

<b>TOPLINE RESULTS</b>	
<b>Date:</b> 26-JAN-2007	
<b>Protocol Number:</b>	PR97-19-002
	<b>Clinical Phase:</b> IV
<b>Title:</b>	AN OPEN-LABEL, RANDOMIZED, PARALLEL-GROUP STUDY TO CONFIRM THE SAFETY AND EFFICACY OF PROCRIT® (EPOETIN ALFA) ADMINISTERED PERIOPERATIVELY VS. THE STANDARD OF CARE IN BLOOD CONSERVATION IN SUBJECTS UNDERGOING MAJOR ELECTIVE SPINAL SURGERY
<b>Trial Design:</b>	<ul style="list-style-type: none"> <li>• Multicenter, randomized, open-label, controlled trial with 2 parallel treatment groups: Standard of Care for blood conservation (SOC); and 600 U/kg PROCRIT® x 4 Doses (Days -21, -14, -7, and the day of surgery).</li> <li>• Study Population: Subjects scheduled to undergo elective adult spinal surgery with pre-treatment hemoglobin &gt;10 and ≤13 g/dL.</li> <li>• Randomization was performed using a central IVRS system.</li> <li>• Primary analysis population for Safety: ITT population (includes all randomized subjects).</li> <li>• Primary safety variable: Proportion of subjects with Deep Vein Thrombosis (DVT) identified by either Color Flow Duplex Imaging (CFDI) on post-operative day 4 or on the day of discharge or by clinical symptoms (at any time during the study: Day -21 to 30 days after discharge).</li> <li>• Primary efficacy variable: Proportion of subjects transfused (transfusion rate) during or after surgery.</li> <li>• Secondary endpoints: Proportion of subjects with Thrombotic Vascular Events (TVEs) and changes in hemoglobin from baseline to post-operative day 4 or day of hospital discharge.</li> <li>• Expected effect size and planned sample size: The estimated DVT incidence rate was assumed to be 3% for both the SOC and PROCRIT® groups. The non-inferiority margin was determined to be 4%. To achieve at least 80% power with a one-sided Type I error rate=0.025, and assuming a 15% dropout rate 674 subjects were planned, with 681 subjects actually enrolled.</li> </ul>

The results in this summary have been verified by the Biometrics statisticians and programmers. Nevertheless, these results may differ slightly from what will appear in the final Clinical Study Report (CSR). Results presented in the CSR will be the final, fully validated results of this trial.

**Primary Objective:**

The primary objective of the study is to demonstrate that there is no clinically important additional risk for deep vein thrombosis (DVT) in adult spine surgery subjects using a peri-surgical regimen of PROCRI<sup>®</sup> versus the standard of care for blood conservation. In addition, the efficacy of PROCRI<sup>®</sup> in protecting subjects from receiving allogeneic red cell transfusions across adult spinal procedures is to be studied.

**Topline Results Summary**

- A total of 681 subjects were randomized. A total of 93 subjects were withdrawn from the study. Demographic and baseline characteristics were well balanced between the SOC and PROCRI<sup>®</sup> groups.
- The non-inferiority of PROCRI<sup>®</sup> compared to the Standard of Care (SOC) regimen in the incidence of deep vein thrombosis in adult spine surgery was not demonstrated. The total number of subjects with any DVT in the PROCRI<sup>®</sup> group was 16 (4.7%) compared to 7 (2.1%) in the SOC arm in the Intent-to-Treat population. As the upper confidence interval of the difference between DVT rates between the two groups was greater than the 4% pre-specified margin, the non-inferiority of PROCRI<sup>®</sup> to Placebo could not be established.
- The efficacy of PROCRI<sup>®</sup> in protecting patients from receiving allogeneic red cell transfusions across adult spinal procedures was demonstrated. Fewer subjects in the PROCRI<sup>®</sup> arm received any blood transfusions (29.7%) compared to subjects in the SOC arm (55%). During the peri-operative and post-operative periods of the study, 25% of subjects in the SOC arm compared to 15.3 % in the PROCRI<sup>®</sup> arm required allogeneic blood transfusions.
- At screening the mean Hb was 12.2 g/dL in both the PROCRI<sup>®</sup> and SOC group. From screening to the day of surgery, Hb decreased to 11.8 g/dL in the SOC arm and increased to 13.5 g/dL in the PROCRI<sup>®</sup> arm. At discharge the mean Hb value was 10 g/dL in the SOC arm and 10.9 in the PROCRI<sup>®</sup> arm.
- A total of 3 subjects died during the study; two in the SOC group and one in the PROCRI<sup>®</sup> group.
- The number of subjects who experienced at least one adverse event or serious adverse event was similar in the SOC and PROCRI<sup>®</sup> groups. The proportion of subjects with adverse events leading to study withdrawal was higher in the PROCRI<sup>®</sup> group (3.5% compared to 1.5% SOC). Vascular and cardiac disorders were also more frequent in the PROCRI<sup>®</sup> group.

## RESULTS

### 1. SUBJECT AND TREATMENT INFORMATION

#### 1.1. Study Completion/Withdrawal Information

A total of 681 subjects were randomized (Table 1.1); one subject was randomized twice and was excluded from the ITT population. The ITT population includes 680 subjects (340 subjects in each treatment group).

A total of 93 subjects were withdrawn from the study: 60 subjects from the PROCRI<sup>®</sup> group and 33 subjects from the Standard of Care (SOC) group. The major reason for withdrawal in both the SOC and PROCRI<sup>®</sup> groups was subject or physician request.

The Per-Protocol (PP) population includes subjects who were randomized, had no major protocol violation, underwent spinal surgery and had an interpretable post-operative Color Flow Duplex Imaging (CFDI) evaluation. In addition, subjects in the PROCRI<sup>®</sup> group received at least 1 of the 4 scheduled PROCRI<sup>®</sup> doses. A total of 543 subjects qualified for the PP-population (284 subjects in the SOC group and 259 in the PROCRI<sup>®</sup> group).

<b>Table 1.1:</b> Study Disposition; Completion/Withdrawal Information (All Randomized Subjects)			
	SOC (N=340)	PROCRI <sup>®</sup> (N=341)	Total (N=681)
<b>Randomized, n (%)</b>	340 (100.0)	341 (100.0)	681 (100.0)
<b>Completed, n (%)</b>	307 (90.3)	280 (82.1)	587 (86.2)
<b>Withdrawn, n (%)</b>	33 (9.7)	60 (17.6)	93 (13.7)
Subject or Physician Request	8 (2.4)	16 (4.7)	24 (3.5)
Lost to follow-up	1 (0.3)	0 (0.0)	1 (0.1)
Adverse event	4 (1.2)	9 (2.6)	13 (1.9)
Significant Delay in Surgery	8 (2.4)	17 (5.0)	25 (3.7)
Death [1]	1 (0.3)	0 (0.0)	1 (0.1)
Other	11 (3.2)	18 (5.3)	29 (4.3)
Intent To Treat (ITT) Population [2]	340 (100.0)	340 (99.7)	680 (99.9)
Per Protocol (PP) Population [3]	284 (83.5)	259 (76.0)	543 (79.7)
[1] In addition one subject in each group died after being discharged from the hospital during the follow-up period. (see Table 3.2)			
[2] ITT Population: All randomized subjects			
[3] PP Population: All randomized subjects with no major protocol violations who were randomly assigned to treatment, had surgery and had an interpretable post-operative Color Flow Duplex Imaging (CFDI) evaluation. Subjects in the PROCRI <sup>®</sup> group received at least 1 of the 4 scheduled PROCRI <sup>®</sup> doses.			

## 1.2. Demographic and Baseline Characteristics

Patient demographics are summarized in Table 1.2. Demographic and Baseline characteristics were well balanced between the SOC and PROCRI<sup>®</sup> groups. Overall, subjects ranged in age from 18 to 88 years, with a mean age of 59.8 years. The majority of subjects were White (85.1%) and Female (88.4%) with a mean weight of 77.8 kg. The mean baseline Hb was 12.2 g/dL in both the SOC and PROCRI<sup>®</sup> group.

<b>Table 1.2: Demographic and Baseline Characteristics (Intent-to Treat Population)</b>			
	SOC (N=340)	PROCRI <sup>®</sup> (N=340)	Total (N=680)
<b>Age (years)</b>			
Mean (SD)	58.6 (14.1)	60.9 (14.3)	59.8 (14.2)
Median	59.5	62.0	61.0
Range	22-84	18-88	18-88
<b>Sex, n (%)</b>			
Male	42 (12.4)	36 (10.6)	78 (11.5)
Female	298 (87.6)	303 (89.1)	601 (88.4)
<b>Race, n (%)</b>			
White	285 (83.8)	294 (86.5)	579 (85.1)
Black	30 (8.8)	29 (8.5)	59 (8.7)
<b>Weight (kg)</b>			
Mean (SD)	77.5 (18.1)	78.1 (17.0)	77.8 (17.5)
Median	75.0	76.4	76.1
Range	43-168	34-132	34-168
<b>Height (cm)</b>			
Mean (SD)	163.9 (8.8)	163.1 (8.0)	163.5 (8.4)
Median	162.6	162.6	162.6
Range	140-193	145-191	140-193
<b>Hemoglobin (g/dL)</b>			
Mean (SD)	12.2 (0.8)	12.2 (0.8)	12.2 (0.8)
Median	12.3	12.3	12.3
Range	9.5-15.3	9.7-15.1	9.5-15.3
<b>Systolic Blood Pressure (mm Hg)</b>			
Mean (SD)	130.7 (17.1)	132.4 (17.7)	131.6 (17.4)
Median	130.0	132.0	130.0
Range	94-192	80-193	80-193
<b>Diastolic Blood Pressure (mm Hg)</b>			
Mean (SD)	77.3 (9.3)	77.2 (9.7)	77.3 (9.5)
Median	78.0	78.0	78.0
Range	48-106	54-120	48-120

### 1.3. Extent of Exposure

Subjects in the PROCRT® group were scheduled to receive 600 U/kg of PROCRT® on day –21, -14, -7 and on the day of surgery (day 0), following the surgical procedure. Out of the 340 subjects randomized to the PROCRT® group, 314 subjects received a mean dose of 46,743 Units of PROCRT® at day –21, 305 subjects 46,872 Units at day –14, 300 subjects 46,380 Units at day –7 and 271 subjects 46,779 Units at the day of surgery.

<b>Table 1.3: Study Medication Administration for PROCRT® Treatment Group (Intent-to-Treat Population)</b>		
Study Day		Total Dose (Units)
Day -21	n	314
	Mean (SD)	46742.9 (10179.3)
	Median	46190
	Range	15000-79200
Day -14	n	305
	Mean (SD)	46871.5 (10049.6)
	Median	46380
	Range	20000-79200
Day -7	n	300
	Mean (SD)	46906.5 (9893.6)
	Median	46380
	Range	24840-79200
Day 0	n	271
	Mean (SD)	46779.4 (9688.0)
	Median	46000
	Range	24840-79200

## 2. END POINTS

### 2.1. Primary Analysis: Incidence of Deep Venous Thrombosis (DVT)

The primary analysis compares the proportion of subjects with any (symptomatic or asymptomatic) DVT between the two treatment arms in the intent-to-treat population.

Table 2.1 summarizes the DVT results in the ITT population. In the PROCRI<sup>®</sup> group, 14 (4.1%) subjects were identified by CFDI at post-operative day 4 or on the day of discharge to be positive for DVT compared to 7 (2.1%) in the SOC group. Two subjects (0.6%) in the PROCRI<sup>®</sup> group reported symptoms of a DVT but the CFDI evaluations were normal. The total number of subjects with any DVT in the PROCRI<sup>®</sup> group was 16 (4.7%) compared to 7 (2.1%) in the SOC arm. As the upper confidence interval of the difference between DVT rates between the two groups was greater than the 4% pre-specified margin, the non-inferiority of PROCRI<sup>®</sup> to Placebo could not be established.

<b>Table 2.1:</b> Primary Analysis: Number (%) of Subjects with Deep Vein Thrombosis (DVT) identified by either Color Flow Duplex Imaging [1] on post-operative day 4 or on the day of discharge or by clinical symptoms (at any time during the study: Day -21 to 30 days after discharge). (Intent-to-Treat Population)				
Diagnosis Category	SOC (N=340) n (%)	PROCRI <sup>®</sup> (N=340) n (%)	Difference	Upper CI of Difference [2]
Subjects with any DVT	7 (2.1)	16 (4.7)	0.026	0.0536
Subjects with DVT identified by CFDI on post-operative day 4 or on the day of discharge	7 (2.1)	14 (4.1)		
Subjects with symptoms of DVT but normal CFDI assessment	0 (0.0)	2 (0.6)		
Normal CFDI	295 (86.8)	272 (80.0)		
Unknown CFDI	2 (0.6)	3 (0.9)		
Not Done/Missing CFDI	36 (10.6)	49 (14.4)		
<p>[1] Any subject with DVT identified by CFDI (in case of discrepancy between local lab or core lab evaluation, DVTs were adjudicated by an independent blinded adjudicator) or reported as an adverse event.</p> <p>[2] One sided 97.5% upper confidence interval on the difference (proportion in the PROCRI<sup>®</sup> group – proportion in the Standard of Care group). Subjects with an unknown/Not Done/Missing results are not counted as DVTs.</p>				

Table 2.2 summarizes the DVT results of the Per-Protocol population. In the PROCRI<sup>®</sup> group, 13 (5%) subjects were identified by CFDI at post-operative day 4 or on the day of discharge to be positive for DVT compared to 7 (2.5%) in the SOC group. Two subjects (0.8%) in the PROCRI<sup>®</sup> group reported symptoms of a DVT but the CFDI evaluations were normal. The total number of subjects with any DVT in the PROCRI<sup>®</sup> group was 15 (5.8%) compared to 7 (2.5%) in the SOC arm. As demonstrated with the IIT population, the upper confidence interval of the difference between DVT rates between the two groups was greater than the 4% pre-specified margin, the non-inferiority of PROCRI<sup>®</sup> to Placebo could not be established in the PP population.

<b>Table 2.2:</b> Secondary Analysis: Number (%) of Subjects with Deep Vein Thrombosis (DVT) identified by either Color Flow Duplex Imaging [1] on post-operative day 4 or on the day of discharge or by clinical symptoms (at any time during the study: Day –21 to 30 days after discharge). (Per Protocol Population)				
Diagnosis Category	SOC (N=284) n (%)	PROCRI <sup>®</sup> (N=259) n (%)	Difference	Upper CI of Difference [2]
Subjects with any DVT	7 (2.5)	15 (5.8)	0.033	0.0669
Subjects with DVT identified by CFDI on post-operative day 4 or on the day of discharge	7 (2.5)	13 (5.0)		
Subjects with symptoms of DVT but normal CFDI assessment	0 (0.0)	2 (0.8)		
Normal CFDI	277 (97.5)	244 (94.2)		
[1] Any subject with DVT identified by CFDI (in case of discrepancy between local lab or core lab evaluation, DVTs were adjudicated by an independent blinded adjudicator) or reported as an adverse event.				
[2] One sided 97.5% upper confidence interval on the difference (proportion in the PROCRI <sup>®</sup> group – proportion in the Standard of Care group). Subjects with an unknown/Not Done/Missing results are not counted as DVTs.				

Table 2.3 summarizes the incidence of any (symptomatic/asymptomatic) DVT by baseline Hb levels. Baseline Hb values of subjects receiving PROCRI<sup>®</sup> did not impact the incidence of DVTs. Subjects in the PROCRI<sup>®</sup> group entering the study with a baseline Hb of 10-12 g/dL had a 4.6 % (6/131) incidence of DVTs compared to 4.8% (10/209) in the > 12 g/dL baseline hemoglobin stratum. In contrast, subjects in the SOC group entering the study with a baseline Hb of 10–12 g/dL had a 0.8 % (1/128) incidence of DVTs compared to 2.8% (6/211) in the > 12 g/dL baseline hemoglobin stratum.

<b>Table 2.3: Baseline Hb Levels and DVT Incidence</b>		
Baseline Hb	SOC	PROCRI <sup>®</sup>
> 12 g/dL	2.8% (6/211)	4.8% (10/209)
10-12 g/dL	0.8% (1/128)	4.6% (6/131)
Odds Ratio	3.72	1.05
(95% CI)	(0.44, 31.23)	(0.37, 2.95)

## **2.2. Secondary Analysis**

### **2.3. Incidence of Thrombotic/Vascular Events (TVEs)**

Table 2.4 summarizes the TVE results in the ITT population. A total of 44 subjects experienced thrombotic vascular events (TVEs): 28 (8.2%) subjects in the PROCRI<sup>®</sup> group and 14 (4.1%) subjects in the SOC group. The most commonly reported TVE was symptomatic/asymptomatic DVT. Of the 42 subjects who develop TVEs, 23 subjects had asymptomatic/asymptomatic DVT (see Table 2.1). Twenty-one (87%) of the 23 subjects with DVTs were asymptomatic and had DVTs identified by CFDI on post-operative day 4 or on the day of discharge. The second most common TVE was chest pain (4 subjects in SOC arm vs. 5 subjects in the PROCRI<sup>®</sup> arm) followed by pulmonary embolism (3 subjects in SOC arm vs. 0 subject in the PROCRI<sup>®</sup> arm).

**Table 2.4:** Secondary Analysis: Number (%) of Subjects Who Had Thrombotic/Vascular Events (TVEs) (Intent-to-Treat Population)

Thrombotic/Vascular Events	SOC (N=340) n (%)	PROCRIT® (N=340) n (%)
Subjects Who Had At Least One TVE	14 (4.1)	28 (8.2)
Symptomatic/Asymptomatic DVT	7 (2.1)	16 (4.7)
Pulmonary Embolism	3 (0.9)	0 (0.0)
Stroke or Transient Ischemic Attack	0 (0.0)	1 (0.3)
Arterial Thrombosis	0 (0.0)	0 (0.0)
Angina or Myocardial Ischemia	0 (0.0)	1 (0.3)
Myocardial Infarction	0 (0.0)	1 (0.3)
Cerebrovascular Accident	0 (0.0)	2 (0.6)
Chest Pain	4 (1.2)	5 (1.5)
Other Thrombosis	0 (0.0)	2 (0.6)

Table 2.5 summarizes the TVE results of the Per-Protocol population. The incidence and distribution of TVEs in the Per-Protocol population is similar to the ITT population.

**Table 2.5:** Secondary Analysis: Number (%) of Subjects Who Had Thrombotic/Vascular Events (TVEs) (Per Protocol Population)

Thrombotic/Vascular Events	SOC (N=284) n (%)	PROCRIT® (N=259) n (%)
Subjects Who Had At Least One TVE	10 (3.5)	22 (8.5)
Symptomatic/Asymptomatic DVT	7 (2.5)	15 (5.8)
Pulmonary Embolism	0 (0)	0 (0.0)
Stroke or Transient Ischemic Attack	0 (0.0)	0 (0.0)
Arterial Thrombosis	0 (0.0)	0 (0.0)
Angina or Myocardial Ischemia	0 (0.0)	0 (0.0)
Myocardial Infarction	0 (0.0)	0 (0.0)
Cerebrovascular Accident	0 (0.0)	2 (0.8)
Chest Pain	3 (1.1)	4 (1.5)
Other Thrombosis	0 (0.0)	1 (0.4)

### 2.3.1. Incidence of Blood Transfusions

Table 2.6 summarizes the blood transfusion results in the ITT population. Fewer subjects in the PROCRIT® arm received any blood transfusions (29.7%) compared to subjects in the SOC arm (55%). During the peri-operative and post-operative period of the study, 25% of subjects in the SOC arm compared to 15.3 % in the PROCRIT® arm required allogeneic blood transfusions.

<b>Table 2.6:</b> Secondary Analysis: Number (%) of Subjects Who Received Blood Transfusions During Peri-operative and Post-operative Periods (Intent-to-Treat Population)				
Period	Transfusion Blood Source	SOC (N=340) n (%)	PROCRIT® (N=340) n (%)	p-value [1]
Peri-operative	Allogeneic	45 (13.2)	34 (10.0)	0.188
	Autologous	99 (29.1)	49 (14.4)	<0.001
	Any Blood Transfusion	120 (35.3)	76 (22.4)	<0.01
Post-operative	Allogeneic	59 (17.4)	31 (9.1)	0.002
	Autologous	55 (16.2)	21 (6.2)	<0.001
	Any Blood Transfusion	110 (32.4)	48 (14.1)	<0.001
Total (both periods)	Allogeneic	85 (25.0)	52 (15.3)	0.002
	Autologous	145 (42.6)	64 (18.8)	<0.001
	Any Blood Transfusion	187 (55.0)	101 (29.7)	<0.001

[1] p-values obtained using Chi-square test.

### 2.3.2. Hemoglobin Levels

Table 2.7 summarizes the Hb changes during the study in the ITT population. At screening the mean Hb was 12.2 g/dL in both the PROCRI<sup>®</sup> and SOC group. From screening to the day of surgery, Hb decreased to 11.8 g/dL in the SOC arm and increased to 13.5 g/dL in the PROCRI<sup>®</sup> arm. At discharge the mean Hb value was 10 g/dL in the SOC arm and 10.9 in the PROCRI<sup>®</sup> arm.

<b>Table 2.7: Secondary Analysis: Hemoglobin Levels (g/dL) from Screening through Discharge [1]</b> (Intent-to-Treat Population)			
Study Period		SOC (N=340) n (%)	PROCRI <sup>®</sup> (N=340) n (%)
Screening	n	337	338
	Mean (SD)	12.2 (0.8)	12.2 (0.8)
	Median	12.3	12.3
	Range	9.5-15.3	9.7-15.1
Surgery	n	270	262
	Mean (SD)	11.8 (1.2)	13.5 (1.5)
	Median	11.8	13.5
	Range	8.2-14.8	8.6-16.9
Post-operative	n	299	271
	Mean (SD)	10.0 (1.2)	11.3 (1.6)
	Median	10.0	11.2
	Range	6.5-12.8	6.5-15.1
Discharge	n	279	263
	Mean (SD)	10.0 (1.1)	10.9 (1.5)
	Median	9.9	10.9
	Range	7.1-13.6	7.3-15

[1] Measured prior to each transfusion in the Operating, Recovery and Post-operative study periods.

### **3. SAFETY**

#### **3.1. Summary of All Adverse Events**

Table 3.1 summarizes all adverse events that occurred during the study. The number of subjects who experienced at least one adverse event was similar in the SOC (73.2%) and PROCRIT® (76.2%) groups. The incidence of subjects who experienced at least one serious adverse event was also similar in the SOC (11.8%) and PROCRIT® (12.9%) groups. The proportion of subjects with adverse events leading to study withdrawal was higher in the PROCRIT® group (3.5% compared to 1.5% SOC). Vascular and cardiac disorders were also more frequent in the PROCRIT® group. A total of 3 subjects died during the study; two in the SOC group and one in the PROCRIT® group. More details about these deaths are provided in the next section.

<b>Table 3.1: Treatment-Emergent Adverse Events in &gt;5% of Subjects by System Organ Class (SOC) and Preferred Term [1] (Intent-to-Treat Population)</b>		
	SOC (N=340) n (%)	PROCRIT® (N=340) n (%)
Number of Subjects with at least one Adverse Event	249 (73.2)	259 (76.2)
Number of Subjects with Serious Adverse Event	40 (11.8)	44 (12.9)
Number of Subjects with Adverse Event Causing Discontinuation	5 (1.5)	12 (3.5)
Number of Subjects who Died	2 (0.6)	1 (0.3)
Adverse Event by System Organ Class (MedDRA version 6.0)		
Gastrointestinal disorders	139 (40.9)	139 (40.9)
Nausea	99 (29.1)	91 (26.8)
Constipation	55 (16.2)	57 (16.8)
Vomiting NOS	23 (6.8)	21 (6.2)
Injury, poisoning and procedural complications	99 (29.1)	91 (26.8)
Post procedural pain	72 (21.2)	71 (20.9)
General disorders and administration site conditions	78 (22.9)	84 (24.7)
Pyrexia	58 (17.1)	57 (16.8)
Skin and subcutaneous tissue disorders	56 (16.5)	51 (15.0)
Pruritus	43 (12.6)	39 (11.5)
Nervous system disorders	46 (13.5)	54 (15.9)
Headache	21 (6.2)	24 (7.1)
Musculoskeletal and connective tissue disorders	41 (12.1)	58 (17.1)
Muscle spasms	21 (6.2)	24 (7.1)
Back pain	7 (2.1)	18 (5.3)
Psychiatric disorders	51 (15.0)	42 (12.4)
Insomnia	23 (6.8)	17 (5.0)
Metabolism and nutrition disorders	41 (12.1)	41 (12.1)
Hypokalemia	19 (5.6)	21 (6.2)
Respiratory, thoracic and mediastinal disorders	38 (11.2)	43 (12.6)
Infections and infestations	31 (9.1)	48 (14.1)
Urinary tract infection NOS	16 (4.7)	22 (6.5)
Vascular disorders	29 (8.5)	43 (12.6)
Investigations	28 (8.2)	29 (8.5)
Renal and urinary disorders	25 (7.4)	23 (6.8)
Blood and lymphatic system disorders	23 (6.8)	18 (5.3)
Cardiac disorders	13 (3.8)	21 (6.2)
[1] Subjects with multiple occurrences of the same adverse event are counted only once for that particular adverse event or body system. SOC is displayed in descending order of total frequency of all treatment groups. Preferred term is displayed in descending order of total frequency of all treatment groups within SOC.		

### 3.2. Deaths

Two subjects in the SOC group and one subject in the PROCRT® group died during the study. Detailed narratives are found below.

Table 3.2: Subjects Who Died							
Treatment Subject No.	Age (yrs) Sex	Day of Death	Last Dose Prior to Death {Units}	Day of Last Dose	Precipitative Adverse Event	Relationship of AE to Study Drug	Duration of Exposure (Units)
<b>SOC</b>							
155-0180	67 F	11/30/02	NA	NA	Sudden cardiac death	Unlikely	NA
185-0501	80 F	04/23/05	NA	NA	Acute myeloid neoplasia NOS	Unlikely	NA
<b>PROCRT®</b>							
101-0270	64 F	08/01/03	40,380	07/09/03	Cryptogenic organizing pneumonia	Unlikely	161,520

**Death due to Sudden Cardiac Arrest:** Subject # 155-0180 is a 67-year old Caucasian female with a height of 156 cm and a weight of 96.8 kg. Her relevant medical history includes controlled hypertension and low back pain. The subject was randomized to standard of care treatment on 11/22/02. Eight days later, prior to the scheduled surgery, she died from sudden cardiac arrest. Her screening Hb on 11/21/02 was 12.6 g/dL.

**Death due to Acute Myeloid Neoplasia:** Subject # 185-0501 is a 80-year old Caucasian female with a height of 152 cm and a weight of 59.1 kg. Her relevant medical history includes controlled hypertension, osteoporosis, hypercholesterolemia and spondylosis. The subject was randomized to standard of care treatment on 3/9/05. On 3/29/05 she underwent a lumbar laminectomy that lasted 1 hour and 38 minutes. She received Propacet and Paracetamol for post procedural pain. On 4/21/05 she was hospitalized and diagnosed with acute myeloid neoplasia. Two days later, on 4/23/05, the subject died. Her Hb values were 11.9 g/dL, 10.2 g/dL, and 11.9 g/dL on 3/4/05, 3/30/05 and 4/1/05, respectively.

**Death due to a Cryptogenic Organizing Pneumonia:** Subject # 101-0270 is a 64-year old Caucasian female with a height of 150 cm, a weight of 67.3 kg and a smoking history. Her medical history includes hypertension, osteoporosis since 1995, restless leg syndrome, diabetes, depression, asthma since 1983, COPD since 1988 and pneumonia. The subject was randomized to receive 40,380 Units of PROCRT® on 6/9/03, 6/17/03, 6/24/03 and 7/1/03, the day of surgery. On 7/1/03 she underwent posterior L4-L5 decompression surgery that lasted 3 hours and 24 minutes. On 7/21/03 she was hospitalized with a cryptogenic organizing pneumonia. She was treated with methylprednisone, bactrim, azithromycin, sodium polystyrene, lasix, calcium gluconate, montelukast sodium, metronidazole and vancomycin but expired on 8/1/03. Her Hb values were 11 g/dL, 11.7 g/dL, 8.7 g/dL and 8.4 g/dL on 7/4/03, 7/9/03, 7/10/03 and 7/11/03, respectively. In the investigator's opinion there was an unlikely relationship between the subject's death and the study drug.

### 3.3. Serious Adverse Events

Table 3.3 lists all serious adverse events that occurred during the study. The overall incidence of serious adverse events was similar in the two groups. Forty-four (12.9%) subjects in the PROCRIT® group and 40 (11.8%) subjects in the SOC group experienced serious adverse events during the study. A difference in incidence of serious adverse events was seen in subjects who were diagnosed with DVT, subjects who developed nervous system disorders and pulmonary embolisms. Six (1.8%) subjects in the PROCRIT® group compared to two (0.6%) subjects in the SOC group reported serious DVTs. Three subjects (0.9%) in the SOC group reported serious pulmonary embolism. No subject in the PROCRIT® group experienced a pulmonary embolism.

<b>Table 3.3:</b> Treatment-Emergent Serious Adverse Events {in >1% of Subjects} by System Organ Class (SOC) and Preferred Term [1] (Intent-to-Treat Population)		
SOC MedDRA version 6.0 Preferred Term	SOC (N=340) n (%)	PROCRIT® (N=340) n (%)
Number of Subjects with at least one Serious Adverse Event	40 (11.8)	44 (12.9)
Injury, poisoning and procedural complications	12 (3.5)	6 (1.8)
Procedural complication	3 (0.9)	0 (0.0)
Infections and infestations	5 (1.5)	9 (2.6)
Wound infection	1 (0.3)	4 (1.2)
Vascular disorders	3 (0.9)	9 (2.6)
Deep vein thrombosis	2 (0.6)	6 (1.8)
Nervous system disorders	2 (0.6)	9 (2.6)
Respiratory, thoracic and mediastinal disorders	6 (1.8)	5 (1.5)
Pulmonary embolism	3 (0.9)	0 (0.0)
Cardiac disorders	3 (0.9)	4 (1.2)
Gastrointestinal disorders	3 (0.9)	4 (1.2)
Musculoskeletal and connective tissue disorders	4 (1.2)	2 (0.6)
Renal and urinary disorders	2 (0.6)	4 (1.2)
[1] Subjects with multiple occurrences of the same serious adverse event are counted only once for that particular serious adverse event or body system. SOC is displayed in descending order of total frequency of all treatment groups. Preferred term is displayed in descending order of total frequency of all treatment groups within SOC.		

### 3.4. Other Safety Observations

Table 3.4.1 and 3.4.2 summarize the results of systolic and diastolic blood pressure measurements (mm Hg) from screening through discharge in the ITT population. The systolic and diastolic measurement results were similar across treatment groups and point of assessment. No increase in systolic or diastolic blood pressure was seen in the PROCRT® group.

<b>Table 3.4.1:</b> Systolic Blood Pressure (mm Hg) from Screening through Discharge [1] (Intent-to-Treat Population)			
Study Period		SOC (N=340) n (%)	PROCRT® (N=340) n (%)
Screening	n	333	335
	Mean (SD)	130.7 (17.1)	132.4 (17.7)
	Median	130	132
	Range	94-192	80-193
Surgery	n	300	278
	Mean (SD)	134.4 (21.8)	136.8 (21.7)
	Median	132	136
	Range	89-200	87-214
Post-operative	n	305	279
	Mean (SD)	123.9 (15.6)	124.2 (15.0)
	Median	123	123
	Range	92-175	74-175
Discharge [1]	n	305	279
	Mean (SD)	126.5 (18.9)	127.3 (19.5)
	Median	126.0	126
	Range	80-191	80-179

[1] Post-operative day 4 or within 24 hours of discharge, whichever is earlier.

<b>Table 3.4.2: Diastolic Blood Pressure (mm Hg) from Screening through Discharge [1] (Intent-to-Treat Population)</b>			
Study Period		SOC (N=340) n (%)	PROCRT® (N=340) n (%)
Screening	n	333	335
	Mean (SD)	77.3 (9.3)	77.2 (9.7)
	Median	78	78
	Range	48-106	54-120
Surgery	n	300	278
	Mean (SD)	72.2 (11.7)	72.7 (12.9)
	Median	71	74
	Range	43-108	36-108
Post-operative	n	305	279
	Mean (SD)	66.8 (7.9)	66.3 (7.8)
	Median	66	66
	Range	50-91	43-93
Discharge [1]	n	305	279
	Mean (SD)	68.8 (10.5)	68.4 (11.1)
	Median	68	69
	Range	38-100	42-99

[1] Post-operative day 4 or within 24 hours of discharge, whichever is earlier.

**Disclaimer**

*Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.*