OASIS: A Phase 2/3 Randomized, Double-blind, Placebo-controlled Study of the Safety and Efficacy of Talactoferrin Alfa in Patients with Severe Sepsis

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON35780

Source
ToetsingOnline

Brief title
OASIS LF-0802

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
Septic shock, Severe sepsis

Research involving
Human

Sponsors and support

Primary sponsor: Agennix Incorporated

Source(s) of monetary or material Support: Pharmaceutical industry

Intervention

Keyword: lactoferrin, recombinant human lactoferrin, severe sepsis, talactoferrin

Outcome measures

Primary outcome

28-day (672-hour post first dose of study drug) all-cause mortality

Secondary outcome

Secundary parameters:

- 3-month all-cause mortality;

- 6-month all-cause mortality;

-12-month all-cause mortality;

- Overall survival;

- Number of ICU-free days during 28-day period (672-hour post first dose of study drug);

- Number of shock-free days during 28-day period (672-hour post first dose of study drug);

- Number of ventilator-free days during 28-day period (672-hour post first dose of study drug); Number of dialysis-free days during 28-day period (672-hour post first dose of study drug);

- Number of organ-dysfunction-free days during 28-day period (672-hour post first dose of study drug); Incidence and severity of additional organ dysfunction* during 28-day period (672-hour post first dose of study drug);

- Incidence of new infections, relapses, and superinfections during 28-day period (672-hour post first dose of study drug);

- Time to initial ICU discharge from first dose of study drug; Duration of

hospitalization from first dose of study drug.

Safety Endpoints:

- Number of treatment-emergent and study agent-related adverse events;

- Number of serious adverse events; Number of study drug discontinuations due

to adverse events; Anti-TLF antibodies.

Additional Parameters:

- Soluble mediators (including, but not limited to IL-6, IL-8, IL-10, TNF-*,

IL-1*);

- Circulating levels of procalcitonin;

- Pharmacogenomic (DNA) collection;

- RNA collection;

- Plasma sample for retention;

- Pharmacoeconomic and quality of life parameters

Study description

Background summary

Sepsis is the clinical syndrome defined by the presence of both infection and a systemic inflammatory response. Severe sepsis is defined as sepsis plus one or more organ dysfunctions. The current sepsis treatment consists of eradicating the underlying infection and providing supportive care of any associated organ dysfunction.
This is a Phase 2/3, double-blind, placebo-controlled, study of oral talactoferrin in patients with severe sepsis (Figure 2). In Part 1 (Phase 2) of the study, 350 patients will be randomized 1:1 to receive either

talactoferrin or placebo in addition to standard care, for up to 28 days or until discharge from the ICU, whichever occurs first. In Part 2 (Phase 3) of the study, 930 patients will be randomized 1:1 to receive either talactoferrin or placebo in addition to standard care, for up to 28 days or until discharge from the ICU, whichever occurs first. The decision to start Part 2 (Phase 3) of the study will be made after reviewing the results of the primary endpoint and safety and tolerability from Part 1 (Phase 2) of the study.

Study objective

The primary objective is to determine the effect of oral talactoferrin alfa on 28-day (672-hour post first dose of study drug) all-cause mortality in patients with severe sepsis.

The secondary efficacy objectives are to determine the effect of oral talactoferrin alfa on:
- 3-month all-cause mortality;
- 6-month all-cause mortality;
- 12-month all-cause mortality;
- Overall survival;
- Number of 28-day intensive-care-unit (ICU) free days;
- Number of 28-day shock-free days;
- Number of 28-day ventilator-free days;
- Number of 28-day dialysis-free days;
- Number of 28-day organ dysfunction-free days;
- Incidence and severity of additional sepsis-related organ dysfunction;
- Incidence of new infections, relapses, and superinfections;
- Time to initial ICU discharge from first dose of study drug;
- Duration of hospitalization from first dose of study drug.

The secondary safety objective is to assess safety and tolerabiliity of oral talactoferrin alfa in patients with severe sepsis.
An additional secondary objective is to assess pharmacoeconomic and quality of life parameters.

Study design

This is a Phase 2/3, double-blind, placebo-controlled, study of oral talactoferrin in patients with severe sepsis. In Part 1 (Phase 2) of the study, 350 patients will be randomized 1:1 to receive either talactoferrin or placebo in addition to standard care, for up to 28 days or until discharge from the ICU, whichever occurs first. In Part 2 (Phase 3) of the study, 930 patients will be randomized 1:1 to receive either talactoferrin or placebo in addition to standard care, for up to 28 days or until discharge from the ICU, whichever occurs first. The decision to start Part 2 (Phase 3) of the study will be made after reviewing the results of the primary endpoint and safety and

tolerability from Part 1 (Phase 2) of the study.

Intervention

One bottle talactoferrin (1.5 g) or placebo 3 times a day (every 8 ±2 hours) oral or via other enteral route for up to 28 days or until discharge from the ICU, whichever occurred first.

Study burden and risks

De risks for the patients are, beside possible side effects and adverse events of the study medication, the risk from blood withdrawals.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Age * 18 years
2.Onset of severe sepsis within the previous 24 hours as defined by meeting all of the following criteria (A, B and C). Organ dysfunction must be present at the time of randomization. Randomization must occur within 24 hours of the first documented organ dysfunction (C) as defined below:
A.Objective evidence of confirmed or suspected infection. Suspected infection must be based on objective clinical evidence such as: (a) neutrophils in a normally sterile body fluid; (b) perforated viscus; (c) radiographic evidence of pneumonia; or (d) a syndrome associated with a high likelihood of infection (e.g., ascending cholangitis). and
B.the presence of at least three manifestations of a systemic inflammatory response syndrome (SIRS) due to infection (only two criteria if patient is on medication that controls heart rate or has a pacemaker):
*Body temperature: i) hyperthermia as indicated by a temperature of *38º C; or ii) hypothermia as indicated by a core temperature *36º C. For defining hypothermia, temperature must be obtained via a rectal temperature, central venous catheter monitor or urinary bladder thermistor, not by oral, tympanic or axillary measurement.
*Heart rate *90/min
*Respiratory rate *20/min or PaCO2 * 32 mmHg; or the use of mechanical ventilation for an acute respiratory process
*WBC *12,000/mm3 or *4,000/mm3, or >10% immature neutrophils (i.e., bands), and
C.at least one acute organ dysfunction due to sepsis, that is newly developed, and not explained by other disease processes or the effects of treatment and is ongoing at the time of randomization, defined as follows:
*Septic shock (Cardiovascular) * the requirement for vasopressors,* despite adequate fluid resuscitation,** to maintain a MAP >65 mm Hg or a systolic pressure >90 mm Hg.
* Vasopressors are defined as dopamine *5 *g/kg/min or any dose of norepinephrine, epinephrine, phenylephrine, or vasopressin, with the intent to support blood pressure. Dobutamine and dopexamine are not considered vasopressors.
**Adequate fluid resuscitation is defined as one of the following: i) a minimum of a 20 mL/kg (ideal body weight) intravenous fluid challenge (crystalloid or equivalent colloid); or ii) if measured, a central venous pressure (CVP) *8 mm Hg or *12 mm Hg if mechanically ventilated; or iii) a pulmonary artery occlusion pressure (PAOP) *12 mm Hg or *16 mm Hg if mechanically ventilated.
*Respiratory * must have mechanical ventilation and PaO2/FiO2 ratio *300 (SpO2/FiO2 *357) or if lung is the primary site of infection a PaO2/FiO2 ratio *200 (SpO2/FiO2 *214). Note: SpO2 may only be used if <97 (see Appendix E).
*Renal * i) an absolute increase in serum creatinine of *0.3 mg/dL within the preceding 48 hours, or ii) a relative increase in serum creatinine *50% within the preceding 48 hours, or iii) a urine output<0.5 mL/kg ideal body weight/hr for *2 hours in the absence of known or suspected urinary tract obstruction. In the presence of preexisting impairment of renal function (defined as a serum creatinine concentration >2 times the upper limit of the normal reference range prior to the onset of sepsis), the patient should meet another organ dysfunction criteria.
Meeting criteria i) or ii) requires *2 creatinine measurements within 48 hours. Criteria i), ii) or

iii) must be met despite adequate fluid resuscitation.** (defined as above for septic shock)
*Hematologic * platelet count <80,000/mm3 or platelet count <120,000/mm3 in association with a PT INR *1.2
*Metabolic * serum lactate *2.0 mmol/L (or equivalent in other units) despite adequate fluid resuscitation** (defined as above for septic shock)
3.Must be receiving antimicrobial therapy
4.Informed-consent form signed by patient or authorized representatives, according to local rules and regulations
5.Able to take liquid medication by mouth or feeding tube

Exclusion criteria

1. Receipt of any investigational medication or device within 4 weeks prior to randomization
2. Severe congestive heart failure (e.g., NYHA Class IV or pre-sepsis ejection fraction <30%)
3. Neutrophils <1,000/mm3 unless due to sepsis
4. Known HIV infection with CD4 <200 cells/mm3 or illnesses associated with end stage AIDS (e.g., disseminated Mycobacterium Avium Complex, Cytomegalovirus and Progressive Multifocal
Leukoencephalopathy)
5. Presence of 3rd-degree burns involving >20% body surface area (unless burn occurred >7 days prior to randomization)
6. Receiving immunosuppressants, such as prednisone 20 mg/day or equivalent for *2 weeks immediately prior to evaluation for enrollment
7. Patient is moribund and whose death is considered imminent by the investigator
8. Life expectancy, due to pre-existing conditions such as cancer, is less than six months
9. Severe hypoxic encephalopathy (e.g., post cardiopulmonary resuscitation) or persistent vegetative state
10. Child-Pugh Class C liver disease pre-sepsis or known portal hypertension or esophageal varices
11. The patient or their legal representative, or the patient*s primary physician are not committed to providing full, aggressive, life support
12. Patients chronically bed-bound prior to the onset of sepsis
13. Pregnant or breast-feeding

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-11-2011
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Talactoferrin Alfa
Generic name:	Talactoferrin

Ethics review

Approved WMO Date:	24-02-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2012
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	EUCTR2010-023986-23-NL
ClinicalTrials.gov	NCT01273779
CCMO	NL35501.029.11