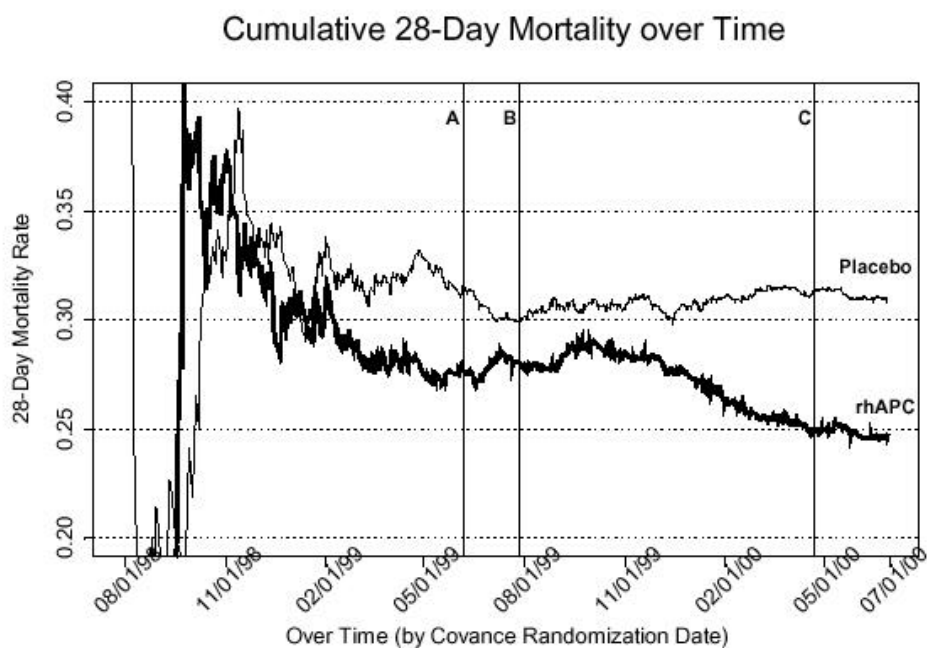
Figure 7. 28-Day cumulative mortality over time for all patients

Presented above (as in clinical report of the license application) are data on the 28 Day cumulative mortality over time. The amended version of the protocol was introduced at Line A, first interim analysis occurred at Line B and the second interim analysis at Line C.

II. Summary of Changes

A. Protocol Amendment Summary

Presented below is a summary of major changes implemented under the amended protocol as compared to the original protocol. Appendix 6 contains a more detailed listing of the protocol amendment changes.

The following are some of the changes:

- Simplify the primary analysis such that the primary analysis was confined to patients meeting the diagnosis of severe sepsis.
- Eliminate a primary planned analysis of Protein C deficiency (analyze as secondary instead) and "septic shock" from the primary and secondary analyses.
- Clarify exclusion criteria for patients with esophageal varices.
- Add exclusion criteria for patients having undergone bone marrow, lung, liver, pancreas, or small bowel transplantation.
- Add exclusion criteria for patients who were considered moribund and where death was imminent (within 24 hours).
- Add exclusion criteria for patients whose family had not committed to aggressive management of the patient.
- Add exclusion criteria for patients with acute pancreatitis without known infection.
- Clarify exclusion criteria for patients with a history of malignancy.
- Add exclusion criteria for patients having organ failure for greater than 24 hours at the time of meeting all inclusion criteria.
- Change placebo from normal saline to 0.1% HSA.
- Replace "septic shock status" with "Protein C activity class" as a covariate for the primary analysis.

B. Impact of Changes Between Protocol Versions and Patient Eligibility

Presented below is a summary of patients not meeting inclusion and exclusion criteria of the amended protocol who were enrolled under the original protocol. This analysis was conducted to assess the impact of changes on the original patients enrolled to determine how many would or would not be eligible in the modified inclusion criteria.

Table 24. 28-Day mortality analyses by clinical evaluation committee determinations of fulfillment of inclusion and exclusion criteria patients enrolled under original protocol

	rhAPC (360)		Placebo (360)		Mortality Relative Risk (RR)	95%CI for RR
	N Total	N (%)	N Total	N (%)		
Meeting New Inclusion Criteria						
No	41	14 (34)	40	17 (43)	0.80	0.46, 1.40
Yes	319	88 (28)	320	92 (29)	0.96	0.75, 1.23
Meeting Criteria A (SIRS)						
Yes	358	101 (28)	360	109 (30)	0.93	0.74, 1.17
Meeting Window 2						
No	20	8 (40)	20	6 (30)	1.33	0.57, 3.14
Yes	340	94 (28)	340	103 (30)	0.91	0.72, 1.16
Meeting Criteria B						
Yes	360	102 (28)	358	109 (30)	0.93	0.74, 1.17
Meeting Criteria C (Suspected or Proven Infection)						
No	9	2 (22)	7	4 (57)	0.39	0.10, 1.55
Yes	351	100 (28)	353	105 (30)	0.96	0.76, 1.21
Meeting Exclusion Criteria						
No	13	5 (38)	16	8 (50)	0.77	0.33, 1.79
Yes	347	97 (28)	344	101 (29)	0.95	0.75, 1.20

CI=Confidence Intervals.

81 patients or 11% eligible for the original protocol would not have been eligible for the amended version of the protocol. This highlights the fact that the amended protocol did enroll a different patient population compared to the original protocol.

C. Site Additions and Deletions

Sites were discontinued and added throughout the study, mostly due to enrollment inability. Under the original protocol, 20 sites enrolling a total of 52 patients were discontinued prior to the implementation of the amended version of the protocol. In addition to discontinuing sites, the sponsor elected to add new sites for enrollment after the start of the study. After the introduction of the amended version 45 sites were included, administering a total of 175 patients.

Differences in mortality rates between the first and second half of the study may also be due to the smaller sites enrolling fewer patients. The relative risks of the patients at individual sites are presented in Appendix 8. Patients enrolled in sites ultimately dropped from the study before its completion were more likely to have a more severe SIRS, as reflected in organ dysfunction scores, have greater PC activity levels and were more independent and required little or no assistance as reflected by the activities of daily living (ADL) scores. An analysis conducted of 705 patients enrolled at US sites, showed a mortality rate of 25% on rhAPC compared to 33% on placebo.

III. Effect of Changes on Mortality

A. Treatment Effect and Original vs. Amended Protocol Versions

Presented below are data on mortality by each protocol version the original and the amendment. The mortality rates with rhAPC under the original protocol were 28% vs. 22% under the amended protocol.

Table 25. Primary 28-Day all-cause mortality analyses stratified by protocol: original and amended

STRATA	THERAPY	Alive at Day 28	Died by Day 28	Total
		N (%)	N (%)	
Protocol: original	Placebo	251 (70)	109 (30)	360
	rhAPC	258 (72)	102 (**28**)	360
		P=0.5665		**720**
Protocol: amended	Placebo	330 (69)	150 (31)	480
	rhAPC	382 (78)	108 (**22**)	490
		P=0.0012		**970**
				1690

Kaplan-Meier Survival Curves for the Original and Amended Protocols

Presented below are the Kaplan-Meier survival curves for both protocol versions. A clearer separation of the survival curves occurs under the amended protocol.

ORIGINAL
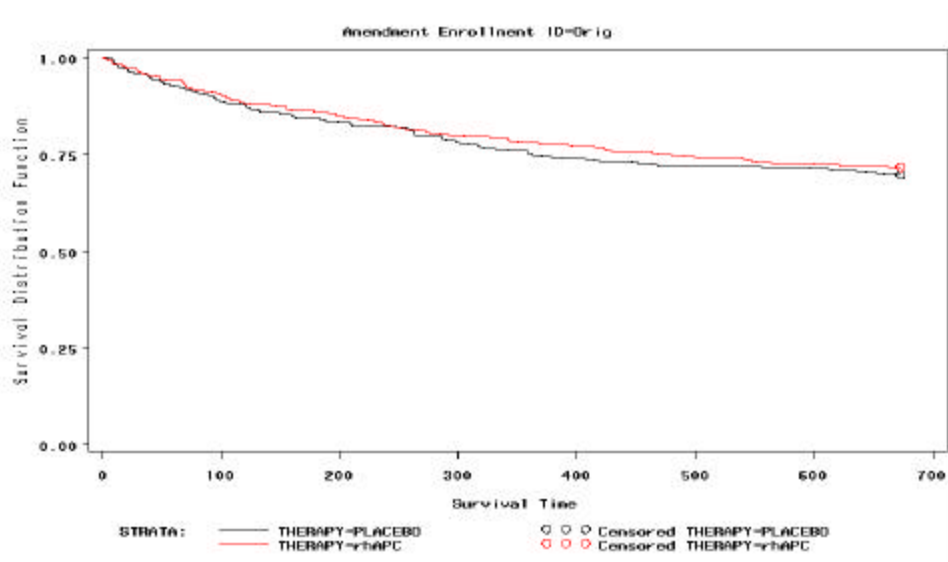
Upper survival curve represents rhAPC and the lower placebo treated patients.

Figure 8. Kaplan-Meier survival curve under original protocol

AMENDMENT
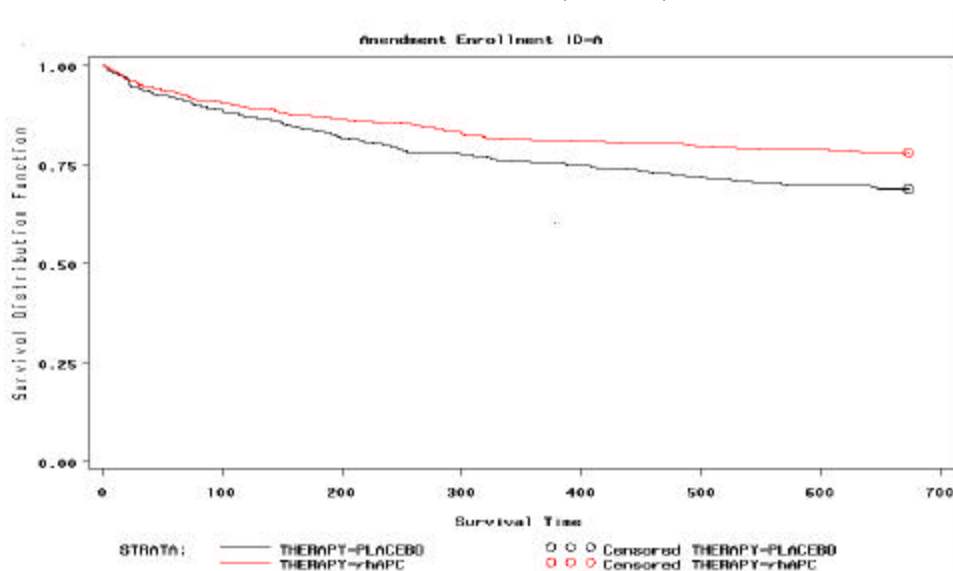
Upper survival curve represents rhAPC and the lower placebo treated patients.

Figure 9. Kaplan-Meier survival curve under amended protocol

Functional Status of Survivors-Do Not Resuscitate Orders

Do not resuscitate (DNR) orders were recorded in both the phase 2 and 3 trials. The phase 2 trial data revealed a rate of DNR orders of ~28% and was well balanced between the rhAPC and the placebo arms.

Table 26. DNR phase 2

	rhAPC (90) N (%)	Placebo (41) N (%)	Total (131) N (%)
DNR during infusion	7 (8)	4 (10)	11 (8)
DNR during 28 days	24 (27)	12 (29)	36 (28)

In the phase 2 trial, there were 36 DNR orders. These subjects had outcomes as listed below.
➢ 30 (83%) died
➢ 1 (3%) discontinued due to patient decision
➢ 1 (3%) discontinued due to physician decision
➢ 4 (11%) completed the study

Though most patients died, this was not universally so. In the phase 3 trial, the data was divided between the first half of the study and the second half as shown below. This division was based on the study material used. In the first half of the study the incidence of obtaining a DNR order was ~17 percent, lower than the phase 2 study but well balanced between treatment arms. In the second half of the study there was a large drop from 16% from 9% in the DNR rate in the rhAPC treated group compared to the placebo group. The placebo rate stayed consistently the same. Whereas the trial was blinded the difference in DNR rates did not reflect bias in how patients were managed, however bleeding events could have led to some unblinding. Higher DNR rates in the placebo arm could simply reflect the fact that more patients did poorly.

Table 27. DNR phase 3

	BDS2 (471) N (%)	First half of the study Placebo (393) N (%)	BDS2+ (355) N (%)	Second half of the study Placebo (447) N (%)	Total (1666) N (%)
Patients with DNR orders	74 (16)	69 (18)	32 (9)	74 (17)	249 (15)

For analyses purposes the study was divided into the "first" and "second half" of the study by date for placebo.

Effect of Changes on Patient Baseline Demographics

Baseline Characteristics Original vs. Amendment

The data on the differences between the baseline demographics of the original and amended versions of the protocol are presented in detail in Appendix 7.

The original and amended protocol versions baseline demographics are strikingly similar. Mean APACHE II scores were both 25. Differences noted included fewer APACHE II chronic health points, acidosis with organ failure met was greater in the original 46% vs. 26%, and a higher mean Il-6 level under the amendment 566 ug/ml vs. 389 ug/ml. A greater number of patients were at home prior to hospitalization, and had an ADL score of zero (independent and required less or no assistance prior).

Solicited patient history and preexisting conditions between the original and amended protocol were examined to determine whether at baseline similar groups of patients were enrolled in both versions.

Summary of Efficacy

The primary efficacy endpoint was 28-day all-cause mortality in patients with severe sepsis. Of the 1728 patients enrolled in the trial, 1690 patients received rhAPC (850 patients) at 24 ug/kg/hr rhAPC iv infusion for 96 hours or placebo (840 patients) for any of time and constituted the ITT population. The observed 28-day all-cause mortality for patients receiving rhAPC was 25% (210/850) as compared with 31% (259/840 patients) in patients receiving placebo. This difference of an absolute 6% reduction in mortality in the rhAPC group was statistically significant (primary stratified p=0.0054; nonstratified p=0.0049).

Of note, the exploratory analyses of important patient subgroups showed a reverse mortality trend in the first APACHE II quartile and less benefit in patients who fell into the second APACHE II quartile compared to the third and fourth APACHE II quartiles. Among the adult patients studied, there was a smaller treatment effect in those younger than 50 years of age. This may have implications for labeling to pediatric patients, where data in the pediatric population are limited. In addition to the APACHE II subgroups, other exploratory analyses indicate a treatment effect in patients with DIC at baseline and no effect in those without DIC at baseline, and almost no treatment effect in patients with less than two organ failures.

Also of note was a significant difference in mortality among patients randomized to rhAPC between the first and second half of the study. This finding resulted in extensive FDA analyses to assess the potential impact of the manufacturing change and the protocol amendment, both of which were instituted at similar time approximately half way through the study.

Section IV-Pediatrics

Introduction

Pediatric data are limited. rhAPC was not introduced into pediatric patients until preliminary data in adults suggested acceptable toxicity and potential for benefit. Thus, at the time the phase 3 trial in adults was initiated, pharmacokinetic studies in children were not ongoing to identify appropriate dose(s) and potential safety concerns. The sponsor proposed that, if the product were to be shown safe and effective based on adult data, the product could be labeled for pediatric use as per regulation (21 CFR 201.57) which states:

> " FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients."

Although the agency did not rule out the possibility of extrapolation of efficacy, Lilly was encouraged to amend the phase 3 protocol to include pediatric patients down to a specific lower age limit. However, the phase 3 trial was stopped after the second interim, based on the mortality benefit observed in adult patients and no placebo controlled data in pediatric patients with sepsis are available. The results of the open label studies are described below.

Two separate studies have accumulated pediatric data. A total of 70 pediatric patients have been treated. 12 have been treated in an open label compassionate use trial in purpura fulminans (EVAS). 58 patients have been treated in an open label pharmacology/safety study in pediatric sepsis (EVAO). There were no pediatric deaths reported in the purpura fulminans study; 3 of 58 patients died in the sepsis study. Demographic, pharmacokinetic, and safety data are presented.

I. Pharmacology and Safety Study in Pediatric Sepsis (EVAO)
This pharmacology and safety study was conducted in pediatric patients with sepsis. The main parameters of the study are listed below. The study included 3 pediatric age groups and was divided into 2 parts:

- **Part 1:** open label dose escalation:
  Newborn to < 1y/o   - 6 patients
  ≥ 1 y/o to < 8 y/o   - 8 patients
  ≥ 8 y/o to 18 y/o   - 7 patients
  Total   - 21 patients

- **Part 2:** open label 96 hr infusion at 24 ug/kg/hr as determined from the part 1 dose escalation phase.

```
Newborn to < 1y/o       - 6 patients
≥ 1 y/o to < 8 y/o      - 23 patients
≥ 8 y/o to 18 y/o       - 8 patients
Total                   - 37 patients
```

Pediatric Demographics

Demographics presented include the site of infection and the type of organ failure at entry into the study. There are more systemic infections, fewer primary lung infections noted in this population compared to the adult population. Additionally organ failure included primarily cardiovascular and respiratory sources. The protocol was later amended to include hematologic and renal failures but no patients were enrolled under the amendment.

Table 28. Pediatric primary site of infection

Site of Infection	Part 1	Part 2
Systemic Infection	9	8
CNS	3	3
Intra-abdominal	3	2
Lung	2	4
Skin	1	0
UTI	1	0
HEENT	1	0
Indwelling Catheter	0	1
Other	1	0

Table 29. Pediatric organ failure

Organ Failure	Part 1	Part 2
Cardiovascular	16	7
Respiratory	2	3
Both CV/Resp	3	8
Hematologic	0	0
Renal	0	0

Pediatric Safety

A. Pediatric Adverse Events

Many adverse events were reported, with the most common being listed below. The pattern of adverse events was similar to the adult study. There were 222 actual events reported. The most common events are listed below.

Table 30. Pediatric adverse events

Adverse Event	# of reports
Necrosis	10
Pleural Effusion	8
Pain	7
Diarrhea	7
Atalectasis	6
Agitation	6
Peripheral Edema	5
Generalized Edema	3
Infection	4
Lung Edema	4
Vomiting	4
Anemia	3
Bradycardia	3
Fever	3
Rash	3
Stridor	3
Thrombocytopenia	3

B. Pediatric Serious Adverse Events

Serious adverse events by study part are listed below. The total number of patients is small so that significant conclusions cannot be made. No obvious trend in serious adverse events is noted.

Table 31. Pediatric serious adverse events

Study Part Enrollment	Patient Number	Serious Adverse Event	Fatal Outcome
Part 1	150	Cerebral Ischemia	No
Part 1	159	Gangrene, Nasopharyngeal Hemorrhage	No
Part 1	450	Intestinal perforation, Abscess	No
Part 1	451	Respiratory distress Syndrome	No
Part 1	751	Choreoathetosis, Apnea	No
Part 1	800	Necrosis	
Part 2	252	Heart arrest, Shock, Peripheral Vascular Disorder	Yes (Study day 4)
Part 2	253	Peripheral Vascular Disorder	No
Part 2	354	Hematuria, PT decreased, Thromboplastin Decreased, Encephalopathy	Yes (study day 8)
Part 2	457	Shock	No
Part 2	459	Hypotension, Apnea	No
Part 2	552	Hypotension, Shock	Yes (Study day 3)
Part 2	754	Bradycardia	No
Part 2	805	Purpura	No

C. Comparative Pediatric and Adult SAE Bleeding Events and Mortality

Serious bleeding adverse events and 14 day mortality is compared to the adult data. The overall number of events is small so that meaningful comparisons are difficult. The overall mortality rate is lower in the pediatric study with a comparable serious bleeding rate.

Table 32. Pediatric and adult SAE bleeding events and mortality

	Pediatric (58) N (%)	Adult rhAPC (850) N (%)	Adult Placebo (840) N (%)
SAE – Bleeding (Infusion)	2 (3)	20 (2)	8 (1)
SAE – Bleeding (28 day)	2 (3)	30 (4)	17 (2)
Mortality – 14 day	3 (5)	166 (20)	201 (24)

II. Compassionate use of APC in Purpura Fulminans (EVAS)

The entry criteria for this study include subjects 1 year of age or older. They received a 96 hr infusion at 24 ug/kg/hr as in the adult study. The study has enrolled 23 adult patients greater than 18 years of age and 12 pediatric patients under 18 years. A total of 35 patients have been treated. There have been 7 deaths (no pediatric) and 8 serious adverse events (2 pediatric). Pediatric patient narratives for the serious adverse events are reported below.

- 15y/o received rhAPC for 168 hrs from 6/8/99 – 6/15/99. On 7/9/99 (24 days post transfusion she experienced bilateral occipital hemorrhages.

- 2y/o during infusion was transferred to a high frequency ventilator and experienced hypoxia and bradycardia leading to cardiac arrest. Patient was resuscitated and the infusion was continued.

Both patients survived these events.

III. Summary of Pediatrics

Limited safety data are available for the pediatric population. No new trends in serious adverse events, bleeding events or mortality were identified from these limited data. These data are derived from open label non placebo controlled studies. Therefore efficacy cannot be inferred from the data at hand in the pediatric population. A similar safety concern exists with a serious adverse event bleeding rate similar to the rhAPC treated adults.

Pharmacokinetic data from adults and pediatric patient with severe sepsis suggests that body weight is an important parameter influencing the clearance C_{ss} of rhAPC. In part 1 of study EVAO, clearance did not vary by age or rate of infusion when normalized by body weight. For ages 0 to <1 year (n=6),   1 to <8 years (n=7) and   8 to <18 years (n=7), clearance was 0.62 (31), 0.59 (46), and 0.53 (21) L/hr/kg when expressed as the mean and CV% when using data from all rates of infusion (6 to 36 ug/kg/hr). In part 2 of study EVAO, C_{ss} was found to be 54.0 ng/kg/ml over 96 hours. In study EVAD the C_{ss} was 54 ng/ml (range 14.1 to 390.6 ng/ml, N=326).

Section V-Safety

Introduction

Safety data from the F1K-MC-EVAD study are summarized below including data on specific patient subpopulations.

I. Important Features of the F1K-MC-EVAD Study

A. Exclusion of Patients at High Risk of Bleeding

Patients were excluded from this trial if they presented with an increased risk for bleeding. The specific high-risk bleeding factors include:

➢ **Platelet count <30,000/mm**
➢ **Increased risk for bleeding (for example):**
  - Major surgery within 12 hrs prior to infusion
  - Severe head trauma, stroke, Tumor
  - Congenital bleeding diathesis
  - GI Bleed within 6 weeks
  - Trauma with increased risk for bleeding
➢ **Patients taking the following medications:**
  - Therapeutic heparin
  - Warfarin within 7 days
  - Acetylsalicylic acid (ASA) >650 mg/day within 3 days
  - Thrombolytic treatment within 3 days.
  - Glycoprotein IIb/IIIa antagonists within 7 days
  - Antithrombin infusion of >10,000 units within 12 hours of study entry.

➢ **Patients with known esophageal varices, chronic jaundice, cirrhosis, or chronic ascites.**

Parameters were outlined to stop and restart the study drug related to specific procedures as described below:

Procedure	Stop Infusion	Restart Infusion
Central venous catheter	1 hour prior to procedure	Immediately after procedure
Chest tube insertion	1 hour prior to procedure	1 hour after procedure
Lumbar puncture	1 hour prior to procedure	1 hour after procedure
Re-intubation (tube change)	1 hour prior to procedure	Immediately after procedure
Sinus puncture	1 hour prior to procedure	Immediately after procedure
Thoracic drainage	1 hour prior to procedure	1 hour after procedure
Tracheostomy	1 hour prior to procedure	1 hour after procedure
Major surgery	1 hour prior to procedure	12 hour after procedure

Additionally, parameters were established to monitor coagulation status during the infusion and guidelines for stopping and re-starting the infusion.

Stop Infusion	Restart Infusion
PTT ≥100 seconds	PTT <100 seconds
INR ≥3.0	INR <3.0
Platelet count ≤15 GI/L.	Platelet count >15 GI/L

II. Summary of Patient Mortality in the F1K-MC-EVAD Study

The overall mortality and classification of cause of death is shown below. Patient summaries for all patients who died were reviewed in a blinded manner by a team of two clinical research physicians at Lilly. The event leading to death was adjudicated for all deaths.

Table 33. Summary of cause of death for all deaths ITT

Cause of Death	rhAPC (850)	Placebo (840)	Total (1690)
Sepsis induced Multi Organ Failure	96	102	198
Refractory Septic Shock	46	63	109
Respiratory Failure	28	46	74
Myocardial Infarction	9	11	20
Primary cardiac Dysrrythmia	6	9	15
Hemorrhage			
Cerebral	2	1	3
Pulmonary	2	0	2
Chest Trauma	1	0	1
Retroperitoneal	1	0	1
Thoracic	0	1	1
Other			
Cardiogenic Shock	5	1	6
Cancer	3	4	7
Cerebral edema	3	1	4
Unknown	2	3	5
Encephalopathy	2	2	4
Cerebral Herniation	1	0	1
Pulmonary embolism	1	0	1
Aortic Valve endocarditis	0	1	1
CNS Event	0	1	1
Cerebral Artery Thrombosis	0	1	1
Cerebral embolism	0	1	1
CHF	0	1	1
Hypoxic Brain Injury	0	1	1
Ischemic Bowel	0	1	1
Large and Small Bowel Infarction	0	1	1
Malignant Hyperthermia	0	1	1
Mitral Valve Rupture/Endocarditis	0	1	1
Renal Failure	0	1	1
Tracheoesophageal Fistula	0	1	1
Total	210	259	469

Deaths that were attributable directly to the study drug as recorded by the investigators are shown below. This includes 6 deaths, 5 in the rhAPC treated group and 1 in the placebo group. 4 of the deaths were related to bleeding, and all of those were in the rhAPC group.

Table 34. Deaths–possibly related to the study drug per investigators

Event	rhAPC (850)	Placebo (840)	Total (1690)
Bleeding			
Neurologic	2	0	2
Cardiovascular	1	0	1
Pulmonary	1	0	1
Non-Bleeding			
Neurologic	1	1	2

Narratives for these patients are presented in Appendix 9. The neurologic-related adverse events included cerebral edema (rhAPC) and cerebral infarcts (placebo) in addition to two cerebral hemorrhages (rhAPC).

Other adverse events listed above include a pulmonary hemorrhage (rhAPC) and an aortic disruption (rhAPC) with a history of an MVA 3 days prior to entering the study.

These cases highlight the potential risk of fatal hemorrhage in the setting of sepsis and the administration of rhAPC. Whether or not there are other cases attributable to rhAPC is unknown due to the severe underlying disease process related to sepsis and the accompanying high overall mortality rate in this patient population.

III. Adverse Events Related to Bleeding

Bleeding adverse events, particularly serious adverse events, were a concern because of the anticoagulant mechanism of action. Narratives of serious bleeding events are presented in Appendix 9. Bleeding events were recorded during the infusion time period and throughout the 28 day study period with more bleeding events overall in the rhAPC arm. However, since the majority of patients were in disseminated intravascular coagulation (DIC) when they entered into the study, there were a number of bleeding events in the placebo group as well. The largest difference between the placebo and active treatment group occurred during the infusion period.

A. Serious Bleeding Events

Below, the serious[3] adverse bleeding events reported during the infusion period are displayed followed by the data from the 28 day study period.

Table 35. Serious bleeding adverse events (during rhAPC infusion period)

Site of Hemorrhage	rhAPC (850)	Placebo (840)	Total (1690)
Gastrointestinal	5	4	9
Intra-thoracic	4	0	4
Retroperitoneal	3	0	0
Intra-abdominal	2	3	5
Cerebral Hemorrhage	2	0	2
Genitourinary	2	0	2
Transfusion-related Serious Bleeding Event	1	1	2
Skin/Soft tissue	1	0	1
Total	20 (2%)	8 (1%)	28 (2%)

Table 36. Serious bleeding events (28 Day study period)

Site of Hemorrhage	rhAPC (850)	Placebo (840)	Total (1690)
Gastrointestinal	9	9	81
Intra-thoracic	6	1	7
Retroperitoneal	4	0	4
Intra-abdominal	3	4	7
Cerebral Hemorrhage	2	1	3
Transfusion-related Serious Bleeding Event	2	2	4
Genitourinary	2	0	2
Skin/Soft tissue	2	0	2
Total	30 (4%)	17 (2.0%)	47 (3%)

The majority of the difference in serious adverse bleeding events can be accounted for during the infusion period.

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[3] "Serious" bleeding adverse event defined as: any intracranial hemorrhage; life-threatening bleed (i.e. one in which at risk of death at time of even, it does not refer to an event which hypothetically might have occurred if it was more severe {ICH guidelines E2A}); patients who received 3 or more units of packed red blood cells per day for 2 consecutive days.

B. All Reported Bleeding Events

Below are listed all bleeding adverse events (including SAEs) during the infusion period, followed by the events reported during the 28 day study period. Again, most of the difference in rate between rhAPC and placebo for adverse bleeding events is accounted for during the infusion period.

Table 37. Adverse events (bleeding) study drug infusion period

Event Classification	rhAPC (850)		Placebo (840)		Total (1690)	
	N	(%)	N	(%)	N	(%)
GI Hemorrhage	46	(5)	25	(3)	71	(4)
Hemorrhage (CV)	45	(5)	21	(3)	66	(4)
Ecchymosis	44	(5)	25	(3)	69	(4)
Hematuria	16	(2)	4	(1)	20	(1)
Thrombocytopenia	14	(2)	6	(1)	20	(1)
Injection Site Hem.	13	(2)	3	(0)	16	(1)
Epistaxis	12	(1)	10	(1)	22	(1)
Melena	11	(1)	2	(0)	13	(1)
Coagulation Disorder	9	(1)	3	(0)	12	(1)
Rectal Hemorrhage	7	(1)	0		7	(0)
Hemoptysis	7	(1)	16	(2)	23	(1)
Petechia	6	(1)	1	(0)	7	(0)
Eye Hemorrhage	6	(1)	2	(0)	8	(1)
Coag Time Increased	4	(1)	1	(0)	5	(0)
Lung Hemmorrhage	3	(0)	1	(0)	4	(0)
Hemothorax	3	(0)	0		3	(0)
Cerebral Hemorrhage	2	(0)	0	(0)	2	(0)
Metrorrhagia	1	(0)	0		1	(0)
Vaginal Hemorrhage	0		1	(0)	1	(0)
Total	249		121		370	

Table 38. Adverse events (bleeding) 28-Day study period

Event Classification	rhAPC (850)		Placebo (840)		Total (1690)	
	N	(%)	N	(%)	N	(%)
GI Hemorrhage	72	(9)	46	(6)	118	(7)
Hemorrhage (CV)	67	(8)	47	(6)	114	(7)
Ecchymosis	60	(7)	36	(4)	96	(6)
Melena	16	(2)	10	(1)	26	(2)
Hemoptysis	14	(2)	24	(3)	38	(2)
Eye Hemorrhage	10	(1)	3	(0)	13	(1)
Rectal Hemorrhage	9	(1)	1	(0)	10	(1)
Gum Hemorrhage	5	(1)	4	(1)	9	(1)
Lung Hemorrhage	5	(1)	3	(0)	8	(1)
Hematemesis	3	(0)	1	(0)	4	(0)
Hemothorax	3	(0)	0		3	(0)
Anemia	2	(0)	0		2	(0)
Muscle Hemorrhage	2	(0)	0		2	(0)
Cerebral Hemorrhage	2	(0)	1	(0)	3	(0)
Retroperitoneal Hemorrhage	1	(0)	0		1	(0)
Esophageal Hemorrhage	1	(0)	2	(0)	3	(0)
Duodenal Ulcer Hemorr.	1	(0)	1	(0)	2	(0)
Stomach Ulcer Hemorrhage	1	(0)	1	(0)	2	(0)
Bloody Diarrhea	1	(0)	0		1	(0)
Hemorrhagic Colitis	1	(0)	0		1	(0)
Hemorrhagic Gastritis	1	(0)	0		1	(0)
Coagulation Disorder	1	(1)	0		1	(0)
Retinal Hemorrhage	1	(0)	0		1	(0)
Hematuria	1	(0)	0		1	(0)
Hemoperitoneum	0		2	(0)	2	(0)
Rupture of Spleen	0		3	(0)	3	(0)
Hemolysis	0		1	(0)	1	(0)
Vaginal Hemorrhage	0		1	(0)	1	(0)
Total	280		187		467	

C. Serious Adverse Events (Bleeding) Related to Heparin

Heparin was used in the study, to a maximum of 15,000 units per day, for prophylaxis of thrombotic events. The rate of bleeding events was similar among rhAPC patients who received heparin compared to those that did not. Increase in bleeding rates was observed between the rhAPC and placebo groups.

Table 39. SAE bleeding events (infusion period) as related to heparin

	rhAPC		Placebo	
Heparin	N (850)	# SAE (%)	N (840)	# SAE (%)
No	216	5 (2)	203	3 (1)
Yes	634	15 (2)	637	5 (1)

Table 40. SAE bleeding events (28 day study period) as related to heparin

	rhAPC		Placebo	
Heparin	N (850)	# SAE (%)	N (840)	# SAE (%)
No	216	8 (4)	203	4 (2)
Yes	634	22 (4)	637	13 (2)

The mortality among patients receiving rhAPC was not affected by the addition of prophylactic heparin administration. The mortality in the placebo arm was higher in those patients who did not receive heparin compared to those that did. The 28% mortality rate in the placebo prophylactic heparin arm approached the overall mortality rate in the rhAPC group.

Table 41. Mortality (28-Day study period) as related to heparin

	rhAPC		Placebo	
Heparin	N (850)	Mortality (%)	N (840)	Mortality (%)
No	216	52 (24)	203	80 (39)
Yes	634	158 (25)	637	179 (28)

IV. Other Adverse Events

Review of other adverse events, both serious and non-serious did not reveal major differences between the study drug and placebo or establish a distinct safety risk in this acutely ill patient population. Data representing serious adverse events related to the study drug (per the investigators rather than the sponsor) in addition to selected adverse events related to infections and neoplasms are presented below. Narrative summaries of the serious adverse events felt to be related to the study drug can be found in Appendix 9.

A. Serious Adverse Events Related to the Study Drug per the Investigator

Table 42. Serious adverse events (non-bleeding)

Event	rhAPC (850)	Placebo (840)	Total (1690)
Neurologic	1	1	2
Cardiovascular	1	1	2
Renal	1	0	1
Coagulation/Sepsis	1	0	1
Hepatic	1	0	1

B. Adverse Events Infusion Period

Relative to the placebo treatment group, the rhAPC treatment group had a greater proportion of patients who experienced the following treatment-emergent adverse events (other than bleeding events) during the study drug infusion
period:
➢   hypertension (2.6% versus 0.6%),
➢   healing abnormal (1.4% versus 0.5%),
➢   hallucinations (1.1% versus 0.1%).

Relative to the rhAPC treatment group, the placebo treatment group had a greater proportion of patients who experienced the following treatment-emergent adverse events (other than bleeding events):
➢   ventricular tachycardia (3.0% versus 1.5%),
➢   peripheral edema (5.5% versus 3.3%),
➢   edema (5.4% versus 3.3%).

C. Adverse Events 28-Day Study Period

All Events

Relative to the placebo treatment group, the rhAPC treatment group had a significantly greater proportion of patients who experienced at least one treatment-emergent adverse event during the 28-day study period.
For the body as a whole, digestive system, and hematologic/lymphatic system, a greater proportion of rhAPC treated patients experienced at least one treatment-emergent adverse event compared with placebo treated. The higher incidence of AEs in patients resulted from the following events that were more common among rhAPC treated patients:
➢   the body as a whole; a higher incidence of abscess and injection site hemorrhage;
➢   the digestive system; a higher incidence of gastrointestinal bleeding events;
➢   the hematologic/lymphatic system; a higher incidence of ecchymosis and thrombocytopenia.

Non-Bleeding Events

Relative to the placebo treatment group, a greater proportion of patients in the rhAPC group experienced the following treatment-emergent adverse events (other than bleeding events) during the 28-day study period:

➤ abscess (3% versus 1%),
➤ hypertension (4% versus 2%),
➤ thrombocytopenia (2% versus 1%), and

Relative to the rhAPC treatment group, the placebo treatment group had a greater proportion of patients who experienced edema during the 28-day study period (7% versus 4%).

V. Infectious Adverse Events and Neoplasms

Below is a summary of selected adverse events related primarily to infections and neoplasms. Also presented are post-baseline culture results. These data were obtained to monitor culture results on an ongoing basis and determine the prevalence of new infections while on study drug.

Table 43. Summary of selected adverse events 28 day study period

Category	rhAPC(850) N (%)	Placebo (840) N (%)	Total (1690) N (%)
Infections			
Pneumonia	69 (8)	61 (7)	130 (8)
UTI	50 (6)	52 (6)	102 (6)
Herpes Simplex	25 (3)	14 (3)	39 (2)
Sinusitis	24 (3)	13 (2)	37 (2)
Oral Monoliasis	21 (3)	12 (1)	33 (2)
Bronchitis	11 (1)	5 (1)	16 (1)
Infection Superimposed	10 (1)	6 (1)	16 (1)
Pancreatitis	8 (1)	10 (1)	18 (1)
Peritonitis	7 (1)	3	10 (1)
Aspiration Pneumonia	6(1)	4	10(1)
Endocarditis	5 (1)	7 (1)	12 (1)
+ HIV	3	1	4
Hepatitis	3	1	4
Aids	2	0	2
Pericarditis	2	2	4
Pseudomem. Colitis	2	2	4
TB Reactivated	1	0	1
Osteomyelitis	1	2	3
Herpes Zoster	1	5	6
Vaginal Monoliasis	1	2	3
Pyelonephritis	1	1	2
Pulmonary Mycosis	0	1	1
Necrotizing Pancreatitis	0	2	2
Neoplasm			
Neoplasm	5	5	10
Carcinoma	2	3	5
Lung CA	2	0	2
Prostate CA	1	0	1
GI carcinoma	1	1	2
Cervix CA	0	1	1

Data were recorded regarding the rate of new infections while in the study. The number of new infections or sequela to the initial infection were tabulated.

Table 44. Post baseline culture data

Category	rhAPC(850) N (%)	Placebo (840) N (%)
> 1 sequela Infection	141 (17)	148 (18)
> 1 new infection	217 (26)	211 (25)

There was no trend noted in acquiring new infections when comparing the rhAPC group to the placebo group.

VI. Analysis of Adverse Events By Sub-Population

Sub-population data are presented below. These include data regarding mortality, serious adverse events and serious adverse bleeding events.

A. Gender

Gender data revealed no major differences between placebo and the rhAPC treated group.

Table 45. Gender

Category	rhAPC		Placebo	
	Total (850)	Events (%)	Total (840)	Events (%)
28 Day Mortality				
F	373	94 (25)	353	108 (31)
M	477	116 (24)	487	151 (31)
SAE				
F	373	50 (13)	353	47 (13)
M	477	56 (12)	487	55 (11)
SAE Bleeding Events				
F	373	18 (5)	353	11 (3)
M	477	12 (3)	487	6 (1)

(F-Female; M-Male)

B. Age Class

Though there was an overall increased mortality with age in both the rhAPC treated group and the placebo group, there was not an increasing trend in SAE or bleeding SAE with increasing age.

Table 46. Age class

Category	rhAPC		Placebo	
	Total (850)	Events (%)	Total (840)	Events (%)
28 Day Mortality				
< 60	375	59 (16)	366	75 (20)
> 60	475	151 (32)	474	184 (39)
<65	437	68 (16)	449	94 (21)
> 65	413	142 (34)	391	165 (42)
SAE				
< 60	375	48 (13)	366	39 (11)
> 60	475	58 (12)	474	63 (13)
<65	437	57 (13)	449	51 (11)
> 65	413	49 (12)	391	51 (13)
SAE Bleeding Events				
< 60	375	16 (4)	366	7 (2)
> 60	475	14 (3)	474	10 (2)
<65	437	18 (4)	449	11 (2)
> 65	413	12 (3)	391	6 (2)

C. Ethnic Origin

The number of subjects of origins other than Caucasian is too small to make meaningful conclusions, though there were no specific trends noted.

Table 47. Origin

Category	rhAPC		Placebo	
	Total (850)	Events (%)	Total (850)	Events (%)
28 Day Mortality				
AF	71	19 (27)	61	23 (38)
AS	5	0 (0)	6	1 (17)
CA	695	170 (24)	689	214 (31)
EA	9	2 (22)	13	4 (31)
HP	34	7 (21)	40	8 (20)
O	37	12 (32)	31	9 (29)
SAE				
AF	71	13 (19)	61	10 (16)
AS	5	0 (0)	6	1 (17)
CA	695	84 (12)	689	80 (12)
EA	9	2 (22)	13	2 (15)
HP	34	34(12)	40	4(10)
O	37	3 (8)	31	5 (16)
SAE Bleeding Events				
AF	71	5 (7)	61	1 (2)
AS (not Listed)	5		6	
CA	695	21 (3)	689	15 (2)
EA	9	2 (22)	13	1 (8)
HP	34	1 (3)	40	0 (0)
O	37	1 (3)	31	0 (0)

(AF-African; AS-Asian; CA-Caucasian; EA East/Southeast Asian; HP-Hispanic; O-Other)

D. First APACHE II Quartile

Safety data divided into APACHE II Quartiles are presented below. Narrative descriptions of individual subjects in the first APACHE II quartile are presented in Appendix 10. There is an increased risk of bleeding adverse event and bleeding serious adverse event in all APACHE II quartiles in the rhAPC treated patients compared to the placebo arm. This difference is most pronounced in the first quartile. The first quartile also has an increased relative risk of mortality in the rhAPC treated patients vs. placebo.

Table 48. Mortality (28-Day) and bleeding events (infusion period) per APACHE II quartile

	APACHE II Quartile							
	First		Second		Third		Fourth	
	rhAPC (218) N (%)	Placebo (210) N (%)	rhAPC (218) N (%)	Placebo (222) N (%)	rhAPC (204) N (%)	Placebo (162) N (%)	rhAPC (210) N (%)	Placebo (241) N (%)
Bleeding AE	38 (17)	17 (8)	36 (17)	20 (9)	40 (20)	19 (12)	46 (22)	35 (15)
Relative Risk	2.2 (1.1, 4.6) P=0.016		1.8 (1.0, 3.7) P=0.052		1.7 (0.9, 3.4) P=0.096		1.5 (0.9, 2.5) P=0.093	
Bleeding SAE	9 (4)	0	2 (1)	5 (2)	6 (3)	0	3 (1)	3 (1)
Relative Risk	18.3 (2.7, *) P=0.003		0.5 (0.004, 6.1) P=1.0		10.3 (1.4, *) P=0.019		1.1 (0.04, 32.2) P=1.0	
Mortality 28 day	33 (15)	26 (12)	49 (23)	57 (26)	48 (24)	58 (36)	80 (38)	118 (49)
Relative Risk	1.3 (0.77, 2.02)		0.87 (0.62,1.22)		0.66 (0.48,0.91)		0.78 (0.65,0.97)	

Relative Risk (95% exact confidence interval), exact P-value
* very large number

A higher mortality was noted in the first quartile in the rhAPC treated group when compared to the placebo group. Additionally, there was a much higher bleeding SAE rate in the rhAPC treated group in the first quartile compared to the placebo group. Narratives of the SAE subjects and the 33 deaths in the first quartile are presented in Appendix 10..

E. DIC

The vast majority of patients were in DIC as defined by the study (see below). The rate of serious adverse bleeding events in DIC mirrors the entire study. There are too few patients that were not in DIC to make meaningful conclusions.

Table 49. DIC

Category	rhAPC		Placebo	
	Total (850)	Events (%)	Total (840)	Events (%)
28 Day Mortality				
DIC – Y	800	196 (25)	774	243 (31)
DIC - N	49	14 (29)	66	16 (24)
SAE				
DIC – Y	800	96 (12)	774	93 (12)
DIC - N	49	10 (20)	66	9 (14)
SAE Bleeding Events				
DIC – Y	800	28 (4)	774	16 (2)
DIC - N	49	2 (4)	66	1 (2)

In this study, a patient was classified as having DIC at baseline if any two of the following criteria were met within the 24 hours prior to study drug initiation:

(a) Platelet count <100,000 mm 3 or a 50% decrease from any value in the previous 3 days.

(b) Prothrombin time or activated partial thromboplastin time >1.2 times the upper limit of normal.

(c) Evidence of procoagulant or fibrinolytic activation based on a D-dimer level greater than the upper limit of normal.

(d) Evidence of inhibitor consumption based on either Protein C activity, Protein S activity, or antithrombin activity below the lower limit of normal.

F. Transfusion

Below is summarized the transfusion requirements in both the rhAPC group and the placebo group. More transfusions were required in the rhAPC group for packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets compared to placebo.

Table 50. Summary of transfusion data (phase 3)

Category		rhAPC 850) N (%)	Placebo (840) N (%)	Total (1690) N (%)
PRBC	Yes	533 (63)	490 (58)	1023 (61)
	No	317 (37)	350 (41)	667 (40)
FFP	Yes	200 (24)	162 (19)	362 (21)
	No	650 (77)	678 (81)	1328 (79)
Platelets	Yes	114 (13)	96 (11)	210 (12)
	No	736 (87)	744 (89)	1480 (88)

There was an increased use in all blood products for the rhAPC treated group compared to the placebo treated group.

G. Coagulation profile

The coagulation profiles represent pooled data from the phase 2 (n=131) and 3 (n=1690) trials. Data are presented for mortality and adverse bleeding events. This table is followed by a table representing the most abnormal PTT, PT or platelet count in days 1-5 and the mortality, and bleeding adverse events recorded for those various groups.

Table 51. Baseline coagulation profile

Category	rhAPC		Placebo	
	Total (940)	Events (%)	Total (881)	Events (%)
28 Day Mortality				
APTT				
Unknown	71	26 (37)	83	18 (22)
$\leq$ ULN	282	54 (19)	251	67 (27)
ULN- $\leq$2xULN	543	139 (26)	510	169 (33)
> 2xULN	44	17 (39)	37	19 (51)
PT				
Unknown	70	24 (34)	86	20 (23)
$\leq$ ULN	92	17 (18)	66	17 (26)
ULN- $\leq$1.2xULN	262	48 (18)	245	66 (27)
> 1.2xULN	516	147 (28)	484	170 (35)
Platelet				
Unknown	150	40 (27)	148	51 (34)
< 50,000	19	7 (36)	24	15 (63)
50,000- LLN	222	57 (26)	190	62 (33)
> LLN	549	132 (24)	519	145 (28)
Adverse Bleeding Events				
APTT				
Unknown	71	12 (17)	83	7 (8)
$\leq$ ULN	282	46 (16)	251	25 (10)
ULN- $\leq$2xULN	543	101 (19)	510	55 (11)
> 2xULN	44	9 (20)	37	5 (14)
PT				
Unknown	70	11 (16)	86	8 (9)
$\leq$ ULN	92	7 (8)	66	7 (11)
ULN- $\leq$1.2xULN	262	42 (16)	245	22 (9)
> 1.2xULN	516	108 (21)	484	55 (11)
Platelet				
Unknown	150	30 (20)	148	14 (9)
< 50,000	19	5 (26)	24	7 (29)
50,000- LLN	222	38 (17)	190	27 (14)
> LLN	549	95 (17)	519	44 (8)

There were more reported bleeding events with abnormal coagulation factors in the rhAPC treated group than the placebo group.

Table 52. Coagulation profile study days 1-5 28-Day study period

Category	rhAPC		Placebo	
	Total (940)	Events (%)	Total (881)	Events (%)
28 Day Mortality				
Maximum APTT				
Unknown	45	33 (73)	53	39 (74)
≤ ULN	104	16 (15)	179	39 (22)
ULN- ≤2xULN	568	112 (20)	526	135 (26)
> 2xULN	223	75 (34)	123	60 (49)
Maximum PT				
Unknown	45	33 (73)	53	39 (74)
≤ ULN	50	9 (18)	59	19 (17)
ULN- ≤1.2xULN	237	29 (12)	256	50 (20)
> 1.2xULN	608	165 (27)	513	174 (34)
Lowest Platelet				
Unknown	226	106 (47)	239	122 (51)
< 50,000	46	15 (32)	47	25 (53)
50,000- LLN	195	51 (26)	171	55 (32)
> LLN	473	64 (14)	424	71 (17)
Adverse Bleeding Events				
Maximum APTT				
Unknown	45	2 (4)	53	1 (2)
≤ ULN	104	14 (13)	179	15 (8)
ULN- ≤2xULN	568	95 (17)	526	57 (11)
> 2xULN	223	57 (26)	123	19 (15)
Maximum PT				
Unknown	45	2 (4)	53	1 (2)
≤ ULN	50	7 (14)	59	3 (5)
ULN- ≤1.2xULN	237	36 (15)	256	23 (9)
> 1.2xULN	608	123 (20)	513	65 (13)
Lowest Platelet				
Unknown	226	43 (19)	239	26 (11)
< 50,000	46	11 (22)	47	7 (15)
50,000- LLN	195	40 (21)	171	22 (13)
> LLN	473	74 (16)	424	37 (9)

Many more patients had increasingly abnormal coagulation profiles in the first 5 days of the illness both in the rhAPC treated group and the placebo group. Overall there was consistent mortality benefit with consistently higher bleeding events in the rhAPC treated group compared to the placebo group.

H. APC Steady – State

Presented below are data on the safety profile of subjects based on the steady state rhAPC level.

Table 53. Safety profile by rhAPC steady-state concentration quartile (total 326)

Variable	1st Quartile (81)		2nd Quartile (83)		3rd Quartile (81)		4th Quartile (81)	
	N	(%)	N	(%)	N	(%)	N	(%)
28 day mortality	12	(15)	14	(17)	16	(20)	27	(33)
28 day SAE	7	(9)	10	(12)	15	(19)	13	(16)
28 day SAE (bleed)	3	(4)	0		3	(4)	3	(4)
Infusion period SAE	4	(5)	4	(5)	6	(7)	6	(7)
Infusion period SAE (bleed)	2	(3)	0		1	(1)	2	(3)

All levels in ng/ml

1st Quartile – 0 – 35
2nd Quartile – 35-45
3rd Quartile – 45 –62
4th Quartile – 62 – 390

Highest Placebo group concentration recorded – 44.1

There was a wide range in the steady state rhAPC concentration, in addition to measurable levels being recorded in the placebo treated patients. It is noted that there was a higher overall mortality in the 4th (highest) quartile though again the numbers are small.

I. Baseline Surgical Status

Presented below are data from phase 2 and phase 3 concerning patients that required surgery, both emergent and non-emergent.

Table 54. Mortality treatment emergent bleeding events and transfusion based on surgical status

Category	rhAPC		Placebo	
	Total (940)	**Events (%)**	**Total (881)**	**Events (%)**
28 Day Mortality				
Elective Post-op	63	20 (32)	59	22 (37)
Relative Risk	0.9 (0.4, 1.6) P=0.657			
Emergency Post-op	186	56 (30)	187	49 (26)
Relative Risk	1.1 (0.8, 1.7) P=0.505			
Non-op	691	160 (23)	635	202 (32)
Relative Risk	0.7 (0.6, 0.9) P=0.003			
Treatment Emergent Bleeding Events				
Elective Post-op	63	12 (19)	59	4 (7)
Relative Risk	2.6 (0.7, 24.3) P=0.178			
Emergency Post-op	186	32 (17)	187	14 (7)
Relative Risk	2.3 (1.1, 5.4) P=0.018			
Non-op	691	124 (18)	635	74 (12)
Relative Risk	1.5 (1.1, 2.1) P=0.005			
Required Transfusion of PRBC				
Elective Post-op	63	54 (86)	59	44 (75)
Relative Risk	1.1 (0.9, 1.5) P=0.287			
Emergency Post-op	186	154 (83)	187	144 (77)
Relative Risk	1.1 (1.0, 1.2) P=0.261			
Non-op	691	384 (56)	635	326 (51)
Relative Risk	1.1 (1.0, 1.2) P=0.159			

Relative Risk (95% exact confidence interval), exact P-values

The mortality rate was higher in rhAPC treatment group emergent post-op surgical patients compared to the placebo rates.

Although bleeding rates were increased in the rhAPC group compared to placebo, this seemed to be unaffected by the patient's surgical status.

There was a higher rate of transfusions in all rhAPC groups, but most pronounced in the post operative groups.

J. Immunogenicity

No Anti-APC antibody response was noted in the phase 1/1B trials. 105 subjects were tested (104 had results reported, 1 patients samples were missing). 87% of patients received multiple doses.
In phase 2/3 trials, 942 patients were exposed to rhAPC (90 phase2; 852 phase3).
Evaluable patients had a baseline determination, and at least 1 determination at day 14 (acceptable day 12-21) and or at day 28 (acceptable day $\geq$22). Out of 942 potential patients, 370 (39%) had specimens suitable for testing (53 (59%) phase 2; 317 (37%) phase 3).

Level 1   Chemilucent binding assay – any patient with a value greater than 124 adjusted relative light units (ARLU) and a 2 fold or greater rise over baseline proceeded to level 2.

Level 2   Specific anti-APC IgG at a level of 1:10. Any sample with a response greater than 40% inhibition at study day 28 was considered positive.

Level 3   Neutralizing antibody to rhAPC and APC using an activated anti-partial thromboplastin time assay

Table 55. Anti-APC antibody data for APC-treated patients with positive level 1 testing

	Level 1 Results		Level 2 Results		Level 3 Results
Patient #	Fold increase over baseline level	ARLU Units for 14 or Day 28 sample	% Inhibition	Anti-APC Antibody Response	Anti-APC Neutralizing Antibody
Phase 2					
003-304	7.9	388	53.0	Positive	Negative
015-1501	2.2	142	27.2	Negative	NA
Phase 3					
045-4502	4.2	189	36	Negative	NA
340-4003	8.1	171	49.1	Positive	Negative
851-5110	4.4	128	7.8	Negative	NA

Incidence of Anti-APC antibody response in patients exposed to rhAPC (defined as positive level 2 testing) was 0.54% (2/370). Patient 003-304 received 24 ug/kg/hr for 48 hours in phase 2, had no clinical sequalae and was antibody negative at 1 year. Patient 340-4003 received 24 ug/kg/hr for 96 hours in the phase 3 trial. This patient was reported to develop superficial and deep vein thrombosis "that were not deemed serious by the investigator." Follow-up past the 28 day study period was obtained. This patient had no further thrombotic episodes but died on day 36 of multi-organ failure.

Summary of Safety

Review of the safety data reveals the following:

- 4 deaths due to bleeding, related to the study drug per the investigators, occurred in the rhAPC, and none in the placebo arm.
- There was an increased rate of bleeding adverse events and bleeding serious adverse events in the rhAPC treated patients compared to placebo.
- There was a higher mortality rate in the first APACHE II quartile in the rhAPC group compared to placebo.
- There was a higher rate of serious bleeding events in the first APACHE II quartile in the rhAPC group compared to placebo.
- There was a higher mortality in patients requiring emergency surgery in the rhAPC group compared to placebo.
- There was a higher mortality rate in the rhAPC steady state 4th quartile (highest concentration) when compared to the first 3 quartiles.
- Anti-APC antibody detection was rare, though one of the two patients with positive results developed superficial and deep vein thrombosis. This patient reportedly died after the 28-day study period.
- Other than bleeding events, there were no other patterns of adverse event noted in the rhAPC group compared to placebo.
- Because of the nature of this population, significant adverse events may have been subsumed in the underlying illness of the patients.

SECTION VI-APPENDICES

Appendix 1

Phase 1 Brief Description of Studies

- **F1K-LC-GUAA Clinical Pharmacology**

This was an open-label, single center study in healthy male adults. Three single 3 hour intravenous (iv) infusions per patient at 0.49-25.7 ug/kg/hr rhAPC in 4 males were studied.

- **F1K-LC-GUAB Clinical Pharmacology**

This was an open-label, single center study in healthy male adults. Three single 3-hour iv infusions per patient, separated by 2 weeks, at 6.04-49.1 ug/kg/hr rhAPC in 4 patients were studied.

- **F1K-LC-GUAC Clinical Pharmacology**

This was an open-label, single center study in healthy adult males and postmenopausal or surgically sterile females, with or without estrogen. Two dosing periods, 6 and 24 hour iv infusions, separated by at least 14 days, at 6.59-24.2 ug/kg/hr rhAPC in 32 patients were studied.

- **F1K-LC-GUAD Clinical Pharmacology**

This was an open-label, single center study in healthy adult males and postmenopausal females, with and without estrogen. Two dosing periods, 6 and 24 hour iv infusions, separated by at least 5 days, at 12.8-49.9 ug/kg/hr rhAPC in 51 patients were studied.

- **F1K-LC-GUAE Clinical Pharmacology**

This was an open-label, single center study in adults with end-stage renal disease (hemodialysis and peritoneal dialysis). One 6 hour infusion at 26.3 ug/kg/hr rhAPC in 12 patients were studied.

- **F1K-LC-GUAF Clinical Pharmacology**

This was an open-label, single center study in healthy adults. There were two parts, Part A, single dose aspirin (500 mg po) alone was studied in 15 patients. Part B, single-blind, crossover design, two treatments, separated by at least 14 days, comparing rhAPC in the presence of aspiring or placebo was studied in 27 patients. Aspirin or placebo (po) was followed by 6 hour infusion at 25.1 ug/kg/hr rhAPC.

- **F1K-LC-EVAK Clinical Pharmacology**

This was an open-label, single center study in healthy adult males. Part A-6 patients, 3 treatments bolus injection; 6 hr constant rate iv infusion; or bolus injection immediately followed by 6 hr constant rate iv infusion. Doses of rhAPC administered were up to 10 ug/kg/hr over 1 minute; 0.5 ug/kg/hr for 6 hours; or at up to 10 ug/kg/hr over 1 minute plus 0.5 ug/kg/hr for 6 hours. Part B-6 patients (from part A 1 reentered), one treatment

bolus over 5 minutes to 2 hours, followed by a 6 hr constant rate iv infusion of rhAPC. Average infusion rates were 12.3 (over 2 infusions) or 12.8 ug/kg/hr (over 3 infusions).

- **F1K-LC-EVAM Clinical Pharmacology**

This was an open-label, single center study in healthy adult males and postmenopausal females in 14 patients. One single 0.5 hour loading dose followed by a 5.5 hour constant rate iv infusion of rhAPC was given. The average infusion rates over two infusions were 12.5, 24.7 or 49.8 ug/kg/hr.

- **F1K-LC-EVAV Clinical Pharmacology**

This was an open-label, single center study in healthy adult controls and patients with end-stage renal disease requiring hemodialysis or peritoneal dialysis for more than 3 months. 13 patients were studied at 6 hour infusions for the control and treatment groups with hemodialysis group receiving two infusions (1 and 2 days after hemodialysis) at 24 ug/kg/hr rhAPC. Objectives of this study were to determine the differences in clearance of rhAPC in patients with chronic renal failure or end-stage renal disease in GUAE can be confirmed.

- **F1K-LC-EVAW Clinical Pharmacology**

This was an open-label, multicenter center study in adults with end-stage renal disease requiring hemodialysis for more than 3 months. 5 patients, with 3 sessions of hemodialysis with control and 3 sessions with rhAPC were evaluated. rhAPC-a loading dose followed by continuous infusion of 24 ug/kg/hr for 6 hours was studied. Control-standard heparin protocol for hemodialysis.

- **F1K-LC-EVAX Clinical Pharmacology**

This was a single-blind, placebo-controlled study in healthy adults. 13 patients with two of three possible infusion rates during 3 separate study periods were evaluated. rhAPC was given infusion rates of 12, 24 or 48 ug/kg/hr and placebo was saline.

- **F1K-MC-EVAB Protein C deficiency noncontrolled study**

This was an open-label, single center study in adults with heterozygous Protein C deficiency (HPCD). Up to three 24 hour iv infusions each, separated by a minimum of 3 weeks in 9 patients were studied. rhAPC was given at a range of doses between 0.48 and 24 ug/kg/hr with each subject possibly receiving three different infusion rates during the study.

- **F1K-MC-EVAS Purpura fulminans, noncontrolled study**

This was an open-label, multicenter study in adults and pediatric patients with purpura fulminans. 35 subjects enrolled, from 8 months to 61 years, at 19 centers. 96 to 168 hour continuous iv infusion of 24 ug/kg/hr rhAPC was studied. Safety profile included 28 day follow up.

Appendix 2

Phase 3 Inclusion and Exclusion Criteria

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A. Phase 3 Inclusion Criteria

For the purposes of this study, patients with severe sepsis were defined as having:

> 1. Three or more SIRS criteria (Criteria A)
> 2. At least one of the five organ failure criteria (Criteria B)
> 3. Evidence of infection (Criteria C)

Criteria A (modified SIRS entry criteria): The patient must have had three or more of the following qualifications during Window I. The events satisfying these criteria must have been attributable to the onset of sepsis and not attributable to an underlying disease process or to the effects of concomitant therapy.

1. Core temperature 38°C (100.4°F) or 36°C (96.8°F). Core temperature was defined as rectal, central catheter, or tympanic. If oral or axillary temperature was used, 0.5°C (1°F) was added to the measured value. Hypothermia (36°C or 96.8°F) must have been confirmed by a rectal or core temperature.
2. Heart rate 90 beats/min. If patients had a known medical condition or were receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they need only have met two of the three remaining Criteria A, excluding heart rate.
3. Respiratory rate 20 breaths/min or a PaCO2 32 mm Hg, or mechanical ventilation or an acute process.
4. White blood cell count of 12,000/mm^3 or 4,000/mm^3 or >10% immature neutrophils.

Criteria B (associated organ failure entry criteria): The patient must have met one or more of the following criteria during Window I. This criterion must have been newly developed in the context of the changes listed in Criteria A, and not explained by underlying disease processes or by effects of concomitant therapy.

1. **Cardiovascular**: An arterial systolic blood pressure (SBP) of 90 mm Hg or a mean arterial pressure (MAP) 70 mm Hg for at least 1 hour despite adequate fluid resuscitation, adequate intravascular volume status, or the need for vasopressors to maintain SBP 90 mm Hg or MAP 70 mm Hg. Adequate fluid resuscitation or adequate intravascular volume was defined as one or more of the following:
   a) Pulmonary arterial wedge pressure 12 mm Hg
   b) Central venous pressure 8 mmHg.
   > Note: Vasopressors were defined as:
   > ▪ Dopamine 5 ug/kg/min

- Norepinephrine, epinephrine, or phenylephrine at any dose.
- Note**:** Dobutamine and Dopexamine were not considered vasopressors.

2. The administration of an intravenous fluid bolus (500 mL of crystalloid solution, 20 g of albumin, or 200 mL of other colloids administered over 30 minutes or less)

3. **Renal**: Urine output <0.5 mL/kg/hr for 1 hour, despite adequate fluid resuscitation as described. In the presence of preexisting impairment of renal function (defined as a serum creatinine concentration >2 times the upper limit of the normal reference range for that institution prior to the onset of sepsis), the patient must have met one of the other four organ failure criteria.

4. **Respiratory**:
    a) PaO_2/FiO_2 250
    b) If the lung was the sole organ meeting criteria as well as the suspected site of infection, the patient must have had a PaO_2/FiO_2 200.

5. **Hematology**: Platelet count of <80,000/mm^3 or a 50% decrease in the platelet count from the highest value recorded over the previous 3 days.

6. **Unexplained metabolic acidosis**, which was defined as:
    a) pH 7.30 or base deficit 5.0 mEq/L and
    b) A plasma lactate level >1.5 times the upper limit of normal for the reporting lab.

Criteria C (infection criteria): The development of SIRS and associated organ failure must have been secondary to an infection.

Suspected or proven infection. Patients with suspected infection must have had evidence of an infection such as white blood cells in a normally sterile body fluid, perforated viscus, chest x-ray consistent with pneumonia and associated with purulent sputum production, or a clinical syndrome associated with a high probability of infection (for example, ascending cholangitis).

B. Phase 3 Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

1. Pregnant or breastfeeding.
2. Less than 18 years of age.
3. Weighing >135 kg.
4. Platelet count < 30,000/mm^3.
5. Increased risk for bleeding (for example):
    a) Any patient who had undergone major surgery, defined as surgery that required general or spinal anesthesia that was performed within the 12-hour period immediately preceding study drug infusion; any postoperative patient who demonstrated evidence of active bleeding; or any patient with planned or anticipated surgery during the study drug infusion period, such as patients with staged surgeries or burn patients with planned excisions and grafting during the study drug infusion period.

b) History of severe head trauma that had required hospitalization, intracranial surgery, or stroke within 3 months of study entry, or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesion. Patients with an epidural catheter or who anticipated receiving an epidural catheter during study drug infusion were also excluded from the study.

c) History of congenital bleeding diatheses, such as hemophilia.

d) Gastrointestinal bleeding within 6 weeks of study entry that required medical intervention unless definitive surgery had been performed.

e) Trauma patients at increased risk of bleeding, for example: flail chest; significant contusion to lung, liver, or spleen; retroperitoneal bleed; pelvic fracture; or compartment syndrome.

6. Patients with a known hypercoagulable condition including activated Protein C resistance; a hereditary deficiency of Protein C, Protein S, or antithrombin; presence of anticardiolipin antibody, antiphospholipid syndrome, lupus anticoagulant or homocysteinemia; or patients with a recently documented (within 3 months of study entry) or highly suspected deep venous thrombosis or pulmonary embolism.

7. Patients taking the following medications:

a) Therapeutic heparin, defined as:

b) Unfractionated heparin dosed to treat an active thrombotic or embolic event within the 8 hours prior to study drug infusion. Low molecular weight heparins used at any dose higher or more frequent than the recommended dose in the product label for prophylaxis within the 12 hours prior to study drug infusion.

c) Note: Prophylactic unfractionated heparin up to 15,000 units/day was permitted.

d) Warfarin, if used within 7 days of study entry and if prothrombin time was prolonged beyond the upper limit of normal for the institution.

e) Acetylsalicylic acid (ASA) >650 mg/day or compounds that contain ASA >650 mg/day within 3 days of study entry.

f) Thrombolytic treatment within 3 days of study entry (for example, streptokinase, tPA, rPA, and urokinase).

g) Note: These agents were permitted for the treatment of intra-catheter thromboses; however, care should have been taken to avoid systemic administration.

h) Glycoprotein IIb/IIIa antagonists within 7 days of study entry.

i) Antithrombin infusion of >10,000 units within 12 hours of study entry.

j) Protein C infusion within 24 hours of study entry.

8. Participation in another therapeutic drug or device trial or use of another investigational agent, such as nitric oxide, within 30 days of study entry without prior approval from the Vanderbilt Coordinating Center (VCC).

9. Patients with known esophageal varices, chronic jaundice, cirrhosis, or chronic ascites.

10. Presence of an advanced directive to withhold life-sustaining treatment with the exception of cardiopulmonary resuscitation (CPR).

11. Patients not expected to survive 28 days given their preexisting, uncorrectable medical condition. This criterion included patients with, or suspected to have, poorly controlled neoplasms or other end-stage processes, such as end-stage cardiac disease, prior cardiac arrest, end-stage lung disease, or end-stage liver disease. Enrollment of patients with known or suspected metastatic cancer was approved by the VCC prior to randomization. Lilly provided guidelines for the VCC to use in determining which patients with malignancy were appropriate for this study.

12. Patients with chronic renal failure on either hemodialysis or peritoneal dialysis.
Note: Patients with acute renal failure were permitted.

13. HIV positive patients who's most recent CD4 count, if known, was 50/mm^3.

14. Patients who had undergone bone marrow, lung, liver, pancreas, or small bowel transplantation.

15. Patients who were moribund and where death was perceived to be imminent (within 24 hours).

16. Presence of the first sepsis-induced organ failure greater than 24 hours prior to the start of Window II.

17. Patients whose family or primary physician had not committed to aggressive management of the patient.

18. Patients with acute clinical pancreatitis without a proven source of infection.

Appendix 3

APACHE II Scoring System

(as provided in the license application)

A   Acute Physiology Points:

Physiologic variable	High Abnormal Range				0	Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (rectal, °C)	≥41	39-40.9		38.5-38.9	36- 38.4	34-35.9	32 -33.9	30 -31.9	≤29.9
Mean Arterial Pressure (mm Hg)	≥160	130 – 155	110-129		70-109		50-69		≤49
Heart rate (ventricular response)	≥ 180	140-179	110-139		70-109		55-69	40-54	≤39
Respiratory rate (non-ventilated orientation)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation: $AaDO_2$ or PaO_2 (mmHg) a. FIO_2 ≥0.5 record only AaDO b. FIO_2 <0.5 record only PaO_2	≥500	350-499	200-349		<200 PO_2 >70	PO_2 61-70		PO_2 55-60	PO_2 <55
Arterial pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Serum sodium (mMd/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
Serum potassium (mMd/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		<2.5
Serum creatinine (mg/100 mL) (double point score for acute renal failure.)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		<20
White Blood Count	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
Glasgow Coma Score (GCS) Score = 15 minus actual GCS									
Total Acute Physiology Score									
Serum HCO_3 (venus, mMd/L) (not preferred, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	<15

B AGE POINTS:

Assign points to age as follows:

Age (yrs)	Points
≥ 44	0
45 – 54	2
56 – 64	3
65 – 74	5
≤ 75	6

C CHRONIC HEALTH POINTS:

If the patient has a history of severe organ insufficiency or is immunocompromised, assign points as follows:

a. nonoperative or emergency post-operative patients: 5 points

b. elective postoperative patients: 2 points

Definitions: Organ insufficiency or immunocompromised state evident prior to this hospital admission and conforming to the following criteria:
LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
CARDIOVASCULAR: New York Heart Association Class IV.
RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, ie, unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mm Hg), or respirator dependency.
RENAL: Receiving chronic dialysis.
IMMUNOCOMPROMISED: Patient has received therapy that suppresses resistance to infection, eg, immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection (eg, leukemia, lymphoma, AIDS)

APACHE II SCORE

Sum of A + B + C

A APS Points   _____
B Age Points   _____
C Chronic Health Points _____

TOTAL APACHE II   _____

Appendix 4

Baseline characteristics

A. Solicited patient history
Table 56. Baseline distribution of solicited patient history

Variable	APC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Hypertension			
No	503 (59)	530 (63)	1033 (61)
Unknown	22 (3)	16 (2)	38 (2)
Yes	325 (38)	294 (35)	619 (37)
Myocardial Infarction			
No	725 (85)	698 (83)	1423 (84)
Unknown	22 (3)	21 (3)	43 (3)
Yes	103 (12)	121 (14)	234 (13)
Congestive Cardiomyopathy			
No	770 (91)	749 (89)	1519 (90)
Unknown	26 (3)	15 (2)	41 (2)
Yes	54 (6)	76 (9)	130 (8)
Diabetes			
No	662 (78)	642 (76)	1304 (77)
Unknown	12 (1)	10 (1)	22 (1)
Yes	176 (21)	188 (22)	364 (22)
Pancreatitis			
No	803 (95)	791 (94)	1594 (94)
Unknown	18 (2)	16 (2)	34 (2)
Yes	29 (3)	33 (4)	62 (4)
Chronic Liver Disease			
No	814 (96)	803 (96)	1617 (96)
Unknown	18 (2)	15 (2)	34 (2)
Yes	18 (2)	22 (3)	62 (4)
COPD			
No	637 (75)	605 (72)	1242 (74)
Unknown	24 (3)	16 (2)	33 (2)
Yes	189 (22)	219 (26)	40 (2)
Malignancy			
No	680 (80)	663 (79)	1343 (80)
Unknown	25 (3)	19 (2)	44 (3)
Yes	145 (17)	158 (19)	303 (18)
Recent Trauma			
No	808 (95)	792 (94)	1600 (95)
Unknown	14 (2)	5 (1)	19 (1)
Yes	28 (3)	43 (5)	71 (4)
Recent Surgery			
No	597 (70)	580 (69)	1177 (70)
Unknown	8 (1)	3 (0)	11 (1)
Yes	245 (29)	257 (31)	502 (30)

COPD=Chronic Obstructive Pulmonary Disease. Recent=Within 30 days.

The groups were balanced with regard to these baseline covariates.

B. Infection data

Table 57. Baseline distribution of infection data

Variable	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Presumed Site of Infection			
Blood	45 (5)	42 (5)	87 (5)
Bone/Joint	3 (0)	8 (1)	11 (1)
Cardiac	6 (1)	3 (0)	9 (1)
CNS	20 (2)	19 (2)	39 (2)
Gynecologic	4 (1)	4 (1)	8 (1)
Head/EENT	4 (1)	4 (1)	8 (1)
Intra-Abdominal	170 (20)	167 (20)	337 (20)
Lung	456 (54)	450 (54)	906 (54)
Other	20 (2)	15 (2)	35 (2)
Pleural	5 (1)	8 (1)	13 (1)
Skin/skin structure	23 (3)	28 (3)	51 (3)
Urinary Tract	85 (10)	86 (10)	171 (10)
Vascular Catheter	9 (1)	6 (1)	15 (1)
Reason Presumed or Known			
Chest X-ray	381 (45)	376 (45)	757 (45)
Other	31 (4)	40 (5)	71 (4)
Polymorphs	24 (3)	33 (4)	57 (3)
Pos Culture/Gram	199 (23)	183 (22)	382 (23)
Underlying Disease/condition	57 (7)	51 (6)	108 (6)
Visual Inspection	158 (19)	157 (19)	315 (19)
At least 1 positive bacterial pathogen culture			
No	285 (34)	271 (32)	556 (33)
Unknown	3 (0)	2 (0)	5 (0)
Yes	562 (66)	576 (68)	1129 (67)
At least 1 positive blood culture			
No	572 (67)	567 (68)	1139 (67)
Yes	278 (33)	273 (33)	551 (33)
Type of Gram stain class of bacterial pathogen cultured			
Mixed Gram	133 (16)	117 (14)	250 (15)
No bacterial Expo	285 (34)	271 (32)	556 (33)
Pure Gram Negative	185 (22)	196 (23)	381 (23)
Pure Gram Positive	219 (26)	211 (25)	430 (25)
Unconfirm Gram	28 (3)	45 (5)	73 (4)
At least 1 positive anaerobic culture pathogen			
Mixed Aero/Anaer	37 (4)	32 (4)	69 (4)
No bacterial Expo	285 (34)	271 (32)	556 (33)
Pure Aerobic	482 (57)	485 (58)	967 (57)
Pure Anaerobic	16 (2)	6 (1)	22 (1)
Unconfirm Aer/Anaer	30 (4)	46 (6)	76 (5)
At least 1 positive fungal culture			
No	772 (91)	767 (91)	1539 (91)
Unknown	6 (1)	9 (1)	15 (1)
Yes	72 (9)	64 (8)	136 (8)
At least 1 positive viral culture			
No	838 (99)	827 (99)	1665 (99)
Unknown	9 (1)	11 (1)	20 (1)

Yes	3 (0)	2 (0)	5 (0)
At least 1 positive parasitic culture			
No	840 (99)	829 (99)	1669 (99)
Unknown	9 (1)	11 (1)	20 (1)
Yes	1 (0)	0	1 (0)
At least 1 pathogen			
No	265 (31)	254 (30)	519 (31)
Yes	585 (69)	586 (70)	1171 (69)

CNS=Central nervous system. EENT=Eye, ear, nose throat. Pos=Positive.

C. Biomarkers

Presented below is a summary of the baseline Protein C activity and deficiency and other laboratory biomarkers in patients.

Table 58. Baseline distribution of central laboratory data

Variable (Baseline)	rhAPC (850) N (%)	Placebo (840) N (%)	Total N (1690) N (%)
Protein C Activity			
40%	330 (39)	285 (34)	615 (36)
>80%	90 (11)	105 (13)	195 (12)
Unknown	51 (6)	65 (8)	116 (7)
41-60%	240 (28)	227 (27)	467 (28)
61-80%	139 (16)	158 (19)	297 (18)
Protein C Deficiency			
Deficient	709 (83)	670 (80)	1379 (82)
Not deficient	90 (11)	105 (13)	195 (12)
Unknown	51 (6)	65 (8)	116 (7)
Severe Protein C Deficiency			
Not severely deficient	183 (22)	210 (25)	393 (23)
Severely deficient	616 (73)	565 (67)	1181 (70)
Unknown	51 (6)	65 (8)	116 (7)
ATIII Quartile			
1 (<0.44)	212 (27)	186 (24)	398 (26)
2 (0.45-0.59)	202 (25)	191 (25)	393 (25)
3 (0.60-0.74)	182 (23)	188 (25)	370 (24)
4 (0.75)	198 (25)	199 (26)	397 (26)
Unknown	56	76	132
ATIII Deficiency			
Deficient	655 (83)	618 (81)	1273 (82)
Not deficient	139 (18)	146 (19)	285 (18)
Unknown	56	76	132
APC resistance factor V Leiden			
Negative	768 (96)	768 (96)	1536 (96)
Positive	33 (4)	32 (4)	65 (4)
Unknown	49	40	89
APC resistance factor V Hong Kong			
Negative	794 (100)	785 (100)	1579 (100)
Positive	1 (0)	2 (0)	3 (0)
Unknown	55	53	108

D. Baseline location prior to hospitalization

Table 59. Subject location at baseline prior to hospitalization

	rhAPC (850)		Placebo (840)		Total (1690)	
	N	(%)	N	(%)	N	(%)
Acute Care Hospital	79	(9)	78	(9)	157	(9)
Home	689	(81)	663	(79)	1352	(80)
Other	34	(4)	28	(3)	62	(4)
Skill Nursing Home	48	(6)	71	(9)	119	(7)

Appendix 5

Treatment Effects and Subgroup Analyses

A. Treatment Effect and Organ Dysfunction

Table 60. Primary 28-Day all-cause mortality analyses stratified by the presence or absence of organ failure at baseline

STRATA	THERAPY	Alive at Day 28	Died by Day 28	Total
		N (%)	N (%)	
Cardiovascular Organ failure: No	Placebo	165 (72)	63 (28)	228
	rhAPC	189 (76)	59 (24)	248
				476
Cardiovascular Organ failure: Yes	Placebo	416 (68)	196 (32)	612
	rhAPC	451 (75)	151 (25)	602
				1214
Hematology Organ failure: No	Placebo	499 (70)	211 (30)	710
	rhAPC	540 (76)	172 (24)	712
				1422
Hematology Organ failure: Yes	Placebo	82 (63)	48 (37)	130
	rhAPC	100 (72)	38 (28)	138
				268
Metabolic Acidosis: No	Placebo	416 (75)	142 (25)	558
	rhAPC	430 (78)	121 (22)	551
				1109
Metabolic Acidosis: Yes	Placebo	165 (59)	117 (41)	282
	rhAPC	210 (70)	89 (30)	299
				581
Renal Failure: No	Placebo	371 (76)	116 (24)	487
	rhAPC	399 (81)	94 (19)	493
				980
Renal Failure: Yes	Placebo	210 (59)	143 (41)	353
	rhAPC	241 (68)	116 (32)	357
				710
Respiratory organ failure: No	Placebo	143 (72)	57 (29)	200
	rhAPC	170 (78)	48 (22)	218
				418
Respiratory organ failure: Yes	Placebo	438 (68)	202 (32)	640
	rhAPC	470 (74)	162 (26)	632
				1272

B. Treatment Effect and Disease

Table 61. 28-Day all-cause mortality subgroup analyses for selected disease severity measures at baseline

	rhAPC (850)		Placebo (840)		Relative	95% CI
	Total N	N (%)	Total N	N (%)	Risk	for RR
Shock						
No	252	53 (21)	238	53 (22)	0.94	0.67, 1.32
Yes	598	157 (26)	602	206 (34)	0.77	0.64, 0.91
DIC						
DIC	800	196 (25)	774	243 (31)	0.78	0.66, 0.92
No DIC	49	14 (29)	66	16 (24)	1.18	0.64, 2.18
ARDS						
No	725	173 (24)	706	216 (31)	0.78	0.66, 0.93
Yes	125	37 (30)	134	43 (32)	0.92	0.64, 1.33
Ventilator						
No	227	40 (18)	188	43 (23)	0.77	0.52, 1.13
Yes	623	170 (27)	652	216 (33)	0.82	0.70, 0.97
Immunocompromised						
No	763	184 (24)	771	235 (31)	0.79	0.67, 0.93
Yes	87	26 (30)	69	24 (35)	0.86	0.54, 1.36

Patients with shock, DIC, ARDS and mechanical ventilation had a lower mortality on rhAPC.

C. Treatment Effect and Microbiology

Presented below is a summary of the site of infection, Gram stain and type of culture obtained at baseline for the treatment groups.

Table 62. 28-Day all-cause mortality subgroup analyses for baseline microbiology data

Variable	rhAPC (850) Total N N (%)		Placebo (840) Total N N (%)		Relative Risk	95% RR for CI
Presumed Site of Infection						
Blood	45	11 (24)	42	20 (48)	0.51	0.28, 0.94
Bone/Joint	3	0 (0)	8	4 (50)	0.25	0.02, 3.62
CNS	20	1 (5)	19	3 (16)	0.32	0.04, 2.79
Gynecologic	4	1 (25)	4	0 (0)	3.00	0.16, 57.37
Head/EENT	4	1 (25)	4	0 (0)	3.00	0.16, 57.37
Intra-Abdominal	170	47 (28)	167	51 (31)	0.91	0.65, 1.26
Lung	456	114 (25)	450	151 (34)	0.75	0.61, 0.91
Other	20	4 (20)	15	1 (7)	3.00	0.37, 24.17
Pleural	5	1 (20)	8	1 (13)	1.60	0.13, 20.22
Skin/skin structure	23	8 (35)	28	8 (29)	1.22	0.54, 2.74
Urinary Tract	85	18 (21)	86	18 (21)	1.01	0.57, 1.81
Vascular Catheter	9	4 (44)	6	2 (33)	1.33	0.35, 5.13
Positive Blood Culture						
No	572	133 (23)	567	166 (29)	0.79	0.65, 0.97
Yes	278	77 (28)	273	93 (34)	0.81	0.63, 1.05
Positive Bacterial Culture						
No	285	73 (26)	271	88 (33)	0.79	0.61, 1.03
Unknown	3	3 (100)	2	1 (50)	2.00	0.50, 8.00
Yes	562	134 (24)	567	170 (30)	0.80	0.66, 0.97
Positive Gram Stain Bacterial Culture						
Mixed Gram	133	29 (22)	32	6 (19)	0.82	0.53, 1.28
No Bacterial Expo	285	73(26)	271	88 (33)	0.79	0.61, 1.03
Pure Gram negative	185	45 (24)	485	147 (30)	0.85	0.61, 1.19
Pure Gram Positive	219	50 (23)	6	2 (33)	0.70	0.51, 0.95
Unconfirmed Gram	28	13 (46)	46	16 (35)	1.39	0.78, 2.47
Positive Anaerobic Bacterial Pathogen Culture						
Mixed Aero/aner	37	5 (14)	32	6 (19)	0.72	0.24, 2.14
No Bacterial Expo	285	73 (26)	271	88 (33)	0.79	0.61, 1.03
Pure Aerobic	482	116 (24)	485	147 (30)	0.79	0.64, 0.98
Pure Anaerobic	16	3 (19)	6	2 (33)	0.56	0.12, 2.58
Unconfirmed Aer/aner	30	13 (43)	46	16 (35)	1.25	0.71, 2.20

Positive Viral Culture						
No	838	204 (24)	827	254 (31)	0.7926	0.68, 0.93
Unknown	9	5 (56)	11	4 (36)	1.5278	0.58, 4.05
Yes	3	1 (33)	2	1 (50)	0.6667	0.08, 5.54
Positive Fungal Culture						
No	772	181 (24)	767	231 (30)	0.7785	0.66, 0.92
Unknown	6	3 (50)	9	3 (33)	1.5000	0.44, 5.09
Yes	72	26 (36)	64	25 (39)	0.9244	0.60, 1.43
Positive Parasite Identification						
No	840	205 (24)	829	255 (31)	0.7934	0.68,0.93
Unknown	9	5 (56)	11	4 (36)	1.5278	0.58, 4.05

Aer=anerobic. Aner=anerobic. EENT=eye, ear, nose and throat.

D. Treatment Effect by APACHE II Half Octiles

Treatment Effect by APACHE II Half Octiles

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Placebo	9	16	15	7	24	27	29	24	25	36	48	38	41	50	56	59
rhAPC	16	17	17	5	17	26	28	23	24	23	28	21	41	30	46	48
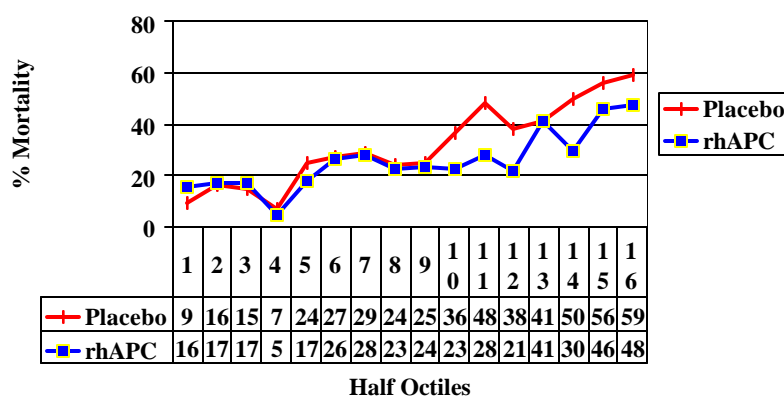
Half Octiles

Figure 10. Treatment effect by APACHE II half octiles

E. Treatment Effect Across the Subgroups Defined by Biochemical Measures

Presented below are mortality results across the subgroups defined by various biochemical measures of baseline disease severity.
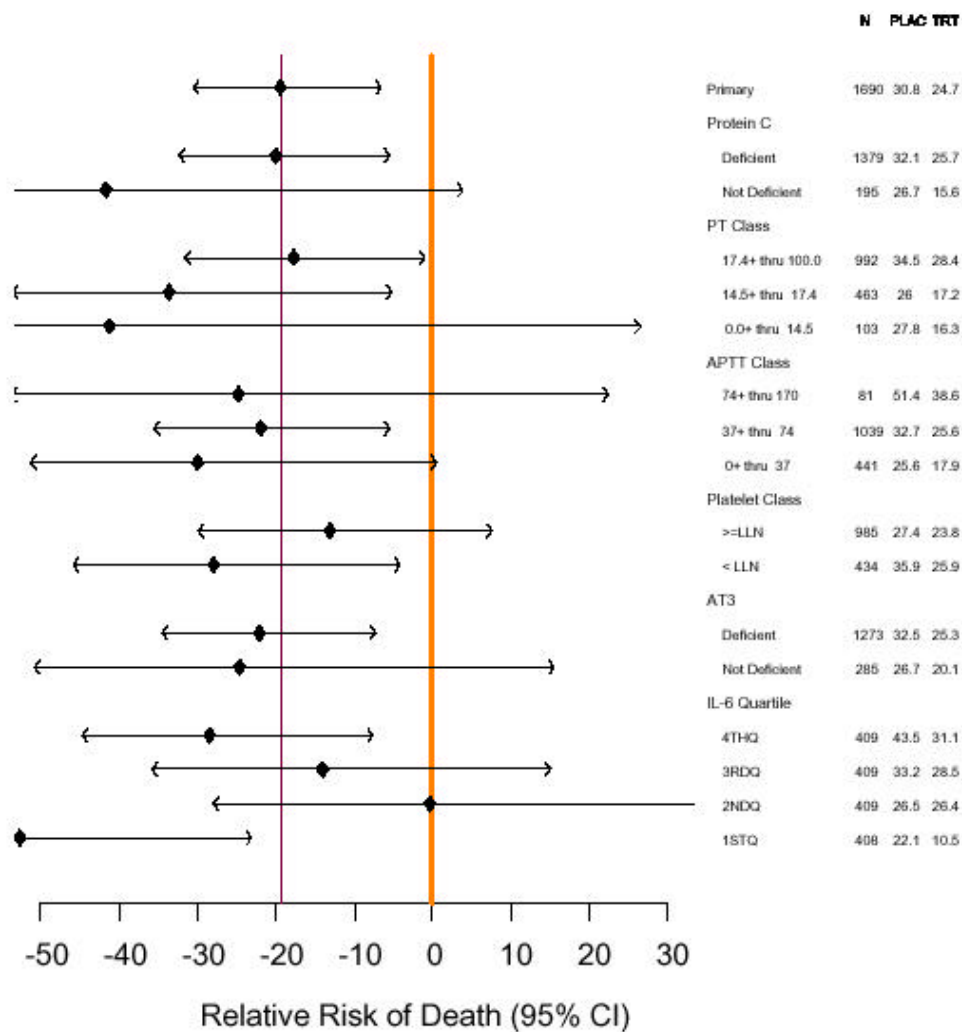
Figure 11. 28-Day all-cause mortality across subgroups defined by biochemical measures of baseline disease severity

F. D-dimer Analyses

Presented below are data on D-dimer levels between the treatment arms.

Figure 12. Median D-dimer levels on Study Days 1 through 7

Appendix 6

Protocol Amendment Summary

- 28-day mortality analysis for protein C-deficient patients will be analyzed as a secondary objective instead of a primary objective in order to simplify the goals and statistical analyses of the study. In addition, the term septic shock has been removed from the primary and secondary objectives.
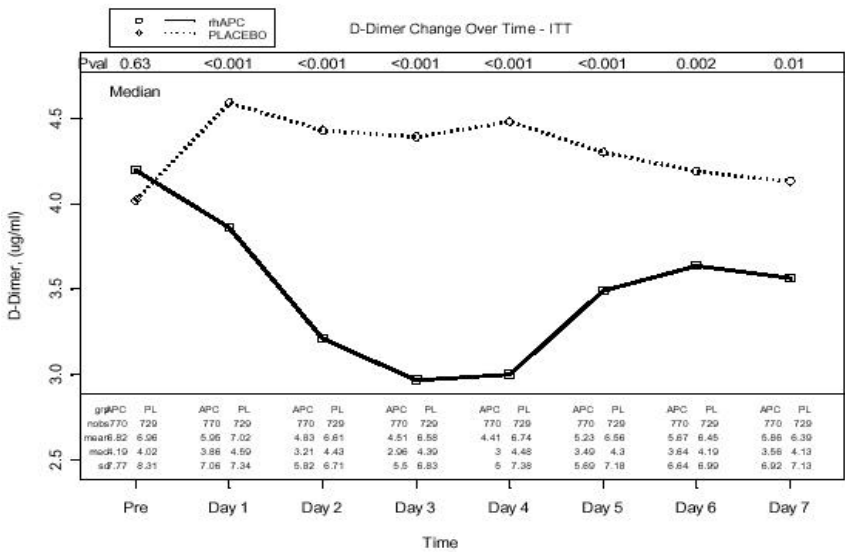- Enrollment criteria have been clarified, explanation for sepsis-induced and non-sepsis induced organ failures and criteria C specially defined.
- Investigative sites should contact the Vanderbilt Coordinating Center (VCC) for questions about patient eligibility.
- Oxygen saturation has been deleted as an acceptable method for evaluating respiratory organ failure.
- Exclusion of patients who are at increased risk for bleeding has been further clarified in exclusion criterion.
- Exclusion of patients with a known hypercoagulable condition has been further defined.
- Exclusion of investigational agents/devices further clarified. Added within 30 days without prior VCC approval.
- Exclusion of patients with esophageal varices has been clarified. This exclusion criterion now includes clinical findings that indicate the presence of portal-hypertension and hence esophageal varices. Patients with esophageal varices are at increased risk for bleeding and must be excluded from this trial.
- In an effort to increase the discriminatory patient population for this sepsis trial the following exclusion criteria have been added: Patients who have undergone bone marrow, lung, liver, pancreas or small bowel transplantation; patients who are moribund and where death is imminent; patients whose family and/or primary physician have not committed to aggressive management of the patient; and patients with acute clinical pancreatitis without a proven source of infection.
- In an effort to increase the discriminatory patient population for this sepsis trial, exclusion criterion has been further defined along with a requirement that the VCC approve the enrollment of any patient with known or suspected metastatic cancer.
- Exclusion criterion has been added to clarify Window I of the entry criteria. This clarifies the duration of sepsis-induced organ failure which makes a patient ineligible for the trial.
- Patients randomized to placebo will now receive 0.1% human serum albumin (HSA) in sterile 0.9% sodium chloride. The institution of HSA as the placebo increases the integrity of the blind for this trial.
- List of excluded medications has been added for clarification of medications which should not be administered to the patient during the infusion of study drug.
- As death is the primary efficacy measure in the study, it is included in the list of clinical outcomes. An event resulting in death is not considered a serious adverse event unless it is thought that the event has a causal relationship to study drug. For

clarification, serious adverse event and mortality reporting requirements have been further defined.

- Protein C activity class will replace septic shock status as a covariate for the primary analysis. Baseline protein C activity class was found to have greater discriminatory ability than septic shock status as a covariate when combined with Apache II quartile and age class.
- Several measures have been enacted to ensure maintenance of the study blind. These include the use of a contract research organization (CRO) to manage patient treatment assignments; the use of an external statistical research organization (SSO) to generate interim reports and present interim data; and the use of an external organization to monitor the handling and reconciliation of study drug.
- A blinded executive subcommittee has been included in the data reporting process. This subcommittee will ensure unbiased decision-making for stopping or continuing the study at the interim analyses.
- The pre-infusion schedule of events has been altered to accurately reflect the current collection of blood for protein S functional activity, ATIII functional activity, APC resistance, and anti-APC antibody tests. A blood draw for plasma and serum storage has been added to enable future testing of biomarkers. A blood draw for serum storage has also been added at Days 14 and 28 to enable future testing of biomarkers.

Appendix 7

Baseline demographics of original and amended protocols

Table 63. Baseline demographics under original vs. amendment

	ORIGINAL	AMENDMENT
Country		
Country of origin USA	334 (46%)	371 (38%)
Demographics		
Hypertension	259 (36%)	360 (37%)
Recent surgery	231 (32%)	271 (28%)
From Nursing Home	58 (8%)	61 (6%)
ADL score 0	479 (67%)	739 (76%)
ADL score 6	86 (12%)	76 (8%)
Patients with $\geq$ 1 condition	321 (45%)	260 (27%)
Patients with no condition	399 (55%)	710 (73%)
Hx of allergic Rxn	80 (11%)	1 (0%)
Hx of pneumonia	46 (6%)	17 (2%)
SIRS Criteria		
# of SIRS criteria met 3	305 (42%)	360 (37%)
# of SIRS criteria met 4	413 (57%)	606 (63%)
Organ Failure (OF)		
# OF criteria met 1	177 (25%)	241 (25%)
# OF criteria met 2	218 (30%)	325 (34%)
# OF criteria met 3	185 (26%)	247 (26%)
# OF criteria met 4	113 (16%)	122 (13%)
# OF criteria met 5	27 (4%)	34 (4%)
1st induced OF Respiratory	237 (33%)	432 (45%)
1st induced OF CV	197 (25%)	295 (30%)
1st induced OF Multi	105 (15%)	87 (9%)
1st induced OF Acidosis	87 (12%)	40 (4%)
1st induced OF Renal	60 (8%)	77 (8%)
1st induced OF Heme	34 (5%)	38 (4%)
OF criteria met Cardiovasc	494 (69%)	720 (74%)
OF criteria met Respiratory	535 (74%)	737 (76%)
OF criteria met Hematology	120 (17%)	148 (15%)
OF criteria met Renal	278 (39%)	432 (45%)
OF criteria met Acidosis	328 (46%)	253 (26%)
Baseline Status		
Baseline status Shock	500 (69%)	700 (72%)
Baseline status ARDS	101 (14%)	158 (16%)
Baseline status DIC	658 (91%)	916 (95%)
Baseline status Ventilation	549 (76%)	726 (75%)

Baseline status Immunocom	81 (11%)	75 (8%)
Baseline status GCS mean	11.8	11.8
APACHE II		
Baseline APACHE Mean	24.8	24.8
APACHE Quartiles First	185 (26%)	248 (26%)
APACHE Quartiles Second	195 (27%)	245 (25%)
APACHE Quartiles Third	144 (20%)	222 (23%)
APACHE Quartiles Fourth	196 (27%)	255 (26%)
APACHE age points 0	136 (19%)	202 (21%)
APACHE age points 2	97 (14%)	145 (15%)
APACHE age points 3	137 (19%)	169 (17%)
APACHE age points 5	179 (25%)	239 (25%)
APACHE age points 6	171 (24%)	215 (22%)
APACHE Chronic Health Points 0	538 (75%)	807 (83%)
APACHE Chronic Health Points 2	15 (2%)	11 (1%)
APACHE Chronic Health Points 5	167 (23%)	152 (16%)
APACHE acute physiology score (mean)	20	21
Laboratory		
Baseline PC activity mean	0.5	0.51
≤40%	271 (38%)	344 (36%)
41-60%	179 (25%)	288 (30%)
61-80%	133 (19%)	164 (17%)
> 80%	76 (11%)	119 (12%)
Unknown	61 (8.5%)	55 (6%)
PC deficient (≤ 80%)	583 (81%)	796 (82%)
PC severelydeficient(≤65%)	492 (68%)	689 (71%)
AT III deficient	555 (85%)	718 (80%)
Protein S mean	0.38	0.43
D-dimer mean	7.2	7
IL-6 mean	10304	10554
Platelets mean	207	196
APC resistance factor V Leiden	21 (3%)	44 (5%)
Time		
Meeting IC to SD mean hrs	15.4	16.1
# of pts >12 hrs	457 (64%)	648 (67%)
Onset 1st OF to SD mean hours	17.7	17.2

OF=organ failure. PC=protein C. IC=inclusion criteria. SD=standard deviation. ADL=Index of Independence Activity of Daily Living. GCS=Glascow coma scale. Hx=history. CV=cardiovascular. Heme=hematology. Mutli=multiple. Rxn=reaction.

Presented below are data on patient history solicited comparing differences between both protocols.

Table 64. Examples of solicited patient history under original vs. amendment

	Original (720) N (%)	Amendment (970) N(%)
Chronic liver disease	22 (3)	18 (2)
Pancreatitis	30 (4)	32 (3)
Malignancy	152 (21)	151 (16)
Recent surgery	231 (32)	271 (28)
Hypertension	259 (36)	360 (37)
Myocardial infarction	112 (16)	112 (12)

Percentages are similar with the exception more patients had malignancy, and myocardial infarction in the original compared to the amended protocol.

Presented below are data on examples of preexisting conditions comparing the differences between the original vs. amended protocol.

Table 65. Examples of preexisting conditions under original vs. amendment

Preexisting conditions	Original (720) N (%)	Amendment (970) N (%)
Cirrhosis	4 (1)	3 (0)
Jaundice	7 (1)	5 (1)
Cholestatic jaundice	2 (0)	1 (0)
Hepatitis	17 (3)	16 (2)
Liver damage	10 (1)	7 (1)
Abnormal liver function test	4 (1)	8 (1)
Pancreatitis	22 (3)	13 (1)
Neoplasma	19 (3)	8 (1)
Anemia	75 (10)	100 (10)
Thrombocytopenia	6 (1)	2 (0)
Kidney function abnormal	26 (4)	35 (4)
Acute kidney failure	8 (1)	7 (1)
Albuminuria	3 (0)	1 (0)
HIV	5 (1)	9 (1)

The incidence of preexisting conditions was similar between the two groups.

Presented below is a comparison of original vs. amended protocol versions from the time in which patients met the inclusion criteria to the time the patient received study drug.

Table 66. Time from meeting the inclusion criteria to start of study drug under the original vs. amendment

	rhAPC N (%)	Placebo N (%)	Total N (%)
Original			
12 hours	138 (38)	125 (35)	263 (37)
>12 hours	222 (62)	235 (65)	457 (64)
Amendment			
12 hours	166 (34)	156 (33)	322 (33)
>12 hours	324 (66)	324 (68)	648 (67)

Presented below are data on the baseline mechanical ventilation status in patients enrolled under the original and amended protocols.

Table 67. Baseline mechanical ventilation status in the original and amended versions of the protocol

	rhAPC N (%)	Placebo N (%)	Total N (%)	P value
Original	260 (72)	289 (80)	549 (76)	0.01
Amendment	363 (74)	363 (76)	726 (75)	0.58

Appendix 8

Sites

Table 68. Number of patients enrolled per site by the observed relative risk reduction

Number of Patients Per Site	Number of Sites (N)	RR for Patients Enrolled Under Original (N)	RR for Patients Enrolled Under Amendment (N)	Interaction
≥25	11 (457)	0.91 (202)	0.83 (255)	0.75
≥20	20 (655)	0.84 (291)	0.67 (364)	0.36
≥15	38 (956)	0.79 (417)	0.69 (539)	0.52
≥10	62 (1255)	0.86 (537)	0.72 (718)	0.40
≥5	105 (1551)	0.89 (664)	0.72 (887)	0.24
Entire Patient Population	164 (1690)	0.94 (720)	0.71 (970)	0.08

N=Number of patients. RR=Relative risk.

Table 69. Relative risk by protocol version

Patient Population (N)	RR under Original	RR under Amendment	Interaction P-Value
Entire Patient Population (1690)	0.94	0.71	0.08
Patients Enrolled at Sites Enrolling under Both Protocols or Amendment Only (1638)	0.87	0.71	0.22
Patients Enrolled at Sites Enrolling under Both Protocols Only (1463)	0.87	0.77	0.50

N=Number of patients. RR=Relative risk.

Appendix 9

Safety

Narratives for deaths and serious adverse events

Narrative summaries for patients treated with rhAPC will be presented below. The placebo summaries are not included.

I. Deaths

Six patients (5 rhAPC-treated and 1 placebo-treated) experienced serious adverse events that were assessed by the investigator as possibly related to study drug and were associated with the outcome of death. Four of these events were bleeding events.

A. Bleeding Events

➢ Patient 004-0409 (rhAPC). This patient experienced a fatal pulmonary hemorrhage 1-day into the study drug infusion. The bleeding event occurred in the presence of a profound coagulopathy with an APTT >150 seconds, a prothrombin time INR of 3.7, and a platelet count of 19 GI/L. The patient's APTT decreased to approximately 50 seconds following discontinuation of the study drug infusion. The patient did not have a history of any mass lesions of the lung and an autopsy was not performed.

➢ Patient 069-6908 (rhAPC). This patient experienced a fatal cerebral hemorrhage diagnosed 14 hours into the study drug infusion. This event occurred in the setting of gram negative sepsis with severe DIC. The patient had an APTT of 49.2 seconds, a platelet count of 18 GI/L, and a prothrombin time-INR of 1.21 at the time of the event. Study drug was discontinued. The patient died approximately 5 hours after study drug discontinuation.

➢ Patient 080-8000 (rhAPC). This patient suffered a fatal bleed as a result of an aortic disruption. The bleeding event was diagnosed 2 hours following completion of the study drug infusion. The patient died approximately 4 hours after the completion of the study drug infusion. The aortic disruption was a result of a motor vehicle accident 3 days prior to study entry. The patient had also sustained the following traumatic injuries: left pulmonary contusion, flail chest, splenic fracture, and an acetabular fracture.

➢ Patient 107-0707 (rhAPC). This patient experienced a fatal cerebral hemorrhage diagnosed 84 hours into the study drug infusion. Study drug was discontinued. The patient died approximately 1.5 hours after study drug discontinuation. During the infusion, the patient developed severe DIC with an APTT of 122 seconds that decreased to 43 seconds after the study drug was interrupted. The patient's platelet count also fell to 27 GI/L during the study drug infusion period.

B. Non-Bleeding Events

➢ Patient 014-1413 (rhAPC). This patient experienced cerebral edema diagnosed 10 days after the completion of the study drug infusion. The patient died 2 days later. The patient had severe hypoxia during the course of her illness, which had required treatment with an extracorporeal membrane oxygenator (ECMO).

II. Serious Adverse Events (Bleeding)

A. Gastrointestinal

A bleeding event was classified as gastrointestinal if there was evidence of bleeding in the lumen of the gastrointestinal tract.

Eighteen patients (9 rhAPC-treated and 9 placebo-treated) experienced gastrointestinal bleeding reported as a serious adverse event.

Upper gastrointestinal - Thirteen patients (7 rhAPC-treated and 6 placebo-treated)

➢ Patient 045-4502 (rhAPC). This patient was readmitted to the hospital with coffee ground emesis secondary to a duodenal ulcer 13 days after the completion of 95 hours of study drug infusion. In the opinion of the investigator, the events were not related to study drug or research conditions, but to the patient's recurrent health problems

➢ Patient 220-2011 (rhAPC). This patient experienced esophageal and gastrointestinal bleeding on the last day of study drug infusion that was thought to be due to erosion from the nasogastric tube. The bleeding occurred in the setting of a platelet count of 77 GI/L. Study drug was not discontinued and the bleeding ceased following the transfusion of 6 units of packed red blood cells. The study drug infusion was not interrupted or discontinued. In the opinion of the investigator, the bleeding event was not related to study drug.

➢ Patient 225-2506 (rhAPC). This patient was readmitted to the hospital with melena 12 days following the completion of study drug infusion. In the opinion of the investigator, this event was not related to study drug.

➢ Patient 241-4102 (rhAPC). This patient experienced a hemorrhage from a duodenal ulcer 13 days following the completion of the study drug infusion. A bleeding vessel at the ulcer site was discovered and clipped. The patient required transfusion with 4 units of whole blood as a result of this event. In the opinion of the investigator, this event was not related to study drug.

➢ Patient 338-3802 (rhAPC). This patient had gastrointestinal bleeding from a gastric ulcer noted 2 days into the study drug infusion. Study drug was discontinued on Study Day 3 after 72.5 hours of infusion. The bleeding resolved

following sclerosis. The patient received 6 units of packed red blood cells. The patient had received low molecular weight heparin for 3 days prior to the event. In the opinion of the investigator the gastric hemorrhage was possibly related to the study drug.

➢   Patient 956-5601 (rhAPC). This patient experienced a hemorrhage at a small bowel anastomotic site 15 hours into the study drug infusion. This patient had had surgical resection of necrotic small bowel secondary to a strangulated umbilical hernia prior to receiving study drug. The study drug infusion was stopped when the patient developed a coagulopathy with an APTT >180 seconds and a prothrombin time INR of 3.4. The patient received heparin on the first day of study drug administration. The patient was returned to surgery for re-exploration and an anastomotic hemorrhage was found with a large clot filling and distending the bowel. The patient improved following the surgery. In the opinion of the investigator, this event was possibly related to study drug.

➢   Patient 991-9121 (rhAPC). This patient was noted to have bleeding from the nasogastric tube 35 hours into the study drug infusion. At the time of the bleeding event, this patient was receiving low molecular weight heparin to maintain the patency of the continuous veno-venous circuit. The heparin drip was discontinued when the APTT lengthened to180 seconds and the platelet count fell to 36 GI/L. The study drug infusion was permanently discontinued when bleeding was observed. The bleeding ceased 3 days later following the transfusion of 11 units of packed red blood cells. The patient died on Study Day 6 of overwhelming sepsis. In the opinion of the investigator, the gastrointestinal bleeding was probably related to the study drug.

Colonic pathology - 2 patients in the rhAPC treatment group

➢   Patient 015-1505 (rhAPC). This patient experienced rectal bleeding77 hours into the study drug infusion. Study drug was permanently discontinued at that time. The patient was receiving low molecular weight heparin at the time of the bleeding event. Ischemic bowel was found on endoscopy. This bleeding event continued for 11 days until the patient was taken to the operating room for a hemicolectomy (Study Day 14). The patient died on Study Day 20 of worsening organ failure from overwhelming sepsis. In the opinion of the investigator, the bleeding event was possibly related to study drug; the patient's death was not related to study drug.

➢   Patient 861-6128 (rhAPC). This patient experienced bleeding from multiple angiodysplastic lesions of the colon 4 days after the termination of the study drug infusion. The bleeding event resolved after a total colectomy was performed. This patient was receiving heparin for renal replacement therapy at the time of the bleeding event. In the opinion of the investigator, this bleeding event was not related to study drug.

B. Intra-abdominal

A bleeding event was defined as intra-abdominal if there was evidence of bleeding into the intra-abdominal cavity.

Intra-abdominal bleeding - 7 patients (3 rhAPC-treated and 4 placebo-treated)

➤ Patient 221-2109 (rhAPC). This patient experienced bleeding following the removal of an abdominal drain that was noticed 2 days following the completion of the 96-hour study drug infusion. The patient had had a gastrectomy and ileo-jejunal bypass prior to entering the study. The patient was taken to surgery for repair of anastomotic vessels on the day of the bleeding event. The patient required 17 units of packed red blood cells. The patient had received low molecular weight heparin for 6 days prior to the event. Two days following surgery the patient died of refractory septic shock. In the opinion of the investigator, neither the bleeding event or the patient's death was related to study drug.

➤ Patient 492-9214 (rhAPC). This patient was admitted into the trial following surgery for a perforated gastric ulcer and peritonitis. One day into the study drug infusion the patient had postoperative bleeding from omental vessels. The bleeding ceased with oversewing of the bleeding vessels and transfusion of 10 units of packed red blood cells. The patient had received heparin during the study drug infusion period. The study drug infusion was completed. In the opinion of the investigator, this event was not related to study drug.

➤ Patient 971-7104 (rhAPC). This patient experienced a 2.5-liter bleed into the abdominal cavity 53 hours into the study drug infusion. Study drug was discontinued at the time of the event. The patient had received low molecular weight heparin for 3 days prior to the event. This bleeding event occurred after removal of a suction drain 1 day following a total abdominal hysterectomy with bilateral salpingo-oophorectomy. The patient was returned to the operating room where pelvic artery bleeders were tied off. The patient required 4 units of packed red blood cells. In the opinion of the investigator, this event was not related to study drug.

C. Intrathoracic

A bleeding event was defined as intrathoracic if there was evidence of bleeding within the thoracic cavity including intrapulmonary hemorrhage.

Intrathoracic bleeding - 7 patients (6 rhAPC-treated and 1 placebo-treated)

➤ Patient 004-0409 (rhAPC). This patient experienced a fatal pulmonary hemorrhage. (see previous discussion)

➢ Patient 044-4440 (rhAPC). This patient experienced intrathoracic bleeding that began following a decortication procedure for a fibrohydrothorax. The patient was receiving low molecular weight heparin at the time of the surgical procedure. The bleeding event was ongoing at the start of the study drug infusion. The patient continued to bleed after the study drug infusion was begun, which required the infusion to be discontinued after approximately 23 hours. The patient was returned to the operating room where bleeding was noted on the visceral surface of the lung. In the opinion of the investigator, this bleeding event was not related to study drug.

➢ Patient 080-8000 (rhAPC). This patient suffered a fatal bleed as a result of an aortic disruption. (see previous discussion)

➢ Patient 087-8707 (rhAPC). This patient experienced hemoptysis approximately 44 hours following the termination of study drug. The study drug infusion had been discontinued after 7.5 hours due to a myocardial infarction. The bleeding event occurred while the patient was receiving systemic heparin for acute myocardial infarction. The bleeding event resolved after the heparin infusion was discontinued. In the opinion of the investigator, the hemoptysis was not related to study drug.

➢ Patient 220-2019 (rhAPC). This patient had a 2.8-liter bleed into the pleural space following an open lung biopsy. This bleeding event occurred 6 days following the completion of the study drug infusion. At the time of the bleeding event, systemic heparin was being administered to maintain the patency of an extracorporeal circuit. The patient died on Study Day 11 of septic shock. In the opinion of the investigator, the bleeding event was not related to study drug.

➢ Patient 974-7405 (rhAPC). This patient was found to have a right-sided hemothorax 2 days following completion of the study drug infusion. The patient had a history of an abdominal gunshot wound with injury to the liver. The patient received low molecular weight heparin during the study drug infusion period. He underwent two thoracentesis during the study drug infusion period for evaluation of a right-sided pleural effusion. The patient's hemoglobin dropped by a total of 4 g/dL during this period and he received 2 units of packed red blood cells. Two days following completion of the study drug infusion, a drainage procedure of the right pleural space yielded 850 cc of old blood. In the opinion of the investigator, the hemothorax was possibly related to study drug.

D. Retroperitoneal

A bleeding event was defined as retroperitoneal if there was evidence of bleeding into the retroperitoneal space.

Retroperitoneal bleeding - 4 patients in the rhAPC treatment group

➢ Patient 045-4514 (rhAPC). This patient experienced a left renal hemorrhage and retroperitoneal bleed diagnosed 41.5 hours into the study drug infusion. This event occurred following the placement of a suprapubic catheter for a neurogenic bladder 3 days prior to the event. This bleeding event occurred at a time when the patient's APTT had risen to 61 seconds during the infusion with no change in the prothrombin time-INR. The patient was receiving heparin in addition to study drug at the time of the event. The study drug infusion and the heparin were stopped when the hemorrhage was diagnosed. The patient did not require surgical intervention but received 1 unit of packed red blood cells. In the opinion of the investigator, these bleeding events were possibly related to study drug.

➢ Patient 244-4406 (rhAPC). This patient experienced a retroperitoneal bleed, which in the assessment of the investigator was related to the inadvertent puncture of the femoral artery during placement of a femoral venous catheter. The inadvertent arterial puncture occurred on the same day as the start of the study drug infusion. This bleeding event was diagnosed by ultrasound 54 hours into the study drug infusion. The event occurred in the setting of a coagulopathy with an APTT of 106.8 seconds and prothrombin time of 16.7 seconds. The patient required transfusion of 8 units of packed red blood cells. The patient died on Study Day 3 from overwhelming sepsis. In the opinion of the investigator, the bleeding event was possibly related to study drug; the patient's death was not related to study drug.

➢ Patient 861-6118 (rhAPC). This patient was diagnosed with a left iliopsoas hematoma 3 days following completion of the study drug infusion. This bleeding event was diagnosed following placement of a left femoral catheter for dialysis. The patient was being treated with heparin at the time of the bleeding event. In the opinion of the investigator, this bleeding event was not related to study drug.

➢ Patient 956-5606 (rhAPC). This patient experienced a left renal hemorrhage and a retroperitoneal bleed 18 hours into the study drug infusion. This bleed occurred following the placement of a nephrostomy tube. The patient stabilized after transfusion of 6 units of packed red blood cells and the administration of fresh frozen plasma. In the opinion of the investigator, the retroperitoneal bleed was possibly related to study drug, to the insertion of the nephrostomy tube, or to both.

E. Cerebral Hemorrhage

A bleeding event was defined as cerebral hemorrhage if there was evidence of bleeding consistent with a cerebral hemorrhage.

Cerebral hemorrhage - 3 patients (2 rhAPC-treated and 1 placebo-treated)

➢ Patient 069-6908 (rhAPC). This patient experienced a fatal cerebral hemorrhage. (see previous discussion)

➢ Patient 107-0707 (rhAPC). This patient experienced a fatal cerebral hemorrhage. (see previous discussion)

F. Transfusion-Related (PRBC SAE)

According to the protocol, patients would be considered to have had a serious bleeding event if they required transfusions of 3 or more units of packed red blood cells/day for 2 consecutive days.

Transfusion - 4 patients (2 rhAPC-treated and 2 placebo-treated)

➢ Patient 014-1401 (rhAPC). This patient met the transfusion criteria for a serious bleeding event 1 day following completion of the study drug infusion. This patient required 4 units of packed red blood cells during tricuspid valve replacement surgery for endocarditis and 4 units postoperative. In the opinion of the investigator, the patient's blood loss was not related to study drug but instead to the nature of the surgery performed. This patient also experienced serious adverse events of renal failure and pleural effusion

➢ Patient 065-6539 (rhAPC). This patient met the transfusion criteria for a serious bleeding event 9 days following completion of the study drug infusion. At the time of the event, the patient was receiving ECMO therapy for ARDS that required heparin therapy to maintain the patency of the extracorporeal circuit. The patient received 21 units of packed red blood cells while undergoing ECMO therapy. The patient died on Study Day 15 of ARDS. In the opinion of the investigator, neither the bleeding event nor the patient's death were related to study drug.

G. Genitourinary

A bleeding event was defined as genitourinary if there was evidence of bleeding into the genitourinary system.

Genitourinary bleeding - 2 patients in the rhAPC treatment group

➢ Patient 040-4005 (rhAPC). This patient experienced a right renal hematoma noted on Study Day 2. Study drug was continued for 47 hours at which time it was discontinued to allow placement of a nephrostomy tube. The nephrostomy tube was placed approximately 1 hour following discontinuation of study drug. Post-procedure, the nephrostomy tube clotted and a hematoma was found to be obstructing the right ureter. Urokinase was instilled in the nephrostomy tube and the patient experienced hematuria. The patient required 2 units of packed red

blood cells. Study drug was not restarted. In the opinion of the investigator, this bleeding event was not related to study drug.

> Patient 070-7006 (rhAPC). This patient was diagnosed with a submucosal hemorrhage of the bladder and a renal capsular hemorrhage on Study Day 20 at the time of postmortem. This patient had a bowel to bladder fistula as a sequela of ovarian cancer. This patient had study drug interrupted for an APTT of 147 seconds. The study drug infusion was restarted when the APTT fell to 50 seconds but was discontinued when the APTT rose to 90 seconds 44 hours into the infusion. The patient experienced persistent DIC following discontinuation of study drug requiring large numbers of blood products. The patient died on Study Day 20 of sepsis. In the opinion of the investigator, neither the bleeding event or the patient's death was related to study drug. This patient was classified as having a packed red blood cell serious adverse event before the site of hemorrhage was discovered on autopsy.

H. Skin/Soft Tissue

A bleeding event was defined as skin or soft tissue if there was evidence of bleeding into the skin or soft tissue structures.

Skin or soft tissue bleeding - 2 patients in the rhAPC treatment group

> Patient 331-3107 (rhAPC). This patient was found to have iliac and psoas muscle hematomas 9 days following the termination of study drug. These hematomas were of unknown etiology but followed 5 days of therapeutic heparin for the treatment of angina. The patient received 4 units of packed red blood cells and required no further treatment. In the opinion of the investigator, these hematomas were not related to study drug.

> Patient 965-6503 (rhAPC). This patient developed bleeding from a debridement site of the buttock and thighs. The study drug infusion was interrupted 1 hour after initiation for the debridement procedure. The patient received low molecular weight heparin on the day of the surgery. This bleeding event required 5 units of packed red blood cells. When study drug was initiated 12 hours after the surgery, the patient had recurrent incisional bleeding requiring the transfusion of 5 units of packed red blood cells. The study drug infusion was permanently discontinued after a total infusion time of 5.5 hours. In the postoperative period the patient had ongoing DIC and died on Study Day 7. In the opinion of the investigator, neither the bleeding event nor the patient's death were related to study drug.

III. Serious Adverse Events (Non-Bleeding)

7 patients (5 rhAPC-treated and 2 placebo-treated) experienced serious (nonbleeding) adverse events that were determined by the investigator to be possibly related to study drug.

➢ Patient 014-1401 (rhAPC). This patient experienced kidney failure and pericardial effusion 5 and 12 days, respectively, following the completion of the study drug infusion. The patient's renal failure developed in the setting of hypotension and multiple concomitant medications with potential nephrotoxicity. The pericardial effusion occurred following cardiac valve replacement. This patient also experienced a transfusion-related bleeding event that was reported as a serious adverse event.

➢ Patient 015-1500 (rhAPC). This patient experienced a left ventricular apical thrombus diagnosed 1 day following the completion of the study drug infusion. The patient had echocardiographic findings of a questionably infected septal segmental wall suggesting endocarditis. The patient did not have a neurologic event as a result of his cardiac thrombus.

➢ Patient 017-1705 (rhAPC). This patient experienced two serious adverse events during study drug infusion: worsening DIC and thrombocytopenia. The patient was enrolled in the trial with an APTT of 58.1 seconds and a platelet count of 59 GI/L. The study drug infusion was interrupted twice because of an APTT of >95 seconds. After stopping study drug and receiving a transfusion of fresh frozen plasma, the patient's APTT returned to approximately 45 seconds. The patient's platelet count fell below 50 GI/L during the infusion. The patient did not experience any bleeding event as the result of the coagulopathy. After the second interruption, the study drug infusion was not restarted. The patient had received study drug for approximately 33 hours. The patient died on Study Day 8 of worsening sepsis.

➢ Patient 856-5619 (rhAPC). This patient experienced a fixed and dilated right pupil on the first day of the study drug infusion suggestive of intracerebral herniation. The patient died on Study Day 1 as a result of refractory sepsis. The patient received the study drug infusion for approximately 16 hours. The patient did not have a CT scan or autopsy performed to determine the cause of the fixed and dilated pupil.

➢ Patient 945-4513 (rhAPC). This patient experienced liver dysfunction noted 18.5 hours into the study drug infusion. The study drug infusion was discontinued. The patient was in profound septic shock and also suffered a myocardial infarction leading to a decreased cardiac output. The patient's ALT rose to 3885 U/L and bilirubin to 63 mmol/L on Study Day 3. The patient died on Study Day 3 of multisystem organ failure.

Appendix 10

Safety and First APACHE II Quartile

There were 9 serious adverse events in the rhAPC treated patients in the first APACHE II quartile. Of these 9, 6 were involved in a surgical procedure around the time of the infusion and 4 had recent surgery or trauma within the preceding 30 days. A brief summary of these individual patients is provided below.

I. Serious Adverse Events in the First Quartile

9 - SAE in the first quartile
Operation- 6; Recent surgery/trauma (30 days) - 4

- 21 y/o male with endocarditis and post op bleeding after valve replacement (OR- 24 hrs after finishing infusion). The patient survived and was discharged from the hospital
- 56 y/o female NH resident developed rectal bleeding from hemorrhagic colitis. She had ischemic bowel, had a hemi-colectomy and eventually was made a DNR on study day 20 and died shortly thereafter.
- 80 y/o had indwelling foley and presumed urosepsis had the study drug stopped for 2 hrs and had a nephrostomy tube placed and subsequently developed an ureteral hematoma which was treated with urokinase. She developed hematuria as well. The patient survived to day 28.
- 27y/o male enrolled due to pneumonia and CV organ failure. He had a recent (1 day prior to study drug) lung decortication procedure done for a fibrohydrothorax. He developed a worsening of a lung hemorrhage on therapy requiring transfusion. Patient survived to day 28.
- 74y/o male with gram- sepsis developed an intracerbral hemorrhage while on study drug. Patient expired.
- 32y/o male s/p significant MVA (broken ribs, pulmonary contusion, splenic laceration and acetabular fracture) entered into study and died of a ruptured aorta while on study drug.
- 47 y/o with sepsis from a thigh cellulitis and myositis, had an I+D while study drug was interrupted. She experienced post op bleeding requiring a total of 24 units PRBC. She died of multi-organ failure on day 7.
- 34 y/o female with sepsis from previous abortion procedure. She developed an intra-abdominal hemorrhage on infusion day 3 requiring surgery. Patient survived to study day 28.
- 40y/o male GSW to ABD 2 days prior to study enrollment. He had pneumonia and respiratory failure. He developed a hemothorax while on study. He survived to discharge

II. Death Summaries of Patients in the first APACHE II Quartile

➢ 33 deaths in the first APACHE II quartile

➢ 12 deaths in the first 120 hrs
  ➢ 5 with a history of trauma or surgery in the past 30 days
  ➢ 2 with operations just prior to or during the infusion time

➢ 21 deaths between 120 hrs and 28 days.
  ➢ 13 with a history of trauma or surgery in the past 30 days
  ➢ 14 with operations just prior to or during the 28 day study period

12 deaths occurred in the first 120 hrs of study drug infusion.
Operation- 2; Recent surgery/trauma (30 days) - 5

012-1202 – 2 organ failure (Resp, Ren)
60 y/o female with COPD and pneumonia 4 hrs into rhAPC treatment developed cardiac dysrythmia and died. Patient's O2 sats had dropped and she had become hypotensive.

035-3501 – 2 organ failure (Resp, MA)
81 y/o female had surgery for esophageal stricture and gastric CA. Perforation leading to sepsis. She received 37 hrs of rhAPC. Developed necrotic bowel. was reoperated on and died after DNR established.

069-6908 – 3 organ failure (Resp, CV, Hem)
74 y/o male with sepsis due to pneumonia and DIC. After 14 hrs of study drug he became unresponsive with CT showing massive intracranial bleed.

080-8000 – 2 organ failure (Resp, Hem)
32 y/o male status post MVA ruptured aorta while on study drug (96.1hrs).

083-8301 – 1 organ failure (CV)
75 y/o female with pneumonia and refractory shock. She received 69 hrs of rhAPC till the family withdrew life support and the patient expired.

945-4513 – 3 organ failure (Resp, CV, Ren)
73 y/o female with pneumonia. She received 18.6 hrs of rhAPC. She developed liver failure as well and died on study day 3.

952-5202 – 2 organ failure (Resp, CV)
80 y/o female with urosepsis and history of transitional cell CA of the Kidney. She received 45 hrs of APC but due to worsening pulmonary status, life support was withdrawn and the patient expired.

965-6521 – 4 organ failure (Resp, CV, Heme, Ren)
69 y/o male with pneumonia and underlying COPD. He received 65 hrs of rhAPC and died of multi-organ failure.

967-6703 – 2 organ failure (Resp, Ren)
77 y/o male with post-op colon CA resection, enrolled with intra-abdominal infection. He received 62.8 hrs of rhAPC with an interruption at 36 hrs for repeat surgery and repair of an anastomotic leak. He died of multiple organ failure.

967-6704 – 3 organ failure (RESP, CV, Ren)
69 y/o male with pneumonia. He received 96 hrs of the study drug and died 10 minutes after the drug was finished of refractory hypoxemia and shock.

967-6710 - 4 organ failure (Resp, CV, Heme, Ren)
67 y/o female with pneumonia died on study day 5 of cardiac arrest and multiple organ failure. She received 96 hrs of rhAPC.

967-6713 – 3 organ failure (Resp, CV. Ren)
21 y/o female with pneumonia. She received 48 hrs of rhAPC. She died of refractory hypoxemia, anuria and acidosis.

21 deaths occurred after 120 hrs from enrollment
Operation- 14; Recent surgery/trauma (30 days) - 13
(data is much more sketchy for these patients)

015-1505 – 1 organ failure (Resp)
56 y/o female form sepsis, with a UTI source. She developed hemorrhagic colitis and died on day 20. She received 70 hrs of study drug. She required surgery and eventually had life support withdrawn with multi-organ failure.

020-2011
77 y/o male with pneumonia and respiratory failure received 96 hrs of rhAPC and died on day 12 of cardiac arrest.

040-4004
86 y/o male post-op surgery for necrotic bowel received 96 hrs of rhAPC and died on day 14 with ARDS.

081-8101
31 y/o female post mediastinal abscess drainage after a traumatic intubation and a perforated esophagus. She received 96 hrs of rhAPC and died on day 11 of ARDS.

087-8709
90 y/o female with sepsis and pneumonia, received 97 hrs of rhAPC and died on day 9 of multi-organ failure.

220-2003 – 3 organ failure (Resp, CV, Ren)
46 y/o male s/p (2 day) esophagectomy developed pneumonia. Hx of CAD died on study day 6 of ischemia and cardiac arrest. Received 96 hrs of study drug.

220-2015
39 y/o male with suspected meningococcal meningitis. He received 96 hrs of therapy and died on day 10 of overwhelming sepsis.

*221-2109 – 2 organ failure (Resp, MA)
46 y/o male sepsis 11 day s/p gastrectomy and jejunal bypass. 96 hrs of rhAPC. Day 6 he developed anastomotic hemorrhage with 9 L blood loss. Patient was re-operated and stabilized. He died of overwhelming sepsis on day 6.

221-2113
51 y/o male received 96 hrs rhAPC, was post-op bowel infarction and sepsis died suddenly on day 13. ? cardiac etiology.

222-2204 – 3 organ failure (Resp, CV, Ren)
61 y/o male with pneumonia, received 31 hrs of therapy at which time he had an MI. Therapy was stopped. He died on day 20 of recurrent pneumonia.

496-9611
79 y/o male post-op rectum resection for CA had perforation and became septic. Re-operated on for persistent leak, died on day 6.

725-2500
47 y/o male with drainage of perianal abscess, developed retroperitoneal abscess and sepsis. Patient died on day 14.

854-5420
81 y/o female s/p surgery for bowel obstruction, developed pneumonia and sepsis. Received 96 hrs of APC. Requested DNR status day 9 and died day 9.

861-6122
79 y/o male s/p surgery for perforated sigmoid diverticula also acute cholecystitis. Patient received 96 hrs APC and recovered. Developed recurrent intra-abdominal abscess, requiring drainage, became septic again and family withdrew care. Patient died day 9.

953-5302
57 y/o male with pneumonia and sepsis. 96 hrs of treatment. Patient died on day 6 of worsening sepsis.

962-6203
78 y/o male lung cancer s/p surgery lobectomy with post op pneumonia. Patient received 96 hrs of treatment and died on day 10 of worsening sepsis.

963-6300
78 y/o female post-op surgery for perforated duodenal ulcer and peritonitis. Received 94 hrs of therapy, and died on day 8 of refractory sepsis.

965-6503 - 4 organ failure (CV, Ren, Heme, MA)
47 y/o female with abscess/cellulitis R thigh due to injection. She had an I+D of the sight, received 5 hrs of rhAPC (had recurrent bleeding from the wound sight) and died on day 7 of refractory shock.

967-6707
67 y/o male with pneumonia and sepsis. Received 101 hrs of therapy. Patient died on day 24 of refractory hypoxia.

970-7001
26 y/o male with abscess of arm (I+D) developed staph sepsis. He received 96 hrs of therapy and died on day 14 of multi-organ failure.

970-7002
44 y/o male with pneumonia and sepsis. He received 97 hrs of rhAPC and died on day 6.