The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: EMD20001 (28-day Primary Analysis Phase)
Title: A Prospective, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study of the Safety and Efficacy of Three Days of Continuous Intravenous Infusion of GR270773 in the Treatment of Suspected or Confirmed Gram-Negative Severe Sepsis in Adults
Rationale: The EMD20001 study was undertaken to evaluate GR270773 in the treatment of new-onset severe sepsis caused by a suspected or confirmed Gram-negative bacterial infection. Although antibiotics and organ support therapies are currently used to treat sepsis, there still remains an unmet medical need in the management of this increasingly prevalent disorder.
Phase: II
Study Period: 02September2004 – 16May2006
Study Design: Prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group study consisting of a 28-day Primary Analysis Phase followed by a 12-month Follow-up Period.
Centers: 235 centers among 31 countries
Indication: Suspected or confirmed Gram-negative severe sepsis
Treatment: GR270773 was administered as a sterile 100mg/mL lipid emulsion for IV administration. Low-dose GR270773 (850mg/kg total dose) was administered as a 75mg/kg/hr loading dose infused over a 2-hour period, followed by a 10mg/kg/hr maintenance dose infused over 70 hours. High-dose GR270773 (1350mg/kg total dose) was infused as a 150mg/kg/hr loading dose, followed by a 15mg/kg/hr maintenance dose infused over 70 hours. The matching placebo emulsion was infused at the same rate as the corresponding active treatment.
Objectives: The primary objective of the study was to estimate the magnitude of the GR270773 treatment effect on 28-day all-cause mortality of two doses of GR270773 Emulsion compared against placebo emulsion in adults with suspected or confirmed Gram-negative severe sepsis.
Primary Outcome/Efficacy Variable: The primary endpoint was mortality, from any cause, within the first 28 days of the study. The proportion of subjects who died within 28 days following the initiation of dosing was compared between each dose of GR270773 and placebo.
Secondary Outcome/Efficacy Variable(s): The secondary endpoint was morbidity, defined as new-onset organ failure (regardless of cause) within the first 28 days of the study. The proportion of subjects with new-onset organ failure (in an organ not in failure at study entry) was compared between each dose of GR270773 and placebo.
Statistical Methods: As per protocol amendment 6 (29 July 2005), the sample size was readjusted to at least 615 subjects per treatment arm from 630 subjects per treatment arm, resulting in a <1% decrease in statistical power as a result of these changes in enrollment. This would provide at least 80% power for each of the 90% one-sided confidence intervals (CI) to detect a difference of 5%, given a 25% mortality rate in the placebo group. However, due to IDMC recommendations following the review of interim safety analyses, enrollment into the high-dose GR270773 treatment arm was paused and then permanently stopped, resulting in only 186 subjects randomized to high-dose GR270773, compared with 612 and 610 randomized subjects in the placebo and low-dose GR270773 treatment groups, respectively. The primary endpoint (28-day all-cause mortality) was evaluated using the Intent-to-Treat (ITT), Efficacy, and Per Protocol analysis populations. Analysis of safety data was performed using the ITT population.
Study Population: Subjects had to be at least 18 years of age and have one of the following new-onset bacterial infections with a suspected or confirmed Gram-negative etiology: 1) confirmed Gram-negative bacteremia, with the pathogen isolated from blood culture prior to study entry; 2) intra-abdominal infection; 3) nosocomial pneumonia, with evidence of a Gram-negative organism from either histological examination or by direct stain of a respiratory specimen prior to study entry; or 4) pyelonephritis. In addition, eligible subjects had to have signs of new-onset severe sepsis as evidenced by at least one hypoperfusion abnormality (i.e., metabolic acidosis or persistent oliguria) or organ failure (respiratory failure; coagulopathy; or cardiovascular failure) caused by the current episode of sepsis. Eligible subjects also had to be receiving new parenteral antibacterial treatment for the infection responsible for the episode of sepsis and receive study drug within 36 hours of commencing treatment with the new antibacterial agent and within 12 hours from onset of the first sepsis-related hypoperfusion abnormality/organ failure.

	Placebo N = 599	**Low-dose GR270773 N = 598**	**High-dose GR270773 N = 182**
Number of Subjects:			
Planned, N		615	615
Randomized, N		610	186
Completed, n (%)		574 (96%)	172 (95%)
Total Number Subjects Withdrawn, N (%)		24(4%)	10(5%)
Withdrawn due to Adverse Events n (%)		9 (2%)	6 (3%)
Withdrawn due to Lack of Efficacy n (%)		-	-
Withdrawn for other reasons n (%)		15 (3%)	4 (2%)
Demographics	**Placebo N = 599**	**Low-dose GR270773 N = 598**	**High-dose GR270773 N = 182**
N (ITT)	599	598	182
Females: Males	254:345	239:359	573:806
Mean Age, years (SD)	63.1 (16.41)	62.8 (16.27)	64.8 (15.47)
Caucasian, n (%)	484 (81%)	494 (83%)	161 (88%)
Primary Efficacy Results:			
	Placebo N = 599	**Low-dose GR270773 N = 598**	**High-dose GR270773 N = 182**
Death Within First 28 Days of Study (ITT Population), n (%)	161 (26.9%)	154 (25.8%)	57 (31.3%)
Difference in rate (Placebo – Active Treatment)		1.1%	-4.4%
One-sided chi-square p-value		0.329	0.879
One-sided 90% Confidence Interval		(-2.1%, -)	(-9.4%, -)
Secondary Outcome Variable(s):			
	Placebo N = 599	**Low-Dose GR270773 N = 598**	**High-Dose GR270773 N = 182**
Any Type of New-Onset Organ Failure Within First 28 Days of Study (ITT Population), n (%)	**122 (20.4%)**	**157 (26.3%)**	**57 (31.3%)**
Respiratory	50/297 (16.8%)	61/333 (18.3%)	23/99 (23.2%)
Cardiovascular	33/150 (22.0%)	48/161 (29.8%)	15/43 (34.9%)
Renal	40/460 (8.7%)	47/474 (9.9%)	22/138 (15.9%)
Coagulopathy	36/344 (10.5%)	41/355 (11.5%)	16/107 (15.0%)
Safety Results:			
	Placebo N = 599	**Low-dose GR270773 N = 598**	**High-dose GR270773 N = 182**
Most Frequent Adverse Events			
Subjects with any AE(s), n(%)	423 (71%)	442 (74%)	144 (79%)
Anemia	79 (13%)	92 (15%)	29 (16%)
Hypokalemia	57 (10%)	54 (9%)	16 (9%)
Metabolic acidosis	52 (9%)	65 (11%)	26 (14%)
Cardiac arrest	46 (8%)	42 (7%)	17 (9%)
Atrial fibrillation	46 (8%)	46 (8%)	11 (6%)
Diarrhea	33 (6%)	50 (8%)	28 (15%)
Mental impairment	38 (6%)	38 (6%)	12 (7%)
Hypoglycemia	27 (5%)	21 (4%)	7 (4%)

Pleural effusion	28 (5%)	18 (3%)	6 (3%)
Nausea	25 (4%)	31 (5%)	15 (8%)
Thrombocytopenia	23 (4%)	12 (2%)	5 (3%)
Hepatic failure	21 (4%)	25 (4%)	17 (9%)
Agitation	21 (4%)	15 (3%)	6 (3%)
Lipase increased	17 (3%)	25 (4%)	2 (1%)
Pyrexia	17 (3%)	10 (2%)	7 (4%)
Confusional state	15 (3%)	11 (2%)	7 (4%)
Serious Adverse Events			
	Placebo N = 599 n (%) [related]	**Low-dose GR270773 N = 598 n (%) [related]**	**High-dose GR270773 N = 182 n (%) [related]**
Subjects with SAEs, n (%)[n considered by the investigator to be related to study medication]	**213 (36%) [27]**	**235 (39%) [34]**	**77 (42%) [8]**
Metabolic acidosis	49 (8%) [0]	61 (10%) [1]	23 (13%) [0]
Cardiac arrest	46 (8%) [0]	42 (7%) [1]	17 (9%) [0]
Mental impairment	38 (6%) [0]	38 (6%) [0]	12 (7%) [0]
Hepatic failure	20 (3%) [2]	25 (4%) [0]	15 (8%) [0]
Hypokalemia	7 (1%) [0]	1 (<1%) [0]	0
Lipase increased	7 (1%) [7]	10 (2%) [9]	1 (<1%) [1]
Septic shock	6 (1%) [0]	2 (<1%) [0]	0
Thrombocytopenia	6 (1%) [0]	2 (<1%) [1]	0
Pneumonia	5 (<1%) [0]	2 (<1%) [0]	2 (1%) [0]
Gamma-glutamyl transferase increased	4 (<1%) [2]	3 (<1%) [0]	0
Hypoglycemia	4 (<1%) [1]	10 (2%) [3]	2 (1%) [0]
Myocardial infarction	4 (<1%) [0]	1 (<1%) [0]	2 (1%) [0]
Ventricular tachycardia	4 (<1%) [2]	0	1 (<1%) [0]
Anemia	3 (<1%) [0]	8 (1%) [2]	1 (<1%) [1]
Atrial fibrillation	3 (<1%) [0]	6 (1%) [0]	1 (<1%) [0]
Gastrointestinal hemorrhage	3 (<1%) [0]	4 (<1%) [0]	0
Heart injury	3 (<1%) [3]	1 (<1%) [1]	0
Hepatic enzyme increased	3 (<1%) [3]	1 (<1%) [0]	0
Multi-organ failure	3 (<1%) [0]	1 (<1%) [0]	1 (<1%) [0]
Pulmonary embolism	3 (<1%) [0]	3 (<1%) [0]	0
Respiratory distress	3 (<1%) [0]	1 (<1%) [1]	1 (<1%) [0]
Shock hemorrhagic	3 (<1%) [0]	0	1 (<1%) [0]
Urinary tract infection	3 (<1%) [0]	0	0
Carbon dioxide decreased	2 (<1%) [0]	0	0
Cardiac failure	2 (<1%) [0]	1 (<1%) [0]	1 (<1%) [0]
Cerebrovascular accident	2 (<1%) [0]	2 (<1%) [0]	1 (<1%) [0]
Deep vein thrombosis	2 (<1%) [0]	2 (<1%) [0]	0
Hemoglobin decreased	2 (<1%) [0]	2 (<1%) [0]	0
Hyperbilirubinemia	2 (<1%) [1]	1 (<1%) [1]	0
Hyperkalemia	2 (<1%) [1]	3 (<1%) [0]	0
Hypernatremia	2 (<1%) [0]	1 (<1%) [0]	0
Intestinal ischemia	2 (<1%) [0]	1 (<1%) [0]	0
Muscle necrosis	2 (<1%) [1]	0	0
Pancreatitis acute	2 (<1%) [1]	1 (<1%) [1]	0
Pyrexia	2 (<1%) [0]	1 (<1%) [0]	1 (<1%) [0]
Rectal hemorrhage	2 (<1%) [1]	1 (<1%) [0]	0
Upper gastrointestinal hemorrhage	2 (<1%) [0]	1 (<1%) [0]	0

Wound dehiscence	2 (<1%) [0]	2 (<1%) [0]	0
Abdominal pain	1 (<1%) [0]	0	0
Acute abdomen	1 (<1%) [0]	0	0
Alanine aminotransferase increased	1 (<1%) [0]	1 (<1%) [0]	0
Anoxic encephalopathy	1 (<1%) [0]	1 (<1%) [0]	0
Arrhythmia	1 (<1%) [0]	0	0
Arthralgia	1 (<1%) [0]	0	0
Aspartate aminotransferase increased	1 (<1%) [0]	2 (<1%) [1]	0
Aspiration	1 (<1%) [0]	0	0
Asthma	1 (<1%) [0]	0	0
Bacteremia	1 (<1%) [0]	0	1 (<1%) [0]
Bladder distension	1 (<1%) [0]	0	0
Blood amylase increased	1 (<1%) [1]	1 (<1%) [1]	1 (<1%) [1]
Bradyarrhythmia	1 (<1%) [1]	0	0
Brain edema	1 (<1%) [0]	2 (<1%) [1]	1 (<1%) [0]
Bronchitis	1 (<1%) [0]	0	0
Bronchopneumonia	1 (<1%) [0]	0	0
Cardiac death	1 (<1%) [0]	0	0
Cardiac failure congestive	1 (<1%) [0]	1 (<1%) [0]	0
Cardiac output decreased	1 (<1%) [1]	0	0
Cardio-respiratory arrest	1 (<1%) [0]	0	0
Cerebral infarction	1 (<1%) [0]	0	0
Cholangitis	1 (<1%) [1]	2 (<1%) [0]	0
Cholecystitis	1 (<1%) [0]	1 (<1%) [1]	1 (<1%) [1]
Cholestasis	1 (<1%) [0]	0	0
Chronic obstructive pulmonary disease	1 (<1%) [0]	0	0
Coma	1 (<1%) [0]	0	0
Cytolytic hepatitis	1 (<1%) [1]	0	0
Decubitus ulcer	1 (<1%) [0]	0	0
Dehydration	1 (<1%) [0]	0	0
Endocarditis bacterial	1 (<1%) [0]	0	0
Extradural abscess	1 (<1%) [0]	0	0
Extremity necrosis	1 (<1%) [0]	0	0
Failure to anastomose	1 (<1%) [0]	0	0
Gastric ulcer hemorrhage	1 (<1%) [0]	0	0
Graft complication	1 (<1%) [0]	1 (<1%) [0]	0
Hematochezia	1 (<1%) [0]	0	0
Hematocrit decreased	1 (<1%) [0]	0	0
Hydronephrosis	1 (<1%) [0]	0	0
Hyperamylasemia	1 (<1%) [0]	3 (<1%) [3]	0
Hyperglycemia	1 (<1%) [0]	2 (<1%) [0]	0
Hypersensitivity	1 (<1%) [1]	0	0
Hypoxic encephalopathy	1 (<1%) [0]	0	0
Ileus paralytic	1 (<1%) [0]	1 (<1%) [0]	0
Infected skin ulcer	1 (<1%) [0]	0	0
Intestinal obstruction	1 (<1%) [0]	1 (<1%) [0]	0
Large intestine perforation	1 (<1%) [0]	0	0
Lobar pneumonia	1 (<1%) [0]	0	0
Localized infection	1 (<1%) [0]	0	0
Mental status changes	1 (<1%) [0]	0	0
Metastases to liver	1 (<1%) [0]	0	0
Myelodysplastic syndrome	1 (<1%) [0]	1 (<1%) [0]	1 (<1%) [0]
Non-Hodgkin's lymphoma	1 (<1%) [0]	0	0
Pain in extremity	1 (<1%) [0]	0	0
Pancreatitis	1 (<1%) [1]	3 (<1%) [2]	0

Pancreatitis necrotizing	1 (<1%) [0]	0	0
Peritoneal necrosis	1 (<1%) [0]	0	0
Platelet count decreased	1 (<1%) [0]	0	0
Pneumothorax	1 (<1%) [0]	0	2 (1%) [0]
Postoperative wound infection	1 (<1%) [0]	0	0
Pulmonary edema	1 (<1%) [0]	0	1 (<1%) [0]
Pyelonephritis	1 (<1%) [0]	0	1 (<1%) [0]
Renal failure	1 (<1%) [0]	1 (<1%) [0]	0
Renal failure acute	1 (<1%) [0]	1 (<1%) [0]	0
Respiratory failure	1 (<1%) [0]	9 (2%) [1]	1 (<1%) [0]
Retroperitoneal hematoma	1 (<1%) [0]	0	0
Retroperitoneal hemorrhage	1 (<1%) [0]	0	0
Sepsis	1 (<1%) [0]	2 (<1%) [0]	1 (<1%) [0]
Shock hypoglycemic	1 (<1%) [1]	0	0
Small intestinal hemorrhage	1 (<1%) [0]	0	0
Splenic rupture	1 (<1%) [0]	0	0
Supraventricular tachycardia	1 (<1%) [0]	0	0
Thrombocytopenic purpura	1 (<1%) [1]	0	0
Tracheal hemorrhage	1 (<1%) [0]	0	0
Transitional cell carcinoma	1 (<1%) [0]	0	0
Troponin increased	1 (<1%) [0]	0	0
Ventricular fibrillation	1 (<1%) [0]	2 (<1%) [0]	0
Wound infection	1 (<1%) [0]	1 (<1%) [0]	0
Abdominal abscess	0	2 (<1%) [0]	0
Abdominal hernia	0	1 (<1%) [0]	0
Acute myocardial infarction	0	3 (<1%) [1]	3 (2%) [1]
Acute pulmonary edema	0	1 (<1%) [0]	1 (<1%) [0]
Acute respiratory failure	0	1 (<1%) [0]	0
Anastomotic leak	0	1 (<1%) [0]	0
Angina pectoris	0	1 (<1%) [0]	0
Aortic aneurysm rupture	0	0	1 (<1%) [0]
Atelectasis	0	0	1 (<1%) [0]
Bile duct cancer	0	0	1 (<1%) [0]
Bile duct stone	0	2 (<1%) [0]	0
Blood bilirubin increased	0	0	1 (<1%) [1]
Blood creatinine increased	0	1 (<1%) [0]	0
Bradycardia	0	3 (<1%) [1]	0
Brain abscess	0	1 (<1%) [0]	0
Cardiac failure acute	0	2 (<1%) [0]	0
Cardiogenic shock	0	1 (<1%) [0]	0
Cerebral ischemia	0	1 (<1%) [0]	0
Citrobacter sepsis	0	0	1 (<1%) [0]
Colitis pseudomembranous	0	1 (<1%) [0]	0
Coombs negative hemolytic anemia	0	1 (<1%) [1]	0
Dizziness	0	1 (<1%) [0]	0
Dizziness postural	0	1 (<1%) [0]	0
Duodenal perforation	0	1 (<1%) [0]	0
Duodenal ulcer perforation	0	0	1 (<1%) [0]
Electromechanical dissociation	0	0	1 (<1%) [1]
Encephalitis	0	1 (<1%) [0]	0
Encephalopathy	0	1 (<1%) [0]	0
Fungemia	0	1 (<1%) [0]	0
General physical health deterioration	0	0	1 (<1%) [0]
Guillain-Barre syndrome	0	1 (<1%) [0]	0
Hematuria	0	1 (<1%) [0]	0

Hemoglobinaemia	0	1 (<1%) [1]	0
Hemolysis	0	1 (<1%) [1]	0
Hemopneumothorax	0	1 (<1%) [0]	0
Hemorrhage	0	2 (<1%) [0]	3 (2%) [1]
Hepatic encephalopathy	0	0	1 (<1%) [0]
Hepatic function abnormal	0	1 (<1%) [0]	0
Hydrocholecystis	0	1 (<1%) [1]	0
Hypercapnia	0	1 (<1%) [0]	0
Hyperpyrexia	0	1 (<1%) [1]	0
Hyperuricemia	0	0	1 (<1%) [0]
Hyponatremia	0	1 (<1%) [0]	0
Hypotension	0	2 (<1%) [0]	0
Hypoventilation	0	1 (<1%) [0]	0
Hypovolemic shock	0	1 (<1%) [0]	1 (<1%) [0]
Hypoxia	0	1 (<1%) [0]	1 (<1%) [0]
Intestinal perforation	0	1 (<1%) [0]	0
Intra-abdominal hemorrhage	0	1 (<1%) [0]	1 (<1%) [0]
Ischemic hepatitis	0	1 (<1%) [0]	0
Ischemic stroke	0	0	1 (<1%) [0]
Jaundice	0	1 (<1%) [0]	0
Jugular vein thrombosis	0	1 (<1%) [0]	0
Left ventricular failure	0	1 (<1%) [0]	0
Leukocytosis	0	1 (<1%) [0]	0
Leukopenia	0	0	1 (<1%) [0]
Liver disorder	0	1 (<1%) [0]	0
Lower gastrointestinal hemorrhage	0	0	1 (<1%) [0]
Lower respiratory tract infection	0	1 (<1%) [0]	0
Lymphopenia	0	1 (<1%) [0]	0
Mesenteric artery thrombosis	0	1 (<1%) [0]	0
Metastases to central nervous system	0	1 (<1%) [0]	0
Multi-organ disorder	0	1 (<1%) [1]	0
Myelocyte present	0	1 (<1%) [0]	0
Necrotizing fasciitis	0	1 (<1%) [0]	0
Nodal arrhythmia	0	1 (<1%) [0]	0
Esophageal rupture	0	0	1 (<1%) [0]
Pancreatic duct obstruction	0	1 (<1%) [0]	0
Pancreatic enzymes increased	0	0	1 (<1%) [1]
Perinephric abscess	0	1 (<1%) [0]	0
Peritoneal hemorrhage	0	1 (<1%) [0]	0
Peritonitis	0	1 (<1%) [0]	0
Pneumonia aspiration	0	0	1 (<1%) [0]
Post procedural bile leak	0	1 (<1%) [0]	0
Post procedural hemorrhage	0	0	1 (<1%) [0]
Red blood cell abnormality	0	1 (<1%) [1]	0
Respiratory arrest	0	2 (<1%) [1]	1 (<1%) [1]
Salivary gland neoplasm	0	1 (<1%) [0]	0
Shock	0	1 (<1%) [1]	0
Sudden cardiac death	0	0	1 (<1%) [1]
Supraventricular tachyarrhythmia	0	1 (<1%) [1]	0
Tachyarrhythmia	0	2 (<1%) [1]	0
Tachypnea	0	1 (<1%) [0]	0
Thoracic hemorrhage	0	0	1 (<1%) [0]
Torsade de pointes	0	1 (<1%) [0]	1 (<1%) [1]
Transaminases increased	0	1 (<1%) [0]	0
Transient ischemic attack	0	0	1 (<1%) [0]

Ventricular tachyarrhythmia	0	1 (<1%) [1]	0
Wound evisceration	0	2 (<1%) [0]	0
	Placebo N = 599 n (%) [related]	**Low-dose GR270773 N = 598 n (%) [related]**	**High-dose GR270773 N = 182 n (%) [related**
Subjects with fatal SAEs, n (%) [n considered by the investigator to be related to study medication]	**85 (14%) [2]**	**70 (12%) [6]**	**33 (18%) [1]**
Cardiac arrest	36 (6%) [0]	35 (6%) [0]	16 (9%) [0]
Metabolic acidosis	13 (2%) [0]	12 (2%) [0]	4 (2%) [0]
Hepatic failure	6 (1%) [0]	5 (<1%) [0]	4 (2%) [0]
Mental impairment	4 (<1%) [0]	4 (<1%) [0]	2 (1%) [0]
Septic shock	4 (<1%) [0]	0	0
Shock hemorrhagic	3 (<1%) [0]	0	1 (<1%) [0]
Ventricular tachycardia	3 (<1%) [1]	0	0
Cardiac failure	2 (<1%) [0]	1 (<1%) [0]	1 (<1%) [0]
Gastrointestinal hemorrhage	2 (<1%) [0]	0	0
Intestinal ischemia	2 (<1%) [0]	1 (<1%) [0]	0
Multi-organ failure	2 (<1%) [0]	1 (<1%) [0]	1 (<1%) [0]
Respiratory distress	2 (<1%) [0]	0	0
Thrombocytopenia	2 (<1%) [0]	1 (<1%) [1]	0
Acute abdomen	1 (<1%) [0]	0	0
Anoxic encephalopathy	1 (<1%) [0]	1 (<1%) [0]	0
Arrhythmia	1 (<1%) [0]	0	0
Bradyarrhythmia	1 (<1%) [1]	0	0
Brain edema	1 (<1%) [0]	2 (<1%) [1]	1 (<1%) [0]
Bronchopneumonia	1 (<1%) [0]	0	0
Carbon dioxide decreased	1 (<1%) [0]	0	0
Cardiac death	1 (<1%) [0]	0	0
Cerebral infarction	1 (<1%) [0]	0	0
Cerebrovascular accident	1 (<1%) [0]	1 (<1%) [0]	0
Chronic obstructive pulmonary disease	1 (<1%) [0]	0	0
Coma	1 (<1%) [0]	0	0
Failure to anastomose	1 (<1%) [0]	0	0
Heart injury	1 (<1%) [1]	0	0
Hypernatremia	1 (<1%) [0]	0	0
Hypoglycemia	1 (<1%) [0]	0	0
Hypoxic encephalopathy	1 (<1%) [0]	0	0
Myocardial infarction	1 (<1%) [0]	1 (<1%) [0]	0
Non-Hodgkin's lymphoma	1 (<1%) [0]	0	0
Peritoneal necrosis	1 (<1%) [0]	0	0
Pulmonary embolism	1 (<1%) [0]	1 (<1%) [0]	0
Respiratory failure	1 (<1%) [0]	4 (<1%) [1]	0
Small intestinal hemorrhage	1 (<1%) [0]	0	0
Transitional cell carcinoma	1 (<1%) [0]	0	0
Troponin increased	1 (<1%) [0]	0	0
Ventricular fibrillation	1 (<1%) [0]	1 (<1%) [0]	0
Acute myocardial infarction	0	2 (<1%) [1]	1 (<1%) [1]
Acute respiratory failure	0	1 (<1%) [0]	0
Aortic aneurysm rupture	0	0	1 (<1%) [0]
Atrial fibrillation	0	1 (<1%) [0]	0
Bacteremia	0	0	1 (<1%) [0]
Bradycardia	0	1 (<1%) [0]	0
Brain abscess	0	1 (<1%) [0]	0

Cardiac failure acute	0	2 (<1%) [0]	0
Cardiogenic shock	0	1 (<1%) [0]	0
Cerebral ischemia	0	1 (<1%) [0]	0
Citrobacter sepsis	0	0	1 (<1%) [0]
Electromechanical dissociation	0	0	1 (<1%) [1]
Encephalitis	0	1 (<1%) [0]	0
General physical health deterioration	0	0	1 (<1%) [0]
Hemoglobin decreased	0	1 (<1%) [0]	0
Hepatic encephalopathy	0	0	1 (<1%) [0]
Hepatic function abnormal	0	1 (<1%) [0]	0
Hydrocholecystis	0	1 (<1%) [1]	0
Hypovolemic shock	0	0	1 (<1%) [0]
Intestinal perforation	0	1 (<1%) [0]	0
Intra-abdominal hemorrhage	0	0	1 (<1%) [0]
Mesenteric artery thrombosis	0	1 (<1%) [0]	0
Multi-organ disorder	0	1 (<1%) [1]	0
Esophageal rupture	0	0	1 (<1%) [0]
Pneumothorax	0	0	1 (<1%) [0]
Post procedural bile leak	0	1 (<1%) [0]	0
Respiratory arrest	0	0	1 (<1%) [1]
Sepsis	0	1 (<1%) [0]	1 (<1%) [0]
Shock	0	1 (<1%) [1]	0
Sudden cardiac death	0	0	1 (<1%) [1]
Tachyarrhythmia	0	1 (<1%) [1]	0
Upper gastrointestinal hemorrhage	0	1 (<1%) [0]	0

Conclusion: Neither dose of GR270773 had a beneficial treatment effect on survival or morbidity during the first 28 days of the study.

Adverse events were reported in 423 (71%) subjects receiving placebo, 442 (74%) subjects receiving low-dose GR270773, and 144 (79%) subjects receiving high-dose GR270773. Anemia was the most frequently-reported AE in all three treatment groups. Serious adverse events were reported in 213 (36%) subjects receiving placebo, 235 (39%) subjects receiving low-dose GR270773, and 77 (42%) subjects receiving high-dose GR270773. The most frequent SAE in all three treatment groups was metabolic acidosis. Fatal SAEs occurred in 85 (14%) subjects receiving placebo, 70 (12%) subjects receiving low-dose GR270773, and 33 (18%) subjects receiving high-dose GR270773.

Date Updated: 18-May-2007