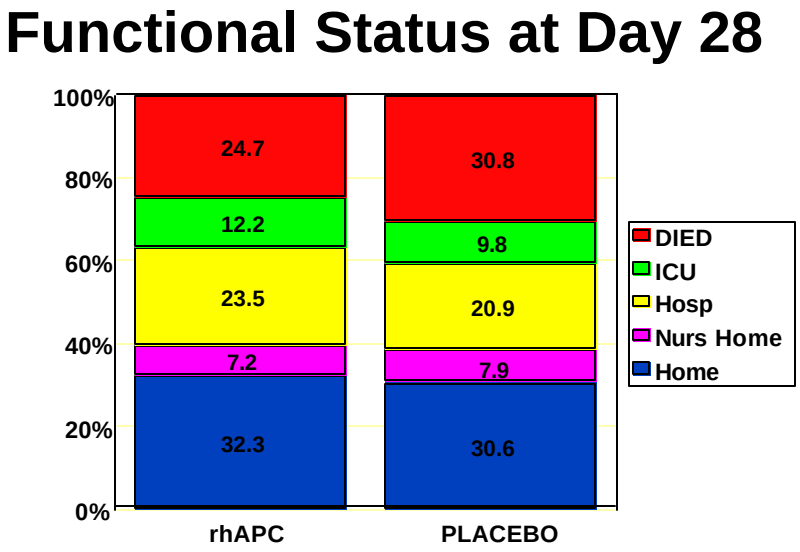
Morbidity Analyses

The figure below is a side-by-side comparison of morbidity and functional status between rhAPC and placebo at day 28. In descending order are proportion of patients who: died, were still in ICU, hospitalized but not in ICU (hosp); at a nursing home (nurs home); and discharged home at the end of the study period.



As shown in this FDA analysis, absolute difference in survival among those in the rhAPC group was 6% compared with the placebo group, but the absolute difference in hospital discharge was only 1%. Thus, the remaining 5% in the rhAPC arm who survived were in the hospital at 28 days, with half in the ICU. Without longer follow up, the ultimate outcomes of the hospitalized patients cannot be determined. The 6% mortality difference at 28 days may overestimate drug effect. However, since the most of the mortality benefit was seen in the subset of patients with APACHE II chronic health points, e.g., symptomatic cirrhosis, renal dialysis, class IV heart failure, immunosuppression, it is not surprising that many of the survivors were hospitalized at day 28.

Section IIIC- Changes to the Clinical Protocol

Overview

In June 1999, a protocol amendment was submitted to the agency and the inclusion and exclusion criteria were modified. 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)2 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 larger rhAPC treatment effect was observed in the second half of the study compared to the first half. 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. The mortality rates for rhAPC for 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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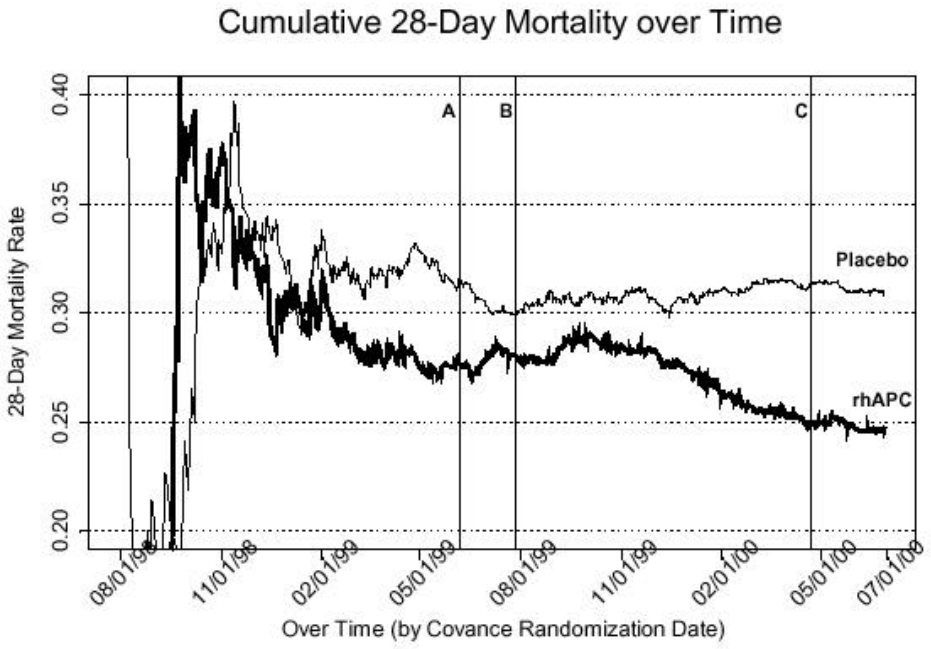

Figure 11. 28-day cumulative mortality over time for all patients

The figure above is 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.

Reviewer comment: The appearance of this graph raised questions about the differences in rhAPC treatment effect. The decrease in relative risk over time could be explained by many factors including chance, as such variability in clinical trials can be observed, a site effect (sites were added or dropped during the course of the trial), changes in patients disease characteristics over time (e.g. enrollment of a greater percentage of patients with a higher probability of dying from severe sepsis as opposed to underlying non-sepsis conditions) or product manufacturing changes. We attempted to explore these different possibilities.

Protocol Amendment Summary

The list below is a summary of major changes implemented under the amended protocol as compared to the original protocol.

- 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 ------- 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.

Reviewer comment: The intent of the protocol amendments were to exclude patients with severe underlying disease who were more likely to die from causes other than sepsis within 28 days.

In the original version of the protocol, investigators were instructed to exclude patients with high probability of dying from their underlying non-sepsis medical condition within the 28-day study period from participation in the study.

In the amended protocol, exclusion criteria was clarified by:

- Clarifying the exclusion criteria for "know or suspected portal hypertension" to include the clinical manifestation of portal hypertension including esophageal varices, chronic jaundice, cirrhosis or chronic ascites.
- Clarifying the exclusion criteria of "not expected to survive 28-days given pre-existing medical condition" to state "not expected to survive 28 days given their pre-existing uncorrectable medical condition". Specific examples of end stage organ failures were provided (e.g., end stage cardiac disease, end stage lung disease). The new exclusion criterion required that enrollment of patients with malignancy must have been approved by the coordinating center.
- Adding exclusion criterion for bone marrow, lung, liver, pancreas or small bowel transplantation.
- Adding exclusion criterion to exclude patients who were moribund and death was imminent.
- Adding exclusion criteria for patients whose family had not committed to aggressive management of the patient.

Additionally, the language of the original protocol and the final amended protocol objectives are provided below.

- The original protocol:

Primary Objectives

The primary objectives of this study are as follows:

- To demonstrate that rhAPC reduces 28-day mortality in patients with severe sepsis and/or septic shock.
- To demonstrate that rhAPC reduces 28-day mortality in protein C deficient patients with severe sepsis and/or septic shock.

Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the effects of rhAPC on organ function (cardiovascular (shock), respiratory, renal, hematologic, and hepatic).
- To evaluate the health economic impact of rhAPC administration in patients with severe sepsis and/or septic shock.
- To further characterize pharmacokinetics of rhAPC administration.

- The amended protocol:

Primary Objectives

The primary objective of this study is:

- To demonstrate that rhAPC reduces 28-day mortality in patients with severe sepsis.

Secondary Objectives

The secondary objectives of this study are as follows:

- To demonstrate that rhAPC reduces 28-day 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.
- To further characterize pharmacokinetics of rhAPC administration.

Reviewer comment: The sponsor stated the rationale for change in primary and secondary objectives from original protocol to amended protocol was to made to clarify that there would be a single primary analysis conducted (as opposed to a possible interpretation that 2 or more primary analyses were being considered). The sponsor stated it was their intent to have the protein C deficient subgroup analysis considered as a secondary objective instead of as a primary objective prior to the first patient being enrolled in the study. The change in covariates for stratification in primary analysis from original protocol to amended protocol was Protein C activity class replaced "shock within 6 hours" status as a covariate for the primary stratified analysis based on a review of the phase 2 study. Baseline protein C activity class was found to have greater discriminatory ability in predicting mortality than "shock within 6 hours" status as a covariate when combined with APACHE II quartile and age class. The analysis

described in the original protocol as primary with stratification for APACHE II quartile, age class, and shock status had a relative risk point estimate of 0.82 (95% confidence interval: 0.71 to 0.95) in favor of rhAPC (p = 0.0085).

Effect of Changes on Patient Baseline Demographics

Baseline Demographics 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 below.

Table 49. 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	0.5
≤40%	271 (38%)	344 (36%)
41-60%	179 (27%)	288 (30%)
61-80%	133 (19%)	164 (17%)
> 80%	76 (11%)	119 (12%)
Unknown	61 (9%)	55 (6%)
PC deficient (≤ 80%)	583 (81%)	796 (82%)
PC severely deficient (≤65%)	492 (68%)	689 (71%)
AT III deficient	555 (85%)	718 (80%)
Protein S mean	0.4	0.4
D-dimer mean	7.2	7.0
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. Multi=multiple. Rxn=reaction.

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 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).

Impact of Changes Between Protocol Versions and Patient Eligibility

A small number of patients (n = 81, 11%) enrolled under the original protocol would not have met the eligibility criteria under the amended protocol. We analyzed the outcome for those 81 patients separately (see table below) to assess the impact of changes in eligibility on outcome.

Table 50. 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.

Reviewer comment: There was a rhAPC treatment effect in those 81 patients who would not be eligible under the amended protocol (RR=0.8). This suggests that there was no systemic attempt to eliminate patients who would be less likely to respond to rhAPC, that elimination of such patients did not increase the observed treatment effect and thus did not account for the larger observed treatment effect in the second half of the trial.

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.

We looked at the baseline characteristics of patients enrolled in sites ultimately dropped from the study before its completion to determine if these patients appeared to be "different". The patients in sites that were ultimately dropped were more likely to have a more severe SIRS, as reflected in organ dysfunction scores. Of note, such patients were ones that had a greater rhAPC treatment effect. These patients also had higher rhAPC activity levels. rhAPC activity levels did not have an impact on treatment response. These patients also were more independent prior to their sepsis [as reflected by the activities of daily living (ADL) scores]. The RR among patients at the smaller sites all favored rhAPC treatment, suggesting deletion of lower enrolling sites was not a major factor contributing to the differences between the first and second halves of the study.

Table 51. Number of patients enrolled per site and 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.

20 sites enrolled and administered study drug to at least 1 patient under the original protocol but were then discontinued from the study prior to enrolling a patient under the amended protocol. In total, these 20 sites enrolled and administered study drug to 52 patients under the original protocol.

The number of patients is too small to conclude effect on mortality. But it could be worrisome as there is a reversal of the effect in this group- mortality was worse in rhAPC treatment among those 52 patients. In this subgroup, although mortality was higher among those 26 randomized to rhAPC compared to the 26 on placebo, the numbers are too small to conclude that there is a reverse effect of rhAPC. In addition, the distribution of APACHE II scores in this subgroup was not balanced in that twice as many patients who received rhAPC had poorer prognosis, as evidence by APACHE II scores in the third and fourth quartiles, compared to placebo patients.

Additionally, the sponsor elected to introduce new investigative sites into the study after the start of the study. Of these, 45 sites began participation in the study after the introduction of the amendment and these sites enrolled and administered study drug to 175 patients.

Reviewer comment: Several sites were closed to enrollment before the protocol amendment, mostly due to poor enrollment or resources, e.g. the principal investigator moved away. Results from the sites that were dropped, the 52 patients in 20 sites, did not show evidence of drug effect. However, we have not found any indication of bias or unblinding in stopping sites. All but 2 that were stopped had fewer than patients enrolled. All 20 sites were closed prior to the first interim efficacy analysis indicating that unblinded outcome-data did not play a role. Several sites were added during the trial reportedly in an attempt to improve accrual. Sites that were added later tended to show stronger evidence of drug effect. There were over 40 such sites. Most only had a few patients as the trial was unexpectedly stopped at interim analysis shortly after the sites were added, about 180 patients were treated at these 45 sites. We did not identify any systemic reason to account for the finding of better treatment effect at those sites, nor to suspect that they biased the study results.

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Effect of Changes on Mortality

Treatment Effect and Original vs. Amended Protocol Versions

The table below shows mortality by treatment arm among patients enrolled on the original and the amended version of the protocol. Of note, the placebo mortality rates were similar (30% original, 31% amended) while rhAPC rates were markedly different pre- and post-amendment (28% vs. 22%).

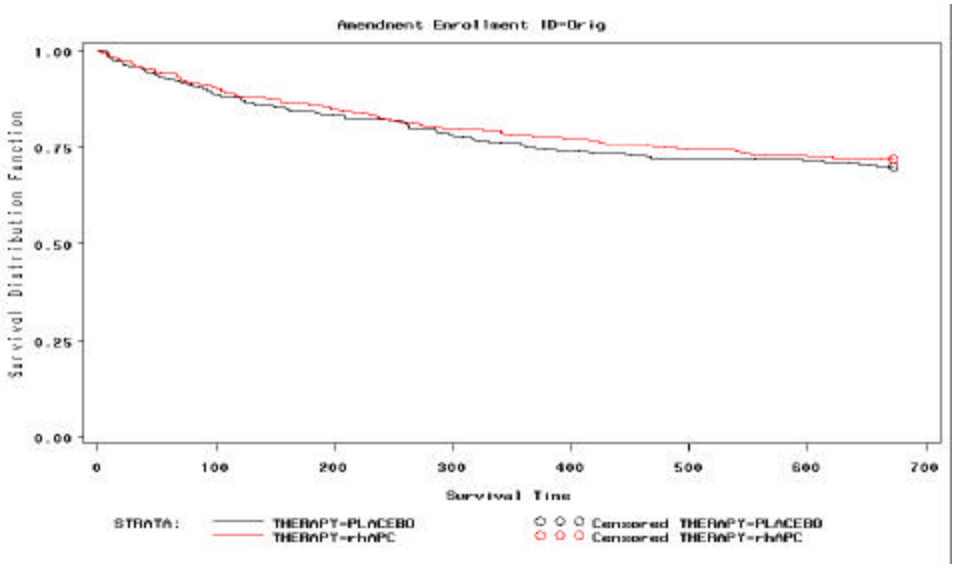
Table 52. Primary 28-day all-cause mortality analyses stratified by protocol: original and amended

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.

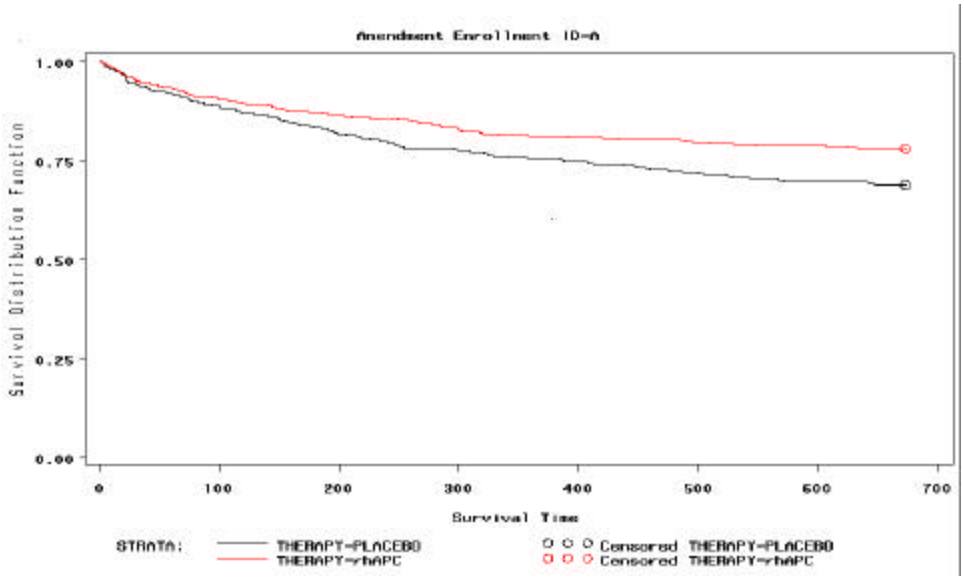
ORIGINAL



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

Figure 12. Kaplan-Meier survival curve under original protocol

AMENDMENT



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

Figure 13. Kaplan-Meier survival curve under amended protocol

The table below shows data on mortality for the original and amended protocols stratified by APACHE II quartiles. A survival benefit was observed in patients enrolled under the original version of the protocol and under the amended protocol for patients in the 3rd and 4th APACHE II quartiles. While a survival benefit was also observed for patients in the 1st and 2nd APACHE II quartile under the amended protocol, less benefit was observed in the 2nd quartile under the original version of the protocol.

Table 53. Mortality by APACHE II quartile and protocol amendment

	rhAPC	Placebo	Relative Risk	95% CI for RR
Original Protocol				
1st Quartile	21/92 (23%)	9/93 (10%)	2.36	1.14, 4.87
2nd Quartile	27/103 (26%)	25/92 (27%)	0.96	0.61, 1.54
3rd Quartile	16/75 (21%)	21/69 (30%)	0.70	0.40,1.23
4th Quartile	38/90 (42%)	54/106 (51%)	0.83	0.61,1.12
				Interaction p=0.03
Amended Protocol				
1st Quartile	12/126 (10%)	17/122 (14%)	0.68	0.34, 1.37
2nd Quartile	22/115 (19%)	32/130 (25%)	0.78	0.48, 1.26
3rd Quartile	32/129 (25%)	37/93 (40%)	0.62	0.42, 0.92
4th Quartile	42/120 (35%)	64/135 (47%)	0.74	0.55, 1.00
				Interaction p=0.85

Reviewer comment: The above analysis of results pre- and post-amendment by APACHE II quartiles suggest the inconsistency between early and late results was essentially limited to the first quartile or low risk patients. In this subset, the RR of 2.36 is in striking contrast to the RR of 0.68 for the first APACHE II quartile group in the amended version of the protocol and the RR among patients in the other APACHE II quartiles in groups in both versions of the protocol. Although the notably worse outcome in the first APACHE II quartile could be due to chance, the magnitude of the difference between rhAPC and placebo in this subset and the p value of 0.03 for the interaction between treatment and APACHE II quartiles strongly suggest that those at lower risk require further study. It should be noted that in the ITT primary analysis this interaction p value is 0.09 which suggests lack of efficacy in patients with lower risk mortality.

Presented below are data on mortality on the APACHE II chronic health points in all patients as well as separated according to whether they were enrolled under the original or the amended protocols.

Table 54. Mortality by treatment group, APACHE II components chronic health points

Chronic Health Points	RhAPC	Placebo
All Patients*		
0	163/681 (24%)	176/664 (27%)
2	3/9 (33%)	10/17 (59%)
5	44/160 (28%)	73/159 (46%)
Original protocol		
0	77/276 (28%)	60/262 (23%)
2	2/5 (40%)	6/10 (60%)
5	23/79 (29%)	43/88 (49%)
Amended protocol		
0	86/405 (21%)	116/402 (29%)
2	1/4 (25%)	4/7 (57%)
5	21/81 (26%)	30/71 (42%)

*Treatment by Age Points Interaction (Logistic Regression) p-value = 0.01

Reviewer comment: APACHE II system assigns chronic health points only to those patients with rather severe underlying diseases predating the acute illness. Patients with chronic health problems experienced most of the beneficial effect. Treatment associated mortality benefit was 3% in the 1345 patients without APACHE II chronic health problems but 25% in the 345 patients with APACHE II chronic health problems. The p value for interaction of drug effect and APACHE II chronic heath points was 0.01. Thus it does not appear that the success of the trial was dependent on the exclusion of patients with underlying disease. Such patients appeared to experience the greatest drug benefit. The effect of the protocol amendment was to decrease the proportion of patients with severe underlying disease.

Table 55 contains mortality results for patients on rhAPC vs placebo according to the other components of the APACHE II score (other than chronic health points) i.e, the acute physiology and age components.

Table 55. Mortality by treatment group, APACHE II components acute physiology score (APS)

APS Points Quartile	rhAPC	Placebo
All patients*		
0 to 15	51/230 (22%)	46/211 (22%)
16 to 20	47/241 (20%)	55/241 (23%)
21 to 25	45/204 (22%)	62/183 (34%)
26 to 48	67/177 (38%)	96/205 (47%)
Original Protocol		
0 to 15	31/102 (30%)	21/99 (21%)
16 to 20	23/101 (23%)	25/103 (24%)
21 to 25	18/89 (20%)	25/74 (34%)
26 to 48	30/68 (44%)	38/84 (45%)
Amended protocol		
0 to 15	20/128 (16%)	25/112 (22%)
16 to 20	24/140 (17%)	30/138 (22%)
21 to 25	27/113 (24%)	37/109 (34%)
26 to 48	37/109 (34%)	58/121 (48%)

*Treatment by APS Points Interaction (Logistic Regression) p-value=0.18

Reviewer comment: In contrast to the findings on the Chronic Health Points, results for APS parallel that for the overall APACHE II scores. There was no apparent treatment difference among patients who had lower APS points in the overall study population and a reversal of the rhAPC benefit among those with the lowest APS enrolled under the original protocol.

Table 56. Mortality by treatment group, APACHE II components age points

AGE Points Quartile	rhAPC	Placebo
All patients*		
0 (<44 years)	23/177 (13%)	21/161 (13%)
2 (45 to 54 years)	20/112 (18%)	31/130 (24%)
3 (55 to 64 years)	25/148 (17%)	42/158 (27%)
5 (65 to 74 years)	73/208 (35%)	76/210 (36%)
6 (≥75 years)	69/205 (34%)	89/181 (49%)
Original protocol		
0 (<44 years)	11/73 (15%)	6/63 (10%)
2 (45 to 54 years)	10/44 (23%)	12/53 (23%)
3 (55 to 64 years)	12/65 (19%)	15/72 (21%)
5 (65 to 74 years)	34/88 (39%)	39/91 (43%)
6 (≥75 years)	35/90 (39%)	37/81 (46%)
Amended protocol		
0 (<44 years)	12/104 (12%)	15/98 (15%)
2 (45 to 54 years)	10/68 (15%)	19/77 (25%)
3 (55 to 64 years)	13/83 (16%)	27/86 (31%)

5 (65 to 74 years)	39/120 (33%)	37/119 (31%)
6 (≥75 years)	34/115 (30%)	52/100 (52%)

*Treatment by Age Points Interaction (Logistic Regression) p-value=0.36

Reviewer comment: In both the original and amended versions of the protocol, the rhAPC treatment benefit was apparent among those patients with the higher age points. Patients with scores of 0 for age points (reflecting ages < 44) did not show a treatment benefit. This outcome was similar to the results of mortality by age, described earlier,

Do Not Resuscitate Orders

Do not resuscitate (DNR) orders were recorded in both the phase 2 and 3 trials. In the phase 2 trial, ~27% of patients had a DNR order either during the 28 days on study. This was balanced between the rhAPC and the placebo arms, as shown in Table 57.

Table 57. DNR phase 2

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

Of the 36 patients with a DNR orders in the phase 2 study, outcomes are listed below:

- 30 (83%) died
- 1 (3%) discontinued due to patient decision
- 1 (3%) discontinued due to physician decision
- 4 (11%) completed the study

We also looked at DNR rates in the phase 3 trial, and particularly, whether there were differences between the first and second halves of the trial. For these analyses, the division for the rhAPC arm only was based on the study material used (BDS2 vs BDS2+). In the first half of the study the incidence of DNR orders was ~17 percent, lower than the phase 2 study but well balanced between treatment arms. In the second half of the study the rate of DNR orders fell to 9% in the rhAPC group while it remained constant in the placebo group. Whereas the trial was blinded (though there could be some unblinding due to bleeding) it was unlikely that the difference in DNR rates reflected bias in how patients were managed. In the second part of the study, the higher DNR rates in the placebo arm compared to the arm that received BDS2+ likely reflect the fact that more placebo patients did poorly.

Table 58. DNR phase 3

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

For analysis purposes placebo was divided into "first" and "second half" of the study.

Efficacy and drug manufacturing process BDS2 and BDS2+

Table 59 depicts mortality rates based on the two drug manufacturing process, BDS2 and BDS2+. The mortality among the 471 patients who received BDS2 was 29% vs. 19% for the 355 patients who received BDS2+. This compares to the 31% mortality among the placebo group and 25% mortality for the rhAPC group.

Table 59. Primary 28-day all-cause mortality in all randomized patients stratified by Bulk Drug Substance (BDS)

THERAPY	Alive at Day 28	Died at Day 28	Total
	N (%)	N (%)	
Placebo	581 (69)	259 (31)	840
BDS2	334 (71)	137 (29)	471
BDS2+	287 (81)	68 (19)	355
BDS2 & BDS2+	19 (83)	4 (17)	23
rhAPC (Total)	640 (75)	209 (25)	849
			1689[6]

Placebo vs BDS2 P = 0.0054 (Fisher's exact)
Placebo vs BDS2+ P< 0.00005 (Fisher's exact)
BDS2 vs BDS2 P = 0.001 (Fisher's exact)
Placebo-BDS2-BDS2+ Trend P=0.0003 (Jonckheere-Terpstra test)

Reviewer comment: Although different mortality rates were observed (29%) with BDS2 vs. (19%) with BDS2+, neither physiochemical nor pharmacokinetic differences were detected between the two manufactured products. It is not known if there exist differences in these macromolecules that escaped detection. Changes in the master cell bank could be substantial and result in changes to a product. Nonetheless, as extensive analysis found no difference, it is unlikely that any differences in product could account for the different clinical outcomes. If the new master cell bank resulted in a product difference that accounts for the improved clinical results, then the newer product is superior and effective. This conclusion would not argue against approval, but rather careful product control to ensure that the desirable characteristics acquired were not lost.

[6] Missing data on one patient.

Summary of Efficacy in Adults Patients with Severe Sepsis

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 either rhAPC (850 patients) or placebo (840 patients) for any of time and constituted the intent-to-treat (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, 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.

In addition to the APACHE II subgroups, other exploratory analyses indicate almost no treatment effect in patients with less than two organ failures. However, additional subset analyses suggested APACHE II, and not number of organ failures, was the strongest predictor of a response to rhAPC. There appeared to be a treatment effect in patients with DIC at baseline and no effect in those without DIC. However, this analysis was confounded by the definition of DIC in this protocol, which differed from more conventional definitions of DIC used in other sepsis trials, as it also incorporated laboratory tests not commonly obtained in clinical settings. When FDA assessed treatment effect only in patients who had low platelet counts as a rough indicator of DIC, a rhAPC treatment benefit was observed in those with and without thrombocytopenia. There was also an apparent treatment effect in patients with shock and little effect in those without shock. As with DIC, however, the sponsor's definition of shock was different than that commonly used in sepsis. Post hoc analyses of patient subgroups according to other criteria to identify patients in shock supported a rhAPC effect in patients with severe sepsis in shock as well as not in shock.

Analyses of prophylactic heparin use suggested that patients who were on heparin did not have as much treatment benefit as patients not on low dose heparin, although such conclusions are difficult to make because heparin use occurred post randomization.

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. We could not find difference in the material BDS2 and BDS2+ and no impact in the eligibility criteria on outcome.

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 had not begun. During the phase 3 study, the pediatric sepsis study was initiated 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. This was not done. The pediatric sepsis study was ongoing when the phase 3 trial was stopped after the second interim analysis, based on the mortality benefit observed in adult patients. No placebo-controlled data in pediatric patients with sepsis are available. At the time of the filing of the BLA, the pediatric sepsis study was ongoing. The purpose of this trial was to study the PK/PD parameters of the drug in the pediatric sepsis patient population, and to establish a pediatric safety database.

Sources of Reviewed Material

This review does not include a completed study report on the primary pediatric sepsis study. At the time of the review, the sponsor had not submitted this and it was to be submitted at a later date. The information used for this report consists of information provided by the sponsor in the initial filing of the BLA which included 51 of the total 83 patients, and no patients enrolled after a protocol amendment was made. Additional information was provided in a 4-month safety update on another 3 patients. Finally, the sponsor's briefing document to the advisory committee contained some preliminary data on the remaining 29 patients in the pediatric study. The complete database, study summary, adverse events and case report forms will be submitted later and will not be a part of this review. The results of the open label studies are described below.

Two separate studies have accumulated pediatric data. A total of 182 pediatric patients have been treated. 14 have been treated in an open label compassionate use trial in purpura fulminans (--------). 83 patients have been treated in an open label pharmacology/safety study in pediatric sepsis (--------). Additionally, 85 patients have been treated in open label ongoing studies, but there has been no data submitted on these

patients. There was one pediatric death reported in the purpura fulminans study (N=14) and 8 of 83 patients died in the sepsis study. Demographic, pharmacokinetic, and safety data are presented.

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 < 1 year - 6 patients
  ≥ 1 year to < 8 years - 8 patients
  ≥ 8 years to 18 years - 7 patients
  Total - 21 patients

- **Part 2:** open label 96 hour infusion at 24 ug/kg/hr as determined from the part 1 dose escalation phase.
  Newborn to < 1y/o - 19 patients
  ≥ 1 year to < 8 years - 26 patients
  ≥ 8 years to 18 years - 17 patients
  Total - 62 patients

Pharmacokinetics

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 ---------, 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 ----------, C_{ss} was found to be 54.0 ng/kg/ml over 96 hours. In study ------- the C_{ss} was 54 ng/ml (range 14.1 to 390.6 ng/ml, N=326).

Pediatric Demographics

Demographics presented include the site of infection, type of pathogen, the type of organ failure, and the number of organ failures at entry into the study. Organ failure included primarily cardiovascular and respiratory sources. The protocol was later amended to include hematologic and renal failures and no patients were enrolled under the amendment with the initial filing of the BLA. Subsequent data has been obtained from the sponsors briefing document as to the nature of the patients enrolled after the protocol amendment (N=32).

Table 60. Pediatric primary site of infection*

Site of Infection	Part 1 (%)	Part 2 (%)
Blood	9/21 (43)	20/62 (32)
Cardiac	0	1/62 (2)
CNS	3/21 (14)	11/62 (18)
Intra-abdominal	3/21 (14)	3/62 (5)
Lung	2/21 (10)	15/62 (24)
UTI	1/21 (5)	2/62 (3)
HEENT	1/21 (5)	3/62 (5)
Indwelling Catheter	0	2/62 (3)
Gynecologic	0	3/62 (5)
Other	2/21 (10)	2/62 (3)

* Obtained from briefing document

Table 61. Type of pathogen*

Pathogen	Part 1 (%)	Part 2 (%)
Gram Positive	5/21 (24)	11/62 (18)
Gram Negative	4/21 (19)	25/62 (40)
Mixed Gram	3/21 (14)	8/62 (13)

*Obtained from briefing document,
Percentages add up to less than 100 as some patients had negative cultures

Table 62. Pediatric organ failure*

Organ Failure	Part 1 (%)	Part 2 (%)
Cardiovascular	19/21 (91)	56/62 (90)
Respiratory	5/21 (24)	24/62 (39)
Hematologic	0	8/62 (13)
Renal	0	4/62 (7)

*Obtained from briefing document,
Percentages add up to greater than 100 as some patients had more than 1 organ failure
Hematologic and renal organ failure are based on the last 32 patients enrolled

Table 63. Number of pediatric organ failure*

Number of Organ Failures	Part 1 (%)	Part 2 (%)
1	18/21 (86)	39/62 (63)
2	3/21 (14)	18/62 (29)
3	0	3/62 (5)
4	0	2/62 (3)

*Obtained from briefing document,
Percentages add up to greater than 100 as some patients had more than 1 organ failure 3 and 4 organ failures include hematologic and renal organ failure and are based on the last 32 patients enrolled

Reviewer comment: The pediatric patient population is noted to have primarily blood infections in addition to a high incidence of CNS infections secondary to the prevalence

of meningitis in this population. Infections with gram negative organisms are more common than gram positive infections. There is a predominance of single organ failure, primarily cardiovascular followed by respiratory failure.

Demographics: Pediatric versus Adult

Pediatric data based on the entire study is compared to the adult data from the phase 3 trial. Site of infection, type of pathogen, type and number of organ failures are compared. The sponsor proposes that pediatric and adult sepsis are similar.

Table 64. Site of infection pediatric versus adult*

Site of Infection	Pediatric (%)	Adult Phase 3 (%)
Blood	29/83 (35)	87/1690 (5)
CNS	14/83 (17)	39/1690 (2)
Intra-abdominal	6/83 (7)	337/1690 (20)
Lung	17/83 (21)	906/1690 (54)
UTI	3/83 (4)	171/1690 (10)
Other	14/83 (17)	150/1690 (9)

*Obtained from briefing document

Table 65. Type of pathogen*

Pathogen	Pediatric (%)	Adult phase 3 (%)
Gram Positive	16/83 (19)	430/1690 (25)
Gram Negative	29/83 (35)	381/1690 (23)
Mixed Gram	11/83 (13)	250/1690 (15)

*Obtained from briefing document,
Percentages add up to less than 100 as some patients had negative cultures

Table 66. Type of organ failure*

Organ Failure	Pediatric (%)	Adult phase 3 (%)
Cardiovascular	29/32 (91)	1214/1690 (72)
Respiratory	12/32 (38)	1272/1690 (75)
Hematologic	8/32 (25)	268/1690 (16)
Renal	4/32 (13)	710/1690 (42)

*Obtained from briefing document,
Percentages add up to greater than 100 as some patients had more than 1 organ failure
Pediatric hematologic and renal organ failure are based on the last 32 patients enrolled

Table 67. Number of pediatric organ failure*

Number of Organ Failures	Pediatric (%)	Adult phase 3 (%)
1	18/32 (56)	418/1690 (25)
2	9/32 (28)	543/1690 (32)
3	3/32 (9)	432/1690 (26)
4	2/32 (6)	235/1690 (14)

*Obtained from briefing document,
Percentages add up to greater than 100 as some patients had more than 1 organ failure
3 and 4 organ failures include hematologic and renal organ failure and are based on the last 32 patients enrolled

Reviewer comment: In comparing the pediatric to adult sepsis patients, several points can be made. First, there is an extremely small data base from which to draw any meaningful conclusions. Second, pediatric sepsis differs from adult sepsis based on the demographic data in several important ways. Blood, lung and CNS infections are most common in the pediatric patients versus lung, intra-abdominal and UTI in adult patients. Pediatric patients more often have gram negative infections versus gram positive for adult patients. Also the number of organ failures are more commonly single for pediatric patients and multiple for adult patients. Respiratory organ failure is less common in the pediatric patients compared to the adult patients. The claim that pediatric sepsis is the same disease process as adult sepsis is not supported by the demographic data.
Disease severity can be estimated by the number of organ failures and as noted above, there were fewer organ failures in the pediatric patients versus the adult patients again suggesting a less ill patient population.

A. Mortality in Pediatric Patients

Mortality in the pediatric study was based on the patient's status at 14 days. There were 8 deaths reported for a 14-day event rate of 10%. The causes of death included multi organ failure, cardiogenic failure, arrhythmia, cerebral edema and one intracranial hemorrhage. The intracranial hemorrhage was "possibly related" to the study drug. It involved a 14 year old with meningococcemia and an intracranial bleed noted on day 14. The patients infusion had been stopped after 10 hours due to anisicoria. A CT scan was not obtained for almost 2 weeks.

Table 68. 14-day mortality pediatric versus adult patients treated with rhAPC

	Pediatric (%)	**Adult phase 3 (%)**
Mortality	8/83 (10)	166/850 (20)

Reviewer comment: As another marker of disease severity, overall observed mortality was half that observed in the adult patients. As with organ failure, this would suggest a less ill patient population in the pediatric study compared to the adult study. As noted in the review of the adult study efficacy, the benefit of rhAPC in patients that were less ill was not clear.

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 69. 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. 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.

Table 70. 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

D. 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 71. Pediatric and adult SAE bleeding events and mortality

	Pediatric (83) N (%)	Adult rhAPC (850) N (%)	Adult Placebo (840) N (%)
SAE – Bleeding (Infusion)	3 (4)	20 (2)	8 (1)
SAE – Bleeding (28 day)	4 (5)	30 (4)	17 (2)
Mortality (14 day)	8 (10)	166 (20)	201 (24)

Reviewer comment: As noted previously, the overall mortality rate was lower in the pediatric study compared to the adult study. This is coupled with a similar rate of serious bleeding adverse events. The potential for benefit in a patient population with a lower overall mortality and a similar serious bleeding adverse event rate is diminished. Additionally, as noted earlier, there is a question as to the efficacy as raised in the review of the adult efficacy data, as to the benefit in patients whom are less ill.

rhAPC in Purpura Fulminans (--------)

The entry criteria for this study include subjects 1 year of age or older. They received a 96-hour 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 14 pediatric patients under 18 years. A total of 35 patients have been treated. There have been 8 deaths (one pediatric, further details have not been submitted) and 8 serious adverse events (2 pediatric). Pediatric patient narratives for the serious adverse events are reported below.

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

- 2-year-old 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.

Summary of Pediatrics

Limited safety data are available for the pediatric population. This review is based on the initial BLA submission of partial data, a safety update, and the sponsors briefing document. The patient populations studied suggest different etiologies for sepsis in the pediatric patients compared to the adult patients. This is based on the demographic data as previously outlined. No new trends in serious adverse events or bleeding events were identified from these limited data. A similar safety concern exists with a serious bleeding event rate similar to the rhAPC treated adults.

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. With a difference in the demographics between pediatric and adult patients, a lower overall mortality rate and a similar adverse event rate profile, licensing for a pediatric indication cannot be recommended. Further studies to establish efficacy based on controlled data is recommended.

- No controlled studies were performed in the pediatric population to support efficacy, characterized by safety profile. The patient population from which to draw any conclusions is limited.
- In comparing pediatric to adult data,
    - drug effects as reflected by the pharmacokinetics and pharmacodynamics were similar.
    - disease characteristics reflected by the type of infections and organisms, and the type and number of organ failures are different.
- Additionally, the mortality rate in the pediatric study was half of the rate observed in the adult phase 3 trial. This low mortality rate is coupled with a similar rate of complications including bleeding events and the occurrence of an intracranial hemorrhage.
- This is important in assessing the benefit versus the risk in the pediatric population
- Further studies to establish efficacy based on controlled data is recommended.

- **A pediatric indication is not recommended based on available data. Further studies in the pediatric populations will be necessary for labeling to support efficacy.**

Reviewer comment: The sponsor submitted the final pediatric study report after the clinical review was performed for the BLA.

Section V-Safety

Introduction

Safety data from the ---------- study are summarized below. The summary includes data on specific patient sub-populations. It is recognized that the primary risk to patients treated with rhAPC is bleeding. This comes in the form of catastrophic bleeds resulting in death, serious bleeding events that may be life threatening at the time but are treatable, and bleeding events that are not serious in nature. In a critically ill patient, a serious bleeding event may be enough to tip the balance between survival and death. Sepsis and the resulting physiologic changes are usually associated with a coagulopathy. There is the potential for bleeding independent of the additive effect of an additional treatment. Besides the inherent risk of bleeding, patients in sepsis are critically ill. This results in a high mortality and, though the overall mortality may be improved with a product, significant adverse events and in particular major bleeding events occurring in non-visible spaces may go undetected. This would include intracranial hemorrhages where a CT scan was never obtained and the patient died suddenly of "sepsis". This could be true of intra-thoracic bleeds and retroperitoneal hemorrhages as well. Bleeding events noted represent the events detected and most likely under-represent the true incidence.

Important Features of the ---------- Study

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 (it was recommended that the Vanderbilt coordinating center (VCC) be contacted as well):

Table 72. Summary infusion guidelines related to procedures

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.

Table 73. Summary of infusion guidelines related to coagulation factors

Stop Infusion	Restart Infusion
PTT $\geq$100 seconds	PTT <100 seconds
INR $\geq$3.0	INR <3.0
Platelet count $\leq$15 GI/L	Platelet count >15 GI/L

Reviewer comment: The protocol describes these parameters as recommendations.

Summary of Patient Mortality in the ---------- 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 74. 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 75. 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 3. 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 intra-thoracic bleed (rhAPC) with a history of an MVA 3 days prior to entering the study.

Reviewer comment: 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.

Adverse Events Related to Bleeding

Bleeding adverse events, particularly serious bleeding events, were a concern because of the anticoagulant mechanism of action. Narratives of serious bleeding events are presented in the Appendix 3. 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 had laboratory evidence of DIC when they entered 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.

Reviewer comment: Much of the focus is on events that occur during the infusion period. rhAPC has a short half-life and clears rapidly from the blood. Based on this, events that occur several days from the end of the infusion up to day 28 are more likely to be related to the underlying disease illness. This is also supported by the similar rate of accrual of adverse events and particularly bleeding event between the rhAPC and placebo treated after the infusion period.

Serious Bleeding Events

Below, the serious[7] bleeding events reported during the infusion period are displayed followed by the data from the 28-day study period. The infusion period is defined as the time period from the initiation of the infusion to the end of the infusion plus the next calendar day. For most patients this would be close to a 5-day period, four for the infusion, plus one day. For patients that had their infusion started and stopped, the infusion period would stretch out to more than 5 days.

Table 76. 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 77. 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%)	47 (3%)

Though GI bleeding events were fairly well balanced, there was an increased incidence of intrathoracic, retroperitoneal and cerebral hemorrhages in the rhAPC treated patients compared to the placebo patients.

[7] "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.

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

All Reported Bleeding Events

Below are listed 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 78. 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 Hemorrhage	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 79. Adverse events (bleeding) 28-day study period

Event Classification	**rhAPC** (850) N (%)	**Placebo** (840) N (%)	**Total** (1690) 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

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 80. 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 81. 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)

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 the.

Serious Adverse Events Related to the Study Drug per the Investigator

Table 82. 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

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%).

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%).

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 83. 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

Reviewer comments: No trends related to the study drug noted were noted.

Data were recorded regarding the rate of new infections while in the study. The number of new infections (or sequelae to the initial infection) was tabulated. The purpose of this analysis was to investigate the possibility that rhAPC would increase the rate of subsequent infections. This was recorded as a patient developing a second infection while still being treated or a patient that had finished treatment and developed a new infection.

Table 84. 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 sequalae infections or new infections when comparing the rhAPC group to the placebo group.

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.

Gender

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

Table 85. 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)

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 86. 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)

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 87. 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)

First APACHE II Quartile

Safety data divided into the lower APACHE II scores versus the higher scores are presented below. Narrative descriptions of individual subjects in the first APACHE II quartile are presented in the Appendix 3. 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. The difference in serious bleeding rates is greatest in the lowest APACHE II patients.

Table 88. Bleeding events per subgroups as defined by APACHE II

	APACHE II 3-25		**APACHE II 25-53**	
	rhAPC (436) N (%)	Placebo (437) N (%)	rhAPC (414) N (%)	Placebo (403) N (%)
Bleeding AE	74 (17)	37 (9)	86 (21)	54 (13)
Bleeding SAE	11 (3)	5 (1)	9 (2)	3 (1)

In particular, the first APACHE II quartile had a much higher rate of serious bleeding events when compared to the overall rate of serious bleeding events as presented below.

Table 89. Bleeding events per first APACHE II quartile

	First APACHE II Quartile (3-19)			
	rhAPC (218) N (%)	Placebo (210) N (%)	RR	95% CI
Bleeding AE	38 (17)	17 (8)	2.2	(1.1, 4.6)
Bleeding SAE	9 (4)	0	18.3	(2.7, *)

Using APACHE II as one measure of disease severity, those patients in the lower scores, particularly with the lowest APACHE II scores had a greater incidence of serious adverse bleeding events. This is coupled with less of a treatment benefit.

Reviewer comment: Based on the data from the phase 3 trial, APACHE II scores were the best predictors of mortality. Those patients with a lower APACHE II score and a lower mortality had at least as great a risk of serious bleeding events as those with higher APACHE II scores. The first APACHE II quartile had the greatest risk of serious bleeding events with the least mortality benefit.

A. DIC

The vast majority of patients had laboratory evidence of DIC as defined by the study (see below). The rate of serious adverse bleeding events in DIC mirrors the entire study.

Table 90. DIC

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

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 91. 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.

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. Serious bleeding events are not combined as the definition of serious bleeding events was developed for the phase 3 trial and differed from the phase 2 trial. 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 92. Baseline coagulation profile

Category	**rhAPC**		**Placebo**	
	Total (940)	Events (%)	Total (881)	Events (%)
28 Day Mortality				
APTT				
Unknown	71	26 (37)	83	18 (22)
≤ ULN	282	54 (19)	251	67 (27)
ULN- ≤2xULN	543	139 (26)	510	169 (33)
> 2xULN	44	17 (39)	37	19 (51)
PT				
Unknown	70	24 (34)	86	20 (23)
≤ ULN	92	17 (18)	66	17 (26)
ULN- ≤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)
≤ ULN	282	46 (16)	251	25 (10)
ULN- ≤2xULN	543	101 (19)	510	55 (11)
> 2xULN	44	9 (20)	37	5 (14)
PT				
Unknown	70	11 (16)	86	8 (9)
≤ ULN	92	7 (8)	66	7 (11)
ULN- ≤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. This trend was consistent across the different coagulation parameters other than the small number of patients with a PT ≤ULN.

Table 93. 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.

Renal

The relationship between renal function and mortality, SAE and Bleeding SAE are displayed below. Whether based on the renal organ failure at baseline or based on SOFA score, no trends were noted.

Table 94. Renal

Category	rhAPC		Placebo	
	Total (850)	Event (%)	Total (840)	Event (%)
28 Day Mortality				
ENTOFREN - Yes	357	116 (32)	353	143 (41)
ENTOFREN - No	493	94 (19)	487	116 (24)
BLSOFREN - 0	323	64 (20)	323	69 (21)
BLSOFREN - 1	235	50 (21)	241	76 (32)
BLSOFREN - 2	188	62 (33)	176	76 (43)
BLSOFREN - 3	73	23 (32)	52	20 (38)
BLSOFREN - 4	30	10 (33)	45	17 (38)
SAE				
ENTOFREN - Yes	357	42 (12)	353	46 (13)
ENTOFREN - No	493	64 (13)	487	56 (12)
BLSOFREN - 0	323	31 (10)	323	30 (9)
BLSOFREN - 1	235	28 (12)	241	30 (12)
BLSOFREN - 2	188	30 (16)	176	26 (15)
BLSOFREN - 3	73	12 (16)	52	6 (12)
BLSOFREN - 4	30	5 (17)	45	9 (20)
SAE Bleeding Events				
ENTOFREN - Yes	357	12 (3)	353	11 (3)
ENTOFREN - No	493	18 (4)	487	6 (1)
BLSOFREN - 0	323	8 (2)	323	2 (1)
BLSOFREN - 1	235	8 (3)	241	4 (2)
BLSOFREN - 2	188	10 (5)	176	8 (5)
BLSOFREN - 3	73	3 (4)	52	1 (2)
BLSOFREN - 4	30	1 (3)	45	2(4)

(ENTOFREN-met entry criteria for renal organ failure; BLSOFREN-baseline renal SOFA score)

Hepatic

As with the renal data, the hepatic data revealed no major trends.

Table 95. Hepatic

Category	rhAPC		Placebo	
	Total (850)	Events (%)	Total (840)	Events (%)
28 Day Mortality				
BLSOFHEP - U	73	22 (30)	77	20 (26)
BLSOFHEP - 0	468	104 (22)	482	145 (30)
BLSOFHEP - 1	172	41 (24)	143	44 (31)
BLSOFHEP - 2	116	33 (28)	117	44 (38)
BLSOFHEP - 3	20	9 (45)	15	4 (27)
BLSOFHEP - 4	1	1 (100)	6	2 (33)
LIVERDIS - N	814	200 (25)	803	245 (31)
LIVERDIS - U	18	8 (44)	15	5 (33)
LIVERDIS - Y	18	2 (11)	22	9 (41)
ALT3X - U	158	88 (56)	158	103 (65)
ALT3X - N	623	102 (16)	622	135 (22)
ALT3X - Y	69	20 (29)	60	21 (35)
AST3X - U	158	88 (56)	158	103 (65)
AST3X - N	645	107 (17)	642	140 (22)
AST3X -Y	47	15 (32)	40	16 (40)
SAE				
BLSOFHEP - U	73	6 (8)	77	8 (10)
BLSOFHEP - 0	468	59 (13)	482	65 (13)
BLSOFHEP - 1	172	22 (13)	143	17 (12)
BLSOFHEP - 2	116	15 (13)	117	12 (10)
BLSOFHEP - 3	20	3 (15)	15	0 (0)
BLSOFHEP - 4	1	1 (100)	6	0 (0)
LIVERDIS - N	814	99 (12)	803	98 (12)
LIVERDIS - U	18	4 (22)	15	2 (13)
LIVERDIS - Y	18	3 (17)	22	2 (9)
ALT3X - U	158	21 (13)	158	14 (9)
ALT3X - N	623	75 (12)	622	74 (12)
ALT3X - Y	69	10 (14)	60	14 (23)
AST3X -U	158	21 (13)	158	14 (9)
AST3X - N	645	80 (12)	642	76 (12)
AST3X - Y	47	5 (11)	40	12 (30)
SAE Bleeding Events				
BLSOFHEP - U	73	2 (3)	77	0 (0)
BLSOFHEP - 0	468	16 (3)	482	11 (2)
BLSOFHEP - 1	172	3 (2)	143	3 (2)
BLSOFHEP - 2	116	8 (7)	117	3 (3)
BLSOFHEP -3 NL	20		15	
BLSOFHEP - 4	1	1 (100)	6	0 (0)
LIVERDIS - N	814	29 (4)	803	16 (2)
LIVERDIS - U	18	0 (0)	15	1 (7)
LIVERDIS - Y	18	1 (6)	22	0 (0)
ALT3X - U	158	8 (5)	158	4 (3)
ALT3X - N	623	21 (3)	622	13 (2)
ALT3X - Y	69	1 (1)	60	0 (0)
AST3X - U	158	8 (5)	158	4 (3)
AST3X - N	645	20 (3)	642	12 (2)
AST3X - Y	47	2 (4)	40	1 (3)

(BLSOFHEP-baseline SOFA hepatic score; LIVERDIS-history of liver disease at baseline; ALT3X- ALT 3 times upper limit of normal on study day 4 (ULN); AST3X-AST 3 times ULN on study day 4; Y-Yes; N-No; U-Unknown; NL-not listed)

rhAPC Steady–State

The table below shows the safety profile of subjects based on the steady state rhAPC level.

Table 96. Safety profile by rhAPC steady-state concentration quartile (total 326)

Variable	1st Quartile (81) N (%)	2nd Quartile (83) N (%)	3rd Quartile (81) N (%)	4th Quartile (81) 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)
Mean APACHE II score	22.3	26.7	25.5	26.2

All levels in ng/ml

1rst Quartile – 0 – 35
2nd Quartile – 35 – 45
3rd Quartile – 45 –62
4th Quartile – 62 – 390 (median 82 ng/ml)

Highest Placebo group concentration recorded – 44.1

There was a wide range in the steady state rhAPC concentration. Some patients in the placebo arm also had measurable levels of rhAPC. It is noted that there was a higher overall mortality in the 4th (highest) quartile though again the numbers are small.

Reviewer comment: There was a wide range of values with the highest rhAPC steady states perhaps representing patients who did not inactivate the product as well. The mean APACHE II scores reflect a lower mortality in the first APACHE II quartile, but no trend in mortality in the remaining APACHE II quartiles. The etiology for these differences do not appear to be based on severity of illness as assessed by the APACHE II scores.

Finally we evaluated this graphically with adverse events and the steady states. There appears to be a higher rate of adverse events outcomes with higher steady states concentrations. This is presented in the below figure. Serious adverse event (SAE) is shown in the figure throughout the study and during the infusion (I) and bleeding events (BE), which are SAE, are shown throughout the study and during the infusion. One possible explanation for the observed relationship between steady-state concentration and SAE incidence, of any severity, may reflect the fact that patients who are sickest may not clear drug as quickly as do patients who are not as sick.

>=1 SAE = patients have at least one SAE
>=1 SAE 1 = at least I SAE during/+1 day infusion
BE-SAE = bleeding event reported as SAE
BE SAE 1 = serious bleeding event during/+1 infusion
Y-axis = % of patients

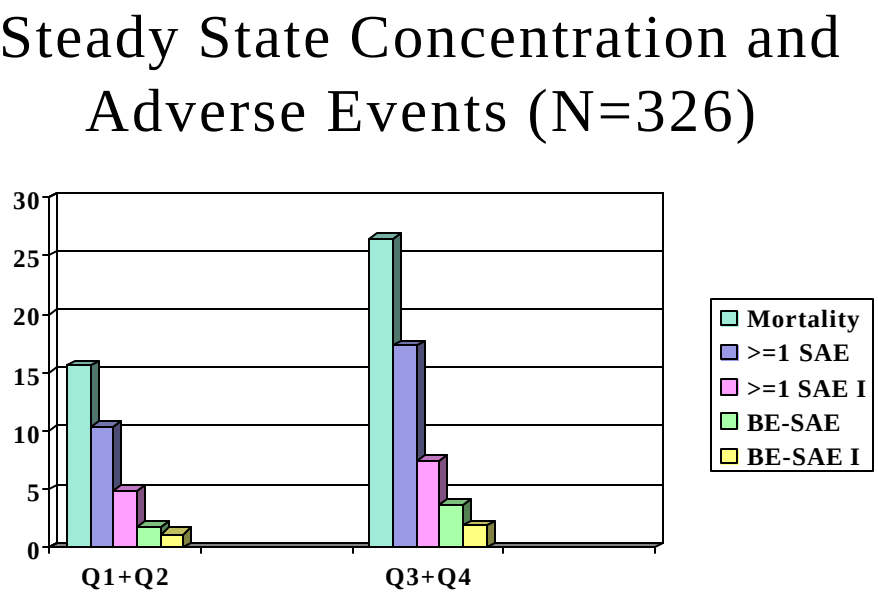


Figure 14. Steady state concentrations and adverse events

Baseline Surgical Status

Presented below are data from phase 2 and phase 3 concerning patients that required surgery, both emergent and non-emergent. Using pooled data from the phase 2 and 3 trials, patients were grouped based on their surgical status - either having had emergency surgery or elective surgery. These patient characteristics were obtained from the APACHE II assessment and were not prospectively defined. Other than recording the APACHE II score at the entry of the trial, the timing of the surgical procedure is unknown.

Table 97. Mortality treatment emergent bleeding events and transfusion based on surgical status

Category	rhAPC		Placebo		RR	CI
	Total (940)	**Events (%)**	**Total (881)**	**Events (%)**		
28 Day Mortality						
Elective Post-op	63	20 (32)	59	22 (37)	0.9	(0.4, 1.6)
Emergency Post-op	186	56 (30)	187	49 (26)	1.1	(0.8, 1.7)
Non-op	691	160 (23)	635	202 (32)	0.7	(0.6, 0.9)
Treatment Emergent Bleeding Events						
Elective Post-op	63	12 (19)	59	4 (7)	2.8	(0.9, 8.2)
Emergency Post-op	186	32 (17)	187	14 (7)	2.3	(1.1, 4.2)
Non-op	691	124 (18)	635	74 (12)	1.5	(1.2, 2.0)
Required Transfusion of PRBC						
Elective Post-op	63	54 (86)	59	44 (75)	1.1	(0.9, 1.5)
Emergency Post-op	186	154 (83)	187	144 (77)	1.1	(1.0, 1.2)
Non-op	691	384 (56)	635	326 (51)	1.1	(1.0, 1.2)

Relative Risk (95% exact confidence interval)

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.

Reviewer comment: Though the numbers are small and the confidence intervals are large, no mortality benefit was observed in the emergency post-operative patients. This was not true in the patients that were post-op from elective surgery. There was a similar rate of bleeding events in the rhAPC groups regardless of their emergent or elective post-operative status.

BDS2 versus BDS2+

Issues were raised concerning the introduction of a re-formulated product midway through the trial. The safety parameters of the two products were compared to determine if there was a difference based on safety profile. BDS2 was used in the first part of the study. BDS2+ was used in the second half of the study.

Table 98. Summary of Adverse Events

Adverse Event	BDS2+ (355) N (%)	BDS2 (471) N (%)	Other (24) N (%)	Placebo (840) N (%)	Total (1690) N (%)
Adverse Events					
Infusion Period	239 (67)	330 (70)	14 (58)	546 (65)	1129 (67)
28-Day Study Period	288 (81)	390 (83)	17 (71)	653 (78)	1348 (80)
Adverse Events (Bleeding)					
Infusion Period	59 (17)	100 (21)	1 (4)	91 (11)	251 (15)
28-Day Study Period	79 (22)	129 (27)	4 (17)	149 (18)	361 (21)
Serious Adverse Events					
Infusion Period	24 (7)	33 (7)	1 (4)	55 (7)	113 (7)
28-Day Study Period	45 (13)	59 (13)	2 (8)	102 (12)	208 (12)
Serious Adverse Events (Bleeding)					
Infusion Period	8 (2)	12 (3)	0	8 (1)	28 (2)
28-Day Study Period	12 (3)	18 (4)	0	17 (2)	47 (3)
Deaths Thought to be Study Drug Related					
28-Day Study Period	2 (.6)	3 (.6)	0	1 (.1)	6 (.4)

Reviewer comment: though there was a slightly lower rate of adverse events and bleeding events in the reformulated product, the overall safety profiles were similar. Data were examined as to the type of adverse events and bleeding events that were reported, and though differences existed, there was no trend observed in these data.

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 phase 2; 852 phase 3).
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).

Combining the phase 2 and 3 trials, 942 patients received rhAPC. Of those 942 patients, 370 patients had adequate blood samples to evaluate immunogenicity. This included a baseline sample, and a sample on or after study day 12.

The testing was done in a tiered manner. The first tier was a chemiluminescent binding assay. If this was positive, it was followed by an inhibition chemiluminescent binding assay. If that was positive, an anti-APC neutralizing antibody test was performed. There are outstanding issues regarding the sensitivity, specificity and quantification of the assays. Based on this, it is difficult to assess the true incidence of Anti-APC antibodies. Recognizing some limitations of these assays, results were obtained in the 370 patients.

Tier 1 Chemiluminescent binding assay – any patient with a value greater than ------ ---------- and a ------- or greater rise over baseline proceeded to level 2.

Tier 2 Specific ---------- at a level of 1:10. Any sample with a response greater than ------ inhibition at study day 28 was considered positive.

Tier 3 Neutralizing antibody to rhAPC and APC using an ---------- assay

Table 99. Anti-APC antibody data for rhAPC-treated patients with positive level 1 testing

	Level 1 Results		Level 2 Results		Level 3 Results
Patient #	Fold increase over baseline level	-------- 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 ---------- received 24 ug/kg/hr for 48 hours in phase 2, had no clinical sequalae and was antibody negative at 1 year. Patient ---------- 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.

Reviewer comments: there are outstanding issues with the assays, so that the true incidence of all antibodies is not known. It is concerning that a DVT occurred in a patient that tested positive for antibodies. The overall incidence of DVT was low in the study (The overall incidence of deep thrombophlebitis reported in the phase 3 trial was 7

cases for an incidence of 0.4%. 3 of these cases occurred in the rhAPC treated patients). The relationship of the antibodies to the DVT is unknown.

Additional Safety Issues from Ongoing Uncontrolled Trials

On August 28, 2001, the company submitted additional preliminary data regarding intracranial hemorrhages (ICH) in ongoing post phase 3 safety studies. These studies, which are separate from the phase 3 trial, have similar entry criteria to minimize the risk of bleeding. Despite these measures, of 551 patients enrolled, 13 new intracranial hemorrhages have been reported with 7 of those occurring during the study drug infusion period (i.e. the infusion period plus the 24 hours immediately following). The remainder occurred beyond the study drug infusion period. For those bleeds occurring during the infusion, the event rate is 1.3%. This compares to a rate of 0.2% in the phase 3 trial.

Additional safety updates followed and initial summary safety data has been submitted related to this patient population in these ongoing studies. That data will be presented following the ICH data. The information presented below is derived from case report forms submitted by the sponsor.

Table 100. Intracranial hemorrhages (ICH) in ongoing open-label trials as of October 25, 2001

Study	ICH during infusion period	ICH after infusion period	Total ICH	Fatal ICH
Ongoing Open-label	7/941 (0.7%)	8/941 (0.9%)	15/941 (1.6%)	6/941 (0.6%)

Below is a summary of case report forms submitted by the sponsor for the additional ICH events that have occurred in the open label trials. The last 5 cases occurred after August 27, 2001.

The entries in italics represent readings that were changed to no hemorrhage by an adjudication process conducted with neuroradiologists.

The entries in bold represent readings that were changed but where a hemorrhage was still present.

Table 101. Preliminary data on intracranial hemorrhages in ongoing open-label trials

Study	Pt. #	Sex	Age	#Days on Drug	Day of Event	Reading and Adjudication findings	Plt. Ct. Initial	Plt. Trans.	Plt. Ct. Event	APTT	PT or INR
--------*	----------	*F*	*55*	*3*	*2/died*	*No Bleed/ cerebral infarct*	*115,000*	*4 units*	*96,000*	*-*	*15-17 PT*
--------*	----------	F	22	3	3/alive	Intracranial hem frontal lobes	28-42-19-34-5	Yes 91 units	19,000	-	10.0 INR
--------*	----------	F	37	3	3/died	Large R frontal lobe bleed	49,000 – 17,000	Yes to 77,000	45,000	45	2.5 INR
--------*	----------	*F*	*19*	*2*	*2/died*	*No Bleed/ edema and hernitaion*	*88,000-31,000*	*yes*	*-*	*59.8*	*2.4-6.5*
--------*	----------	**M**	**43**	**4**	**8/alive**	**L brain hematoma changed to L globbus pallidus hem.**	**51,000**	**-**	**138,000**	**37.4**	**1.5 INR**
--------*	----------	F	40	4	13/died	R frontal ischemia with parietal hem and herniation	65,000	-	170,000	38	1.5 INR
--------*	----------	F	62	4	11/died	Basilar tip bleed with aneurysm	178,000-57,000	-	-	27-132	1.4-1.5
--------*	----------	**F**	**14**	**3**	**3/alive**	**ICH changed to left subdural and infarct**	**-**	**Yes**	**24,000**	**>100**	**8.2 INR**
--------*	----------	M	48	2	2/alive	Intraparenchymal hem	-	-	35,000	58	1.1
--------*	----------	M	69	3	3/died	Disseminated intracerebral bleed	32,000, 49-67	Yes	49,000	-	-
--------*	----------	M	49	4	12/died	Ischemic stroke with hem	Low plt.	-	-	-	Inc INR
--------	----------	*M*	*69*	*4*	*5/alive*	*Bilateral cerebral ischemia with hemorrhage*	-	-	-	*41.8*	*14 PT*
--------*	----------	F	74	4	7/died	Ischemic stroke with subarachnoid bleed	-	-	-	-	-
--------	----------	M	63	1	1/died	parenchymal hemorrhage	48,000	Yes	28,000	64	1.4
--------	----------	F	43	4	5-sym/ 7-CT/ alive	Brain stem Hem	111,000	No	240,000	36	-
--------	----------	M	47	2	2/died	parenchymal hem	90,000	No	84,000	>200	13
--------	----------	F	32 w	2	9/died	Infarcts initially then hemorrhage	31,000	Yes		148	2.2 INR
--------	----------	M	74	4	25/died	L intracerebral Hem					

The sponsor provided additional data with the CT scans being reread by a pair of neuroradiologists. Based on their readings, 4 of the CT scans were reclassified. Patients ---------- and ---------- did not have evidence of a bleed on review (both were "bleeds" during the infusion period). Patients ---------- and ---------- had bleeds still but also evidence of different CT findings.

Patients in italics had a change in their CT scan reading from a bleed to no bleed as adjudicated by 2 independent neuroradiologists. Subjects in bold had changes in their CT scan readings, but still had evidence of a bleed on review.

Additional events have been reported and additional patients have been enrolled. These numbers are preliminary at this point. The best estimate based on the most current data would be a bleeding rate during infusion of approximately 1%.

Reviewer comment: These data are problematic. It reveals a rate of ICH that may be up to 5 times higher than seen in the phase 3 trial. These patients were enrolled with similar precautions as were taken in the phase 3 trial to minimize the risk of bleeding. It is a worrisome trend if in fact the open label trials are not as tightly controlled as the phase 3 trial. If the product were licensed, there would be less control and perhaps a greater incidence of ICH. This is only speculative, but still of concern. The sponsor has provided data and re-evaluations to minimize these numbers. Since many patients may never have a CT scan done if they have a catastrophic event in an ICU setting with multiple organ failure, these figures most likely represent an under-estimation of the true rate.

Preliminary safety data have also been submitted with summary tables as to the rate of serious bleeding events occurring during the infusion period and after the infusion. These data are presented below.

Table 102. Serious bleeding events reported in ongoing open-label studies

	Ongoing Studies	**Phase 3 Study rhAPC**	**Phase 3 Study Placebo**
During Infusion	30/941 (3.2%)	20/850 (2.4%)	8/840 (1.0%)
After Infusion	46/941 (4.9%)	30/850 (3.5%)	17/840 (2.0%)

Reviewer comment: As is noted with the increased rate of ICHs in the ongoing open label trials, there is a greater percentage of serious bleeding events in the open label trials compared to the phase 3 trials. These data are difficult to interpret because they are preliminary in nature. They highlight the need for post-marketing surveillance and ongoing studies do better define the risk of serious bleeding events and ICHs.

Summary of Safety

Sepsis is a difficult condition in which to detect adverse events due to the large and varied number of events associated with sepsis itself. In evaluating products for the treatment of sepsis, important safety events can easily be attributed to the underlying illness. There is a clearly identified increased risk of bleeding in patients treated with rhAPC.

Intracranial hemorrhages were identified in only 2 patients treated with rhAPC in the phase 3 trial. Additional uncontrolled data suggests this may under represent the actual rate. Additional intracranial hemorrhages may go undetected in situations where a CT scan, for practical reasons, is not performed. Thus, it is unclear what the true rate of intracranial hemorrhages may be.

Other major bleeding events occurring in contained non visible sites could be difficult to detect for the same reasons.
Though major bleeding events were identified as being, the true risk of these events remains somewhat uncertain.

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 similar rate of serious bleeding events in patients with a lower mortality risk compared to those with a higher mortality risk.
- There was a higher rate of serious bleeding events in the first APACHE II quartile in the rhAPC group compared to placebo.
- There was no mortality benefit observed in patients requiring emergency surgery in the rhAPC group compared to placebo.
- There was a higher mortality rate in the rhAPC steady state 4^{th} 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 attributed to the underlying illness of the patients.
- The rate of ICH may be significantly higher based on preliminary data submitted to the reviewer. This issue will be critical to define in future evaluations and use of the product.

Section VI-Advisory Committee, Approval and Labeling

Advisory Committee

The Anti Infective Drugs Advisory Committee (AIDAC) met on October 16, 2001 to render advice to the FDA and public on the safety and approval on drotrecogin alfa for use in patients with severe sepsis. The committee was divided regarding an approval recommendation. See Appendix 1 for in-depth discussion of the issues raised by AIDAC.

Approval

The FDA approved Xigris for use in patients with severe sepsis and high risk of death, e.g., as determined by the APACHE II score on November 21, 2001.

Labeling

Proposed Indication

The sponsor proposed "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".

Reviewer comment: The FDA approved the indication:

"Xigris is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II). Efficacy has not been established in adult patients with severe sepsis and lower risk of death. Safety and efficacy have not been established in pediatric patients with severe sepsis."

Proposed Contraindications

The sponsor proposed, "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."

Reviewer comment: The FDA approved contraindications are:

"Xigris increases the risk of bleeding. Xigris is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

- *Active internal bleeding*
- *Recent (within 3 months) hemorrhagic stroke*
- *Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma*
- *Trauma with an increased risk of life-threatening bleeding*
- *Presence of an epidural catheter*
- *Intracranial neoplasm or mass lesion or evidence of cerebral herniation*
- *Xigris is contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated) or any component of this product."*

Appendix 1

Rockville, MD
November 29, 2001

Dear AIDAC members and consultants,

On October 16, 2001, the members of AIDAC provided an extremely valuable service to the FDA and the American public through its deliberations regarding Xigris for the treatment of patients with severe sepsis. As you know, the committee was divided regarding approval and made many valuable and insightful comments. Subsequent to that time, some of you have contacted some of us at the FDA further expressing your opinions.

The deliberations of the AIDAC and the opinions of its members have been carefully considered by FDA. The concerns raised by those who did not favor approval at this time were taken very seriously and investigated to the extent we could. In the period since the meeting, many more analyses have been performed and some additional issues have been identified.

Last Wednesday, FDA approved Xigris for use in patients with severe sepsis and high risk of death, e.g., as determined by the APACHE II score. After full evaluation of the application, the committee's deliberations, and subsequent analyses, we are comfortable that the drug had been shown to be safe and effective in reducing mortality in these patients. While cognizant of important questions that remain unanswered we are confident that this drug can be used in a safe and effective manner at the present time. Given the importance of this drug and indication and the divided opinions on the committee, I felt it would be useful to explain how the agency dealt with some of the concerns expressed.

In analyzing notes from the meeting, the apparent reasons behind opposition to approval by some of the members included the following:

1. Inconsistencies between the first and second half of the trial, potentially attributable to
   - Changes in the product
   - Changes in the entry criteria
   - Changes in the endpoints
   - Changes in study sites
2. A feeling that the population studied was not representative of typical severe sepsis patients with regard to lack of chronic illness.
3. Concern about lack of reproducibility in sepsis trials in general
4. Concern about cost
5. Concern about unsafe off-label use
6. Concern about lack of efficacy in less severely ill patients.
7. Concern about limitations on benefit: survival increase was accompanied by much small increase in hospital discharge by day 28.

I will address each of these issues and how we took them into account in our review.

I would be interested in any feedback you might want to provide as to whether it would be useful to write up some of the materials herein for public dissemination or on any other matter. In preparing this memo, I have not made efforts to distinguish information that is in the public domain, e.g., discussed at AIDAC or posted in the briefing material or in the approved label, and information that is not, and it might be that some of the information herein is not publicly disclosable. However, it is my anticipation that if any is not currently disclosable it will be so very soon.

Inconsistencies between the first and second half of the trial

The p value for the interaction between the trial results pre- and post-amendment is 0.08. While this p value suggests that the impact of changes in the trial should be looked into, it is also not inconsistent with chance variation.

Analyses of various factors that might have led to outcome differences between the trial halves did not support concerns that any of the factors likely accounted for these differences. We have therefore concluded that the differences most likely did arise by chance and that the most appropriate assessment of the data does not involve dividing the trial into two portions.

Product Changes: The FDA requested and reviewed extensive data from studies of the product, both physicochemical and pharmacokinetic. We found no detectable differences between the materials produced before and after changes in the master cell bank. The results of these studies had not been presented in any significant detail to AIDAC as, given the negative findings, we had not thought believe the committee would have much interest. Further, the committee had been selected largely for clinical expertise, not protein chemistry expertise.

We are aware that differences in macromolecules may escape detection and that changes in master cell bank are substantial changes that can change the product. Nonetheless, as extensive analysis finds no difference, we deem it highly unlikely such differences account for different clinical outcomes. If, in fact, the new master cell bank results in a product difference and that difference accounts for the improved clinical results, then the newer product (i.e., product from the current master cell bank) is superior and effective. This conclusion would not argue against approval, it would only argue for careful product control to ensure that the desirable characteristics acquired were not lost.

Entry criteria: Several protocol amendments were made with the intent to exclude more effectively those patients with severe underlying disease who were likely to die from causes other than sepsis within 28 days. Analysis of the study population indicates the newer entry criteria were more effective in reducing the numbers of patients with severe underlying disease than had been the original criteria. Nonetheless, two avenues of analysis argue strongly that this factor did not account for the improved study outcomes after the amendment.

First, as discussed at the AIDAC meeting, an analysis of the subset enrolled in the first half who would have been excluded by the newer entry criteria showed a RR of 0.8 in favor of the drug. Thus this group was showing more evidence of drug effect than was

the group that would not have been excluded by the new criteria (RR=0.99). Since the potentially excluded population showed greater evidence of drug benefit, one can conclude both that the sponsor did not exclude this population on the basis of unblinding of interim data and that the exclusion of this population would not likely have accounted for the greater drug benefit seen after the amendment.

Second, and even more compelling, new analyses performed by FDA subsequent to the AIDAC meeting compared drug effect in patients who had chronic health problems as defined by APACHE II to the effect in those who had not. The APACHE II system assigns chronic health points only to those patients with rather severe underlying diseases predating the acute illness (FDA briefing book, appendix 3; Crit. Care Med., 1985, 13:818-829). Although patients with chronic health problems comprised only about 20% of the total population, this group experienced most of the beneficial effect. Treatment associated mortality benefit was 2.6% in the 1345 patients without APACHE II chronic health points (26.5% on placebo, 23.9% on Xigris, relative risk = 0.90) but 24.8% (47.2% on placebo, and 22.4% on Xigris, relative risk = 0.47) in the 345 patients with such chronic health problems. The p value for the interaction of drug effect and APACHE chronic health points was 0.01. Thus, it does not appear that the success of this trial was dependent upon exclusion of patients with underlying chronic disease. Such patients appeared to experience the greatest drug benefit and the effect of the protocol amendment was to decrease the proportion of such patients enrolled. These finding argue very strongly against the hypothesis that the exclusion of patients with severe underlying disease might account for the greater drug benefit observed in the second half of the study.

Endpoint changes: Some concern was expressed at the AIDAC meeting about what seem to have been changing from two endpoints to one. Further exploration of trial records confirmed that there had always been only one primary endpoint, adjusted 28 mortality in all patients randomized. In the original protocol, there had been 2 efficacy *objectives*, one to assess mortality in all patients randomized, another to assess mortality in the subset with APC deficiency. However, from the start, the only primary endpoint was the analysis of all patients randomized and the analysis of the subset with APC was a secondary endpoint. For the explicit purpose of avoiding any possible confusion regarding multiplicity of endpoints, the sponsor proposed and the FDA accepted modifications of the protocol objectives to better reflect the endpoint. Thus, the assessment of mortality in the subset with APC deficiency became a secondary objective rather than a primary objective. This change was harmless and of little significance as FDA routinely follows the endpoints specified as endpoints in the analysis plan. In any case, the analysis of all patients and the subset analysis give rather similar results.

The protocol amendment also made a minor change the mechanisms of analysis of the endpoints slightly. Protein C activity class replaced septic show as a covariate for the analysis. This change had negligible effect on the analysis.

Changes in study sites: Several sites were closed to enrollment before the protocol amendment, mostly due to poor enrollment or due to resource issues (e.g., the PI moved away). Results from sites that were dropped (52 pts in 20 sites) did not show evidence of drug effect. However, we have not found any indication of bias or unblinding in stopping sites. All but 2 that were stopped were had 4 or fewer patients enrolled. All 20 were

dropped prior to the first interim efficacy analysis indicating that unblended outcome data did not play a role. Even had data had been unblinded, there were too few patients at any one of these sites at the time of closing to enrollment to lead one to conclude that it was not achieving good drug effect. The 2 sites dropped after larger enrollment (7 and 9 patients) were dropped because an investigator moved away and because enrollment had slowed. FDA contacted these sites and investigators and confirmed that there were no suspicious reasons for closing enrollment at the sites.

Several sites were added during the trial, reportedly in an attempt to improve accrual. Sites that were added later tended to show stronger evidence of drug effect. The sites that were added were sites that had enrolled and performed well in another Lilly sepsis trial. There were over 40 such sites. Most had only a few patients as the trial was unexpectedly stopped at interim analysis shortly after the sites were added. About 180 patients were treated at these 45 sites. We did not identify any systematic reason to account for the finding of better treatment effect at those sites, nor to suspect that they biased the study results.

Other observations: Also noteworthy is the analysis of results pre- and post-amendment by APACHE quartile. The suggested inconsistency between early and late results was essentially limited to the first quartile (i.e., low risk patients) which had a relative risk of 2.3 (favoring placebo) early and 0.7 (favoring drug) late. Treatment effect in the 4th and 3rd quartiles, the population that will be targeted by the labeling, was quite consistent over time in the extent to which the data favored treatment.

We are left believing that most or all of the difference in results between early in the trial and later in the trial was attributable to chance effects as reflected by the p value of 0.08.

Population not representative of severe of sepsis due to exclusion of those with anticipated early mortality

As discussed, this study attempted to exclude patients at high risk for mortality from underlying disease. Thus, data were not generated in this population, probably a significant share of sepsis patients in some institutions, and the labeling so indicates. However, the data argue strongly against a conclusion that the drug may not work in patients with underlying serious disease.

As noted above, the majority of the treatment effect was observed in the small subset of patients with serious chronic illness as defined by APACHE II. Indeed, the relative risk for patients with underlying disease was much lower than in patients without such disease suggesting much more benefit in the former group. There was a relative risk of 0.47 in patients with chronic health problems (a 53% relative reduction in mortality) vs. 0.90 in others (a 10% relative reduction in mortality); the p value for interaction of treatment effect with APACHE II chronic health evaluation was 0.01. This finding, unknown at the time of AIDAC, argues strongly against labeling restricted to patients without severe underlying disease. It also indicates that, while such patients may be underrepresented in the study population, the underrepresentation probably does not create a problem with generalization to most patients with chronic health problems.

A subset of patients with chronic health problems of particular interest are those with immunosuppression since one would have somewhat larger concerns that a drug that could alter immune responses might act differently in such a population. In the small

population with immunosuppression, mortality was 35% on placebo and 30% on APC. While too small to be conclusive, these numbers do not suggest a problem of atypical drug effect in this group

Another group excluded from the trial in which one would have high concerns about differing drug responses, especially safety, are those at high risk of bleeding. One should not assume favorable risk-benefit in such patients. This concern about the risks of treatment in such patients has been dealt with through contraindications and warnings.

Concern about lack of reproducibility of results in sepsis trials in general

This concern, expressed at AIDAC and elsewhere, results on the fact that data suggesting efficacy for a variety of products (e.g----------) were not borne out by subsequent trials. The situations in those cases were vastly different from this situation. In none of those cases did the suggestions of benefit come from a prospectively defined primary endpoint in an adequately powered trial. The suggestions of benefit came from secondary or post-hoc subset analyses based on shock, APACHE score, IL-6 level, or bacteriological results and/or from small phase 2 studies. The fact that such suggestions were not borne out by further trials is not surprising and does not suggest inconsistencies between early trials and late trials; it simply highlights the fact that secondary and post-hoc analyses can often be misleading and findings should be confirmed before being relied upon.

The PROWESS trial had 1690 patients and a p value of 0.005 on the prospectively defined primary endpoint. This places it among the most powerful demonstrations of mortality benefit in the history of clinical trials. (Indeed, more powerful demonstrations are improbable as data monitoring committees tend to stop trials for ethical reasons when strong mortality differences occur as happened in this case.) Thus, this outcome is far different from the suggestions of benefit in earlier trials and the likelihood the results would not be reproduced is far, far lower.

A single mortality trial with p=0.005 is well within the range of efficacy evidence upon which FDA approvals are made; it is often deemed unethical to continue placebo controls after such a finding. Indeed, in stopping the PROWESS trial early, the DMC had made such a determination.

Cost

One committee member noted cost considerations as a key factor in his vote against approval. FDA does not consider such issues in approval decisions.

Off-label use

One advisor expressed the opinion that the drug may benefit some patients but there was substantial concern that it might be used too broadly, doing more harm than good. FDA shares this concern. We are particularly concerned that use in pediatric patients, use in patients with severe sepsis and lower risk of mortality (e.g., APACHE <25), use in patients who do not have severe sepsis with end organ dysfunction, and use in patients with elevated risk of bleeding might do more harm than good. We believe FDA and Lilly have written a label that will minimize inappropriate use. I strongly encourage the members and consultants of AIDAC, as thought leaders in this field, to assist in efforts to minimize off-label use. Assuming the drug will, in fact, be costly, it is likely that use will be carefully overseen by payers and that off-label use will be limited. Of note, Lilly has

made commitments, as recommended by AIDAC, to perform rather large post marketing controlled studies that will address use in lower risk patients and pediatric patients, key populations in which off-label use may occur and in which it is unknown whether net benefit or net harm would accrue.

Lack of efficacy in less severely ill patients – limited indication

Despite persistent arguments to the contrary from Lilly, the advisory committee gave a very strong endorsement to the FDA determination that there was strong suggestion of treatment interaction such that treatment effect appeared substantially greater in those patients with higher risk of mortality. Notwithstanding assertions at AIDAC by Lilly to the contrary, analysis by APACHE II subsets was not only prospectively planned but a critical prospective analysis. Also notwithstanding implications to the contrary, the APACHE II, as administered in this trial, was a powerful predictor of mortality - the best by far, of covariates measured. The suggestion of a treatment effect interaction with APACHE II was supported by suggestions of interaction with each component of the APACHE II (age, acute physiology score, and chronic health score) and with other critical predictors of outcome, notably the number of organ failures. Thus, in the PROWESS study, there was a prior hypothesis, very strong biologic plausibility, and strong and consistent evidence in favor of the interaction of treatment effect with risk of death.

The committee members endorsed the FDA interpretation that the data strongly suggested a treatment interaction with risk such that the drug might not be effective in patients at lower risk of death. Most voted that, were the drug approved, it should be limited to patients with higher risk. One even commented that the evidence for interaction was sufficiently strong that further study in lower risk patients might not be safe. However, a few advisors, despite their concern that the drug did not work in such patients, said that if approved, the drug should be approved for all patients eligible to enroll. Those same advisors then voted against approval. Based on the comments made at AIDAC, it is clear this group felt a drug should be either approved for the entire population eligible for the study or it should not be approved and that it inappropriate to approve a drug for a subset of those enrolled. This feeling, together with concerns about less severe patients appeared to contribute to a decision to vote against approval. I strongly disagree that approval for a subset of those studied is not an appropriate option.

Were it the case that an indication can only be identical to the entry criteria, in successful trials in situations in which true subset differences exist, the agency and society would have to chose between not approving a drug despite existence of a subpopulation in which efficacy was not in doubt or approval including a population in which safety and efficacy were significantly in doubt. Further, were that the case, we would be vulnerable to a sponsor practice of artificially designing very broad criteria in order to expand the potential market and then enrolling largely those patients in a smaller subset in whom benefit is expected. For these reasons, FDA must explore not only the entry criteria but the nature of the population enrolled and, the plausibility of and the evidence in support of potentially different treatment effects within that population studied (and, in some cases, the evidence supporting generalizablity beyond the populated studied) before determining the breadth of the indication.

There is no inconsistency here. FDA, and the scientific community in general, view subset findings as hypothesis generating. Therefore, in a failed trial, the suggestion of efficacy in a subset hardly meets the legal standard for evidence of efficacy – the appropriate course is not to approve and (perhaps) to conduct further trials. When an overall result indicates efficacy and meets legal standards for approval, analysis suggesting lack of efficacy in a subset is also considered hypothesis-generating, entirely consistent with the other situation. When there is a valid and highly plausible hypothesis that a drug does not work and perhaps may be harmful in a population, the proper regulatory action is often to limit the indication. If the drug were approved for an indication involving lowering mortality, including in the subset, the likelihood that the hypothesis of lack of efficacy could be appropriately tested in the subset would be substantially diminished. In the particular case at hand, as discussed at AIDAC, there was rather strong evidence, consistency from various analyses, and biologic plausibility supporting the hypothesis that treatment effect is substantially reduced, absent, or reversed in lower risk patients. Thus, the FDA approach is quite consistent in treating subset findings and hypothesis-generating.

As with nearly all subset analyses, it would generally be risky to draw definitive conclusions about lack of efficacy in a subpopulation of a study demonstrating efficacy. However, such analyses can clearly raise doubts (or generate hypotheses) so strong that the legal standard for demonstration of efficacy in the subpopulation is not met and that it is in the interest of public health to limit the indication to exclude the subpopulation. Further, in such cases, a broad indication for mortality benefit including a population of patients in whom safety and/or efficacy were substantially in doubt would likely inhibit or preclude further testing in that population and could lead to substantial harm. The hypothesis generated would not be tested. Thus, in situations such as this one, the limited approval can be consistent with the law and in the interest of science and medicine as well as public health.

Based upon comments at the AIDAC meeting, I believe that some of the advisors restricted their choices to approval for the broad population or non-approval, inappropriately rejecting on methodological grounds the option of limited approval. Indeed, one advisor indicated such an approval would be inconsistent with the situation for the ----------. I find the situations quite consistent - in the ----------, we considered the suggestion of efficacy in a subset to be hypothesis-generating and required another study to test the hypothesis, in the rhAPC study, we considered the lack of efficacy in a subset to be hypothesis generating and we similarly have required another study to test the hypothesis, limiting the approval accordingly.

Limitations on benefit

As shown in FDA analyses, while survival in the Xigris arm was higher by 6% in the APC arm, hospital discharge was only 1% higher (1.7% more were at home, 0.7% fewer in a nursing home). Thus, 5% more patients were in the hospital at 28 days (half in ICU) and only one percent more discharged. This suggests that the 6% mortality difference at 28 days may overestimate drug effect. Some light was shed on this phenomenon by the new analyses indicating that most of the mortality benefit was in the subset of patients

with APACHE chronic health points. For patients with this level of disease (symptomatic cirrhosis, renal dialysis, class IV heart failure, immunosuppression), it is not surprising that many of the survivors were hospitalized at day 28.

Lilly has committed to obtain longer-term follow up in the PROWESS patients and this should be achievable in a few months. While this will be quite informative, I do not believe it critical to the approval decision. Reduced mortality is perhaps the most important clinical benefit endpoint, demonstrated by only a limited number of drugs. The agency believes the substantial effect on mortality demonstrated for this drug provides sufficient evidence of efficacy, even in light of its significant toxicities and the fact that some of the excess survival may be in hospital and could turn out to be short-lived.

Post marketing studies

In keeping with the advice of AIDAC and with FDA requests, Lilly has committed, inter alia, to conduct rather extensive post-marketing studies in the following areas:

- Controlled trials in patients at lower risk
- Controlled trials in children
- Controlled trials as to whether rhAPC is best used with or without low dose heparin.
- Obtaining follow-up data on PROWESS patients to confirm hospital discharge status and other longer term outcomes.

Summary

In summary, all the concerns of the members of the advisory committee, and in particular those concerns that formulated the basis for some to oppose approval, were taken very seriously and considered in light of all the data including new analyses. After this process, we concluded that none of the concerns negated the fact that safety and efficacy had been demonstrated to the appropriate legal and scientific standard. Indeed, this trial, stopped early with a p value of 0.005, has one of the most powerful findings of mortality benefit amongst drug development trials. The findings seem quite robust. With the restrictions, contraindications, and warning in the label (e.g., APACHE), this drug can be targeted to patients for whom the evidence of substantial net benefit is strong. Meanwhile, controlled studies in selected other groups will proceed.

Sincerely,

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Appendix 2

Financial Conflict of Interest

Presented below are sites in which there was a significant equity interest in the sponsor. Less than 1% of patients were enrolled at these sites.
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Table 103. Financial disclosure sites with significant equity interest

	Placebo		rhAPC	
Site	Alive	Died	Alive	Died
------	1	0	0	0
------	5	2	5	1
------	4	2	6	2

Reviewer comment: Three investigators at 3 sites had a significant ($25,000 or more) equity interest. The total number of patients at these three enrolled less than 1% of patients. Numbers of patients were few, so there appears to be minimal impact and no selection bias.

Appendix 3

Narratives for deaths and serious adverse events

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

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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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).

Serious Bleeding Events

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 ---------- (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 ---------- (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.
- ----------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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (rhAPC). This patient experienced a fatal pulmonary hemorrhage. (see previous discussion)

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

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

- Patient ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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.

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 ---------- (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 ---------- (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 ---------- (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 ---------- (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 ---------- (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.

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 nine, 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-year-old male with endocarditis and post-op bleeding after valve replacement (OR- 24 hours after finishing infusion). The patient survived and was discharged from the hospital
- 56-year-old 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-year-old had indwelling foley and presumed urosepsis had the study drug stopped for 2 hours 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.
- 27-year-old 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.
- 74-year-old male with gram- sepsis developed an intracerebral hemorrhage while on study drug. Patient expired.
- 32-year-old male s/p significant MVA (broken ribs, pulmonary contusion, splenic laceration and acetabular fracture) entered into study and died of an intrathoracic bleed while on study drug.
- 47-year-old 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-year-old 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.
- 40-year-old 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 hours
  - 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 hours 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

---------- – 2 organ failure (Resp, Ren)
60-year-old female with COPD and pneumonia 4 hours into rhAPC treatment developed cardiac dysrythmia and died. Patient's O2 sats had dropped and she had become hypotensive.

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

---------- – 3 organ failure (Resp, CV, Hem)
74-year-old male with sepsis due to pneumonia and DIC. After 14 hours of study drug he became unresponsive with CT showing massive intracranial bleed.

---------- – 2 organ failure (Resp, Hem)
32-year-old male status post MVA ruptured aorta while on study drug (96.1 hours).

---------- – 1 organ failure (CV)
75-year-old female with pneumonia and refractory shock. She received 69 hours of rhAPC till the family withdrew life support and the patient expired.

---------- – 3 organ failure (Resp, CV, Ren)
73-year-old female with pneumonia. She received 18.6 hours of rhAPC. She developed liver failure as well and died on study day 3.

---------- – 2 organ failure (Resp, CV)
80-year-old female with urosepsis and history of transitional cell CA of the kidney. She received 45 hours of rhAPC but due to worsening pulmonary status, life support was withdrawn and the patient expired.

---------- – 4 organ failure (Resp, CV, Heme, Ren)
69-year-old male with pneumonia and underlying COPD. He received 65 hours of rhAPC and died of multi-organ failure.

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

---------- – 3 organ failure (RESP, CV, Ren)
69-year-old male with pneumonia. He received 96 hours of the study drug and died 10 minutes after the drug was finished of refractory hypoxemia and shock.

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

---------- – 3 organ failure (Resp, CV. Ren)
21-year-old female with pneumonia. She received 48 hours of rhAPC. She died of refractory hypoxemia, anuria and acidosis.

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

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

77-year-old male with pneumonia and respiratory failure received 96 hours of rhAPC and died on day 12 of cardiac arrest.

86-year-old male post-op surgery for necrotic bowel received 96 hours of rhAPC and died on day 14 with ARDS.

31-year-old female post mediastinal abscess drainage after a traumatic intubation and a perforated esophagus. She received 96 hours of rhAPC and died on day 11 of ARDS.

90-year-old female with sepsis and pneumonia, received 97 hours of rhAPC and died on day 9 of multi-organ failure.

---------- – 3 organ failure (Resp, CV, Ren)
46-year-old male s/p (2 day) esophagectomy developed pneumonia. History of CAD died on study day 6 of ischemia and cardiac arrest. Received 96 hours of study drug.

39-year-old male with suspected meningococcal meningitis. He received 96 hours of therapy and died on day 10 of overwhelming sepsis.

*---------- – 2 organ failure (Resp, MA)
46-year-old male sepsis 11 day s/p gastrectomy and jejunal bypass. 96 hours 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.

51-year-old male received 96 hours rhAPC, was post-op bowel infarction and sepsis died suddenly on day 13. ? cardiac etiology.

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

79-year-old male post-op rectum resection for CA had perforation and became septic. Re-operated on for persistent leak, died on day 6.

47-year-old male with drainage of perianal abscess, developed retroperitoneal abscess and sepsis. Patient died on day 14.

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81-year-old female s/p surgery for bowel obstruction, developed pneumonia and sepsis. Received 96 hours of rhAPC. Requested DNR status day 9 and died day 9.

79-year-old male s/p surgery for perforated sigmoid diverticula also acute cholecystitis. Patient received 96 hours rhAPC and recovered. Developed recurrent intra-abdominal abscess, requiring drainage, became septic again and family withdrew care. Patient died day 9.

57-year-old male with pneumonia and sepsis. 96 hours of treatment. Patient died on day 6 of worsening sepsis.

78-year-old male lung cancer s/p surgery lobectomy with post-op pneumonia. Patient received 96 hours of treatment and died on day 10 of worsening sepsis.

78-year-old female post-op surgery for perforated duodenal ulcer and peritonitis. Received 94 hours of therapy, and died on day 8 of refractory sepsis.

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

67-year-old male with pneumonia and sepsis. Received 101 hours of therapy. Patient died on day 24 of refractory hypoxia.

26-year-old male with abscess of arm (I+D) developed staph sepsis. He received 96 hours of therapy and died on day 14 of multi-organ failure.

44-year-old male with pneumonia and sepsis. He received 97 hours of rhAPC and died on day 6.