QUESTIONS FOR AIDAC - DROTRECOGIN ALFA (ACTIVATED) FOR THE TREATMENT OF SEVERE SEPSIS

I. PATIENT ENTRY CRITERIA

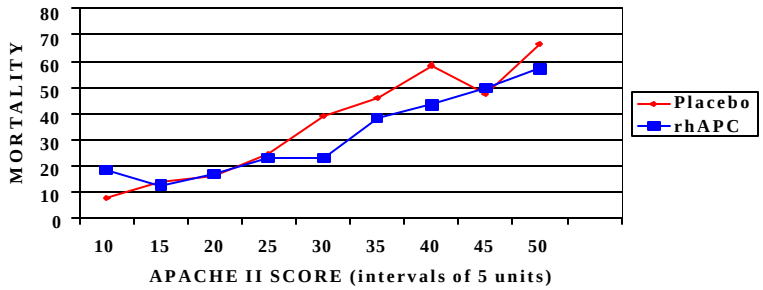
Data supporting the efficacy of drotrecogin alfa (activated) were derived from a single phase 3 randomized, placebo controlled trial of nearly 1700 adult patients with severe sepsis. Treatment with drotrecogin alfa (activated) resulted in a significant reduction in 28 day all cause mortality compare to placebo treated patients (25% vs 31%, respectively, p= 0.005). Eligibility required meeting three or more SIRS criteria, at least one of five organ failure criteria, and with evidence of infection. Midway through the trial, the eligibility criteria were modified to more clearly exclude patients who had a high probability of dying from an underlying non-sepsis related condition within the 28-day study period. As a result of the modifications, fewer patients with malignancy, chronic APACHE II health points, who were immunocompromised, etc. were enrolled.

1. Please comment on the entry criteria, and the implications of the modified criteria. Do the entry criteria define a population appropriately described as having severe sepsis?

II. TREATMENT EFFECT IN SUBGROUPS DEFINED BY DISEASE SEVERITY

The reduction in mortality was not consistent across all prospectively defined patient subgroups. The data suggest there may be a different mortality effect in less severely ill patients with better survival prognosis. Mortality in patients in the lowest APACHE II quartile was higher in the drotrecogin alfa (activated) group compared to placebo patients, and a smaller treatment benefit was observed in those in the second APACHE II quartile compared to patients who were in the 3rd and 4th APACHE II quartiles as shown in the table and figure below.

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



2. Please comment on the implications of the analysis of treatment effect and disease severity (i.e., mortality by APACHE II quartile subgroup analysis). Should the sponsor conduct further controlled studies of the effects of drotrecogin alfa (activated) in patients with severe sepsis and more favorable prognosis (e.g., lower APACHE II scores)?
3. If licensed, should the indication for drotrecogin alfa (activated) be limited to the subset of patients with severe sepsis who have a poorer prognosis?
    a) If so, how might the indicated population be described?
    b) If not, will an indication for severe sepsis without such limitations adversely impact the ability to conduct a placebo controlled trial in the population with less poor prognosis?

III. TREATMENT EFFECT IN PATIENTS WITH DISSEMINATED INTRAVASCULAR COAGULATION

Drotrecogin alfa (activated) has anti-thrombotic and pro-fibrinolytic properties that may contribute to its mortality effects in patients with severe sepsis. Thus, one might see different effects in patients with sepsis who have DIC from those who do not. The majority of patients in the trial (> 90%) had laboratory evidence of DIC at study entry, as defined by the presence of 2 or more of the following laboratory findings:

1. platelet count <100,000/mm^3 or 50% decrease in the past three days
2. PT or APTT >1.2 x ULN
3. D-dimer >ULN (0.4 ng/ml)
4. Protein C, Protein S or Anti-thrombin <LLN

Of note, in 2 individuals who did not have DIC at baseline and 113 patients in whom insufficient laboratory data were available to determine DIC, there was little suggestion of a treatment effect.

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

4. Should drotrecogin alfa (activated) be further evaluated in controlled studies in patients with severe sepsis who do not have laboratory evidence of DIC?
5. Given the limited information available about treatment effects in patients not diagnosed with DIC, if licensed, should the indication for drotrecogin alfa (activated) be limited to those patients with severe sepsis who have laboratory evidence of DIC?

IV. TREATMENT EFFECT AND HEPARIN USE

A. Low Dose Heparin

Many patients received low dose heparin for prophylaxis of deep venous thrombosis. Both heparin and drotrecogin alfa (activated) have anti-thrombotic effects. Mortality was lower in patients who received drotrecogin alfa (activated) than in those receiving placebo regardless of whether low dose heparin was used, but the treatment effect was several fold greater in patients not on low dose heparin, as seen in the table below.

On Heparin	rhAPC		Placebo		
	N	Mortality N (%)	N	Mortality N (%)	Mortality difference %
At baseline	532	138 (26)	559	170 (30)	4
During infusion	634	158 (25)	637	179 (28)	3
By day 1*	567	134 (24)	578	154 (27)	3
Not on Heparin	rhAPC		Placebo		
	N	Mortality N (%)	N	Mortality %	Mortality difference %
At baseline	318	72 (23)	281	89 (32)	9
During infusion	216	52 (24)	203	80 (39)	15
By day 1*	252	45 (18)	222	65 (29)	11

*****pts who died by day 1 are excluded from this analysis

If the differences between drotrecogin alfa (activated) effects in patients on low dose heparin (3-4%) and patients not on low dose heparin (9-15%) are real, then the question of whether to administer low dose heparin when using drotrecogin alfa (activated) could be very important. Potential mechanisms by which low dose heparin might influence the drotrecogin alfa (activated) effect include: low dose heparin may provide some benefits, leaving less residual benefit for the addition of drotrecogin alfa (activated), and low dose heparin use might abrogate some of the benefits from drotrecogin alfa (activated), perhaps through synergistic toxicity.

6. Should more studies be done addressing whether and how low dose heparin should be used in patients receiving drotrecogin alfa (activated)?

B. Therapeutic Heparin

The role of therapeutic doses of heparin (i.e., high dose, intravenous) in sepsis-related DIC is controversial. There have been no adequate controlled trials of therapeutic heparin in this setting. However, some clinicians favor its use there is high concern about thrombotic complications. Clearly, therapeutic heparin and drotrecogin alfa (activated) should not be administered simultaneously because of bleeding risks. In the phase 3 trial, therapeutic heparin use was an exclusion criterion. If any patient subsequently required therapeutic heparin, the protocol specified that the drotrecogin alfa (activated) (or placebo) infusion be discontinued.

Were drotrecogin alfa (activated) approved, clinicians treating patients with severe sepsis and DIC will face a choice of therapy with drotrecogin alfa (activated) or therapeutic heparin, but not both due to bleeding risks.

7. Please discuss how such a choice might be made. Are there situations in which heparin use rather than drotrecogin alpha (activated) might be appropriate? Is there need for further studies and, if so what types of studies would best address this question?

V. SAFETY OF DROTRECOGIN ALFA (ACTIVATED)

Patients with severe sepsis who were at increased risk for bleeding were excluded from the phase 3 trial, including:

- Any patient who had undergone major surgery[1], any postoperative patient who demonstrated evidence of active bleeding; or any patient with planned or anticipated surgery during the study drug infusion period[2],
- History of severe head trauma that had required hospitalization, intracranial surgery, or stroke within 3 months of study entry, or any history of intracerebral arteriovenous malformation, cerebral aneurysm, or central nervous system mass lesion. Patients with an epidural catheter or who anticipated receiving an epidural catheter during study drug infusion
- History of congenital bleeding diatheses, such as hemophilia.
- Gastrointestinal bleeding within 6 weeks of study entry that required medical intervention unless definitive surgery had been performed.
- Trauma patients at increased risk of bleeding[3],
- Patients taking the medications with known bleeding risks[4]

The number of patients experiencing serious bleeding adverse events[5] (AEs) during the phase 3 study was 3.5% (30/850) in those receiving drotrecogin alfa (activated) and 2% (17/840) in those

[1] defined as surgery that required general or spinal anesthesia that was performed within the 12-hour period immediately preceding study drug infusion;

[2] such as patients with staged surgeries or burn patients with planned excisions and grafting during the study drug infusion period.

[3] for example: flail chest; significant contusion to lung, liver, or spleen; retroperitoneal bleed; pelvic fracture; or compartment syndrome.

[4] Therapeutic heparin (Note**:** Prophylactic unfractionated heparin up to 15,000 units/day was permitted), Warfarin, if used within 7 days of study entry and if prothrombin time was prolonged beyond the upper limit of normal for the institution, Acetylsalicylic acid (ASA) >650 mg/day or compounds that contain ASA >650 mg/day within 3 days of study entry, Thrombolytic treatment within 3 days of study entry, Glycoprotein IIb/IIIa antagonists within 7 days of study entry.

receiving placebo. 20 of the 30 bleeding events in the drotrecogin alfa (activated) group occurred during days 1-5 (during or immediately after the infusion) for a rate of 2.3% (20/850) compared to a placebo rate of 1% (8/840). Of these, 12 occurred during days 1-2 and the rest days 3-4(or 5). Four patients receiving drotrecogin alfa (activated) in the phase 3 study were recorded by investigators as having died from bleeding complications (intracranial, pulmonary or intra-thoracic related bleeds) attributable to study drug, while no patients receiving placebo in this study were thus identified. In the uncontrolled studies, where monitoring and or entry criteria may be somewhat different from the phase 3 trial, 13 of 520 patients have developed intracranial bleeds while on study, 8 of whom had the bleed during the infusion or within one day of stopping the infusion.

8. Given that the bleeding events are greatest during the drotrecogin alfa (activated) infusion, should further dose optimization studies be conducted, for example of infusion duration, with the goal to minimize major bleeds while preserving efficacy?
9. If licensed, should drotrecogin alfa (activated) be contra-indicated in patients with conditions that led to exclusion from the phase 3 trial because of high risk for bleeding? What, if any other, characteristics of patients at high risk for bleeding (e.g., thrombocytopenia) should be specifically identified in product labeling?

VI. OVERALL BENEFIT/RISK ASSESSMENT

10. Do the available safety and efficacy data support an indication for use of drotrecogin alfa (activated) in adult patients with severe sepsis (with any of the limitations discussed above)?

VII. PEDIATRIC STUDIES

The sponsor is seeking an indication for use of drotrecogin alfa (activated) in pediatric patients, and cites the regulations which state "that the FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use…(when the agency has) 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 to pediatric patients". The sponsor asserts that sepsis is sufficiently similar in pediatric and adult patients and that similarity of effects between pediatric and adult patients could be sufficiently demonstrated by studying pharmacodynamic parameters, primarily D-dimer formation, following drotrecogin alfa (activated) treatment.

Limited pediatric data are available, all uncontrolled. The majority of the data are derived from a safety and pharmacokinetic/pharmacodynamic (PK/PD) study in patients age 0 to 18 years with sepsis. Additional small numbers of pediatric patients with sepsis and/or purpura fulminans were enrolled in other studies. The dose and duration selected for pediatric patients was based on the ability of dotrecogin alfa (activated) to reduce D-dimer levels to a similar degree as was found in the studies in adult patients. In general, the pediatric experience indicated similar PD effects

[5] Bleeding events defined as serious adverse events included any intracranial hemorrhage, any life threatening bleed, any bleed that required 3 or more transfusions of PRBCs on 2 consecutive days, or was reported as a bleeding event and met SAE reporting criteria (prolonged hospitalization, etc.)

with respect to the adult experience but the absence of controlled data and the small numbers of pediatric patients studied preclude meaningful conclusions. Of note, mortality in the pediatric study was 10%, lower than the overall mortality in the adult study. As discussed, data from the adult study suggest the possibility that the drug effect is absent in the subpopulation with most favorable prognosis and lowest mortality.

11. Is severe sepsis in children sufficiently similar to severe sepsis in adults such that it would support extrapolation of the efficacy of drotrecogin alfa (activated) from adults to children based on PK and PD data in lieu of adequate and well-controlled efficacy data in pediatric patients?
12. If the answer to the above is yes, then is D-dimer formation an appropriate PD marker to indicate a similar drug effect? If D-dimer is not an appropriate PD marker, please discuss other potential PK/PD markers that could establish similarity of effect between adult and pediatric populations.
13. If the answer to #11 is no, please discuss the types of additional clinical data that should be generated to support an indication for pediatric sepsis.