ACCESS: A Controlled Comparison of Eritoran Tetrasodium and Placebo in Patients with Severe Sepsis

Published: 16-08-2006
Last updated: 13-05-2024

The primary objective of this study is to demonstrate that eritoran tetrasodium treatment of patients with severe sepsis results in a reduction in 28-day all-cause mortality.The secondary objectives are to confirm eritoran*s safety profile, and to...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Ancillary infectious topics
Study type	Interventional

Summary

ID

NL-OMON31790

Source
ToetsingOnline

Brief title
ACCESS

Condition

- Ancillary infectious topics

Synonym
Septic shock, Severe sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Eisai

Intervention

Keyword: Septic Shock, Severe Sepsis

Outcome measures

Primary outcome

The primary objective of this study is to demonstrate that eritoran tetrasodium treatment of patients with severe sepsis results in a reduction in 28-day all-cause mortality.

Secondary outcome

The secondary objectives are to confirm eritoran*s safety profile, and to demonstrate the long-term benefit of eritoran treatment (reduction in 12-month mortality), and to determine the population PK profile of eritoran.
Exploratory objectives are to determine the effects of eritoran treatment on duration of ICU and overall hospital stay; on the duration of dialysis, mechanical ventilation, or use of vasopressors within 28 days; on inflammatory marker (cytokine) responses, SOFA scores, 3- and 6-month mortality, subsequent infectious
episodes, and pharmacoeconomic and quality-of-life (QoL) measures.
Appropriateness of initial antibiotic regimen will also be explored. In addition, efficacy and safety measures may be examined using an exploratory population PK/PD analysis.

Study description

Background summary

Hypothesis: The intravenous administration of Eritoran Tetrasodium, total dose is 105 mg, to patients with severe sepsis over een period of a maximum of 6 days shall lead to a reduction in the all cause mortality over a period of 28 days after first administration.

Study objective

The primary objective of this study is to demonstrate that eritoran tetrasodium treatment of patients with severe sepsis results in a reduction in 28-day all-cause mortality.
The secondary objectives are to confirm eritoran*s safety profile, and to demonstrate the long-term benefit of eritoran treatment (reduction in 12-month mortality), and to determine the population PK profile of eritoran.
Exploratory objectives are to determine the effects of eritoran treatment on duration of ICU and overall hospital stay; on the duration of dialysis, mechanical ventilation, or use of vasopressors within 28 days; on inflammatory marker (cytokine) responses, SOFA scores, 3- and 6-month mortality, subsequent infectious
episodes, and pharmacoeconomic and quality-of-life (QoL) measures. Appropriateness of initial antibiotic regimen will also be explored. In addition, efficacy and safety measures may be examined using an exploratory population PK/PD analysis.

Study design

Hospitalized patients in the ICU, or who are about to be transferred to the ICU, who have early severe sepsis will be screened and baseline evaluations will be conducted. Following randomization, patients will receive study drug for a maximum of 6 days. Patients will be assessed for organ failures for 28 days or until hospital discharge, whichever occurs first. During that period safety,
quality of life and pharmacoeconomic assessments will be recorded at selected time points. Patients may be discharged from the ICU or hospital if their condition permits. The primary efficacy outcome will be based on Day 28 mortality status. Extended follow-ups for long-term mortality status will be reported separately.

This is a randomized, double-blind, placebo-controlled study. Patients will be randomized to either eritoran or placebo in a 2:1 ratio.

Intervention

Eritoran (E5564) intravenous infusion total dose 105 mg, administered as one 28.0-mg loading dose (7.0 mg/hr x 4 hours) followed by a second, 14.0-mg loading dose (7.0 mg/hr x 2 hr) at 12 hours, and nine 7.0-mg maintenance doses (3.5 mg/hr x 2 hr) every 12 hours thereafter.

The matching placebo is administered with the same schedule.

Study burden and risks

No specific restrictions on activities beyond the unknown, unidentified and harmfull side effects that have not yet been identified.

Contacts

Public
Eisai

3 Shortlands
London W6 8EE
United Kingdom
Scientific
Eisai

3 Shortlands
London W6 8EE
United Kingdom

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age *18 years; no upper age limit;2. Confirmed early-onset severe sepsis defined as:
a. Objective evidence of infection likely to be caused by a bacterial or fungal pathogen. Examples of objective evidence may include clinical findings (eg, cellulitis or abscesses),

cultures, Gram stains, X-rays, and surgical pathology specimens. A positive culture is not a requirement for entry into the trial.
b. Occurrence of at least three of the four SIRS criteria below
These criteria should have occurred between 12 hours before and 4 hours after the onset of the qualifying organ dysfunction.
* Core (central, urinary, esophageal, or rectal) body temperature *36°C or core (preferred), oral, or tympanic body temperature *38°C
Non-core temperatures are not to be adjusted. (revised per Amendment 01)
* Heart rate *90 beats/minute (patients who cannot be assessed for sepsis-induced tachycardia due to another medical condition known to increase heart rate, or those receiving treatment that prevents tachycardia, must have 2 of the remaining 3 SIRS criteria)
* Respiratory rate >20 breaths per minute or a PaCO(2) <32 mm Hg, or mechanical ventilation
* WBC count *12,000 cells/*L, *4000 cells/*L, or >10% band forms;3. At least one of the following organ dysfunctions:
a. Acute Lung Injury (ALI) / Acute Respiratory Distress Syndrome (ARDS):
* Acute onset of all four criteria below must occur together within a 24-hour interval, and the time of organ dysfunction is defined as the time that the final (fourth) criterion occurred:
- PaO(2)/FiO(2) *300 (<200 in patients with pneumonia). If altitude >1000 m, then PaO(2)/FiO(2) *300 x (PB/760).
- Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates may be patchy, diffuse, homogeneous, or asymmetric.
- Requirement for positive pressure ventilation via endotracheal tube or tracheostomy tube.
- No clinical evidence of left atrial hypertension.
* No history of severe chronic respiratory disease:
- FEV(1) less than 20 mL/kg PBW (eg, 1.4 L for 70 kg), or
- FEV(1)/VC less than 50% predicted, or
- Chronic hypercapnia (PaCO(2) greater than 45 mm Hg) and/or chronic hypoxemia (PaO(2) <55 mm Hg) on FiO(2) <= 0.21, or
- Radiographic evidence of chronic over-inflation or chronic interstitial infiltration, or
- Hospitalization within the past 6 months for respiratory failure (PaCO(2) >50 mm Hg or PaO(2) <55 mm Hg or O(2)-Sat <88% on FiO(2) <= .21).
- Chronic restrictive, obstructive, neuromuscular, chest wall or pulmonary vascular disease resulting in severe exercise restriction (eg. unable to climb stairs or perform household duties), secondary polycythemia, severe pulmonary hypertension (mean >40 mm Hg), or ventilator dependency.
b. Thrombocytopenia:
* Acute onset of platelet count <100,000 or a reduction of 50% or more from prior known levels, without past history of thrombocytopenia, and without attributable cause other than infection.
c.
* Lactic acidosis: (revised per Amendment 01)
* Unexplained metabolic acidosis (pH <7.30 or a base deficit >5.0 mmol/L) in association with a plasma lactate level >2.2 mmol/L (19.8 mg/dL)
* Subjects receiving parenteral fluids containing lactate are not eligible for inclusion under this criterion.
d. Shock:

* Acute onset of systolic blood pressure <90 mm Hg or mean arterial pressure <65 mm Hg. Blood pressure is poorly responsive to at least one hour of aggressive fluid resuscitation with a crystalloid or colloid, and vasopressors are required to maintain mean arterial pressure >65 mm Hg.
* Mechanically ventilated patients must exhibit hypotension due to sepsis before the institution of mechanical ventilation or be hypotensive for at least 60 minutes following intubation to qualify for the study on the basis of shock.
e.
* Acute Renal Failure:
*Urine output <0.5 mL/kg/hr for at least two hours, despite administration of at least 500 mL crystalloid or 200 mL colloid over a 30 minute period;4. A reasonable likelihood that administration of study drug can be started within 12 hours of documented organ dysfunction;5. Baseline APACHE II Score of 21 to 37, inclusive;6. There must be a commitment to full patient support. If a patient*s family has not committed to aggressive management of the patient*s condition or has requested that the patient be classified as *Do not resuscitate* or *Do not treat,* the patient is excluded. If a family directive allows all resuscitative efforts other than chest compression, the patient may be enrolled.

Exclusion criteria

1. Pregnancy or breast feeding;2. Extensive (>20% body surface area) third-degree burns within prior 7 days;3. Patients whose death from sepsis or an underlying condition is considered imminent;4. Patients with an expected survival of less than 2 months due to a pre-existing and uncorrectable medical condition, or those in a chronic vegetative state;5. Patients currently receiving immunosuppressive therapy
Consult Appendix 9 for a list of representative excluded therapies. Any subsequent modification to this list will be in the form of memos to the study sites. For agents not listed, patients should be off such therapies for a time sufficient to restore immune function. (revised per Amendment 02);6. Patients with granulocyte counts <1000/mm(3) unless the decreased count is believed to be due to sepsis;7. Patients who required cardiopulmonary resuscitation in the 4 weeks prior to evaluation for enrollment;8. HIV-positive patients with a last known CD4 count *50/mm(3), or end-stage processes (eg, systemic M. avium infection, progressive multifocal leukoencephalopathy);9. Patients with significant hepatic impairment (Child-Pugh class C), portal hypertension, or esophageal varices;10. Patients with severe congestive heart failure (eg, NYHA Class IV, ejection fraction <35%);11. Weight >150 kg at admission;12. Any one of the following (revised per Amendment 01):
* Ongoing or planned high-flux continuous hemofiltration or hemodiafiltration for the indication of sepsis in the absence of renal impairment
NOTE: Continuous hemofiltration or hemodiafiltration using ultracentrifugation volumes *35 mL/kg/hr for renal replacement therapy, and hemodialysis, are permissible.
* Ongoing or planned use of endotoxin removal devices, such as polymyxin B columns or cartridges
* Ongoing or planned plasma exchange performed for the indication of sepsis;13. IL-2 or interferon therapy within 30 days prior to enrollment ;14. Patients must not have taken any investigational medications or been treated with an investigational device (ie, not approved

by the relevant regulatory agency for any indication) within the 30-day period prior to enrollment into the study.;15. Cancer patients with active disease# or who have not completed their chemotherapy regimen (added per Amendment 01)
* Patients without evidence of active disease may be eligible, provided they have received no cancer chemotherapy or other cancer treatment for a minimum of 3 months (unless a longer exclusionary period is specified for an agent used in treatment) (see Appendix 9).
* Prophylactic use of tamoxifen for prevention of breast cancer is permitted.
* Adjuvant hormonal therapy is permitted.
#Subjects with basal cell carcinoma, cervical carcinoma in situ, or low-grade prostate cancer are eligible.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2006
Enrollment:	100
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Eritoran tetrasodium
Generic name:	Eritoran

Ethics review

Approved WMO Date:	16-08-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-03-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2007
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-06-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2009

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-02-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-03-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2005-005537-35-NL
CCMO	NL13311.029.06