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Clinical Study Summary: Study F1K-MC-EVBQ

A Phase IIIb Study to Determine Efficacy and Safety of Extended Drotrecogin Alfa (Activated) Therapy in Patients with Persistent Requirement for Vasopressor Support After 96-Hour Infusion with Commercial Drotrecogin Alfa (Activated)

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Title of Study: A Phase IIIb Study to Determine Efficacy and Safety of Extended Drotrecogin Alfa (Activated) Therapy in Patients with Persistent Requirement for Vasopressor Support After 96-Hour Infusion with Commercial Drotrecogin Alfa (Activated)	
Investigators: This multicenter study included 64 principal investigators.	
Study Centers: This study was conducted at 64 study centers in 9 countries.	
Length of Study: 2 years, 10 months Date of first patient enrolled: 26 June 2004 Date of last patient completed: 8 May 2007	**Phase of Development:** 3b
Objectives: The primary objective was to investigate, in severe sepsis patients with persistent vasopressor-dependent hypotension at the end of a 96-hour infusion of commercial drotrecogin alfa (activated), whether continued administration of drotrecogin alfa (activated) for up to 72 additional hours resulted in more rapid resolution of vasopressor-dependent hypotension versus placebo. Secondary objectives were (1) to evaluate if extended treatment with drotrecogin alfa (activated) compared with placebo reduced 28-day, all-cause mortality [28-day period began at the start of commercial drotrecogin alfa (activated) infusion] and in-hospital mortality, (2) to evaluate the effects of extended drotrecogin alfa (activated) compared with placebo on organ function status, (3) to evaluate the effects of extended drotrecogin alfa (activated) compared with placebo on various biomarkers, and (4) to investigate the safety profile of an extended infusion of drotrecogin alfa (activated).	
Study Design: This study was a multicenter, double-blind, randomized, placebo-controlled study of adult patients with severe sepsis and persistent vasopressor-dependent hypotension who received commercial drotrecogin alfa (activated) 24 µg/kg/h. An extended infusion of drotrecogin alfa (activated) or placebo was administered for up to 72 hours following the 96-hour infusion of commercial drotrecogin alfa (activated). Patients were treated in a hospital intensive care unit. Patients were followed until discharge from the study hospital or Study Day 90, whichever came first. Survival status was assessed at 28 days from the start of the commercial drotrecogin alfa (activated) infusion.	

Number of Patients: It was originally planned to enroll 270 patients in the study; however, the protocol was amended and the planned enrollment was reduced to 200 patients because of slow recruitment. Planned: total 200; drotrecogin alfa (activated) 100; placebo 100 Randomized: total 199; drotrecogin alfa (activated) 98; placebo 101 Received study drug: total 193; drotrecogin alfa (activated) 94; placebo 99 Completed: total 191; drotrecogin alfa (activated) 94; placebo 97
Diagnosis and Main Criteria for Inclusion: Eligible patients were adult patients (at least 18 years old) with severe sepsis who had received at least 84 hours of a planned 96-hour infusion of commercial drotrecogin alfa (activated) and who continued to require vasopressor support.
Test Product, Dose, and Mode of Administration: Drotrecogin alfa (activated) 24 μg/kg/h administered as a continuous intravenous infusion.
Reference Therapy, Dose, and Mode of Administration: Placebo, sterile 0.9% sodium chloride, administered as a continuous intravenous infusion.
Duration of Treatment: Patients received study drug for a maximum of 72 hours.
Variables: **Efficacy.** The primary efficacy endpoint was the time to resolution of vasopressor-dependent hypotension. Secondary efficacy endpoints were 28-day all-cause mortality, in-hospital mortality, change in organ function as measured by Sequential Organ Failure Assessment (SOFA) scores, and evaluation of biomarkers (protein C activity level, D-dimer level, and prothrombin time). **Safety.** Safety was assessed by evaluating the occurrence of the following adverse events: serious adverse events, including serious bleeding events, nonserious bleeding events that led to or contributed to the need for transfusion of packed red blood cells, study-drug-related nonserious adverse events, and adverse events that led to the discontinuation of the study drug infusion. Events leading to the clinical outcomes that were associated with the severe sepsis syndrome (for example, death, organ dysfunction, or systemic inflammatory response syndrome) were not recorded as adverse events unless the investigator believed the events may have been caused by study drug.
Evaluation Methods: A sample size of 200 patients (100 in each treatment group) had 81% power to detect a difference in time to resolution of vasopressor-dependent hypotension using the log rank statistic with a two-sided significance level of 0.1 if the true hazard ration is 0.59. A hazard ratio of 0.59 corresponds to a difference of about 19% between the two treatment groups in the percentage of patients whose cardiovascular failure resolved after 72 hours of extended therapy with drotrecogin alfa (activated). The intention-to-treat population was defined as all randomized patients who received study drug for any length of time. For the primary analysis, time to resolution of vasopressor-dependent hypotension was estimated for each treatment group using the product-limit (Kaplan-Meier) method. A two-sided log-rank test was used for the primary comparison of time to resolution of vasopressor-dependent hypotension. Differences in estimated resolution rates at various time points were tested using the proportions test. For mortality, relative risk and odds ratio estimates with associated 95% confidence intervals were calculated. For other key efficacy variables (organ function status and biomarker assessments), comparisons between treatment groups were assessed with analysis of variance (ANOVA). Treatment differences for safety measurements were compared using a Fisher's exact test.

Summary:

Patient Disposition

It was originally planned to enroll 270 patients in the study; however, the protocol was amended and the planned enrollment was reduced to 200 patients because of slow

recruitment. A total of 201 patients were entered into the study (signed informed consent); 199 patients were randomly assigned to treatment and 193 received study drug and made up the intention-to-treat population [94 drotrecogin alfa (activated) and 99 placebo]. Six patients did not receive study drug because they met an exclusion criterion or died. Two patients did not complete the study: 1 patient withdrew consent and 1 patient was lost to follow-up.

Baseline Characteristics

There were no statistically significant differences between the two treatment groups in baseline demographic characteristics; however, there were statistically significant differences in the clinical characteristics related to cardiovascular dysfunction. There were statistically significant differences in cardiovascular Sequential Organ Failure Assessment (SOFA) score, the requirement for norepinephrine (the most common vasopressor administered), and cumulative vasopressor index, a measure of vasopressor support determined from the dosages of vasopressors that the patient received. A greater percentage of drotrecogin alfa (activated) patients had a cardiovascular SOFA score of 4 compared with placebo patients (79% versus 64%) and drotrecogin alfa (activated) patients had a higher median norepinephrine requirement (0.26 μg/kg/min versus 0.16 μg/kg/min) and a higher cumulative vasopressor index compared with placebo patients [4.2 for drotrecogin alfa (activated) patients versus 3.8 for placebo patients]. In addition, drotrecogin alfa (activated) patients had lower baseline levels of protein C compared with placebo patients (67% and 73%, respectively) although this difference was not statistically significant.

The average age of the study patients was 62 years and the majority of patients were male (61%) and Caucasian (92%). The mean number of baseline organ dysfunctions was 2.8 for drotrecogin alfa (activated) patients and 2.9 for placebo patients.

Exposure to Commercial Drotrecogin Alfa (Activated)

The mean duration of commercial drug infusion was 99 hours (median 96 hours) in both treatment groups and a mean of 0.5 hours elapsed between the end of the commercial drug infusion and the start of the study drug infusion (median 0 hours).

Primary Analysis

In the ITT population, 32 drotrecogin alfa (activated) patients (34%) experienced resolution of vasopressor-dependent hypotension and 40 placebo patients (40%). The difference between the two treatment groups was not statistically significant (p=0.42; see Figure 1) The majority of patients in both groups continued to require vasopressor support after 72 hours of study treatment and were, therefore, censored at their last observation.

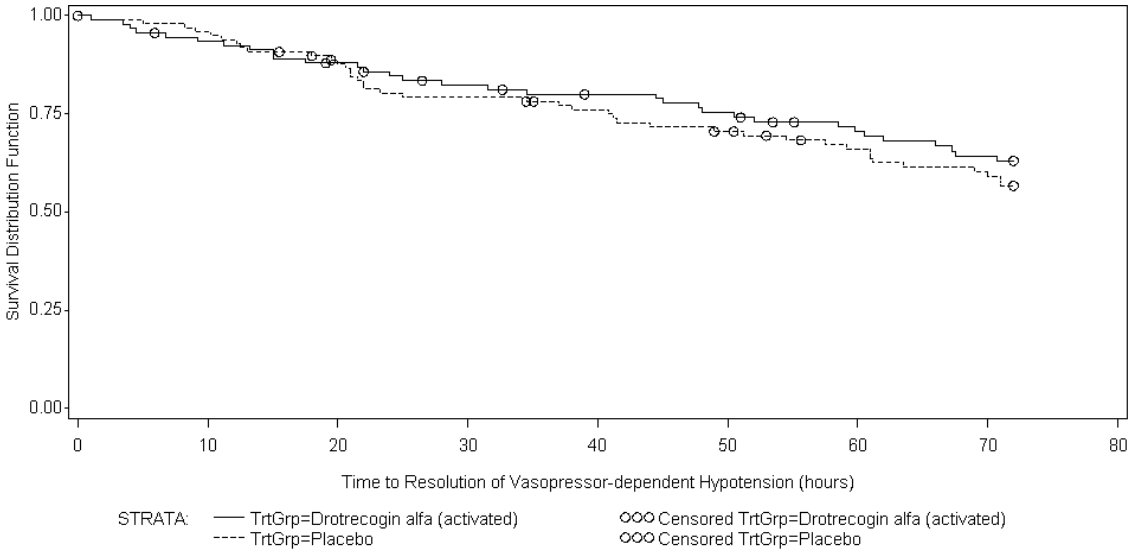

Figure EVBQ.1. Time to resolution of vasopressor-dependent hypotension.

Secondary Analyses

Mortality. The differences between the two treatment groups in 28-day mortality and hospital mortality were not statistically significant (Table 1).

Table 1. Mortality Endpoints

Endpoint	DRO Mortality % (n/N)	PLA Mortality % (n/N)	Odds Ratio (CI)	Relative Risk (CI)	p-Value
28-Day	39.8 (37/93)	32.3 (31/96)	1.39 (0.76 – 2.51)	1.23 (0.84 – 1.81)	0.28
Hospital	54.3 (51/94)	43.9 (43/98)	1.53 (0.86 – 2.68)	1.24 (0.92 – 1.65)	0.15

Abbreviations: CI = confidence interval; DRO = drotrecogin alfa (activated); PLA = placebo.

Organ function. Mean cardiovascular, coagulation, and renal SOFA scores decreased (improved organ function) from baseline in both the drotrecogin alfa (activated) and placebo groups and mean respiration and liver SOFA score were increased (worsened organ function) (Table 2). There were no statistically significant differences between the two treatment groups in the average 10-day cardiovascular, respiration, renal, liver, and coagulation SOFA scores.

Table 2. Change in Sequential Organ Failure Assessment

	Drotrecogin Alfa (Activated)			Placebo			
	Baseline	Day 10	Average 10 Day	Baseline	Day 10	Average 10 Day	p-Value[a]
Cardiovascular	3.7	1.9	2.4	3.5	1.5	2.2	0.77
Respiration	2.3	2.6	2.5	2.2	2.3	2.4	0.57
Renal	2.0	1.8	1.8	2.1	2.0	2.0	0.30
Liver	1.0	1.5	1.2	1.0	1.2	1.1	0.64
Coagulation	1.2	1.2	1.1	1.2	1.1	1.0	0.82

a Mean 10-day SOFA scores are analyzed using analysis of variance (ANOVA).

Biomarkers. Mean thrombin generation (D-dimer level) was essentially unchanged from baseline to endpoint (5.2 to 5.1) in drotrecogin alfa (activated) patients, but increased in placebo-treated patients (4.6 to 6.3); the difference between the treatment groups was significant ($p<0.001$). There were no statistically significant differences in change in prothrombin time or protein C levels between the two treatment groups. Drotrecogin alfa (activated) patients had a greater increase in protein C level from baseline to endpoint compared with placebo patients. However, endpoint levels were similar between the treatment groups because of lower baseline protein C levels among drotrecogin alfa (activated) patients.

Exploratory Analyses by Protein C Level. Analyses of time to resolution of vasopressor-dependent hypotension and 28-day mortality by baseline protein C level were conducted. Patients with a protein C level >40% had a statistically significantly lower mortality rate compared with patients with a baseline protein C level ≤40% ($p=0.03$).

Patients were defined as responders or nonresponders based on the change in protein C level from baseline to endpoint: patients were considered nonresponders if there was no difference or a negative difference between their baseline and endpoint protein C levels; patients were considered responders if there was a positive difference between baseline and endpoint levels, that is, protein C increased from baseline to endpoint. In the drotrecogin alfa (activated) group, 58.1% of patient were classified as responders; in the placebo group, 41.9% of patients were classified as responders ($p=0.07$).

Patients classified as responders had a lower mortality rate compared with patients classified as nonresponders although the difference between the two groups was not statistically significant ($p=0.10$). There was no difference between patients classified as responders and patients classified as nonresponders in time to resolution of vasopressor-dependent hypotension ($p=0.25$).

Safety

Table 3 contains a summary of the adverse events that were reported during the study. A similar number of drotrecogin alfa (activated) and placebo patients experienced at least one serious adverse event or serious bleeding event, or any adverse event or any bleeding event.

Table 3. Summary of Adverse Events ITT Population

Adverse Event Study Period	Drotrecogin Alfa (Activated) N=94 n (%)	Placebo N=99 n (%)
Serious adverse events		
Infusion period	2 (2.1)	3 (3.0)
24-day study period	9 (9.6)	9 (9.1)
Serious bleeding events		
Infusion period	1 (1.1)	1 (1.0)
24-day study period	1 (1.1)	2 (2.0)
All adverse events		
Infusion period	5 (5.3)	3 (3.0)
24-day study period	12 (12.8)	12 (12.1)
All bleeding events		
Infusion period	3 (3.2)	1 (1.0)
24-day study period	3 (3.2)	2 (2.0)

Summary

There were statistically significant differences in baseline characteristics between the treatment groups in measurements of cardiovascular dysfunction. Drotrecogin alfa (activated) patients had a greater degree of cardiovascular dysfunction compared with placebo patients: a greater percentage of drotrecogin alfa (activated) patients had a cardiovascular SOFA score of 4, drotrecogin alfa (activated) patients had a higher median requirement for norepinephrine, and a higher cumulative vasopressor index.

There was no difference between the treatment groups in the primary endpoint, time to resolution of vasopressor-dependent hyoptension. The majority of patients continued to require vasopressor support after 72 hours of study drug infusion. There was no difference between the treatment groups in the secondary endpoints of 28-day mortality, hospital mortality, and change in organ function.

A similar number of drotrecogin alfa (activated) and placebo patients experienced serious adverse events, serious bleeding events, any adverse event, or any bleeding event during the study.

In exploratory analyses by protein C level, patients with a baseline protein C level >40% had statistically significantly lower mortality compared with patients with a protein C level ≤40%. Treatment with drotrecogin alfa (activated) resulted in greater, although not statistically significant, improvement in protein C level: a greater percentage of drotrecogin alfa (activated) patients had increased protein C levels from baseline to endpoint compared with placebo patients.