

A Phase II/III, Randomized, Double-Blind,
Placebo-Controlled Trial of Lisofylline in Patients
with Acute Lung Injury and Adult Respiratory
Distress Syndrome

ARDS Clinical Network
ARDSNet Study 03, Version I

September 25, 1998

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Contents

Part I

Study Summary

- **Study Design:** Multicenter, Phase II/III, randomized, double-blind, placebo-controlled study. Patients will be randomly assigned to receive lisofylline (LSF) 3.0 mg/kg or placebo. Patients will be stratified according to center and ventilator strategy.
- **Primary Objective:** To compare the effect of LSF to placebo on the incidence of Day 28 mortality in patients with ALI or ARDS.
- **Secondary Objectives:** To compare the number of days of unassisted breathing during the 28 day study period.
- To examine the effect of LSF on the incidence of serious infections during the 28 day study period.
- To evaluate the effect of LSF on the incidence of infection-related mortality.
- To evaluate the effect of LSF on the number of organ-failure-free days during the 28 day study period.
- To evaluate the safety of LSF in patients with ALI or ARDS.
- **Study Population:** Patients with ALI or ARDS who are eligible and enrolled on ARDSNet Study 01.
- **Number of Subjects:** 800 patients; interim analyses will be performed after approximately 200, 400, and 600 patients have completed treatment.
- **Duration of Patient Participation:** LSF study drug treatment for 21 days or until 2 consecutive calendar days of unassisted breathing, whichever occurs first. Acute evaluation for 28 days and safety follow up for 60 days after study entry.
- **Study Medication:** Lisofylline or placebo.
- **Dosage Form:** Injection solution (60 mg/mL) in 10 mL ampuls.
- **Dosage:** 3.0 mg/kg, patients weighing ≥ 100 kg will receive the maximum dose of 300 mg.
- **Dosage Regimen:** Ten minute intravenous infusion every 6 hours.

- **Procedures:** Patients will receive LSF 3.0 mg/kg or placebo every 6 hours beginning on Day 0 and continuing through Day 20 (or when the patient has achieved two consecutive calendar days of unassisted breathing), whichever comes first.
- Blood samples will be drawn to determine surrogate marker levels on Day 0 prior to the first dose of LSF study drug and on Day 3 prior to a dose of LSF study drug and 4 hours after the completion of the LSF study drug dose.
- Blood samples to determine LSF and LSF metabolite levels will be drawn immediately before and immediately after the completion of a LSF study drug dose on Day 0 and Day 3. If a patient develops renal or hepatic impairment (creatinine > 2.5 or bilirubin > 3.0), pre- and post- study drug infusion samples will be drawn daily for three days and then weekly until day 28.
- Assessments including monitoring of vital signs, ventilator settings, laboratory studies and diagnostic testing will be performed during the study period.

1 Study Objectives

1.1 Primary Objective

To compare the effect of LSF to placebo on the incidence of Day 28 mortality in patients with ALI or ARDS.

1.2 Secondary Objectives

To compare the number of days of unassisted breathing during the 28 day study period in patients with ALI or ARDS.

To examine the effect of LSF on the incidence of serious infections during the 28 day study period.

To evaluate the effect of LSF on the incidence of infection-related mortality.

To evaluate the effect of LSF on the number of organ failure-free days during the 28 day study period.

To evaluate the safety of LSF in patients with ALI or ARDS.

Since this study involves the same patients as ARDSnet Study 01 in a factorial design, the data analyses comparing 6ml/kg to 12ml/kg ventilation will be performed comparing LSF to Placebo. Furthermore it will be a secondary objective to determine if LSF effects mortality or the number of days of unassisted breathing to Day 28, on the two forms of ventilation differently.

Part II

Study Description

A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Trial of Lisofylline in Patients with Acute Lung Injury and Adult Respiratory Distress Syndrome

ARDSNet Study 03, Version I

2 BACKGROUND

2.1 Acute Lung Injury (ALI) and Adult Respiratory Distress Syndrome (ARDS)

The recent American-European Consensus Conference on ARDS ([?]) define ALI according to the following criteria: 1) acute onset, 2) $\text{PaO}_2/\text{FiO}_2 \leq 300$, 3) Bilateral infiltrates on frontal chest radiograph, and 4) no evidence of left atrial hypertension (pulmonary capillary wedge pressure ≤ 18 when measured). The definition of ARDS is the same except for $\text{PaO}_2/\text{FiO}_2 \leq 200$.

ALI or ARDS occurs when an event such as sepsis or massive aspiration causes inflammation, increased pulmonary vascular permeability, and extravasation of fluid and inflammatory cells into the pulmonary interstitium and alveolar space ([?]). The inflammatory process leads to inactivation, destruction, and decreased production of surfactant ([?],[?],[?]). This causes increased surface tension at the alveolar air-fluid interface, leading to diffuse microatelectasis. Alveolar flooding and atelectasis cause hypoxemia from shunt. Management of hypoxemic respiratory failure frequently requires positive pressure ventilation. Traditional ventilator management in ALI/ARDS employs positive end-expiratory pressure (PEEP) and generous tidal volumes of 10-15 ml/kg ([?],[?]). Despite aggressive treatments for the conditions that precipitate ARDS, many patients die without resolution of the lung injury.

2.2 Lisofylline

ARDS is now thought to be a consequence of an over-aggressive inflammatory response with associated oxidant injury. Increased release of

cytokines and chemokines, with enhanced expression of adhesion molecules produces an acute inflammatory response in the lungs, involving neutrophil infiltration. These neutrophils migrate across the interstitial space into the intra-alveolar space where they, secondary to activation upon adherence, release proteases and reactive oxygen intermediates.

2.2.1 Lisofylline Mechanism of Action

The biomolecular target for lisofylline (LSF) is unknown. In normal human volunteers, lisofylline causes a prolonged and marked decrease (approximately 70%) in the levels of circulating free fatty acids including levels of the major oxidizable species, linoleic acid (unpublished data). In patients treated with IL-2 or in patients with septic shock, circulating levels of free fatty acids increase by several fold ([?],[?]). This increase is inhibited by therapy with lisofylline. During oxidative stress, linoleic acid is peroxidized to the highly bioactive derivative species, 9 and 13 hydroperoxyoctadecadienoic acids (HPODEs). Exposure of cultured endothelial cells to HPODEs increases their permeability to albumin and causes cellular activation as evidenced by upregulation of vascular cell adhesion molecule (VCAM) expression ([?],[?]). In a prospective study of 50 patients undergoing chemotherapy and radiation for bone marrow transplantation who were on a placebo-controlled trial with lisofylline at either 2.0 mg/kg or 3.0 mg/kg given every 6 hours, lisofylline suppressed formation of serum HPODEs in a dose-dependent manner (unpublished data). HPODE levels in circulation on the day of the transplant were highly predictive for subsequent mortality $p \leq (0.01)$. These data, in conjunction with preclinical data indicating LSF efficacy in protecting against tissue injury mediated by oxidation, suggest that LSF may exert its major effect by decreasing cellular lipid peroxidation and subsequent activation of stress-associated signaling pathways, thereby suppressing production of a number of cytokine mediators that amplify the inflammatory process.

2.3 Pre-clinical Studies with Lisofylline

2.3.1 Hemorrhagic shock induced lung injury (*in vivo*)

Lisofylline was investigated in a murine model of lung injury. Control and treated mice were bled one-third of their blood volume with re-transfusion of stored blood after one hour. Treated animals received lisofylline at the time of transfusion. At clinically achievable concentrations, lisofylline significantly inhibited the release of TNF, gamma interferon (INF), IL-6,

and IL-1 into fluid recovered by bronchoalveolar lavage (BAL). Other than mild accumulation of neutrophils, lisofylline treated animals had no histologic evidence of alveolar edema or hemorrhage, unlike control animals which had extensive air space damage, hemorrhage, edema and neutrophil infiltration ([?]).

2.3.2 Cytokine and neutrophil-mediated lung injury (*in vivo*)

A highly fatal and relatively common complication of severe trauma and hemorrhagic shock is the development of acute non-cardiogenic lung injury (ARDS). IL-1, IL-8 and neutrophils are increased in lungs of patients with ARDS and are thought to contribute to lung injury. The effect of lisofylline on cytokines and neutrophils in acute lung injury was evaluated in a series of experiments in intact and isolated rat lung. Lisofylline inhibited lung edema when lungs were perfused with human neutrophils and treated intratracheally with IL-8. Lisofylline also suppressed neutrophil accumulation in lungs treated with intratracheal IL-1. Taken together, these studies suggest that lisofylline may prevent acute lung injury following severe trauma by inhibiting the response to hypoxic injury and the subsequent inflammatory cytokine cascade.

2.3.3 Antibiotic/antimicrobial effects (*in vivo*)

A series of experiments were conducted to evaluate the effect of lisofylline on antimicrobial activity of twelve commonly used antibiotics. Concentrations of lisofylline up to 50 μM (which exceeds planned clinical concentrations), do not appear to antagonize or potentiate the activity of antimicrobial agents in recent blood bacterial isolates. In an *in vivo* model, mice were infected intratracheally with *Pseudomonas* and treated with either sub-therapeutic or therapeutic doses of a cephalosporin antibiotic with or without lisofylline. Lisofylline had no effect on the number of bacterial CFU/g of lung tissue suggesting it had no antagonistic effects on antimicrobial activity *in vivo*. These findings suggest that concomitantly administered lisofylline did not interfere with antimicrobial therapy.

2.3.4 Endotoxic shock (*in vivo*)

Lisofylline was examined in a murine model of endotoxic shock. In these studies, a lipopolysaccharide (LPS) dose sufficient to induce 90-100% lethality in 24-48 hours was utilized. Lisofylline, administered simultaneously or 2 hours after a lethal dose of LPS resulted in 80-100%

survival. Even when lisofylline was administered 4 or 6 hours following an otherwise lethal dose of endotoxin, 37% and 25% of treated animals survived respectively ([?]).

2.3.5 Platelet function (*ex vivo*)

To determine if lisofylline interferes with platelet function and, thus, might increase the hemorrhagic diathesis in patients following trauma, its effect on platelet aggregation was analyzed. Aggregation of normal human donor platelets induced by thrombin, adenosine diphosphate (ADP), ristocetin or collagen, was not affected by lisofylline, at concentrations up to 50 μ M. These data along with data indicating that lisofylline had no effect on either a prothrombin time or a partial thromboplastin time assay indicated that it should not increase bleeding tendencies in patients with septic shock.

2.3.6 Wound healing (*in vivo*)

Using a standard wound healing model, incisional wound tensile strength was measured in rats treated BID with 25 mg/kg and 50 mg/kg of lisofylline. On post-operative days 4 and 8 there were no significant differences between the two groups treated with lisofylline and the control group.

2.4 Clinical Studies with Lisofylline

More than 600 subjects have been enrolled in clinical trials with lisofylline, including greater than 350 subjects treated with active drug. In these trials, lisofylline has been studied for its potential ability to reduce the toxicity and to improve the outcome of cytotoxic antineoplastic therapy. Patients undergoing intensive chemotherapy and/or radiation therapy for bone marrow transplantation, for induction therapy in acute myeloid leukemia or biological therapy for other oncologic diseases have been included in clinical trials. LSF has been found to be safe in these trials, compared with the expected background level of adverse events in these patient populations.

Sixty patients with hematological malignancies undergoing bone marrow transplantation from HLA-identical sibling donors were enrolled in a Phase II study of LSF. Patients were randomized to receive placebo, 2.0 mg/kg LSF, or 3.0 mg/kg LSF diluted in 50 mL normal saline delivered as a 10

minute intravenous infusion every 6 hours from the start of conditioning to Day 21 post-transplant or hospital discharge, whichever occurred first. Trial endpoints included hematopoietic recovery, incidence of infections, incidence and severity of mucositis and survival. Eighteen patients received placebo, 23 patients received 2.0 mg/kg LSF, and 19 patients received 3.0 mg/kg LSF. Seventeen of 19 patients (89%) in the 3.0 mg/kg group survived to Day 100 compared to 11 of 23 patients (48%) in the 2.0 mg/kg group and 10 of 18 (56%) in the placebo group. The difference in the total number of patient deaths to Day 100 post-BMT is statistically significantly different ($p=0.022$) between the 3.0 mg/kg group and the placebo group. There was no statistically significant difference in Day 100 survival between the 2.0 mg/kg group and the placebo group.

There were significantly fewer infections ($p<0.01$) in patients who received 3.0 mg/kg LSF compared to placebo. No patients receiving 3.0 mg/kg developed an infection as defined by the study criteria from Day 0 through Day 35 compared to 8 (35%) patients treated with 2.0 mg/kg and 7 (39%) patients treated with placebo. There were 5 (28%) serious infections in the placebo group, 5 (22%) in the 2.0 mg/kg group and 0% in the 3.0 mg/kg group. In addition, no patient receiving 3.0 mg/kg developed a serious or fatal infection through Day 100 compared to 6 (26%) infections in the 2.0 mg/kg group and 7 (39%) in the placebo group.

Overall, mucositis was less severe and occurred in lower frequencies in the 3.0 mg/kg group and the placebo group ($p=0.1$). All placebo treated patients experienced some degree of mucositis whereas 13 (57%) of the 2.0 mg/kg group and 16 (84%) of the 3.0 mg/kg group reported no mucositis. There was a statistically significant benefit observed in the 3.0 mg/kg group for decreased infectious episodes, including life threatening infections and a higher overall Day 100 survival than placebo patients despite the fact that the LSF treatment groups had significantly higher proportion of high risk patients (older age, poorer performance status) than the placebo recipients. The incidence of reported adverse experiences was similar among the treatment groups indicating that LSF was safe and well-tolerated. In a single center, Phase II trial patients with newly diagnosed AML undergoing induction chemotherapy with idarubicin and cytarabine were randomized to receive placebo or LSF 3 mg/kg beginning prior to the first dose of chemotherapy and continuing through the 28 day treatment cycle for a maximum of 2 cycles. Patients were stratified by age and disease (AML or RAEB/RAEBt). Seventy patients ages 19-73 were enrolled and able to be evaluated. The endpoints of this study included the incidence of neutropenic infections (serious and non-serious) and mortality at Day 60. In this Phase II study, compared to treatment with placebo, treatment with lisofylline at 3 mg/kg did not significantly affect the incidence of any neutropenia-related infections ($p=0.337$) but did

result in a statistically significant reduction in serious neutropenia-associated infections (17% vs. 34%; $p=0.047$) and serious neutropenic fungal infections (0% vs. 14%; $p=0.021$). All cause mortality at Day 60 was not different between the LSF and placebo groups ($p=0.75$). Lisofylline's protective effect against serious infections is consistent with its presumed effects on mucosal barrier integrity since pathogenic organisms associated with serious infections are typically associated with breakdown of mucosal barriers in the gastrointestinal tract or in the lung. Lisofylline did not protect against infections from skin or intravenous catheters.

2.5 Rationale for LSF Dose

Recently completed pharmacokinetic studies of lisofylline in human normal volunteers have demonstrated that a dose up to 5.0 mg/kg given by IV infusion over 10 minutes is well tolerated in most subjects. Symptoms that occur at doses higher than 5.0 mg/kg IV infusion over 10 minutes are light headedness or dizziness and mild nausea. Dose progression leads to pronounced nausea and vomiting. Four of 25 subjects in LSF pharmacokinetic studies experienced light headedness, two experienced nausea at both the 3.0 mg/kg and the 6.0 mg/kg oral doses, and two patients experienced hypotension (decreased systolic blood pressure by approximately 25 for baseline) at a dose of 3.0 mg/kg. All symptoms generally resolved within 60 minutes of completion of the LSF study drug administration.

Clinical studies of lisofylline conducted in patients have utilized doses up to 4.8 mg/kg given by IV infusion over 10 minutes every six hours, for up to 28 days post BMT. Of 42 patients in a Phase II BMT study treated with LSF study drug, either 2.0 or 3.0 mg/kg, 6 who received LSF discontinued study drug due to nausea or nausea with vomiting. None of the 18 patients receiving placebo withdrew from the study due to nausea or vomiting. Other adverse events reported in clinical trials with lisofylline have been consistent with the adverse events expected in this patient population. There were no significant hemodynamic effects observed in seven patients with septic shock who received 1.5 mg/kg lisofylline every six hours for up to 5 days. Accumulation of LSF or of two of its primary metabolites was not observed in the six patients treated on this study. Although LSF doses of up to 5.0 mg/kg by 10 minute infusion have been tolerated in both normal volunteers and in patients undergoing bone marrow transplantation, 3.0 mg/kg proved efficacious in Phase II studies in bone marrow transplantation and induction chemotherapy for AML. Because the 3.0 mg/kg lisofylline dose has been well tolerated in clinical studies to date, a 3.0 mg/kg IV infusion over 10 minutes, every six hours has been chosen as the dose for this study.

3 STUDY OBJECTIVES

3.1 Primary Objective

To compare the effect of LSF to placebo on the incidence of Day 28 mortality in patients with ALI or ARDS.

3.2 Secondary Objectives

To compare the number of days of unassisted breathing during the 28 day study period in patients with ALI or ARDS.

To examine the effect of LSF on the incidence of serious infections during the 28 day study period.

To evaluate the effect of LSF on the incidence of infection-related mortality.

To evaluate the effect of LSF on the number of organ failure-free days during the 28 day study period.

To evaluate the safety of LSF in patients with ALI or ARDS.

Since this study involves the same patients as ARDSnet Study 01 in a factorial design, the data analyses comparing 6ml/kg to 12ml/kg ventilation will be performed comparing LSF to Placebo. Furthermore it will be a secondary objective to determine if LSF effects mortality or the number of days of unassisted breathing to Day 28, on the two forms of ventilation differently.

4 STUDY DESIGN AND ENDPOINT DEFINITIONS

4.1 Study Design

This is a multi-center, Phase II/III, randomized, double-blind, placebo-controlled study of LSF in patients with acute lung injury or adult respiratory distress syndrome. An estimated 800 patients will be enrolled in the study. Approximately 400 patients will be randomized to be treated with LSF 3.0 mg/kg and approximately 400 patients will be randomized to receive placebo. Patients will be stratified according to the ventilator strategy they have been assigned to receive on ARDSNet Study 01, (12 mL/kg or 6 mL/kg (randomized), 6 mL/kg directly assigned), and by center. This study was a factorial study with ARDSNet 01. Now that ARDSNet 01 has ended patients will be treated on 6 mL/kg. The data will

be analyzed in three strata, 12 mL/kg or 6 mL/kg, (randomized) or 6 mL/kg directly assigned. Furthermore, we will test for interactions of LSF with ventilator strategy on mortality and VFD (Vent-Free-Days). After approximately 200, 400, 600 and 800 patients, the primary efficacy and safety variables will be reviewed by an independent Data and Safety Monitoring Board to determine whether the randomization between lisofylline and placebo should stop for futility, lack of safety, or proven efficacy. Stopping for futility or efficacy will be based on a formal group sequential stopping boundary.

When study eligibility has been confirmed, patients will be randomized to receive either LSF 3.0 mg/kg or placebo. LSF or placebo study drug administration will begin within 36 hours of the time the final pulmonary inclusion criteria is met. The day of the first dose of LSF or placebo study drug will be Study Day 0. Study drug administration will continue every 6 hours for 21 days, or until the patient has been on unassisted breathing for 2 consecutive calendar days, whichever occurs first. Assessments including vital signs, hemodynamic measurements, ventilator settings, laboratory studies, and diagnostic testing will be performed during the study period. Patients will also be followed beyond Day 28 if serious adverse experiences have occurred prior to the last day of dosing until the event resolves or stabilizes.

4.2 Endpoint Definitions

Days of unassisted breathing (VFD, denoting Vent-Free-Days) to Day 28 is defined as the number of days after initiating unassisted breathing to Day 28 after randomization, assuming a patient survives for at least 2 consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to Day 28, VFD will be counted from the end of the last period of assisted breathing to Day 28 unless a period of assisted breathing was < twenty-four hours and the purpose of assisted breathing was for a surgical procedure. If the patient is receiving assisted ventilation at Day 28 or dies prior to Day 28, VFD will be zero.

Unassisted breathing is defined as breathing with face mask or nasal prong oxygen (or room air) following extubation, T tube breathing, breathing with CPAP at ≤ 5 cm H₂O pressure, or tracheostomy mask breathing.

Organ failure is defined as present on any date when the most abnormal vital sign/abnormal lab value meets the definition of Clinically Significant Organ Failure (CSOF) according to the Brussels Organ Failure Table ([?]).

Patients will be followed for 28 days, with each day scored for the presence of clinically significant organ failure (renal, hepatic, coagulation, pulmonary, cardiovascular). Each day a patient is alive and free of a given clinically significant organ failure will be scored as a failure free day, e.g., a renal failure free day (maximum number is 29 allowing for the day of study entry plus 28 follow-up days, minimum is zero). Any day that a patient is alive and free of ALL five organ failures will represent days alive and free of all organ failure. Central nervous system dysfunction is evaluated using the Glasgow Coma Scale at study entry (Day 0), Day 14 and Day 28.

Microbiologically documented bacterial or fungal infections are those for which a pathogen is isolated or identified from blood, normally sterile tissue or body fluid. If isolated from blood, the pathogen should be present from one or more blood cultures with the exception of coagulase-negative (or thermonuclease-negative) staphylococci or corynebacteria which require the isolation of these organisms from at least two blood cultures drawn within 24 hours of each other containing the same organism in order to be deemed significant.

Culture negative septic shock is defined as sepsis (two or more of the following: $T > 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$, $\text{HR} > 90$ bpm, $\text{RR} > 20/\text{min}$, $\text{PaCO}_2 < 32$ mmHg, *or* white blood cell count $> 12,000/\text{mm}^3$ or $< 4,000/\text{mm}^3$ or $> 10\%$ immature (band) forms.), with hypotension ($\text{BP} < 90$ mmHg systolic or a drop of ≥ 40 mmHg) lasting ≥ 2 hours despite adequate fluid resuscitation (e.g., 500 ml saline challenge) *or* a requirement for vasopressor support accompanied by the presence of perfusion abnormalities (i.e., lactic acidosis, oliguria, acute alteration in mental status), but without positive blood cultures.

Serious infections and the duration of an infectious episode are defined in Appendix ???. Culture negative septic shock episodes are classified as serious infections due to the severity of the clinical symptoms. Both number of patients with infections and number of infectious events will be considered in the analysis. Infections present 72 hours prior to randomization are not considered as endpoints. However, active treated or untreated infections present during the 72 hours prior to enrollment will be recorded on the case report forms. The infections that will be recorded are defined in Appendix ???.

5 PATIENT SELECTION

5.1 Inclusion Criteria

1. Concurrent enrollment in ARDSNet Study 01.
2. $\text{PaO}_2/\text{FiO}_2 \leq 300$. If altitude $> 1000\text{m}$, then $\text{PaO}_2/\text{FiO}_2 \leq 300 \times (\text{BP}/760)$.
3. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric.
4. Requirement for positive pressure ventilation via endotracheal tube.
5. No clinical evidence of left atrial hypertension. (If the patient has a pulmonary artery catheter, the wedge pressure ≤ 18 mmHg).

5.2 Exclusion Criteria

1. Age < 18 years.
2. A history of allergy to methylxanthines (e.g., theophylline, pentoxifylline). Treatment with methylxanthines must be discontinued at least 4 hours prior to first dose of LSF study drug. If theophylline was administered within 24 hours of first LSF study dose, theophylline level must be less than $10\mu\text{mol/L}$.
3. Participation in other experimental medication or intervention trials within the past 30 days.
4. Planned use of investigational agents or procedures during the 28 day study period.
5. Any other condition which in the investigator's opinion would not make the patient a good candidate for the trial.
6. Positive pregnancy test.

6 STUDY PROCEDURES

6.1 Screening Period

Potential patients will be evaluated in the intensive care units of approximately 24 hospitals that comprise the NIH ARDS Network. Study

coordinators will evaluate all patients who meet the eligibility criteria. Informed consent will be obtained from each patient or surrogate. Patients must be enrolled, randomized and receive LSF study drug within 36 hours of meeting all clinical inclusion criteria (section 5.1. Pre-treatment screening procedures including a clinical evaluation, 12-lead ECG, CBC, blood chemistries and pregnancy test (if applicable) will be obtained. After the results of the screening procedures have been reviewed and a patient is determined to meet all eligibility criteria and informed consent has been signed, the study coordinator will register the patient utilizing telephone randomization systems. Patients will be randomized on the ARDSNet Study 01 first. The ventilator strategy randomization must be known prior to randomization to LSF or placebo. The patient will be assigned a LSF kit number which will correlate to a blinded patient study number.

6.2 Treatment Period

LSF or placebo study drug will be administered as a single agent by a 10 minute intravenous infusion through a central venous catheter every 6 hours. LSF study drug administration will continue for 21 days or until the patient has achieved two consecutive calendar days of unassisted breathing, whichever occurs first.

Patients will be evaluated daily during the 28 day study period. Vital signs, laboratory parameters, ventilator and hemodynamic status and clinical changes will be monitored as outlined in the schedule of events (see Appendix ??). On the day that LSF is discontinued, the next scheduled vital signs, CBC, and serum chemistry evaluations will be required. If unassisted breathing is achieved prior to Day 28, the patient should remain hospitalized for a minimum of two consecutive calendar days following extubation, if possible, to document the achievement of the endpoint.

If a patient prematurely discontinues LSF study drug administration, study assessments including a clinical evaluation and the next scheduled laboratory evaluation must be performed prior to the institution of other therapy, if possible. If any study drug-related adverse experiences or toxicities are present at Day 20 or at the time of withdrawal from the study, the patient must be re-evaluated for the specific clinical or laboratory abnormality until the abnormality resolves or stabilizes. Patients will be evaluated for the development of serious adverse events for 14 days after study drug discontinuation. All deaths occurring within 60 days of study entry will be recorded (see section ??).

7 LABORATORY AND CLINICAL EVALUATIONS

7.1 Screening Evaluations

Pre-treatment evaluations which should be performed within 24 hours of initiating therapy include:

1. Resting 12-lead electrocardiogram (ECG).
2. History and clinical evaluation.
3. Laboratory evaluation: complete blood count (CBC) and platelet count, creatinine, blood urea nitrogen (BUN), albumin, sodium, potassium, chloride, bicarbonate, glucose, total bilirubin, AST, ALT, and alkaline phosphatase.
4. Pregnancy test (serum or urine) for females for child-bearing potential.

7.2 Treatment Period Evaluations

7.2.1 Organ Failure Criteria and Scoring

The Brussels Organ Failure Table (Appendix ??) will be utilized to document the development and reversal of multi-system organ failure throughout the 28 day study period. Laboratory values (creatinine, bilirubin, platelets), and vital signs generated as part of the patient's routine care will be used for these evaluations. The most aberrant value for any day for which data are available will be recorded during the first 28 days of the study period. Organ systems followed on a daily basis include cardiovascular (shock), pulmonary, renal, hepatic, and coagulation. Presence of shock will be evaluated throughout the study period on a daily basis using a clinical evaluation process that takes into account the dose of pressors being administered. Central nervous system dysfunction will be evaluated only at study entry, Day 14, Day 28 and study withdrawal.

7.2.2 Laboratory Evaluations

On Day 0 (prior to first dose of LSF study drug), 1, 2, 3, 4, 7, 14 and 21 the following laboratory tests will be performed: CBC and platelets, creatinine, BUN, albumin, sodium, potassium, chloride, bicarbonate,