# A Phase 2, Multi-Center, Randomized, Placebo-Controlled, Dose-Finding Study Evaluating Efficacy, Safety and Tolerability of Different Doses and Regimens of Allocetra-OTS for the Treatment of Organ Failure in Adult Sepsis Patients

Published: 23-09-2022
Last updated: 18-01-2025

To compare the safety and efficacy of different doses and regimens of Allocetra-OTS to that of Placebo in the treatment of organ failure in adult sepsis patients

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Infections - pathogen unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53483

**Source**
ToetsingOnline

**Brief title**
Efficacy and safety of Allocetra-OTS in patients with sepsis

### Condition

- Infections - pathogen unspecified

**Synonym**
1. Sepsis; 2. A life-threatening, medical emergency caused by an infection in the blood stream that can affect different organs

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Enlivex Therapeutics R&D Ltd;
**Source(s) of monetary or material Support:** Enlivex Therapeutics R&D;Ltd.

## Intervention

**Keyword:** Allocetra-OTS, cell therapy, organ failure, sepsis

## Outcome measures

### Primary outcome

Efficacy: Change from baseline in SOFA score throughout 28 days.

Safety: Number and severity of AEs and Serious Adverse Events (SAEs) throughout

28 days follow up period.

### Secondary outcome

- Ventilator-free days over 28 days

- Vasopressor-free days over 28 days

- Days without renal replacement therapy (dialysis)

- Time in ICU and time in hospital

- Number of days with creatinine <= Baseline levels +20%

- All-cause mortality at Day 28 following first dose

- Changes from baseline in C-reactive protein (CRP) levels

- Number and severity of AEs and SAEs throughout 12 months follow-up period

- Detection of autoimmune and human leukocyte antigen (HLA) antibodies

# Study description

## Background summary

Sepsis has been identified by the World Health Organization (WHO) as a global health priority and has no proven pharmacologic treatment other than appropriate antibiotic agents, fluids, and vasopressors as needed.
Allocetra-OTS is a cell-based therapeutic composed of allogeneic healthy donor mononuclear enriched cells, brought to an apoptotic state. Allocetra-OTS is provided in cryopreservation bags, each containing 50% PlasmaLyte and 50% CryoStor5®.
Allocetra-OTS represents a more holistic novel approach to the treatment of sepsis, leading to rebalancing pro- and anti-inflammatory cytokines and chemokines, growth factors, and other immunomodulating agents, by reprogramming of monocytes/macrophages and dendritic cells. Allocetra-OTS was shown to have a beneficial effect on downregulation of anti- and pro-inflammatory cytokines both in animal models and in vitro models. Furthermore, in a completed Phase 1b open label study utilizing Allocetra-OTS for the prevention of sepsis-related organ dysfunction, Allocetra-OTS has been shown to be safe and demonstrated a potentially significant clinical efficacy via immune rebalancing effect.

## Study objective

To compare the safety and efficacy of different doses and regimens of Allocetra-OTS to that of Placebo in the treatment of organ failure in adult sepsis patients

## Study design

This is a multi-center, randomized, placebo-controlled, dose-finding study comparing the efficacy, safety and tolerability of different dosing regimens of Allocetra-OTS, in up to 160 adult patients with sepsis. Potential patients with organ dysfunction will be identified and screened in the respective department or ward. In part 2 of the study (starting from protocol version 10), after completion of informed consenting process per local regulation, and patient eligibility confirmation, the patient will be randomized to either Cohort 1 (Placebo) or Cohort 4 (Single or two IV doses of Allocetra-OTS, 10x109 cells in each dose).

## Intervention

Allocetra-OTS is a cell-based therapeutic composed of allogeneic healthy donor mononuclear enriched cells, brought to an apoptotic state. Allocetra-OTS is provided in cryopreservation bags, each containing 2.5x10^9 cells, suspended in a solution containing 50% Plasma-Lyte and 50 CryoStor5® (final DMSO concentration of 2.5%), to a total volume of 100ml (per bag). Allocetra-OTS is stored for longterm storage at <= -150°C (in liquid nitrogen). Short-term storage is possible at -80°C, according to secondary label. Prior to IV

administration, each Allocetra-OTS bag is thawed separately and infused within 2 hours. The Placebo contains a solution containing 50% Plasma-Lyte and 50% CryoStor5® (final DMSO concentration of 2.5%) and will be thawed and administered IV.

**Study burden and risks**

The most common AEs assessed as related to Allocetra-OTS as reported in previous Sepsis and COVID-19 clinical studies were potential AEs associated with IV infusions. As Allocetra-OTS is a blood product, a transfusion reaction may potentially occur. Allocetra-OTS contains low levels of platelets. Mild febrile non-hemolytic transfusion reaction (FNHTR) (rigors) assessed and reported as possibly related to Allocetra-OTS in 2 patients in phase 1b clinical trial. This risk was mitigated by reducing the administration rate.
The trial DSMB has reviewed 28 days data of the first 16 dosed patients (approximately 4 patients in each Cohort) and has confirmed that the study may proceed according to plan. periodic and ad hoc DSMB meetings will also be held during the study to provide guidance regarding the safe conduct of the study based on the study safety information.
The safety of the subjects will be monitored by the investigators as well as the medical monitors. Patient will be closely monitored during and after the infusion for vital signs and AEs including allergic reaction. Patient experiencing allergic reaction may be treated with conventional treatment according to the investigator*s judgment by adrenaline, corticosteroids and antihistamines.
The novel mode of action of Allocetra-OTS and the supportive non-clinical and preliminary clinical data suggest a potential advantage in efficacy over existing methods that may induce aggressive immune suppression and is associated with high safety profile in contrast to aggressive agents used today.
Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with Allocetra-OTS are justified by the anticipated benefits that may be afforded to patients with sepsis.

# Contacts

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**Scientific**
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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. Male or female >=18 years and <=90 years of age.
2. Diagnosis of Sepsis meeting Sepsis 3 criteria, defined by the presence of organ dysfunction as identified by a total SOFA score >=5 points above pre-admission (pre-illness) SOFA. Patients in septic shock with SOFA score up to 13 may be included.
3. Initiation of antibiotics treatment for the suspected infection causing sepsis.
4. Sepsis due to infection in at least one of the below organs:
4.1. Suspected, presumed or documented Community-Acquired Pneumonia (CAP).
4.2 Urinary tract infection/urosepsis
4.3. Acute cholecystitis
4.4. Acute cholangitis
4.5. Other Intra-Abdominal Infections (IAI)
4.6. Skin or soft tissue infection
5. Adequate infectious source control if necessary as determined by the investigator, or source control is scheduled to be completed prior to IP administration. In case source control will not be completed prior to IP administration, Sponsor pre-approval is required for IP administration.
6. Signed written informed consent by the patient, or consent obtained according to local regulations if the patient is unable to provide informed consent.
7. Women of childbearing potential and all men must agree to use 2 methods of an adequate contraception: One barrier method (e.g. diaphragm, or condom or sponge, each of which are to be combined with a spermicide) and one hormonal

method (e.g. oral, transdermal patch, implanted contraceptives or intrauterine device) prior to study entry and for the duration of study participation through 4 weeks following IP administration. Subjects that are highly unlikely to conceive (e.g. surgically sterile, postmenopausal, or not heterosexually active) are exempt.
Non-childbearing potential is defined as (by other than medical reasons):
>=45 years of age and has not had menses for over 2 years.
<45 years of age and amenorrhoeic for > 2 years without a hysterectomy and oophorectomy and a Follicle Stimulating Hormone (FSH) value in the postmenopausal range upon pre-trial (screening) evaluation.
For women, post hysterectomy, bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation and vasectomy for men at least 6 weeks prior to screening. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure.

## Exclusion criteria

1. Sepsis due to infection other than lung infection, UTI, IAI, skin/soft tissue infection or sepsis patients where site of infection is unclear or unknown.
2. Patients on chronic dialysis.
3. Patients with acute pancreatitis (serum amylase > 3 ULN with clinical abdominal pain).
4. Moribund patients at a high risk of death within 48 hours of treatment.
5. Weight < 50 kg of >120 kg or Body Mass Index (BMI) > 40 kg/m2.
6. SOFA score >= 14 at screening.
7. Patients with risk of nosocomial infection due to hospitalization or surgery within 30 days prior to diagnosis of sepsis.
8. A known malignancy that is progressing or has required active treatment within the past 3 months.
9. Patient with end-stage disease (unrelated to sepsis) defined as patients who prior to the current hospitalization are expected to live < 6 months (as assessed by the study physician).
10. Known active symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or chronic viral infections, such as, hepatitis B virus (HBV) or hepatitis C virus (HCV), human immunodeficiency virus (HIV) or other chronic infections.
11. Chronic respiratory disease requiring home oxygen therapy on a regular basis for > 6 h/day.
12. Known active upper gastrointestinal (GI) tract ulceration or hepatic dysfunction including but not limited to biopsy-proven cirrhosis; End-stage cirrhosis (Child Pugh Class C); portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure, encephalopathy, or coma.

13. Known New York Heart Association (NYHA) class IV heart failure or unstable angina, ventricular arrhythmias, acute coronary disease, or myocardial infarction within six months prior to diagnosis of sepsis.
14. Known immunocompromised state or medications known to be immunosuppressive as follows:
• Hydrocortisone (for the treatment of septic shock) > 300 mg /d
• Cyclophosphamide in the last 60 days;
• Chemotherapy in the last 3 months;
• Anti-tumor necrosis factor (TNF) agents, interleukin (IL)-1 receptor antagonists (IL-1-RA), CTLA-4 fusion proteins, anti-CD20, anti-CD52, anti-IL-2, anti-IL-6R, anti-IL-12/23, or integrin inhibitor agents within the last 8 weeks.
15. Organ allograft or previous history of stem cell transplantation.
16. Women who are pregnant or breastfeeding. Child-bearing potential females must have a negative serum ß-hCG or hCG blood test at screening. Pregnancy testing is not required for postmenopausal or surgically sterilized women.
17. Known hypersensitivity to any component of study treatment or excipients.
18. Participation in an interventional investigational study within 30 days prior to diagnosis of sepsis.
19. Likely to be non-compliant or uncooperative during the study (e.g. substance abuse such as drug or alcohol abuse, uncontrolled psychiatric disorder or any chronic condition that may interfere with study conduct).

# Study design

## Design

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| Study phase: | 2 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Will not start |
| Enrollment: | 7 |
| Type: | Actual |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Generic name: | Somatic cels allogenic |
| Product type: | Medicine |
| Brand name: | n/a |
| Generic name: | Allocetra-OTS |

## Ethics review

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| Approved WMO Date: | 23-09-2022 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 25-01-2023 |
| Application type: | First submission |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 23-02-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 14-04-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 24-05-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 16-06-2023 |

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| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |
| Approved WMO Date: | 11-10-2023 |
| Application type: | Amendment |
| Review commission: | CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag) |

# 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 | EUCTR2021-003273-66-NL |
| ClinicalTrials.gov | NCT04612413 |
| CCMO | NL82318.000.22 |

# Study results

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| Date completed: | 18-09-2024 |
| Actual enrolment: | 3 |

**Summary results**
Trial never started