2. EVDP Synopsis

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Clinical Study Report Synopsis: Study F1K-MC-EVDP

Title of Study: Efficacy and Safety of Drotrecogin Alfa (Activated) in Adult Patients with Septic Shock	
Number of Investigators: This multicenter study included 221 principal investigators.	
Study Centers: This study was conducted at 208 study centers in 18 countries.	
Publications Based on the Study: Finfer S, Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Gardlund B, Marshall JC, Rhodes A. Design, conduct, analysis and reporting of a multi-national placebo-controlled trial of activated protein C for persistent septic shock. Intensive Care Med 2008;34(11):1935–1947. Thompson BT, Ranieri VM, Finfer S, Barie PS, Dhainaut JF, Douglas IS, Gardlund B, Marshall JC, Rhodes A. Statistical analysis plan of PROWESS-SHOCK study. Intensive Care Med 2010;36(11):1972–1973. Ranieri VM, Thompson BT, Finfer S, Barie PS, Dhainaut JF, Douglas IS, Gardlund B, Marshall JC, Rhodes A; PROWESS-SHOCK Academic Steering Committee. Unblinding plan of PROWESS-SHOCK trial. Intensive Care Med 2011;37(8):1384–1385.	
Length of Study: Date first patient enrolled: 20 March 2008 Date last patient completed 28-day follow-up: 27 September 2011	**Phase of Development:** 3
Objectives: Analyses of the following objectives are included in this condensed 28-day study report: the primary objective was to determine that treatment with drotrecogin alfa (activated) reduced 28-day, all-cause mortality compared with placebo; the secondary objectives were to demonstrate that drotrecogin alfa (activated) reduced 28-day, all-cause mortality in patients with severe protein C deficiency (baseline protein C level less than or equal to half the lower limit of normal) compared with placebo, and had an acceptable safety profile.	
Study Design: A randomized, double-blind, parallel, placebo-controlled, multicenter, Phase 3 study of drotrecogin alfa (activated) administered as a 96-hour infusion to adult patients with persistent septic shock. Patients were followed for 180 days and survival status was assessed at 28, 90, and 180 days.	
Number of Patients: Planned: 1696 patients; 848 drotrecogin alfa (activated) and 848 placebo Randomized: 1696 patients; 851 drotrecogin alfa (activated) and 845 placebo Treated: 1666 patients; 833 drotrecogin alfa (activated) and 833 placebo Completed 28-day follow-up: 1680 patients, 846 drotrecogin alfa (activated) and 834 placebo	
Diagnosis and Main Criteria for Inclusion: Patients eligible for the study must have been adults (18 years or older), have had evidence of an infection, must have met 2 of 4 criteria for systemic inflammatory response syndrome, must have met criteria for vasopressor-dependent septic shock, and must have remained vasopressor dependent throughout the pretreatment period.	
Test Product, Dose, and Mode of Administration: Drotrecogin alfa (activated) 24 mcg/kg/h was administered as an intravenous infusion.	
Reference Therapy, Dose, and Mode of Administration: Placebo of sterile 0.9% sodium chloride was administered as an intravenous infusion.	
Duration of Treatment: Study drug was administered for a total infusion time of 96 hours ± 1 hour.	
Variables: Efficacy: mortality at 28-days (alive or dead). The 28-day timepoint was defined as 672 hours from randomization. Safety: The occurrence of the following adverse events were assessed: serious adverse events, nonserious adverse events considered to be study drug related, adverse events that led to discontinuation of study drug, thrombotic events (serious and nonserious), and bleeding events (serious and nonserious).	

Statistical Evaluation Methods:

Efficacy: The primary endpoint was a comparison of 28-day all-cause mortality between the drotrecogin alfa (activated) and placebo treatment groups using a 2-sided Pearson's chi-square test unadjusted for continuity. Relative risk (risk ratio) and odds ratio estimates with associated 95% confidence intervals are presented. Differences between the drotrecogin alfa (activated) and placebo treatment groups in the time to death from randomization through 28 days were assessed using a log-rank test. Survival curves were produced using the method of Kaplan and Meier. For subgroup analyses, nonstratified treatment comparisons were performed using chi-square (nonstratified) tests and Cochran-Mantel-Haenszel tests for adjusted treatment comparisons. Adjusted relative risks and 95% confidence intervals were calculated using the Cochran-Mantel-Haenszel method. Breslow-Day tests for homogeneity of odds ratios across strata were also performed.

Safety: Adverse events are presented as MedDRA preferred terms by system/organ class. The proportion of patients who experienced adverse events in each treatment group was compared using Fisher's exact test.

Summary: The PROWESS-SHOCK study was designed to investigate the benefit/risk of drotrecogin alfa (activated) in patients with septic shock. This report is a condensed report of the 28-day data from the PROWESS-SHOCK study and includes the following analyses: the primary analysis of 28-day mortality, the secondary analysis of 28-day mortality in patients with severe protein C deficiency at baseline, subgroup analyses of 28-day mortality, and safety analyses of adverse events. The remaining analyses of 28-day data will be included in a second study report to be written after the completion of 180-day follow-up.

The final reporting database included 1696 randomly assigned patients who made up the intention-to-treat (ITT) population. Mortality analyses of this population included 1680 patients; 16 patients were lost to follow-up or withdrew consent and were excluded from landmark mortality analyses. Thirty patients did not receive study drug and were excluded from safety analyses leaving 1666 patients in the all treated patients population. Six hundred seventy-eight patients had a baseline protein C level and were severely protein C deficient (protein C level less than or equal to 40%); these patients make up the ITT-severe protein C deficiency population.

The baseline characteristics of the treatment groups were generally well-balanced. There were statistically significant differences in the proportion of patients who had an identified infecting agent and had a history of thrombophilia: 73% of drotrecogin alfa (activated) and 68% of placebo patients had an identified infecting agent ($p=0.020$), and 4 placebo patients versus no drotrecogin alfa (activated) had a history of thrombophilia ($p=0.045$).

The study was designed to enroll a severely ill septic shock patient population at high risk of death. Approximately 51% of patients enrolled had 4 or 5 organ dysfunctions, 82% were on mechanical ventilation, 74% had renal dysfunction, and 70% had metabolic acidosis. The mean APACHE II score was 25.

In the primary efficacy analysis of 28-day mortality, drotrecogin alfa (activated) and placebo patients had a similar mortality rate: 26.4% (223/846) and 24.2% (202/834), respectively ($p=0.313$). Mortality rates in the drotrecogin alfa (activated) and placebo groups were also similar in the severely protein C deficient population: 28.7% (98/342) and 30.8% (102/331), respectively ($p=0.540$).

There were no statistically significant differences between the 2 treatment groups in patient location at Study Day 28. Forty-nine percent of surviving drotrecogin alfa (activated) and 43% of surviving placebo patients remained in the study hospital; 36% of drotrecogin alfa (activated) and 39% of placebo patients were at home.

Analysis of change in protein C level from baseline to Study Day 4 show the pharmacodynamic effect of drotrecogin alfa (activated): the mean protein C level was similar at baseline in both treatment groups; however, at Study Day 4, drotrecogin alfa (activated) patients had a mean increase of 28 percentage points versus 18 percentage points for placebo patients ($p<0.001$).

The mean duration of infusion was 84 hours and the majority of patients (76%) completed the infusion. Four and a half percent of drotrecogin alfa (activated) patients and 3% of placebo patients discontinued the infusion because of an adverse event. This difference was not statistically significant. The majority of events that caused discontinuation were nonbleeding events and an equal number of patients in each treatment group discontinued because of a nonbleeding event. The difference between the treatment groups was in the number of patients who discontinued because of a bleeding event: 17 drotrecogin alfa (activated) and 5 placebo patients.

A similar proportion of drotrecogin alfa (activated) and placebo patients experienced a serious bleeding event during Study Days 0 through 6 (1.2% and 1.0%; respectively, p=0.814) and during Study Days 0 through 28 (2.4% and 2.8%, respectively; p=0.758). A similar number of drotrecogin alfa (activated) and placebo patients experienced a central nervous system bleeding event during both study periods: 2 drotrecogin alfa (activated) and no placebo patients (p=0.500) during Study Days 0 through 6 and 3 patients in each treatment group during Study Days 0 through 28 (p=1.000). A similar number of patients in each treatment group died from a hemorrhagic event: 3 drotrecogin alfa (activated) patients and 5 placebo patients. There were no statistically significant differences between the treatment groups in the proportion of patients who experienced a serious adverse event, serious thrombotic event, or nonserious thrombotic event during Study Days 0 through 6 or Study Days 0 through 28. The only statistically significant differences in the occurrence of adverse events were in the proportion of patients who experienced a nonserious bleeding events during Study Days 0 through 6 [8.6% of drotrecogin alfa (activated) and 4.8% of placebo patients, p=0.002] and study-drug-related nonserious adverse events during Study Days 0 through 6 [8.9% of drotrecogin alfa (activated) and 4.0% of placebo patients, p<0.001] and Study Days 0 through 28 [9.4% of drotrecogin alfa (activated) and 4.4% of placebo patients, p<0.001].

Conclusions: The study failed to meet its primary objective of demonstrating that treatment with drotrecogin alfa (activated) reduces 28-day, all-cause mortality in patients with septic shock compared with placebo. The study also failed to meet its secondary objective of demonstrating a reduction in mortality in the population of patients with severe protein C deficiency.

No new safety findings were noted in this study. Bleeding is the primary safety finding associated with drotrecogin alfa (activated) administration and rates of serious bleeding and central nervous system bleeding were low and similar in both treatment groups during both study periods, (Study Days 0 through 6 and Study Days 0 through 28). Three drotrecogin alfa (activated) and 5 placebo patients had a hemorrhage-related cause of death; all of these fatal events occurred after the infusion was completed. Although the events of greatest concern, serious and fatal bleeding, were similar in both treatment groups, nonserious bleeding was more common among drotrecogin alfa (activated) patients and occurred primarily during Study Days 0 through 6.

In summary, PROWESS-SHOCK enrolled a high disease severity population, demonstrated a pharmacodynamic effect, yet failed to show a mortality benefit in a high disease severity, persistent septic shock population. No new safety findings were noted; rates of serious bleeding were similar in both treatment groups.