CLINICAL STUDY REPORT

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

Protocol Number:	ENX-CL-02-002
Investigational Medicinal Product:	Allocetra-OTS
Indication:	Sepsis
Phase:	2
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Coordinating investigator:	Bruno Francois Limoges Clinical Investigation Center (Limoges, France)
First Patient, First visit:	16 December 2020
Cut-off date for Day 28 Analysis:	28 February 2024
Last Patient Last Visit:	16 December 2024
Version; date:	1.0, 08 May 2025

The study was conducted according to the protocol and in compliance with GCP, with the Declaration of Helsinki, and with other applicable regulatory requirements.

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Study Title: 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

Enlivex Therapeutics R&D Ltd.

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2. SYNOPSIS

Name of Company: Enlivex Therapeutics R&D Ltd.	**Volume:**	(For national authority use only)
Name of Finished Product: Allocetra-OTS	**Page:**	
Name of Active Ingredient(s): Allocetra-OTS		

Title of Study: 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

Protocol Number: ENX-CL-02-002

Study Period: **Study Phase:** 2

Date of first patient, first visit: 16 Dec2020

Cut-off date for Day 28 Analysis: 28 Feb 2024

Date of last patient, last visit: 16 Dec 2024

Study Centers:

Thirty sites located in 6 countries (Israel, Serbia, Spain, France, Belgium, and the Netherlands) enrolled study patients.

Publication:

Not applicable

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• 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	• Efficacy: Change from baseline in sequential organ failure assessment (SOFA) score throughout 28 days. • Safety: Number and severity of AEs and Serious Adverse Events (SAEs) throughout 28 days follow up period.
Secondary	
• To compare other clinical manifestations of different doses and regimens of Allocetra-OTS associated with organ failure in sepsis patients and assess long term safety follow-up	• Ventilator-free days over 28 days. • Vasopressor-free days over 28 days. • Days without renal replacement therapy (dialysis). • Time in intensive care unit (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 adverse events (AEs) and serious adverse events (SAEs) throughout 12-months follow-up period. • Detection of autoimmune and human leukocyte antigen (HLA) antibodies
Exploratory	
• To assess exploratory safety outcomes in sepsis patients • To assess exploratory efficacy outcomes in sepsis patients • To assess immunological profile parameters in sepsis patients	Clinical Safety: • Time to normal (up to +20%) lactate levels. • Number of days with platelets count $\geq 100 \times 10^9$/L. • Number of days with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$3 times upper limit of normal (ULN). • Number of days with bilirubin levels $\leq 2 \times$ ULN. Clinical Efficacy Outcomes: • Days with Glasgow Coma Scale (GCS) 15. • Change in partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2) ratio throughout 28 days. • Single Organ SOFA changes from baseline throughout 28 days. • Responder analysis of SOFA change over 28 days. • Change in quality of life (QoL) from baseline to Day 28, 3 months, and 12 months by using the EURO-5 QoL tool. Immune Profile Parameters: • Cytokines/chemokines and other immune modulators. • Lymphocyte profile.

Study Design:

This was planned as 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 were identified and screened in the respective department (emergency departments, intensive care units, or operating rooms).

Part 1: Up to Protocol Version 10.0: Up to Protocol Version 10.0, eligible patients were randomized to one of the 4 treatment groups in a 1:1:1:1 ratio between the 4 Cohorts (up to 40 patients in each Cohort).

Cohort	**Placebo/Allocetra-OTS**
1	Placebo
2	Single IV dose of Allocetra-OTS, 5×10^9 cells
3	Single IV dose of Allocetra-OTS, 10×10^9 cells
4	Single or two IV doses of Allocetra-OTS, 10×10^9 cells in each dose

Randomization was implemented in a double blinded fashion which was kept until Day 4. On Day 4, until Protocol Version 10.0, the investigator became unblinded to Cohort 4 patients to assess patient eligibility for a second dose of investigational product (IP). Cohort 4 patients could also be unblinded as a result of the second dose

administration. The remaining Cohorts 1 to 3 were kept blinded throughout the entire study period unless requested and justified by the investigator.

For the first 3 patients enrolled in each site, a central eligibility review was also conducted by the Study Medical Monitor, before the patients were randomized.

Randomization was stratified by screening SOFA score (until Protocol Version 10.0: 2-6 vs. 7-9).

The "screening" SOFA score was the SOFA score assessed following patient's signed consent and was required to confirm patient eligibility prior to randomization.

Prior to IP administration, investigator had to reassess the patient to determine baseline SOFA score. The "Baseline" SOFA score was the SOFA score considered as the reference score calculated on Day 1, before administration of the IP. Up to Protocol Version 10.0, in the following cases, the IP was not to be administered, and the patient was to be considered a randomization failure:

- Improvement of SOFA score: demonstrated by a baseline SOFA score less than 2 points above pre-admission SOFA score (the SOFA score calculated from the patient's clinical condition prior to the infection); OR
- Deterioration of SOFA score ≥10.

Part 2: Starting from Protocol Version 10.0: Starting from Protocol Version 10.0, after completion of informed consenting process per local regulation, and patient eligibility confirmation, the patient was randomized to either Cohort 1 (placebo) or Cohort 4 (Single or two IV doses of Allocetra-OTS, 10×10^9 cells in each dose).

Randomization occurred in a double blinded fashion and was maintained until Day 4.

Starting from Protocol Version 10.0, on Day 4 the investigator had to assess eligibility of all patients for a second dose and would become unblinded to the patient's allocation only in case the patient met eligibility for a second dose. If the patient was allocated to Cohort 4 and eligible for a second dose, the patient was treated with a second dose, thus potentially becoming unblinded. The blind was kept for the remaining patients throughout the entire study period unless unblinding was requested and justified by the investigator.

Starting from Protocol Version 10.0, a central eligibility review was conducted for all patients by an expert reviewer, before the patients were randomized.

Randomization was stratified by screening SOFA score (starting from Protocol Version 10.0: 5-9 vs. 10-13).

Prior to IP administration, the patient was assessed to determine baseline SOFA score.

Starting from Protocol Version 10.0, in the following cases, the IP was not to be administered, and the patient was to be considered a randomization failure:

- Improvement of SOFA score: demonstrated by a baseline SOFA score less than 5 points above pre-admission SOFA score (the SOFA score calculated from the patient's clinical condition prior to the infection); OR
- Deterioration of SOFA score ≥14

In both Part 1 and Part 2:

The time of initial sepsis diagnosis was captured as time 0 (prior to screening). IP administration was to occur on Day 1 within 36 hours from time 0. This timeframe could be extended up to 48 hours from time 0 to allow completion of infectious source control intervention.

Cohort 4 patients who were found eligible on Day 4, received a second dose treatment on Day 5, 24+6 hours from the eligibility determination.

The following was to be confirmed by the investigator on Day 4 for second dose eligibility:

- The patient's screening SOFA of 6 or below deteriorates (Day 4 SOFA > Screening SOFA), OR The patient's screening SOFA of 7 or above had no improvement (Day 4 SOFA ≥ Screening SOFA), SOFA of Day 4
- No detrimental effect which was considered drug related was indicated following first dose administration. Detrimental effect means any serious adverse reaction, or any severe (CTCAE Grade 3 or above) infusion-related reaction or severe allergic reaction observed after the first Allocetra-OTS administration.

Post-treatment Follow-up Period: Overall patients were followed for efficacy assessments over 28 days following IP administration and continued safety follow-up for 12 months.

Patients participating in this study, regardless of whether hospitalized or discharged, were followed daily through Day 7 (inclusive, short-term follow-up), then on Days 10 (only for patients receiving 2nd dose), 14, and 28 (medium-term follow-up), and then at 3 months, 6 months, and 12 months (long-term safety follow-up).

The safety data over 28 days of the first 6, 12, 16, 30 and 80 dosed patients was reviewed by the Data Safety Monitoring Board (DSMB).

Number of Patients (planned and analyzed): Up to approximately 160 patients planned, 148 patients analyzed.

Diagnosis and Main Criteria for Inclusion:

1. Were able to comprehend and willing to provide written informed consent for the study.
2. Male or female patients ≥18 years and ≤90 years of age.
3. 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 could be included.
4. Sepsis due to infection in at least one of the below organs:

4.1. Suspected, presumed, or documented Community-Acquired Pneumonia (CAP). Community-Acquired Pneumonia diagnosis or suspicion was based on clinical signs (cough, purulent sputum, chest pain, fever and dyspnea) and radiological results, and could also be supported by microbiological results.

4.2. Urinary tract infection/ urosepsis diagnosed by:

4.2.1. Any of the following signs and symptoms of urinary tract infection (UTI): urinary frequency, urinary urgency, pain or burning on micturition, flank pain or suprapubic pain or costovertebral angle (CVA) tenderness, gross hematuria or other signs and symptoms of UTI. AND,

4.2.2. A Mid-Stream Clean-Catch (MSCC) or catheterized urine specimen (or nephrostomy obtained sample) with a dipstick analysis positive for nitrite OR evidence of pyuria such as:

- a dipstick analysis positive for leukocytes or leukocyte esterase, AND/OR
- at least 10 white blood cells per cubic millimeter (mm^3) on microscopic analysis of unspun urine, AND/OR
- White blood cell count (WBC) ≥5 cells/HPF in the sediment of a spun urine.

4.3. Acute cholecystitis diagnosed by the below Tokyo criteria (in case one of the parameters was not available, pre-approval is required by the Eligibility Reviewer):

4.3.1. At least one of the following (or other) local signs of inflammation:

- Murphy's sign, AND/OR

- Right upper quadrant (RUQ) mass/pain/tenderness.

AND

4.3.2. At least one of the following systemic signs of inflammation:
- Fever (body temperature >38°C), AND/OR
- Elevated CRP (CRP >1mg/dL), AND/OR
- Abnormal white blood cell (WBC) counts (WBC <4 or >10 × 10^3/μL).

AND

4.3.3. Imaging findings characteristic of acute cholecystitis.

4.4. Acute cholangitis diagnosed by the below Tokyo criteria (in case one of the parameters was not available, pre-approval was required by the Eligibility Reviewer):

4.4.1. At least one of the following systemic signs of inflammation:

4.4.1.1. Fever (body temperature >38°)/or shaking chills, AND/OR

4.4.1.2. Laboratory data: evidence of inflammatory response [Abnormal WBC counts (WBC <4 or >10 × 10^3/μL) OR increased serum CRP levels (CRP ≥1 mg/dL), and other changes indicating inflammation]

AND

4.4.2. At least one of the following signs of cholestasis:

4.4.2.1. Jaundice (total bilirubin ≥2 mg/dL), AND/OR

4.4.2.2. Laboratory data: abnormal liver function tests >1.5 ULN (Increased serum alkaline phosphatase [ALP], γ- guanosine triphosphate [GTP] gamma-glutamyl transferase [GGT], AST, and ALT levels)

AND

4.4.3. At least one of the following imaging findings:

4.4.3.1. Biliary dilatation, AND/OR

4.4.3.2. Evidence of the etiology on imaging (stricture, stone, stent etc.)

4.5. Other intra-abdominal infections (IAI), diagnosed by at least one of the below documented, following adequate infectious source control by surgical intervention (including open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery:

4.5.1. Diverticular disease with perforation or abscess.

4.5.2. Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gallbladder wall.

4.5.3. Appendiceal perforation or peri-appendiceal abscess.

4.5.4. Acute gastric and duodenal perforations, only if operated on <24 hours after perforation is diagnosed.

4.5.5. Traumatic perforation of the intestines, only if operated on <12 hours after perforation is diagnosed.

4.5.6. Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites).

4.5.7. Intra-abdominal abscess (including of liver and spleen provided that there is extension beyond the organ with evidence of intraperitoneal involvement).

4.6. Skin or soft tissue infection: presumed bacterial infection (necrotizing cellulitis [most commonly group A strep], necrotizing fasciitis, necrotizing myositis and myonecrosis, skin and soft tissue infection of the perineum, bacterial synergistic gangrene, clostridial gas gangrene) that could be supported by specific signs and symptoms (e.g. tense edema outside area of compromised skin, pain disproportionate to appearance, skin discoloration, ecchymosis, blisters/bullae, necrosis, tense edema, crepitus and/or subcutaneous gas).

Test Product, Dose and Mode of Administration, and Lot Number(s): Test product: Allocetra-OTS which contained apoptotic cell suspension cryopreserved in a solution containing 50% PlasmaLyte and 50% CryoStor5® at a total volume of 400 mL. [Note: up to Protocol Version 8.0 Allocetra-OTS was provided as a fresh formulation in Ringer's Lactate Solution] Doses: Part 1: Patients in Cohort 2 received a single dose of Allocetra-OTS, 5×10^9 cells, patients in Cohort 3 received single dose of Allocetra-OTS, 10×10^9 cells, and patients in Cohort 4 received single or 2 doses of Allocetra-OTS, 10×10^9 cells in each dose. Part 2: Patients in Cohort 4 received single or 2 doses of Allocetra-OTS, 10×10^9 cells in each dose. Mode of administration: Intravenous (IV) Batch Numbers: Batch per patient and hence included in Appendix 16.1.7.
Reference Therapy, Dose and Mode of Administration, and Lot Number(s): Reference Product: Matching placebo which contained a solution containing 50% Plasma-Lyte and 50% CryoStor5® (final DMSO concentration of 2.5%) Doses: Part 1 and Part 2: Patients in Cohort 1 received 400 mL placebo solution. Mode of Administration: IV Batch Number: Not applicable
Duration of Treatment: For each participating patient, the duration in the study was up to 12 months as follows: Screening (Days -2 to -1): 1-2 days Treatment Day Cohorts 1 to 3 (Day 1): 1 day Treatment Day Cohort 4 (Day 1 and Day 5): 1 or 2 days Short term follow-up (Day 2 to Day 7): 6 days Medium term follow-up (Day 8 to Day 28): 21 days Long-term Follow-up (Day 29 to 1 year): Approximately 11 months

Criteria for Evaluation:

Efficacy:

The SOFA score was assessed, which is a validated ICU mortality prediction score that is based on the degree of dysfunction of six organ systems: respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems, each scored from 0 to 4 with an increasing score reflecting worsening organ dysfunction.

For the purpose of secondary efficacy analysis, the investigator was required to report in the electronic case report form (eCRF) and patients' source documents the use of ventilator, vasopressor, renal replacement therapy (dialysis), hospitalization days in ICU or intensive monitoring unit (IMU) and in the hospital.

Exploratory and Immunogenicity:

Human Leukocyte Antigen antibodies and autoimmune antibodies anti-nuclear antibodies (ANA) and anticardiolipin were collected.

Exploratory biomarkers were evaluated during this study by central laboratory:

- Cytokine/chemokine and other immune modulators levels.
- Lymphocyte profile.

Safety:

Acute Physiology and Chronic Health Evaluation II (APACHE II) and CURB-65 criteria were assessed within 24 hours of admission of a patient to an ICU. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 (or higher) terminology and reported by severity and relationship to study products. The number of patients who experienced each AE while on treatment were presented. AE was to be captured until the end of the study. Comprehensive physical examination was performed at screening. Targeted physical examinations were conducted as clinically indicated throughout the study.

Vital signs were taken throughout the study. These included blood pressure, pulse, respiratory rate, oxygen saturation at room air, and body temperature.

Twelve-lead electrocardiogram was performed at short term and medium-term follow-up.

Euro-QOL 5 Dimensions Questionnaire were to be collected at Day 28 and at the 3-month follow-up visit.

Clinical laboratory assessments were performed throughout the study, including chemistry, hematology, coagulation, and urinalysis.

Statistical Methods:

Efficacy: The primary efficacy endpoint was the change from baseline in SOFA score over 28 days. The SOFA score was evaluated during screening, at baseline on Day 1 prior to dosing, and on Days 2, 3, 4, 5 (prior to dosing for patients in Cohort 4 receiving 2nd dose), 6, 7, 10 (for patients who received a 2nd dose), 14, and 28.

For the primary efficacy endpoint analysis, the following parameters based on the SOFA score were analyzed:

- Change from Baseline in SOFA Score.
- Change from Baseline SOFA Score to Maximum SOFA Score from Day 2-28.
- Percentage of Patients with an Increase of ≥2 or ≥4 Points Above the Baseline SOFA Score.
- Change in Daily Average SOFA Score from Baseline.
- Time to Mortality or SOFA ≥ 2 Above Baseline SOFA Score Over 28 Days.
- Distribution of the Time to SOFA Score within <2 Above the Pre-Admission SOFA Score.

Safety:

Safety analyses are based on the Safety Population, unless stated otherwise. All AEs were coded by using Medical Dictionary for Regulatory Activities (MedDRA), version 23.1. Treatment emergent AEs (TEAEs) were considered those AEs with an onset date and time after the initiation of the IP infusion. All summaries of AEs were based on TEAEs. The incidence of TEAEs were summarized for each cohort. All-Active arms combined and overall, by system organ class and preferred term. All AEs recorded on the eCRF, whether treatment emergent or not, were presented in the data listing. Non-TEAEs were identified in the listings.

The severity of an AE was categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

In addition to the overview of TEAEs, the following summaries of TEAEs were provided:

- TEAEs by System Organ Class and Preferred Term.
- TEAEs by System Organ Class, Preferred Term and CTCAE Severity Grade.
- TEAEs by System Organ Class, Preferred Term and Relationship to Investigational Product.
- Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term.
- TEAEs Leading to Treatment Discontinuation by System Organ Class and Preferred Term.

Summary statistics for hematology, chemistry, urinalysis, and coagulation measurements were calculated for all the scheduled visits. The same statistics were generated for these changes from baseline for each measurement. Vital signs collected included temperature, heart rate, respiratory rate, oxygen saturation, mean arterial pressure, and blood pressure. Vital signs were collected during screening, at baseline on Day 1 prior to dosing, and on Days 2, 3, 4, 5, 6, 7, 10, 14, and 28 including unscheduled visits. Electrocardiogram (ECG) data was collected during screening, on Days 2, 6, 7, 14 and 28. Also note the following details for ECG data collection.

Analysis Populations:

- Screen Failures/Randomization Failures were defined as patients who consented to participate in the clinical study but were not subsequently randomly assigned to study intervention because they did not meet the criteria for study participation. Screen failures were not rescreened.
- Modified Intent-to-Treat Population included all patients who were randomized, received any dose of Allocetra-OTS or placebo, had a Screening total SOFA score ≥5 points above pre-admission total SOFA score, and had at least one post-baseline total SOFA score. Patients in this population were analyzed according to the cohort to which they are randomized, regardless of the cohort actually received.
- Per-Protocol (PP) Population included all patients in the Modified Intent-to-Treat Population (mITT) population who satisfied the following conditions: received at least 75% of one dose of Allocetra-OTS or placebo and had no sponsor-defined exclusionary protocol deviations, including deviation of study inclusion/exclusion criteria.
- Safety Population included all patients who received any dose of Allocetra-OTS or placebo. Patients in this population were analyzed according to the cohort they actually received regardless of the cohort assigned at randomization.

Subgroup Analysis:

No formal subgroup analyses were conducted due to insufficient sample sizes. However, summaries of descriptive statistics based on change from baseline in SOFA score by visit using the following subgroups: Age, gender, race, country, BMI, Screening SOFA Score Category, Combined Use of Vasopressor and Ventilator, Source of Pneumonia, Time from Initial Sepsis Diagnosis to Antibiotics, Sepsis Source, Occurrence of Septic Shock, Protocol Version at Time of Randomization, and Type of Antibiotics (Post hoc analysis) were provided for the mITT Population.

Study Population Results:

For ease of reference, the cohorts are referred to as below in text: Placebo is referred to as Placebo-Cohort 1, Single IV dose 5×10^9 Cells is referred to as Allocetra-Cohort 2, Single IV dose 10×10^9 cells is referred to as Allocetra-Cohort 3, and Single or two IV doses 10×10^9 cells is referred to as Allocetra-Cohort 4.

- Out of 148 screened patients, a total of 131 patients were enrolled in the study; 17 patients were screen failures, and 11 patients were randomized but not treated.
- A total of 120 patients (91.6%) received Allocetra or placebo per study protocol and were included in the Safety Population.
- By Day 28, a total of 12 patients (10.0%) discontinued from the study prematurely; the main cause being death in 10 patients (83.3%).

- Overall, 48 patients were randomized to Placebo-Cohort 1, 18 patients were randomized to Allocetra-Cohort 2, 20 patients were randomized to Allocetra-Cohort 3, and 45 patients were randomized to Allocetra-Cohort 4.
- In the mITT Population, the overall mean standard deviation (SD) age of patients enrolled in the study was 64.6 (13.48) years, and 50.6% were male. The majority of the study population was White (74.7%). Countries with the highest rates of patients recruited were France (48.3%), Belgium (19.5%), Israel and Spain (11.5%) each. Mean (SD) SOFA score at baseline was 7.6 (2.27) for the mITT Population. For the same population, scores were of comparable magnitude between Placebo-Cohort 1 and Allocetra-Cohort 4.
- In the Safety Population, the overall mean (SD) age of patients enrolled in the study was 63.5 (14.57) years, and 56.7% were male. The majority of the study population was White 75%. Countries with the highest rates of patients recruited were France (43.3%), Israel (19.2%), Belgium (17.5%), and Spain (13.3%). Mean (SD) SOFA score at Baseline was 6.5 (2.88). Scores were of comparable magnitude between Placebo-Cohort 1 and the All-active arms combined.

Efficacy Results for the 28-Day Follow-up Period:

- In Allocetra-Cohort 4, 70.0% of patients compared to 53.3% of patients in Placebo-Cohort 1 showed signs of septic shock at screening. This finding was further substantiated by additional post-hoc assessments of septic shock at baseline in the mITT Population, by Investigator determination, or by the use of vasopressors at IP infusion, demonstrating ~30% higher rate of septic shock in Allocetra-Cohort 4 compared to Placebo-Cohort 1. The imbalance in the rate of septic shock, was further supported by the post-hoc evaluation of the need for invasive mechanical ventilation at baseline, indicating a ~20% higher rate of this indicator of sepsis severity in Allocetra-Cohort 4 compared to Placebo-Cohort 1. This imbalance makes it difficult to fully understand the treatment effect of Allocetra compared to placebo.
- At Day 28, the LS Mean difference of the change from baseline of total SOFA score between Placebo-Cohort 1 and Allocetra-Cohort 4 in the mITT Population was 1.6 (95% CI: 0.19, 3.44) with the mean scores difference being borderline statistically significant (rank based Analysis of Covariance [ANCOVA] p-value=0.0502) in favor of placebo.
- Based on the observed cases post-hoc analyses, the LS Mean difference at Day 28 proved to be 0.63 with the mean scores difference being no longer statistically significant (rank based ANCOVA p-value=0.6851) thereby demonstrating the bias of the LOCF imputation in the primary analysis caused by the notably higher number of dropouts/deaths in Allocetra-Cohort 4 group versus Placebo-Cohort 1. While the intent of the LOCF imputation was to minimize the risk of a survival bias, since ultimately the majority of the deaths were not related to sepsis, or occurred in patients subsequently determined to be ineligible, the bias is considered to be meaningful from a clinical perspective.
- Based on the worst-case imputation sensitivity analysis, the LS Mean difference of the change from baseline of total SOFA score was statistically significant in regard to change of SOFA scores from Baseline to Day 28. The LS Mean difference between Placebo-Cohort 1 and Allocetra-Cohort 4 was 3.2 (95% CI: 0.06, 6.25). There was also a statistically significant difference between Placebo-Cohort 1 and Allocetra-Cohort 4 based on the rank based ANCOVA model (p-value =0.0382). Statistically significant differences were also noted at Days 5 and 6 in favor of placebo. These results are also impacted by the LOCF imputation as noted above.
- The mean change from baseline in SOFA score at Day 28 was marginally better in Allocetra-Cohort 4 compared to Placebo-Cohort 1 (i.e., -7.4 versus -6.8, respectively) among patients with sepsis source of urinary tract infection; however, the sample sizes are insufficient to draw any firm conclusions regarding the efficacy of Allocetra-Cohort 4 in this patient subgroup. A post-hoc subgroup analysis of patients with high-risk sepsis (SOFA score of at least 7 at screening) resulting from urinary tract infections demonstrated that patients in the Allocetra-Cohort 4 high-risk UTI subgroup had a 25% higher improvement of the SOFA score from baseline to 14 days following treatment, and a 24% higher improvement of the SOFA score from baseline to 28 days after treatment, compared to Placebo-Cohort 1. These differences were noted despite a higher severity of disease in the Allocetra-treated patients, as reflected by a higher rate of septic shock at screening (100.0% vs. 77.8% in Placebo-treated patients, as well as other indicators of sepsis severity. Given the changes from baseline values in the urinary tract infection subgroup category for both arms were the largest (i.e., largest reduction) among all sepsis source

subgroup categories, exploration in future studies of a possible study drug effect of Allocetra among patients with sepsis source of urinary tract infection may be insightful.

- The LS Mean difference for change from baseline in SOFA score to Maximum SOFA score from Day 2 to 28 between Placebo-Cohort 1 and Allocetra-Cohort 4 was 0.7 (95% CI: -0.37, 1.87) and (rank based ANCOVA p-value=0.1649). Both arms had an overall worsening of mean SOFA scores at some point post baseline. There were no statistically significant differences in change of SOFA scores from Day 2 to 28 based on the rank based ANCOVA model.
- The pre-admission SOFA score reflects chronic comorbidities which are unrelated to the acute sepsis condition, however they impact the SOFA score inadvertently. The LS Mean difference between Placebo-Cohort 1 and Allocetra-Cohort 4 was 1.5 (95% CI: -0.35, 3.37) (rank based ANCOVA p-value=0.1952). No statistically significant differences were noted based on the rank based ANCOVA model but change from pre-admission was consistently higher in Allocetra-Cohort 4 than Placebo-Cohort 1.
- There were no statistically significant differences in the number of ventilator and vasopressor-free days, number of days without renal replacement therapy over 28 days, and in the time the patients spent in the ICU and hospital between Placebo-Cohort 1 and Allocetra-Cohort 4.
- No statistically significant differences were observed at Day 28 in changes from baseline in renal, respiration, coagulation, liver, cardiovascular hypotension, and central nervous system (CNS) SOFA score components between Placebo Cohort 1 and Allocetra Cohort 4.
- The percentages of responders were generally higher in all responder categories for Placebo-Cohort 1 compared to Allocetra-Cohort 4. However, no statistically significant differences were noted except at Day 2 for ≥1 point reduction from baseline (p value=0.0047) and Days 2 and 5 for ≥2 point reduction from baseline (p-value=0.0158 and 0.0333, respectively) which were in favor of placebo.

Immunogenicity:

- Overall, no significant difference was noted in the detection of Autoimmune and HLA antibodies between the Placebo Cohorts and the Allocetra Cohort**.**

Safety Results for the 28-Day and 12-Month Follow-up Periods:

- In the Initial 28-Day follow-up period, a total of 281 TEAEs were reported in 62 patients (82.7%) in the All-active arms combined group in the Initial 28-Day analysis period, and 152 TEAEs were reported in 36 patients (80.0%) in Placebo-Cohort 1. Mild, moderate, and severe SAEs were comparable in both the Placebo and Allocetra groups.
- In the 12-month follow-up period, a total of 391 TEAEs were reported in 67 patients (89.3%) in the All-active arms combined group, and 187 TEAEs were reported in 38 patients (84.4%) in Placebo-Cohort 1. Mild, moderate, and severe SAEs were comparable in both the Placebo and Allocetra groups.
- The most common TEAEs reported in Placebo-Cohort 1 in the Initial 28-Day analysis period were anaemia and pneumonia in 6 patients (13.3%) each, pleural effusion, atrial fibrillation, and thrombocytosis in 5 patients (11.1%), and thrombocytopenia and hypokalaemia in 4 patients (8.9%) each. The most common TEAEs reported in the All-active arms combined group were anaemia and atrial fibrillation in 11 patients (14.7%) each, hypertension in 8 patients (10.7%), respiratory failure in 7 patients (9.3%), and delirium and hypokalaemia in 6 patients (8.0%) each. These events are known to occur in the patient population hospitalized for sepsis due to an underlying infection, and with resulting cardiovascular, respiratory and other organ function dysfunction.
- The most common reported TEAEs in the 12-month follow-up period by SOC in Placebo-Cohort 1 were Respiratory, thoracic, and mediastinal disorders in 18 (40.0%) patients, Infections and infestations in 17 patients (37.8%), Cardiac disorders in 14 patients (31.1%), Blood and lymphatic system disorders in 13 patients (28.9%), Metabolism and nutrition disorders in 12 patients (26.7%). The most common reported TEAEs by SOC in the All-active arms combined group were Infections and infestations in 34 patients (45.3%), Respiratory, thoracic, and mediastinal disorders in 32 patients (42.7%), Vascular Disorders in 22 patients (29.3%), and Cardiac disorders in 21 patients (28.0%). No new safety signals were detected in the 12-month follow-up period.
- A total of 22 serious TEAEs in 17 patients (37.8%) in Placebo-Cohort 1 and 37 serious TEAEs in 27 patients (36.0%) were reported in the All-active arms combined group in the initial 28-day analysis period. None of the serious TEAEs were considered related to study drug.

- A total of 41 serious TEAEs in 24 patients (53.3%) in Placebo-Cohort 1 and 65 serious TEAEs in 39 patients (52.0%) were reported in the All-active arms combined group in the 12-month follow-up period. None of the serious TEAEs were considered related to study drug.
- There were no serious TEAEs leading to study drug interruption in either the 28-day or 12-month follow-up periods.
- A total of 11 deaths (1 death in Placebo-Cohort 1 and 10 deaths in the All-active arms combined group) were reported in the Initial 28-Day analysis period. All the deaths were not related to study treatment, as determined in a blinded manner by the Investigator and the Sponsor medical reviewers. The lack of relationship to study treatment was reviewed and confirmed by the independent study DSMB, and death events were further adjudicated by a blinded committee of sepsis experts.
- A total of 18 deaths were reported in the 12-month follow-up period. In Placebo Cohort 1, 6 patients (13.3%) died and in the All-active arms combined group, 12 patients (16.0%) were reported to have died. All the deaths were not related to study treatment, as determined by the Investigator and the Sponsor medical reviewers.
- The most commonly reported severity category among TEAEs in both Placebo-Cohort 1 and the All-active arms combined group was Grade 3 - Severe. In Placebo-Cohort 1, 15 patients (33.3%) and 21 patients (28.0%) in the All-active arms combined group experienced severe TEAEs.
- Two treatment emergent SAEs of thrombocytopenia were reported in the placebo group of which one was considered probably related to the study drug.
- Phlebitis was the only related TEAE reported in a total of 2 patients (2.7%) in Allocetra-Cohort 3 and Allocetra-Cohort 4 in the initial 28-day analysis period. Thrombocytosis was reported as a probably related TEAE in a total of 3 patients (4.0%) in Allocetra-Cohort 3 and Allocetra-Cohort 4. Thrombocytosis was also reported as probably related in Placebo-Cohort 1 in 4 patients (8.9%). Other probably related TEAEs that were reported in one patient each among the Allocetra-treated patients were rash and liver disorder.
- In the 12-month follow-up period no additional new related or probably related TEAEs were reported.
- In the initial-28-day follow-up period, the most common serious TEAEs reported in Placebo-Cohort 1 were respiratory failure and pneumonia in 3 patients (6.7%) each. The most common serious TEAEs reported in the All-active arms combined group were respiratory failure in 6 patients (8.0%) and septic shock in 3 patients (4.0%).
- The most common serious TEAEs in the 12-month follow-up period reported in Placebo-Cohort 1 were respiratory failure and pneumonia in 3 patients (6.7%) each, and acute respiratory distress syndrome, pleural effusion, cardiac arrest, cardio-respiratory arrest, and thrombocytopenia in 2 patients each (4.4%). The most common serious TEAEs reported in the All-active arms combined group were respiratory failure in 6 patients (8.0%) and pneumonia and septic shock in 4 patients each (5.3%).
- One patient in Allocetra-Cohort 4 had drug withdrawn because of a TEAE of parkinsonism.
- Most of the laboratory evaluations and vital signs were abnormal due to the underlying sepsis condition, which is associated with substantial end-organ compromise and associated physiologic disruptions. This profile is further exacerbated in patients enrolled following the latest protocol amendment, which expanded the patient eligibility criteria to more include more severe sepsis patients. The physiological abnormalities that are associated with sepsis and the impact on plethora of body systems thus manifest as highly disrupted laboratory abnormalities and vital signs.
- A higher percentage of patients experienced significantly elevated QT Interval Corrected Using Fridericia's Formula and QT Interval Corrected Using Bazett’s Formula values in Allocetra-Cohort 4 compared to placebo. However, a detailed inspection of the findings in the first week after study treatment demonstrate multiple risk factors associated with the risk of QT interval prolongation, namely concomitant medications given as supportive care for sepsis, electrolyte imbalances and renal/hepatic dysfunction. Cellular therapies have generally not been associated with a risk of QT interval prolongation, and in fact have been researched for their potential beneficial anti-arrhythmic effects.[1] In light of this, and especially in consideration of the rapid clearance of Allocetra-OTS it is unlikely that these findings reflect a safety risk.

Overall, the results support an adequate safety profile following Allocetra-OTS infusion, especially considering the severity of morbidity associated with the underlying disease, with acute organ failures and functional impairments requiring extensive supportive care measures, with their associated complications.

Conclusions:

The patients enrolled in this study were those with severe sepsis or with septic shock. Hence, the results are complex due to the fact that these patients are heterogenous in the dynamics of their underlying sepsis, depending on multiple factors impacting the progression of the underlying disease with extreme disruptions of multiple body systems – many of these are depicted by the sub-components of the SOFA score (cardiovascular, respiratory, coagulation, renal, hepatic, CNS), but also others that go beyond the extent of the scoring. A shift in focus on community acquired pneumonia to include other sources of infection including urinary tract infections, intra-abdominal infections, biliary infections, and skin and soft tissue infections occurred mid-study.

The other notable change related to patient population was that the recruitment began with patients who had mild to moderate sepsis and then moved to moderate to severe sepsis which is reflected by a change in the minimum allowed SOFA score from 2 to 5, and the maximum allowed SOFA score from 9 to 13 at Screening. Patients with comorbidities and the underlying effect of sepsis should be considered when assessing the AEs and other safety parameters (e.g., labs, vital signs). Owing to the small sample sizes, it is also difficult to draw any firm conclusions regarding the efficacy of Allocetra in this subset of patients.

The randomized arms were stratified according to the SOFA score at screening and were overall balanced with regards to the main demographic and baseline characteristics. However, in Allocetra-Cohort 4, 70.0% of patients showed signs of septic shock at screening, compared to 53.3% of patients in Placebo-Cohort 1. This finding was further substantiated by additional post-hoc assessments of septic shock at baseline in the mITT Population, by Investigator determination, or by the use of vasopressors at IP infusion, demonstrating ~30% higher rate of septic shock in Allocetra-Cohort 4 compared to Placebo-Cohort 1. The imbalance in the rate of septic shock, was further supported by the post-hoc evaluation of the need for invasive mechanical ventilation at baseline, indicating a ~20% higher rate of this indicator of sepsis severity in Allocetra-Cohort 4 compared to Placebo-Cohort 1. This imbalance makes it difficult to fully understand the treatment effect of Allocetra compared to placebo.

After considering all primary, secondary, and exploratory endpoints, there is no compelling clinical or inferential evidence that Allocetra differs from placebo with regard to efficacy by Day 28 for the specific patient population defined by the study eligibility criteria.

Overall, the results support an adequate safety profile following Allocetra-OTS infusion with no serious adverse events reported to be related to Allocetra-OTS both at 28 days and 12 months follow-up period post injection. This conclusion is particularly noteworthy considering the severity of morbidity associated with the underlying disease, with acute organ failures and functional impairments requiring extensive supportive care measures, with their associated complications.

To prevent a treatment imbalance concerning patients with septic shock, future studies could consider including presence of septic shock at baseline as a randomization stratification factor.

Given the changes from baseline values in the urinary tract infection subgroup category for both arms were the largest (i.e., largest reduction) among all sepsis source subgroup categories, exploration in future studies of a possible study drug effect of Allocetra among patients with sepsis source of urinary tract infection may be insightful.

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