The SOAP network of investigators was initiated by the European Society of Intensive Care Medicine (ESICM) to set up multicentric studies in Europe.

The initial Sepsis Occurrence in Acutely Ill Patients (SOAP) study was a cohort, multicenter, observational study in which laboratory, hemodynamic, and diagnostic data were collected prospectively until death, hospital discharge, or for 60 days, on all 3147 adult patients admitted to one of the 198 ICUs in 24 European countries between May 1 and May 15, 2002.

The SOAP network continues multicentric studies on vasoactive drugs, transfusions and other interventions.
Publications

**Original articles**

**Is albumin administration in the acutely ill associated with worse outcomes? Results of the SOAP study**
Vincent JL, Sakr Y, Reinhart K, Sprung C, Gerlach H, Ranieri MV, on behalf of the "Sepsis Occurrence in Acutely Ill Patient" investigators
*Critical Care 9*:R745-754, 2005

**High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury**
Sakr Y, Vincent JL, Reinhart K, J Groeneveld, Michalopoulos A, Sprung CL, Artigas A, Ranieri VM, on behalf of the "Sepsis Occurrence in Acutely Ill Patient" investigators
*Chest* 128:3098-3108, 2005

**Use of the pulmonary artery catheter is not associated with worse outcome in the ICU**
Sakr Y, Vincent JL, Reinhard K, Payen D, Wiedermann CJ, Zandstra KF, Sprung CL, on behalf of the "Sepsis Occurrence in Acutely Ill Patients" investigators
*Chest* 128:2722-2731, 2005

**Sepsis in European intensive care units: Results of the SOAP study**
Vincent JL, Sakr Y, Sprung C, Ranieri VM, Reinhart K, Gerlach H, Payen D, Moreno R, Carlet J, Le Gall JR, on behalf of the “Sepsis Occurrence in Acutely Ill Patient” investigators
*Critical Care Medicine* 34:344-353, 2006

**An evaluation of systemic inflammatory response syndrome (SIRS) signs in the Sepsis Occurrence in Acutely ill Patients (SOAP) study**

**Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) study**
Sakr Y, Reinhart K, Vincent JL, Sprung CL, R Moreno, VM Ranieri, De Backer D, Payen D, on behalf of the "Sepsis Occurrence in Acutely Ill Patient" investigators
*Critical Care Medicine* 34:589-597, 2006

**Effects of hydroxyethyl starch administration on renal function in critically ill patients.**
Sakr Y, Payen D, Reinhart K, Sipmann FS, Zavala E, Marx G, Vincent JL, on behalf of the "Sepsis Occurrence in Acutely Ill Patient" investigators
*British Journal of Anaesthesia (in press)*

**Sepsis and organ system failure are major determinants of post ICU mortality**
*(submitted for publication)*

**Early vs late onset shock in European ICUs**
*(submitted for publication)*
Manuscripts in preparation

A positive fluid balance is associated with a worse outcome in patients with acute renal failure
Payen D, de Pont AC, Sakr Y, Reinhart K, Vincent JL

Are blood transfusions associated with a worse outcome?
Vincent JL, Sakr Y, Payen D, Reinhart K, Gerlach H

Outcome from sepsis: Does sex matter?
Vincent JL, x, y, z......

How do major therapeutic interventions influence outcome?
x, y, z,......

Influence of age on outcome
x, y, z,......

The time course of organ dysfunction
x, y, z,......

Characteristics of patients with cancer
Taccone F, x, y, z,......

Neurological alterations in the ICU patient
Mascia L, x, y, z,......

Outcome patterns according to the ICU length of stay (LOS)
x, y, z,......

The epidemiology of mechanical ventilation in European ICUs
x, y, z,......

Influence of body mass index
x, y, z,......

Epidemiology and outcome of patients receiving massive transfusions
x, y, z,......

Microorganisms (resistance, fungi,...)
x, y, z,......
Abstracts

1. **Sepsis occurrence in the acutely ill patient (SOAP): Results of a large European multicentric study**
   *Critical Care Medicine 31: A130, 2003*

2. **Pseudomonas infection in ICU: Results of the SOAP study**
   *American Journal of Respiratory and Critical Care Medicine 167:A548, 2003*

3. **Incidence of organ failure in European ICUs: Results of the SOAP study**
   *American Journal of Respiratory and Critical Care Medicine 167:A548, 2003*

4. **Shock in the ICU: Results of the SOAP study**
   *American Journal of Respiratory and Critical Care Medicine 167:A548, 2003*

5. **Predictors of mortality from ALI/ARDS: Results of the SOAP study**
   Sakr Y, Vincent JL, Gerlach H, Payen D, Le Gall JR, Moreno R, Reinhart K, Carlet J, Sprung C, Ranieri VM, on behalf of the SOAP Investigators
   *American Journal of Respiratory and Critical Care Medicine 167:A737, 2003*

6. **Does dopamine administration in shock influence outcome? Results of the SOAP study**
   *American Journal of Respiratory and Critical Care Medicine 167:A551, 2003*

7. **Sepsis occurrence in the acutely ill patient (SOAP). Results of a large European multicenter study**
   *American Journal of Respiratory and Critical Care Medicine 167:A837, 2003*

8. **Early and late renal failure (RF) in ICU: incidence and predictors of mortality and morbidity**
   *Intensive Care Medicine 29:S160, 2003*

9. **Extracranial complications in acute brain injured patients: results of a large european multicenter study**
   *Intensive Care Medicine 29:S11, 2003*
10. The use of pulmonary artery catheter is not associated with worse outcome in the ICU; results of the SOAP study

11. Female gender is associated with worse ICU outcome; results of the SOAP study

12. Is albumin administration associated with worse outcome? results of the SOAP study

13. Does albumin administration influence outcome? Results of the SOAP study
*Chest* 124:91S,2003

14. High tidal volume and positive fluid balance in acute lung injury are associated with worse outcome
*Chest* 124:180S,2003

15. Is red blood cell transfusion associated with worse outcome?; results of the soap study
*Chest* 124:125S,2003

16. Early vs late shock in the ICU: Results of the SOAP study
*Critical Care Medicine* 31:A15,2003

17. Time course of respiratory failure in ALI/ARDS: Results of the SOAP study
Sakr Y, Vincent JL, Gerlach H, Payen D, Le Gall JR, Moreno R, Reinhart K, Carlet J, Sprung C, Ranieri VM, on behalf of the SOAP investigators
*Critical Care Medicine* 31:A100,2003

18. Epidemiology of ICU acquired infection: Results of the SOAP study
*Critical Care Medicine* 31:A126,2003

19. Patterns of infection in European intensive care units: Results of the SOAP study
Vincent JL, Sakr Y, Sprung C, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D, Reinhart K, Ranieri VM, on behalf of the SOAP investigators
20. **Outcome patterns according to the ICU length of stay (LOS): Results of the SOAP study**
*American Journal of Respiratory and Critical Care Medicine 169:A42, 2004*

21. **The epidemiology of mechanical ventilation in European ICUs: Results of the SOAP Study**
*American Journal of Respiratory and Critical Care Medicine 169:A42, 2004*

22. **Changes in microvascular blood flow are not related with changes in cardiac index during dobutamine**
De Backer D, Creteur J, Koch M, Dubois MJ, Sakr Y, Chierego M, Verdant C, Vincent JL, on behalf of the SOAP investigators
*Intensive Care Medicine 30:S26, 2004*

23. **Outcome of early late, and recurrent shock in the ICU: Results of the SOAP study**
Brunkhorst F, Sakr Y, Vincent JL, Reinhart K, Payen D, Gerlach H, Moreno R, Sprung C, Ranieri VM, on behalf of the SOAP investigators
*Intensive Care Medicine 30:S47, 2004*

24. **Predictors of poor outcome in various age groups: Results of the SOAP study**
Moreno R, Sakr Y, Vincent JL, Ranieri VM, Gerlach H, Payen D, Sprung C, Reinhart K, on behalf of the SOAP investigators
*Intensive Care Medicine 30:S53, 2004*

25. **Medical admissions are associated with worse ICU outcome: Results of the SOAP study**
Sakr Y, Vincent JL, Reinhart K, Gerlach H, Moreno R, Ranieri V, Sprung C, Payen D, on behalf of the SOAP investigators
*Intensive Care Medicine 30:S31, 2004*

26. **A SOFA score based index at ICU discharge predicts subsequent mortality on referral to general floors**
*Critical Care Medicine 32:A83, 2004*

27. **Patterns of organ failure preceding death in the ICU: Results of the SOAP study**
*Intensive Care Medicine 31:S48, 2005*

28. **Are massive red blood cell (RBC) transfusions associated with increased rates of sepsis and mortality?**
Vincent JL, de Bel E, Mallick A, Malledant Y, Sakr Y, Reinhart K, on behalf of the SOAP investigators
*Critical Care Medicine 33:A175, 2005*
29. **Patterns of organ failure preceding death in the ICU: Results of the SOAP study**  
*Intensive Care Medicine* 31:S48, 2005

30. **Are massive red blood cell (RBC) transfusions associated with increased rates of sepsis and mortality?**  
Vincent JL, de Bel E, Mallick A, Malledant Y, Sakr Y, Reinhart K, on behalf of the SOAP investigators  
*Critical Care Medicine* 33:A175, 2005

31. **Effects of hydroxyethyl starch administration on renal function in critically ill patients**  
Sakr Y, Payen D, Sipmann F, Reinhart K, Fraipont V, Gerard I, Vincent JL, on behalf of the SOAP investigators  
*Critical Care Medicine* 33:A175, 2005

32. **Pattern of infection in cancer patients admitted in the ICU**  
Taccone F, Sakr Y, Vincent JL, Lei K, Spies C, Reinhart K, on behalf of the SOAP investigators  
*Critical Care Medicine* 33:A156, 2005

33. **Patterns of organ failure preceding death in the ICU: Results of the SOAP study**  
*Intensive Care Medicine* 31:S48, 2005

34. **Are massive red blood cell (RBC) transfusions associated with increased rates of sepsis and mortality?**  
Vincent JL, de Bel E, Mallick A, Malledant Y, Sakr Y, Reinhart K, on behalf of the SOAP investigators  
*Critical Care Medicine* 33:A175, 2005

35. **Effects of hydroxyethyl starch administration on renal function in critically ill patients**  
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*Critical Care Medicine* 33:A175, 2005

36. **Pattern of infection in cancer patients admitted in the ICU**  
Taccone F, Sakr Y, Vincent JL, Lei K, Spies C, Reinhart K, on behalf of the SOAP investigators  
*Critical Care Medicine* 33:A156, 2005
ONGOING STUDIES

You are invited to contribute!

Comparison of dopamine and norepinephrine as the first vasoactive agent in the management of shock
(D De Backer)

Transfusion thresholds in the ICU
(Y Sakr)

Industry sponsored (with financial support)

- A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Investigational Drug Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-Resistant Staphylococcus aureus
(Theravance)

- A double-blind, randomized, placebo-controlled study to investigate the clinical efficacy and safety of two doses of Alkaline Phosphatase administered for three days in patients with severe sepsis and septic shock
(AM Pharma)

If you are interested to participate, please contact Mrs Marie-Rose André
(secrjlv@ulb.ac.be)
COMPARISON OF DOPAMINE AND NOREPINEPHRINE AS THE FIRST VASOACTIVE AGENT IN THE MANAGEMENT OF SHOCK

Dopamine and norepinephrine are widely used to correct hypotension in patients with acute circulatory failure, and several consensus or expert recommendations still recommend the use of both agents. The results of the SOAP study indicated that dopamine may be associated with higher mortality rates than norepinephrine, but various uncontrolled factors may have influenced these results. Therefore, we will address this issue in a prospective, randomized, double blind study. We hypothesize that both agents have similar effects on survival.

A total of 1600 consecutive patients with hypotension requiring the administration of vasopressors will be included (power of 80% to detect a 15% relative reduction in mortality with one agent). Patients will be randomized immediately, with the use of sealed envelopes placed near the supplies of dopamine and norepinephrine. If the patient is already being treated with one agent, randomization can still take place provided that it is within a 4 hour period.

Consent will be obtained from the patient before entering the study, if possible, or from the next of kin as soon as possible after starting vasopressor therapy. Indeed, in such cases, vasopressor therapy should anyway be started, either with dopamine or with norepinephrine, and these 2 therapies are currently equally valid 1st choices.

**Blood pressure goal:** defined by the physician in charge, according to each unit's recommendations

**Administration of vasoactive drugs:** Double blind administration of a solution of norepinephrine or dopamine. Each solution will be labeled with its randomly allocated number and will be prepared by the nurses in charge. The rate of administration of the blind solution will be determined according to a scale and using the estimated body weight. The maximal dose with the 2 agents will be 20 µg/kg.min for dopamine and 0.19 mcg/kg.min for norepinephrine. When the maximal dose of the blinded solution is achieved, an open label perfusion of norepinephrine can be added to achieve the desired blood pressure. Epinephrine or vasopressin may be used only as rescue therapy. Weaning of vasopressor agents will begin by weaning of the open label norepinephrine, followed by weaning of the blinded solution.

Dobutamine, dopexamine, and inhibitors of phosphodiesterase III can be used, if needed, to optimize cardiac output according to local practices.

**General therapeutic guidelines:** All therapies will be performed according to local guidelines.

**Randomization:** Randomization by blocks of 10 for each participating ICU, using a computer generated list to allocate treatments A or B, put in sealed envelopes near the drug supplies.

**End-points:** Primary end-point: 28 day survival. Secondary end-points: ICU and hospital survival; severity of organ dysfunction in the ICU (SOFA score), duration of ICU stay, time spent on vasopressors (vasopressor free days), on mechanical ventilation (ventilator free days) and on renal replacement (renal replacement free days), efficacy of dopamine to correct hypotension, tolerance: arrhythmia (incidence of ventricular tachycardia, ventricular fibrillation and atrial fibrillation), myocardial necrosis, skin necrosis, limb or distal extremity ischemia. occurrence of secondary infections, impact of target blood pressure on outcome

**Interim analysis:** Sequential analysis after 50, 100, and then every 100 included patients, allowing premature stop of the study in case of significant difference in 28-day survival between the two treatments.
TRANSFUSION THRESHOLDS IN THE ICU

**Aim of the study:** To determine whether restrictive and liberal strategies of red blood cell (RBC) transfusion produce equivalent results in critically ill patients.

**Background:** A multicenter study by Hebert et al (published in the *N Engl J Med* in February 1999) indicated that a restrictive blood transfusion strategy (hemoglobin threshold of 7 g/dL) was possibly superior to a more liberal approach (hemoglobin threshold of 10 g/dL). However the deleukocytation of transfused blood was uncommon at that time, and routine deleukocytation may result in better outcomes (Hebert et al, *JAMA* 2002). The ABC study conducted in 1999 (published in *JAMA* in 2002) indicated worse outcomes for transfused patients, while the SOAP study conducted in 2002 indicated that this may no longer be the case. The major difference between the ABC study and the SOAP study was that blood deleukocytation was much more commonly implemented in 2002 than in 1999. Hence the time has come to repeat a prospective controlled randomized study to compare hemoglobin thresholds of 7 vs 9 g/dL.

**Type of study:** Multicenter, controlled, randomized open study

**Inclusion criteria:** All patients expected to stay in the ICU for more than 24 hours with a hemoglobin  \( \leq 9 \text{ g/dL} \) within 72 hours after admission and who are considered to be euvolemic.

**Exclusion criteria:**
- age less than 16 years,
- inability to receive blood products,
- active blood loss (ongoing blood losses with 3 g/dL decrease in hemoglobin or need for 3 units of red blood cells in the preceding 12 hours)
- chronic anemia (hemoglobin concentration less than 9 g/dL on at least one occasion more than one month before admission to the hospital)
- pregnancy
- imminent death within 24 hours
- significant therapeutic limitations (DNR)

**Ethical issues** The study must be approved by the institutional review board and informed consent must be obtained from either the patient or the closest family member.

**Statistical analysis** sequential design
A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, MULTINATIONAL TRIAL OF INTRAVENOUS INVESTIGATIONAL DRUG VERSUS VANCOMYCIN FOR TREATMENT OF HOSPITAL-ACQUIRED PNEUMONIA WITH A FOCUS ON PATIENTS WITH INFECTIONS DUE TO METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

<table>
<thead>
<tr>
<th>Title:</th>
<th>A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Investigational Drug Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to Meticillin-Resistant <em>Staphylococcus aureus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Development Phase:</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Primary Objective:</td>
<td>To compare the efficacy and safety of investigational drug to vancomycin in the treatment of adults with Gram-positive hospital-acquired pneumonia (HAP) with an emphasis on patients with infections due to meticillin-resistant <em>Staphylococcus aureus</em> (MRSA).</td>
</tr>
<tr>
<td>Study Population:</td>
<td>Males and non-pregnant, non-lactating females ≥ 18 years old with Gram-positive pneumonia acquired while residing in a health care facility.</td>
</tr>
<tr>
<td>Design:</td>
<td>Multicenter, double-blind, parallel-group, randomized trial comparing investigational drug to vancomycin in patients with Gram-positive HAP. The target enrollment is 625 patients; however, additional patients (to total approximately 750 patients) may need to be enrolled to ensure that at least 100 evaluable patients infected with MRSA are available for analysis.</td>
</tr>
<tr>
<td>Treatments:</td>
<td>Group 1 - Investigational drug 10 mg/kg once a day IV for 7-21 days Group 2 - Vancomycin 1 g q 12 hr IV for 7-21 days Dummy infusions of Dextrose 5% (Glucose 5%) or normal saline will be used to maintain the blind between the two study groups. While a focus of the study is to demonstrate superiority of treatment with investigational drug compared to vancomycin in patients with HAP due to MRSA, patients with other Gram-positive pathogens will be enrolled and treated unless they meet other exclusion criteria. Since this study is designed to compare investigational drug to vancomycin for the treatment of HAP due to Gram-positive bacteria, all patients will be randomized to investigational drug or vancomycin. For patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria in addition to the Gram-positive organisms for which study medication therapy is used, aztreonam and/or metronidazole therapy, respectively, should be used. Piperacillin-tazobactam may be administered for Gram-negative coverage only if aztreonam is not appropriate due to an unacceptable level of resistance among Gram-negative bacteria. However, as piperacillin-tazobactam has activity against MSSA and <em>Streptococcus pneumoniae</em>, patients with those organisms and no MRSA, who require more than 24 hours of treatment with this medication, should not be enrolled. For such patients already enrolled, wherever possible, the piperacillin-tazobactam should be discontinued or switched to aztreonam as soon as possible. Finally, metronidazole is unnecessary if piperacillin-tazobactam is administered due to its activity against anaerobic bacteria. The vancomycin regimen may be monitored, and dosage adjusted, according to the institutional policy at each investigative site, by personnel who are not blinded to study treatment. In a similar manner, unblinded personnel should adjust the dosage of investigational drug for renal function. Other antibiotics permitted in the regimen should be adjusted according to manufacturer package inserts.</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>Patients who meet all of the following criteria will be eligible for study enrollment. 1. Male and female patients ≥ 18 years old 2. Clinical signs and symptoms consistent with pneumonia acquired after at least 48 hours of continuous stay in an inpatient acute or chronic-care facility, or acquired within 7 days after being discharged from a hospitalization of = 3 days duration • At least two of the following signs and symptoms must be present:</td>
</tr>
<tr>
<td>Selected Exclusion Criteria</td>
<td>Patients who satisfy any of the following criteria are not eligible for study enrollment.</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>1.</td>
<td>Received more than 24 hours of potentially effective systemic (IV/IM or PO) antibiotic therapy for Gram-positive pneumonia immediately prior to randomization, (unless documented to have not responded to at least 3 days of treatment or if the isolated pathogen for the current pneumonia was resistant in vitro to previous treatment).</td>
</tr>
<tr>
<td>2.</td>
<td>Respiratory tract specimens or sputum with only Gram-negative bacteria seen on Gram stain or culture</td>
</tr>
<tr>
<td>3.</td>
<td>Known infection with MSSA or <em>S. pneumoniae</em> and patient will require more than 24 hours of concomitant study medication therapy with an antibiotic for Gram-negative coverage that has activity versus MSSA or <em>S. pneumoniae</em> (e.g., piperacillin-tazobactam)</td>
</tr>
<tr>
<td>4.</td>
<td>Known or suspected pulmonary disease that precludes evaluation of therapeutic response (e.g., granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs); cystic fibrosis or active tuberculosis</td>
</tr>
<tr>
<td>5.</td>
<td>Known or suspected <em>Legionella pneumophila</em> pneumonia</td>
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<tr>
<td>6.</td>
<td>Known or suspected infection with an organism that is not susceptible to medications permitted by the protocol</td>
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<tr>
<td>7.</td>
<td>Documented or suspected meningitis, endocarditis, or osteomyelitis</td>
</tr>
<tr>
<td>8.</td>
<td>Refractory shock defined as supine systolic blood pressure &lt; 90 mm Hg for &gt; 2 hours with evidence of hypoperfusion or requirement for high-dose sympathomimetic agents</td>
</tr>
<tr>
<td>9.</td>
<td>Baseline QTc &gt; 500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K+ or Mg++ blood levels that cannot be corrected</td>
</tr>
</tbody>
</table>
10. Severely neutropenic (absolute neutrophil count < 500/mm³) or anticipated to develop severe neutropenia during the study treatment period due to prior or planned chemotherapy, or have HIV with CD4 count < 100/mm³ during the last 6 months

11. a) Female patients of childbearing potential if they are pregnant, nursing, or unable to use a highly effective method of birth control during the study and for at least one complete menstrual cycle following the last dose of study medication. A negative serum pregnancy result must be documented prior to treatment.

   b) Male patients must agree to use medically acceptable birth control for at least three months following last dose of study medication.

12. Considered unlikely to survive at least 7 days due to underlying illness

13. Any other condition that in the opinion of an investigator, would confound or interfere with evaluation of safety or efficacy of the investigational medication, or prevent compliance with the study protocol

| Primary Efficacy Endpoint: | Clinical response at Test-of-Cure evaluation (Cure, Failure or Indeterminate) |
A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY TO INVESTIGATE THE CLINICAL EFFICACY AND SAFETY OF TWO DOSES OF ALKALINE PHOSPHATASE ADMINISTERED FOR THREE DAYS IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK

Objectives

Primary Objectives

- To investigate the clinical efficacy on 28 day all cause mortality and survival rate of a high and a low dosage of iv Alkaline Phosphatase (AP) in comparison to placebo in patients with severe sepsis and septic shock.

Secondary Objectives

- To investigate the effect of a high and low dosage of AP in comparison to placebo in patients with severe sepsis and septic shock, on clinical efficacy variables like:
  - Day 28 clinical condition defined as:
    - The number of patients without mechanical ventilation
    - The number of patients without extra corporal hemodialysis
    - The number of patients without any intensive Care (IC) support
    - In-hospital mortality.
  - Per patient variable:
    - Change from baseline of APACHE II- score
    - Change from baseline of SOFA-score
    - ICU length of stay
    - Hospital length of stay
    - Number of days on mechanical ventilation
    - Number of days on extra-renal support.

- To investigate the effect of a high and low dosage of AP in comparison to placebo in patients with severe sepsis and septic shock, on surrogate efficacy variables like:
  - Per patient change from baseline of:
    - Inflammation variables
    - Pharmacokinetics
    - Immunological variables

- To investigate the safety and tolerability of a high and low AP dosage in comparison to placebo, in patients with severe sepsis and septic shock

Patient Population

Eligible for inclusion into this clinical trial are severe sepsis patients and patients in septic shock who should meet all of the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria

Clinical defined sepsis:

- Proven or suspected bacterial infection and
- Minimally 2 out of 4 SIRS criteria of systemic inflammation positive:
  - Core temperature $\leq 36^\circ$Celsius or $\geq 38^\circ$Celsius
  - Heart rate $\geq 90$ beats/min (unless the patient has a medical condition known to increase heart rate or is receiving treatment that would prevent tachycardia)
  - Respiratory rate $\geq 20$ breaths/min or a PaCO$_2$ $\leq 4.3$ kPa or the use of mechanical ventilation for an acute respiratory process
  - White-cell count $\leq 4^* 10^9$/L or $\geq 12^* 10^9$/L or a differential count showing $> 10$ percent immature neutrophils.

and
Acute onset of minimal 1 end-organ dysfunction in the preceding 36 hours:

- unrelated to the primary septic focus and
- not explained by any underlying primary chronic disease and
- as described by at least one of the following 7 underlying conditions:

1. Sustained hypotension, defined as:
2. Acute renal failure, defined by:
3. Acute alteration in mental state
4. Acute hypoxemic respiratory failure, defined by:
5. Disseminated intravascular coagulopathy (DIC), defined by:
6. Metabolic acidosis, defined as:
7. Acute hepatic failure, defined by = 2 of the following criteria:

and

≥ 18 years

and

Body weight = 125 kg

and

Being committed to - and treated with full intensive care support

and

Written informed consent obtained.

Exclusion Criteria

1. Patients being treated for transplantation of bone marrow, lung, liver, pancreas or other condition
2. Known confirmed gram-positive sepsis
3. Known confirmed fungal sepsis
4. Chronic renal failure requiring hemodialysis or peritoneal dialysis
5. Acute pancreatitis with no established source of infection
6. Patients expected to have rapidly fatal disease within 24 hours
7. Patients not expected to survive for 28 days, due to other medical conditions such as end-stage neoplasm or other diseases
8. Patients being treated with cancer related chemotherapy
9. Participation in another investigational study which clearly and documented interferes with this study within 30 days prior to start of the study
10. Previous administration of AP.
11. Allergy for cow milk
12. Known HIV patients with CD4-count < 50
13. Pregnant and lactating women

Introduction and rationale

Alkaline Phosphatase (AP) is a common endogenous enzyme, which is present in many cells and/or organs (e.g. intestines, placenta, liver, bone, kidney and neutrophilic granulocytes). Although the role of the enzyme is not fully elucidated, there is a growing body of evidence that it plays a significant role in host defense and innate immunity particularly against inflammatory reactions due to lipopolysaccharide (LPS or endotoxin) release. LPS or endotoxins are constituents of the cell wall of
gram-negative bacteria and are released when these bacteria disintegrate. It is a group of negatively charged molecules, of which the Lipid A moiety binds through two, for this purpose essential, phosphate groups, the MD2-CD14-TLR4 complex. These receptors are present on the surface of leukocytes (macrophages, white blood cells) and endothelial cells, and once activated these cells secrete a number of inflammatory cytokines. These in turn can cause a devastating and life-threatening derailment of the human innate immune system. AP has been shown to have a dual mode of action. First of all it binds and subsequently dephosphorylates LPS, thereby eliminating the root cause of the SIRS. Secondly, the enzymatic reaction product, Dephosphorylated LPS is a non-toxic substance for mammals, and acts as a partial antagonist on the LPS receptor complex. Unlike other potential treatments, AP has been shown to act at the front end of the inflammatory cascade. Furthermore, in ongoing sepsis, it cuts out the peaks of inflammatory responses induced by new LPS, which enters the systemic circulation after a septic insult.

To explore AP further for human therapeutic interventions, it is necessary to have sufficient amounts of AP that can be administered to animals and humans. As intestinal tissues contain a particularly high content of AP, technology has been developed to obtain the enzyme from bovine intestines. Certified BSE-free Bovine Intestinal Alkaline Phosphatase is derived from the intestinal mucosa of crop-fed South African cattle younger than 24 months of age.

In addition to \textit{in vitro} studies, the main evidence has been obtained in mouse and piglets models. AP was found to have a protective effect in mice that were administered lethal intraperitoneal doses of E. coli. In the non-treated group of mice 20 % survival was observed, compared to 80 % in the AP treated group. In addition, a profound effect was seen on temperature in the AP-treated group leading to normalization of body temperature. In piglets, a deterioration of well-being was observed following LPS administration, which was not seen when AP was co-administered. In addition, clear reductions in TNF\textalpha release, an inflammatory cytokine, were seen when AP was given together with LPS. Reductions in TNF\textalpha levels of 84-100 % were observed, indicating a significant pharmacological effect of AP on inflammatory response markers.

In a double-blind, randomized, placebo-controlled Phase I clinical study, AP was administered to 32 healthy volunteers in order to study its safety, tolerability and pharmacokinetics. In the first part three groups of 8 subjects received AP (n=6 per group) or matching placebo (n=2 per group). Subjects received AP intravenously given as a 10-minute infusion in a dose of 7.5 U/kg, 22.5 U/kg and 67.5 U/kg, respectively. The three dose levels resulted in mean peak concentrations of 68.5 U/l, 155 U/l and 488 U/l, respectively. The median terminal half-life revealed to be around 4 hours. In the second part, an additional group of 8 subjects received a dose of 200 U/kg (n=6) or placebo (n=2), administered continuously over 24 hours, in order to assess whether administered AP is well tolerated when given over prolonged time intervals. The continuous infusion of 200 U/kg resulted in a steady state concentration of about 60 U/l in plasma. There were no safety or intolerability problems with any of these dose regimens. The most commonly observed adverse events were headache, abnormal feeling, and diarrhea, which were assessed as not likely related to the study drug.

A Phase Ib clinical study was performed to test the safety and the effect on LPS of AP in healthy volunteers. In this study, one half of the subjects received a 10-min infusion of AP 67.5 U/kg vs. the other half of the subjects receiving placebo. Furthermore, all subjects received LPS (4 ng/kg) 2 minutes after start of study medication administration. The subject who received AP subsequently showed suppression of pro-inflammatory cytokines (TNFa, IL-6, and IL-8) and less severe clinical signs and symptoms resulting from LPS administration when compared to the placebo subject. Furthermore, administration of AP was proven to be safe in a series of 8 subjects.

Currently, a phase Ila study in being performed in 10 centers in Belgium and The Netherlands. This study will enclose 32 patients with severe sepsis and or septic shock, who will have a one day infusion of AP or placebo. 24 Patients receive active study medication, 200 U/kg per day, 12 patients receive placebo, and there will be a follow-up of 28 days. The primary endpoint is safety, the secondary endpoints are surrogate efficacy parameters (cytokines). The study is expected to be completed end of April 2006. End of February 2006, an interim analysis on safety will be performed.

\textbf{Design of new study}

This is a double-blind, randomized, placebo-controlled, multi-center, adaptive group sequential study with three parallel treatment groups (group comparative design). Eligible patients will receive either AP in a low or a high dose or matching placebo intravenously for
72 hours in a 1:1:1 allocation ratio. All study medication will be given as add-on (on top of) standard care. Patient follow-up will be 28 days after the start of study medication.