2. EVDK Synopsis

Clinical Study Report Synopsis: Study F1K-MC-EVDK

Title of Study: A Phase 2 Study to Evaluate Dose and Duration of Treatment of Drotrecogin Alfa (Activated) Using Serial Measurements of Protein C in Patients with Severe Sepsis and Multiple Organ Dysfunctions	
Number of Investigators: This multicenter study included 52 principal investigators.	
Study Centers: This study was conducted at 52 study centers in 11 countries.	
Publications Based on the Study: None as of 15 June 2010.	
Length of Study: Date of first patient enrolled: 26 November 2006 Date of last patient completed: 29 August 2009	**Phase of Development:** 2
Objectives: The primary objective was to demonstrate that, in patients with protein C levels less than the lower limit of normal, alternative therapy resulted in a greater increase in protein C level from Study Day 1 to Study Day 7 compared with patients receiving standard therapy with drotrecogin alfa (activated). Secondary objectives were to compare treatment groups with respect to (1) change in protein C level from Study Day 1 to Study Day 7 in patients with severe protein C deficiency and moderate protein C deficiency on Study Day 1, (2) safety, (3) 28-day all-cause mortality and in-hospital mortality, (4) organ function, (5) pharmacokinetic/pharmacodynamic relationships, and (6) to investigate whether achieving a normal protein C level was associated with lower 28-day all-cause mortality compared with a protein C level remaining below the lower limit of normal regardless of treatment.	
Study Design: The study was a randomized, double-blind, parallel, controlled, dose comparison study of alternative therapy (variable duration of infusion in patients with moderate protein C deficiency and higher dose/variable duration of infusion in patients with severe protein C deficiency) and standard therapy (24 mcg/kg/h for 96 hours) with drotrecogin alfa (activated). Randomized patients received 24 hours of common therapy (24 mcg/kg/h) and then received their randomized therapy for the remainder of the infusion. Protein C deficiency class (severe or moderate) was based on the 24-hour local laboratory protein C measurement. The intention-to-treat (ITT) population was defined as those patients who received any amount of randomized therapy. Patients who entered the study with a normal protein C level and remained normal through the pretreatment period were followed in a non-drug-interventional arm.	
Number of Patients: Planned: 488 patients: 449 randomized (422 ITT) and 39 non-drug interventional Randomized: 496 patients: 242 alternative therapy, 254 standard therapy Treated (at least 1 dose): 486 patients: 236 alternative therapy, 250 standard therapy ITT Population: 433 patients: 206 alternative therapy, 227 standard therapy	
Diagnosis and Main Criteria for Inclusion: Patients were eligible for the study if they were at least 18 years old and had severe sepsis and multiple organ dysfunction. Severe sepsis was defined as the presence of a suspected or proven infection and at least 2 sepsis-induced organ dysfunctions.	
Study Drug, Dose, and Mode of Administration: Study drug was administered as a continuous intravenous infusion. Patients assigned to alternative therapy received drotrecogin alfa (activated) 24 mcg/kg/h during the common therapy lead-in period and then randomized therapy of drotrecogin alfa (activated) 24 mcg/kg/h (moderate protein C deficiency strata), 30 mcg/kg/h or 36 mcg/kg/h (severe protein C deficiency strata).	
Reference Therapy, Dose, and Mode of Administration: Patients assigned to standard therapy received drotrecogin alfa (activated) 24 mcg/kg/h administered as a continuous intravenous infusion. Placebo (sterile 0.9% sodium chloride) was administered to maintain the study blind.	

Duration of Treatment: Standard therapy: patients received study drug for 96 hours. Alternative therapy: patients received a variable duration of study drug infusion from a minimum of 48 hours to a maximum of 168 hours. Study drug was administered until the patient had 2 consecutive normal protein C measurements or 168 hours. Placebo was administered to standard therapy patients after completion of 96 hours of study drug infusion until the patient had 2 consecutive normal protein C measurements or 168 hours. Under the original protocol, alternative therapy patients received placebo if they normalized their protein C before the completion of 96 hours of infusion. Under the amended protocol, alternative therapy patients received at least 96 hours of study drug infusion. All patients were followed for 28 days from the start of the infusion or until hospital discharge, death, or 90 days from the start of the infusion, if the patient remained in the study hospital at Study Day 28

Variables:

Efficacy: The primary efficacy measure was the mean change in protein C from Study Day 1 to Study Day 7. Secondary efficacy measures include 28-day all-cause mortality, hospital mortality, and evaluation of organ function using the Sequential Organ Failure Assessment (SOFA) scoring system.

Safety: Safety was assessed through the occurrence of the following adverse events: (1) serious adverse events, including serious bleeding events, (2) nonserious bleeding events that occurred during the treatment period (Study Days 0 through 8), (3) study-drug-related nonserious adverse events, (4) adverse events that led to discontinuation of study drug, and (5) episodes of new infection.

Pharmacokinetic/Pharmacodynamic: The primary pharmacokinetic parameters were weight-normalized plasma clearance and steady-state plasma concentration.

Statistical Methods:

Efficacy: The mean change in protein C from Study Day 1 to Study Day 7 in each treatment groups was compared using an unadjusted 2-sample t-test. Twenty-eight-day and hospital mortality rates in each treatment group were compared using Fisher's exact test. Cardiovascular, respiratory, hematologic, liver, and renal function were assessed using SOFA methodology. Eight day and 28-day time-averaged scores were calculated for each organ system. Mean scores for each treatment group were compared using an unadjusted two-sample t test.

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.

Pharmacokinetic/Pharmacodynamic: The primary pharmacokinetic parameters were the weight-normalized plasma clearance (CL_p) of drotrecogin alfa (activated) and the steady-state plasma concentration (C_{SS}) of activated protein C (APC).

Summary: A total of 557 patients were entered into the study, including 20 patients who discontinued from the study before randomization and 41 patients who entered the study with a normal protein C level and were followed in the non-drug-interventional arm. Four hundred ninety-six patients were randomly assigned to treatment; 486 patients received study drug, and 433 patients completed the 24-hour common therapy lead-in period and received randomized therapy. These 433 patients made up the ITT population (206 alternative therapy and 227 standard therapy). The treatment groups were generally well-balanced with regard to baseline characteristics: the only statistically significant difference was in the history of thrombosis (2 alternative therapy patients versus 13 standard therapy patients), and the difference in hematology SOFA score approached significance: alternative therapy patients had a mean score of 0.75 and standard therapy patients, 0.59. Other nonstatistically significant imbalances included patients requiring vasopressor support (88.8% alternative, 83.7% standard), with lung as the primary site of infection (51.5% alternative, 38.3% standard), with severe protein C deficiency at baseline (54.1% alternative, 48.5% standard), patients with renal dysfunction (55.3% alternative, 61.2% standard), and disseminated intravascular coagulation (30.8% alternative, 39.5% standard). Alternative therapy patients had a lower mean protein C level (41%) compared with standard therapy patients (44%).

In the analysis of the primary endpoint, patients receiving alternative therapy had a statistically significantly greater increase in protein C level from Study Day 1 to Study Day 7 compared with patients receiving standard therapy. Among alternative therapy patients, the mean change in protein C activity was 31% activity and, among standard therapy patients, 24% activity (p=0.011). In addition, a greater percentage of patients in the alternative therapy group had protein C levels that increased compared with patients in the standard therapy group (81.2% versus 72.3%; chi-square p=0.03). In the strata of severe protein C deficiency and moderate protein C deficiency, alternative therapy patients had a greater increase in protein C activity compared with standard therapy patients (severe deficiency: 38% versus 25%; p=0.063; moderate deficiency: 30% versus 24%, p=0.047). In both strata, a greater percentage of alternative therapy patients had increased protein C compared with standard therapy patients (severe deficiency: 90.4% versus 67.4%, moderate deficiency: 79.5% versus 73.7%) The moderate deficiency strata contained approximately 80% of ITT patients and the severe deficiency strata, 20%.

The mortality rate in the standard therapy group was lower than the alternative therapy group at both 28 days and in-hospital (28-day: 16.1% versus 24.9%, p=0.030; in-hospital: 20.5% versus 27.8%, p=0.090). This difference in mortality was driven by the results in the moderate protein C deficiency strata in which the standard therapy group had a lower than anticipated 28-day mortality rate (11.6% versus 25.0%; p=0.001). In the severe protein C deficiency strata, 28-day mortality in the alternative therapy group was lower than in the standard therapy group (24.2% versus 31.4%, p=0.662). To better understand the mortality results observed in the moderately deficient strata, a post hoc analysis was performed based on the duration of study drug received: <97 hours versus ≥97 hours (the standard infusion duration of 96 hours ± 1 hour) in the Switch-No population (patients who did not switch to placebo after an infusion of less than 96 hours). In this analysis, infusion duration is total infusion of drotrecogin alfa (activated) and placebo (if administered). Patients in the alternative therapy group who received less than 97 hours of infusion received the equivalent of standard therapy. Therefore, outcomes in standard and alternative therapy patients who received an infusion for less than 97 hours would be expected to be similar as both groups received the same dose and duration of drotrecogin alfa (activated). This analysis showed similar results: in the <97 hours subgroup, mortality in the alternative therapy group was 28.2% versus 13.8% in the standard therapy group and in the ≥97 hours subgroup, 23.9% versus 11.4%. It is unclear why the alternative and standard therapy groups that essentially received the same standard therapy [drotrecogin alfa (activated) 24 mcg/kg/h for less than 97 hours] would have such widely different mortality rates. Although this analysis does not specifically explain why alternative therapy patients receiving an infusion of greater than 97 hours also experienced higher mortality, it does bring into question the reliability of mortality results from this relatively small subgroup of patients. Similarly large differences in mortality were observed in the randomized non-ITT population (patients who were randomly assigned to therapy and received study drug during the common therapy lead-in period, but did not receive randomized therapy) where both treatment groups were exposed only to the same standard treatment during the common therapy lead-in period (24 mcg/kg/h for up to 24 hours): mortality was 86.7% in the alternative therapy group and 69.6% in the standard therapy group. Mortality was also higher in the alternative therapy group that normalized their protein C levels and switched early to placebo (received an infusion of less than 96 hours) compared to standard therapy patients who continued the infusion and received 96 hours of drotrecogin alfa (activated) (20.0% versus 7.3%, respectively).

In the analysis of mortality by normalization of protein C regardless of treatment assignment, normalization of protein C through Study Day 7 was associated with statistically significantly lower mortality: patients who normalized their protein C had a mortality rate of 10.3% versus 32.0% for patients who did not normalize (p<0.0001).

Median APC concentrations in patients in the severe protein C deficiency strata was higher than that in patients in the moderate protein C deficiency strata (62.2 ng/mL and 71.8 ng/mL, respectively), which is consistent with the higher infusion rates of 30 and 36 mcg/kg/h received by patients in the severe protein C deficiency strata. The median plasma clearance showed no clear relationship with infusion rate: 31.1 L/h, 23.5 L/h, and 35.2 L/h with infusion rates of 24 mcg/kg/h, 30 mcg/kg/h, and 36 mcg/kg/h, respectively.

During the treatment period (Study Days 0 through 8), 5.3% (11 patients) of alternative therapy patients and 1.3% (3 patients) of standard therapy patients experienced a serious bleeding event. No patients who received a higher dose experienced a serious bleeding event. To further characterize the bleeding risk associated with alternative therapy, the treatment period was divided into Study Days 0 through 4 and Study Days 5 through 8. During Study Days 0 through 4, patients in the moderate deficiency strata received the same treatment in both arms [drotrecogin alfa (activated) 24 mcg/kg/h]. Treatment differed during Study Days 5 through 8, when alternative therapy patients could receive a longer infusion duration. In the moderate protein C deficiency strata, most serious bleeding events occurred during Study Days 0 through 4 (9 alternative therapy patients and 2 standard therapy patients) when patients were receiving the same therapy; during Study Days 5 through 8, 3 alternative therapy patients and no standard therapy patients experienced an event. Three central nervous system bleeding events occurred: 2 among alternative therapy patients (on Study Days 7 and 32) and 1 in a standard therapy patient (on Study Day 11). All were considered by the investigator to be related to study drug, none were fatal. One fatal bleeding event occurred in an alternative therapy patient, an arterial haemorrhage on Study Day 24. This event was not considered by the investigator to be related to study drug.

Conclusions: Alternative therapy was associated with statistically significantly greater increases in protein C levels compared with standard therapy in the overall ITT population and in the moderate protein C deficiency strata. Alternative therapy was also associated with greater increases in protein C levels in the severe protein C deficiency, but the difference between the treatment groups was not statistically significant. As well as resulting in a greater mean increase in protein C from Study Day 1 to Study Day 7, alternative therapy was also associated with more patients increasing their protein C levels. Normalization of protein C levels was associated with improved outcome. Patients who normalized their protein C (had 2 consecutive normal protein C levels by Study Day 7) had statistically significantly lower 28-day mortality than patients who did not normalize regardless of treatment group.

Higher mortality was observed in the alternative therapy group in patients receiving a standard dose of 24 mcg/kg/h whether they received shorter, longer, or the same infusion duration as the standard therapy group. These findings do not support a link between infusion duration and the observed mortality in the alternative therapy group. This study was not powered to a mortality endpoint and the mortality results may not be reliable. Overall baseline markers of disease severity were fairly similar between treatment groups; however, there were notable differences in protein C levels present at baseline, and also largely remaining at Study Day 4, that disfavored both alternative therapy groups. Given the link demonstrated in this and other studies between lower protein C levels and higher mortality, it is possible that these baseline differences in protein C may have contributed, at least in part, to the observed mortality differences.

Alternative therapy was associated with an increased rate of serious bleeding compared with standard therapy. No serious bleeding events were reported in patients treated with higher doses of drotrecogin alfa (activated). Nearly all serious bleeding was confined to the moderate protein C deficiency strata. Analyses of the moderate deficiency strata indicated that the excess events occurred primarily during Study Days 0 through 4, when patients in both treatment groups would have received the same therapy (24 mcg/kg/h for 96 hours). There did not appear to be any differences between the alternative and standard therapy groups in the occurrence of nonserious bleeding events. It is not possible to clearly conclude that alternative therapy in the form of a longer infusion duration is associated with an increased risk of bleeding.

The results of this study confirm the primary hypothesis of the study that, by giving higher doses and longer infusion durations of drotrecogin alfa (activated), protein C levels can be improved with alternative therapy compared to those achieved with the current standard regimen.