SYNOPSIS

Name of Company:
Enlivex Therapeutics R&D Ltd.

Name of Finished Product:
Allocetra-OTS

Name of Active Ingredient(s):
Allocetra-OTS

Title of Study: A Phase 2b Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study, Evaluating Efficacy and Safety of Allocetra-OTS in Patients with Severe or Critical COVID-19 with Associated Acute Respiratory Distress Syndrome

Protocol Number: ENX-CL-03-002

Study Phase: 2
Date of first patient, first visit: September 19, 2021
Date of last patient, last visit: March 16, 2023

Study Centers:

All study patients were recruited in centers in Israel.

Publication:

Not applicable

Objectives and Endpoints:

Primary Objective:

To assess the efficacy and safety of Allocetra-OTS on ventilation-free survival and recovery in the treatment of COVID-19 patients.

Secondary Objective:

To assess additional efficacy parameters and the safety of Allocetra-OTS in the treatment of COVID-19 patients.

Primary Endpoint:

Efficacy:

A primary composite endpoint was to be assessed, as compared to placebo, separately for the two study subpopulations (severely ill and critically ill patients).

- Time (days) to improvement, defined as the first day, during the period of 28 days post study treatment administration, when a patient reached the score of 6, 7 or 8 on the 8-point ordinal scale. The 8-point ordinal scale of the clinical severity status scores were as follows:
  - Death=1
  - Hospitalized, on Invasive Mechanical Ventilation (IMV) or Extracorporeal Membrane Oxygenation (ECMO)=2
  - Hospitalized, on noninvasive ventilation or high-flow oxygen devices=3
  - Hospitalized, requiring supplemental oxygen by mask or nasal canula=4
  - Hospitalized, not requiring supplemental oxygen=5
  - Hospitalized, not requiring supplemental oxygen and not requiring ongoing inpatient medical care=6
  - Not hospitalized, limitations on activities=7
  - Not hospitalized, no limitations on activities=8
- Patients with no improvement after the period of 28 days post study treatment administration were to be scored with a nominal value of 29.
- Support by IMV/ECMO. If required during the period of 28 days post study treatment administration, a patient ~~was~~ to be assigned the maximal score of 30.

- Mortality by Day 28 post study treatment administration. Deceased patients were to be assigned the maximal score of 31.

Safety:

- Number and severity of Adverse Events (AEs) and Serious Adverse Events (SAEs) throughout the 28-day period.

Secondary Endpoints:

- Time (days) to improvement, defined as the first day, during a period of 28 days, 60 days and 90 days post study treatment administration, when the patient reached the score of 6, 7 or 8 on the 8-point ordinal scale.
- All-cause mortality during the period of 28 days, 60 days and 90 days.
- Proportion of patients alive and free of respiratory failure, defined as need for IMV, ECMO, noninvasive ventilation, or high-flow nasal cannula oxygen delivery on Days 28, 60 and 90.
- Cumulative number of days on score 6 and/or 7 and/or 8 during the period of 28 days.
- Cumulative number of vasopressor-free days during the period of 28 days, 60 days and 90 days.
- Cumulative number of days in the hospital during the period of 28 days, 60 days and 90 days.
- Cumulative number of days in the Intensive Care Unit (ICU) or Intermediate Care Unit (IMU) during the period of 28 days, 60 days and 90 days.
- [redacted]
- Number and severity of AEs and SAEs throughout the 60-day and 90-day period.
- Number and severity of AEs and SAEs throughout the 365-day period.

[redacted]

Study Design:

This study was planned to be a Phase 2b multi-center, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of Intravenous (IV) Allocetra-OTS 10×10^9 cells vs placebo (1:1) in adult patients hospitalized with severe or critical COVID-19 with associated Acute Respiratory Distress Syndrome (ARDS).

Severe and critical COVID-19 were defined as follows:

Severe COVID-19 –shortness of breath at rest, or respiratory distress, or Respiratory Rate (RR) ≥30 per minute, or SpO2 ≤93% on room air at sea level.

Critical COVID-19 –respiratory failure, requiring at least one of the following: oxygen delivered by high-flow nasal cannula or noninvasive positive pressure ventilation.

After a patient had signed the Informed Consent Form (ICF), and after confirmation that the patient had met all eligibility criteria, the patient was to be enrolled in the study. The two subpopulations, severely ill and critically

ill patients, were to be randomized 1:1 into the active treatment and placebo groups via two separate randomizations schemes.

Study treatment administration was to occur on Day 1 as close as possible to and no later than 48 hours from randomization. Assessments performed on Day 1 prior to study treatment administration were to be considered as baseline assessments.

Patients were to be followed for efficacy and safety through 12 months.

Following study treatment (investigational product [IP] or placebo) administration, patients were to be assessed daily for a period of 7 days. The next visits were planned to occur on Days 14, 28 and 60. Patients that remained hospitalized during this 60-day period were to be monitored daily.

Safety follow-up phone calls were scheduled to occur 3 months and 6 months after study treatment administration. In addition, the last follow-up visit was to occur 12 months after study treatment administration.

The trial was planned to include periodic and ad-hoc Data Safety Monitoring Board (DSMB) review during the study period.

Number of Patients (planned and analyzed): The sample size for this trial was planned to be 152 patients: 120 severely ill and 32 critically ill patients. Until the termination of study recruitment, a total of 12 patients were randomized and dosed.

Diagnosis and Main Criteria for Inclusion:

The study population was planned to include patients hospitalized with severe or critical COVID-19 with associated ARDS.

Included patients were planned to be >18 and <85 years of age, with a laboratory confirmation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) infection by Reverse Transcription Polymerase Chain Reaction (RT-PCR). To be included in the study, a patient had to be hospitalized due to COVID-19 within 7 days prior to enrollment, meeting the criteria for severe or critical COVID-19 as follows:

Severe COVID-19 – defined as shortness of breath at rest, or respiratory distress, or RR ≥30 per minute, or SpO2 ≤93% on room air at sea level.

Critical COVID-19 – defined as respiratory failure, requiring at least one of the following: oxygen delivered by high-flow nasal cannula or noninvasive positive pressure ventilation.

Patients were required to have mild to moderate ARDS confirmed by chest imaging, defined as 100< PaO2/FiO2 ≤300; based on the Berlin Definition of ARDS, or 148< SpO2/FiO2 ≤315; based on the Kigali modification for ARDS.

Patients on IMV/ECMO, or patients with protocol-specified comorbidities were to be excluded from the study.

Test Product, Dose and Mode of Administration, and Lot Number(s):

Allocetra-OTS is a cell-based therapeutic comprised of allogeneic non-human leukocyte antigen (HLA) matched peripheral blood mononuclear cells induced to an apoptotic state. The suspension was prepared with Ringer's lactate solution and administered IV. Allocetra-OTS treatment was a fixed dose, containing 10×10^9 cells (manufacturing approved range is ±20%), [redacted]

Study treatment was to be administered in addition to the Standard of Care (SoC) for COVID-19. The SoC for COVID-19 was to be according to institutional standards including heparin-based anticoagulants and antiviral agents such as remdesivir up to 10 days, dexamethasone, corticosteroids, tocilizumab, or other agents.

Reference Therapy, Dose and Mode of Administration, and Lot Number(s):

The placebo contained only [redacted] and was to be administered IV, in a way identical to that of the IP.

Duration of Treatment: The overall study duration was designed as 12 months duration for each participating patient, comprised of one day for screening, one day for treatment (to be administered as close as possible to and no later than 48 hours from randomization), 28 days for Coronavirus Disease 2019 (COVID-19) monitoring, short term follow-up to 6 months, and long term follow-up to 12 months.

Study Population Results:

Until the termination of study recruitment, [redacted], and 12 patients were randomized and dosed. Among the 12 patients, 4 patients were treated with Allocetra (3 severely ill patients and

one critically ill patient), and 8 patients were treated with placebo (5 severely ill patients and 3 critically ill patients).

No patients discontinued treatment. Most of the study patients completed the protocol required one year follow-up following dosing.

All the patients were White and most patients were females (3/4 Allocetra-treated, 5/8 placebo-treated). The overall mean patient age was 61 years (range 22 – 84 years), with no substantial differences between the groups apart for one 22 year old critically ill patient treated with Allocetra-OTS.

Efficacy Results:

[redacted]

Safety Results:

Twelve patients were treated on the study, [redacted]. No related SAEs were reported, there were no adverse events leading to treatment discontinuation or study discontinuation, and no fatal events were reported.

The study Data Safety Monitoring Board reviewed the safety data of 28-day follow-up for the first 8 patients on the study and concluded that the review showed no potential safety signals.

[redacted]

[redacted] the overall profile of adverse events, laboratory findings and physical examination findings appears to be consistent with the expected safety profile of a population of severely ill and critically ill patients with COVID-19, with clinical signs, symptoms and abnormal laboratory parameters gradually trending back towards normal levels as recovery from COVID-19 proceeds.

Conclusions:

With the development and widespread implementation of COVID-19 vaccines, the reduced virulency of the existing variants and the overall severity of the clinical manifestation, the need to develop new therapies for COVID-19 decreased. As a result, the study was terminated early and consequently only 12 patients were treated, [redacted] The small number of patients substantially limits the ability to analyse and interpret the results. Therefore, no clear conclusions can be drawn from the comparison of Allocetra-OTS treatment to placebo.

[redacted].

The results described for the [redacted] patients treated with Allocetra are overall consistent with the reported outcomes for prior completed clinical trials of 21 patients treated with Allocetra infusion for severe or critical COVID-19 disease. In this study (van Heerden et. al. 2023) patients with severe-critical COVID-19 of Gamma, Alpha and Delta variants, were treated with Allocetra-OTS, similarly to the current study. 19/21 patients had mild-to-severe ARDS at presentation. All 21 study subjects survived to day 28 (end of study); 19/21 recovered completely.

Consistent with the results described for the [redacted] patients treated with Allocetra on the current study, among the 21 previously described patients treated with Allocetra there were 19 patients with ARDS, of whom 17/19 (89.5%) completely recovered. Median total hospitalization after treatment was 6 days (range 2–28) for all the patients (10 critical, 11 severe patients), and the average was 7.6 ± 7 days. The average time for discharge from the hospital after treatment for the 19/21 patients who were discharged was 5.5 ± 2.4 days (range 2–12, median 6 days). Only 2/21 critically ill patients were admitted to the ICU, where they remained until the end of the study at 28 days.

In terms of safety, among the [redacted] Allocetra-treated patients in the current study no related SAEs were reported and no fatal SAEs were reported. [redacted] Similarly to the reported safety profile, among the 21 previously reported patients treated with Allocetra all patients survived 28 days of follow-up. Among the 21 previously described patients, 3 unrelated SAEs were documented in two patients who required mechanical ventilation. One AE was reported as possibly related to Allocetra - shivering following treatment administration.

Overall among all the study patients, either treated with Allocetra or placebo, nearly half the reported events were considered related to the underlying COVID-19. As such, the profile of adverse events reported in the weeks following study inclusion is considered to reflect a population of severely ill or critically ill patients hospitalized with COVID-19. [redacted] he efficacy results are inconclusive due to the small number of patients treated with Allocetra, however,taken together with our previous report of Allocetra therapy in 21 patients, they are encouraging for future trials investigation.

Date of Report: March 11, 2024