Title: A Randomized, Double-Blind, Placebo-Controlled, Phase-3 Study to Assess the Safety and Efficacy of ART-123 in Subjects with Severe Sepsis and Coagulopathy

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Sponsor: Asahi Kasei Pharma America Corporation

Purpose of Research
The goal of this research is to see if ART-123 can reduce death in patients who have severe sepsis. Even though scientists have learned a lot over the past several years, death from sepsis remains very high. This study will determine the safety of the experimental drug, ART-123, and will also determine if ART-123 can help the organs that may be affected by sepsis work properly again. Some people who received the experimental drug, ART-123, have developed antibodies.

Severe sepsis may have caused the subject’s blood pressure to drop very low and the subject’s lungs to stop working well. It may have also caused problems with the way the subject’s blood clots which could lead to a decrease in platelets. If the subject has a decrease in platelets it may take longer to stop bleeding. The bleeding problems may cause temporary or permanent damage to the subject’s organs.

The experimental drug, ART-123, has not been approved by the U.S. Food and Drug Administration (FDA) for sale by prescription. It has been developed by Asahi Kasei Pharma America Corporation. ART-123 is a protein similar to one found in blood called thrombomodulin. This protein helps to prevent clotting in the subject’s blood and prevents the loss of cells in the subject’s blood called platelets. ART-123 is produced by genetic engineering. A worldwide Phase IIB trial in patients with sepsis and another medical problem called Disseminated Intravascular Coagulopathy (DIC) showed a lower rate of death in patients that were treated with ART-123. DIC is a serious, life threatening sickness which causes the proteins that help your blood to clot become more active than normal. ART-123 has been given to almost 1000 subjects in research studies. In addition, more than 25,000 patients have received Recomodulin® (the approved name for ART-123 in Japan) since the drug was approved in Japan in January 2008. Japan continues to collect facts from patients treated with ART-123 to see how they are doing. These facts are used to help us learn more about how well ART-123 works.

Inclusion Criteria
This study targets critically ill subjects with severe sepsis requiring the level of care (patient to nurse ratio) that is normally associated with the treatment in the ICU setting:

1. Subject must be receiving treatment in an ICU, or in an acute care setting (e.g., ER, Recovery Room) with documented orders to transfer to the ICU.
2. Subjects who have clinical evidence of bacterial infection and a known site of infection* (with or without confirmation by culture) and all of the following:
   a. Currently receiving treatment with antibiotics.
   b. WBC >12,000/mm3 or <4,000/mm3 or Bandemia >10%.
   c. Platelet counts in the range of >30,000/mm3 to <150,000/mm3.
   d. Fever with core temperature of <36ºC or >38ºC (If the subject received an antipyretic agent within 24 hours prior to screening, there must be a documented temperature of greater than 38ºC within 24 hours prior to administration of the antipyretic agent in order to still qualify for study participation).
      Axillary temperatures will not be acceptable.
      Note: the presence of concurrent fungal or viral infection is allowed provided that the primary reason for treatment is bacterial infection.
3. Subjects with inflammatory changes due to sepsis defined by at least one of the following:
   I. Cardiovascular Dysfunction defined as receiving vasopressors to maintain Mean Arterial Pressure (MAP) greater than or equal to (> 65 mmHg for adequate tissue perfusion after adequate fluid resuscitation, where adequate fluid resuscitation is defined as:
      a. Intravenous administration of 20 mL/kg crystalloid or 10 mL/kg colloid infusion for up to but no more than 6 hours

b. Adequate right atrial filling pressure if measured by Central Venous Pressure (CVP) of greater than (>) 8 mmHg or Pulmonary Artery Wedge Pressure (PAWP) of greater than (>) 12 mmHg.

II. Respiratory Failure is defined as the acute need for mechanical ventilation and PaO2/FiO2 ratio is <250 mmHg (or < 200 mmHg when lung is the site of infection). For the purpose(s) of this protocol, mechanical ventilation is defined as any type of ventilation administered via an endotracheal tube or nasotracheal intubation. This applies to all modes of mechanical ventilation such as Volume Assist (VA), Volume Control (VC) or Pressure Control (PC), Pressure Support Ventilation (PSV) is permissible. A simple administration of supplemental oxygen is NOT considered as mechanical ventilation for the purposes of this study.

4. Subjects with coagulopathy characterized by an INR >1.40 without other known etiology (e.g., anticoagulant therapy).

Exclusion Criteria:
Candidates for the study will be excluded if ANY of the following criteria are present:

1. Subject has a known allergy to ART-123 or any components of the drug product
2. Subject is unwilling to allow transfusion of blood or blood products
4. Subject has had previous treatment with ART-123
5. Body weight ≥ 175 kg
6. PT prolongation or thrombocytopenia that is not due to sepsis (e.g. AML or ALL in induction therapy, acute leukemia of the M3 type, myeloablative therapy within 4 weeks prior to enrollment, AIDS with persistent thrombocytopenia and/or bleeding disorder, pre-existing thrombocytopenia or coagulopathy)
7. Intra-thoracic or intra-abdominal surgery within the 12 hours prior to consent, or ongoing impairment of hemostasis as a result of one of these procedures
8. A history of head trauma, spinal trauma, or other acute trauma with an increased risk of bleeding within 3 months prior to consent (subjects with minor head trauma may be enrolled if there is a normal neurological examination and a normal CT scan of the head/spine post injury documented in the medical record)
9. Cerebral Vascular Accident (CVA) within 3 months prior to consent
10. Any history of Intracerebral Arteriovenous Malformation (AVM), cerebral aneurysm, or mass lesions of the central nervous system
11. A history of congenital bleeding diatheses (e.g. hemophilia)
12. Significant gastrointestinal bleeding (e.g., melena, hematemesis) within 6 weeks prior to consent unless a corrective interventional procedure has been performed (i.e. endoscopy)
13. Subject is diagnosed with a known medical condition associated with a hypercoagulable state, including:
   a. Resistance to activated protein C or known Factor V Leiden
   b. Hereditary deficiency of protein C or protein S
   c. Presence of anticardiolipin antibody, antiphospholipid antibody, or prothrombin gene mutation
   d. Deep-vein thrombosis or pulmonary embolism within 3 months prior to consent (if evaluation is in progress, this should be completed before consideration for this trial)
   e. Any disorder with a requirement for full anticoagulation
14. Child-Pugh score of 10-15 (Class C)
15. Portosystemic hypertension or known history of bleeding esophageal varices
16. History of solid organ, allogeneic bone marrow, or stem cell transplantation within the 6 months prior to consent (uncomplicated kidney and autologous stem cell/bone marrow transplant subjects may be enrolled at any time after they have recovered from their transplant procedure)
17. Acute pancreatitis where infection has not been documented by a positive blood or abdominal fluid culture. Also, in the opinion of the treating physician the subject is at an increased risk for developing hemorrhagic pancreatitis over the duration of the study
18. Severe renal failure characterized by chronic or acute need of hemodialysis, hemofiltration or peritoneal dialysis
Exclusion Criteria (continued)

19. Use of anticoagulants, antiplatelet agents, antithrombotics and thrombolytics within the 72 hours prior to consent with the exception of:
   a. Heparin locks/flushes
   b. DVT Prophylaxis with either unfractionated heparin at total daily doses no higher than 15,000 U SQ or LMWH at a total daily dose no higher than 15,000 U SQ or 40 mg SQ
   c. Up to 325mg of aspirin daily for cardiac prophylaxis only

20. Life expectancy < 90 days due to underlying conditions such as, but not limited to, the following:
   a. Poorly controlled neoplasms
   b. New York Heart Association class IV subjects or pulmonary vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties), or chronic restrictive or obstructive pulmonary disease that also results in severe exercise restriction, or documented chronic hypoxia (needs continuous home oxygen treatment), hypercapnia, secondary polycythemia, severe pulmonary hypertension (Mean Arterial Pulmonary pressure level of >40 mmHg) or respiratory dependency
   c. Prior cardiac arrest requiring CPR without fully demonstrated neurological recovery, or subject with imminent death
   d. End-stage neurological disorders (e.g., amyotrophic lateral sclerosis – Lou Gehrig's disease)

21. Current use of any chemotherapy agent likely to cause myeloablation

22. Participation in another research study involving an investigational agent within 30 days prior to consent