Clinical Study Report SYNOPSIS
Clinical Trial BST-COVID-01 (COVIDMES Study)
EudraCT: 2020-001505-22
December 20, 2022

Name of Sponsor/Company:: Banc de Sang i Teixits	Individual Study Table Referring to Part of the Dossier **Volume:**	*(For National Authority Use only)*
Name of Finished Product: XCEL-UMC-BETA **(MSC,WJ)**		
Name of Active Ingredient: Expanded and cryopreserved Wharton's Jelly mesenchymal stromal cells from umbilical cord	**Page:**	

Study code: BST-COVID-01

Title of Study:
A Prospective, Double-blind, Randomized, Parallel, Placebo-controlled Pilot Clinical Trial for the Evaluation of the Efficacy and Safety of Two Doses of WJ-MSC in Patients With Acute Respiratory Distress Syndrome Secondary to Infection by COVID-19

Investigators: Dr. Antoni Torres (IP coordinator)

Study centre(s):

1. Hospital Universitari Vall d'Hebron
2. Hospital Clinic i Provincial de Barcelona
3. Hospital Mútua de Terrassa
4. Hospital del Mar
5. Hospital de Bellvitge
6. Hospital de Sant Joan Despí Moisès Broggi
7. Hospital Universitari Sagrat Cor

Publication (reference): None

Studied period (years): (date of first enrolment) 15.07.2020 (First patient in) (date of last completed) 26.07.2021 (Last patient out)	Phase of development: I/IIa

Objectives:

<u>Primary:</u>
All-cause mortality at day 28

<u>Secondary:</u>
To assess the effect of the administration of WJ-MSC compared to placebo in the treatment of patients with SARS-CoV-2 infection and ARDS on:

- Safety and feasibility of the administration of MSC,WJ compared to placebo in the treatment of patients with SARS-CoV-2 infection and ARDS.
- Need to use rescue medication
- Need and duration of mechanical ventilation
- Days free of mechanical ventilation
- Oxygenation index (PaO2/FiO2)
- Evaluation of the SOFA index
- Assessment of the APACHE II score
- Duration of hospitalization in the ICU / semi-critical-intermediate units
- Markers of disease progression: RT-PCR, LDH, D-dimer, Ferritin, procalcitonin.
- Immune response (leukocyte and neutrophil count) at baseline and on days 3, 5, 7, 14, 21 and 28 after the start of treatment.

Additional objectives:

- Analysis of subpopulations of lymphocytes and immunoglobulins
- Evaluation of the in vitro response of recipient lymphocytes at different periods using commercial viral antigens (Miltenyi Botech).
- Study of reactivity against SARS-CoV-2 peptides using ELISPOT
- Immunophenotypic study of memory cells in response to SARS-CoV-2 peptides
- Study of the effect of the genetic variability of the patients and the SARS-CoV-2 genotype on the evolution of the disease and response to treatment.

Methodology:
Double-blind, multicentre, randomised, parallel and placebo-controlled (PL) pilot clinical trial to evaluate the efficacy and safety of two doses of MSC,WJ in patients with moderate ARDS secondary to SARS-CoV-2 infection. Eligible subjects were randomized to receive treatment with MSC,WJ/MSC,WJ or PL/PL in a 1:1 ratio.

Number of patients planned: 30 patients.

Number of patients analysed:
Planed: 30 patients
Recruited: 26 patients
Treated: 25 patients

- Men/women: 17 / 8
- Men/women (percentage): 68% / 32%

Analysed for efficacy: 25
Analysed for safety: 25

Diagnosis and main criteria for inclusion

Inclusion Criteria:

1. Positive PCR for SARS-CoV-2
2. Intensive Care Unit admission for less than 3 days
3. Moderate acute respiratory distress (Berlin criteria definition with 100 mmHg < PaO2/FiO2 ≤ 200 mmHg)
4. Male or female, aged 18 to 70 years old
5. Signed informed consent by the patient or by a legal representative

Exclusion Criteria:

1. Expected survival less than 3 days
2. Neoplastic disease either active or without complete remission
3. Immunosuppressed patients (except treatment with corticosteroids for respiratory distress)
4. Pregnant or lactating women
5. Participation in another clinical trial with an experimental drug in the last 30 days
6. Other pathologies that, in medical judgment, contraindicate participation in the study

Test product: XCEL-UMC-BETA (cell therapy product)

Dose: 1E6/Kg WJ-MSC ± 20% per dose (2 doses)
Mode of administration: Intravenous
Duration of treatment: 2 days

The 2 doses were administered on day 1 (D1) and on D3, obtaining baseline follow-up data (prior to the 1st infusion) and on days 3, 5, 7, 14, 21 and 28. Once the study was completed, controls at 3 months, 6 months and 12 months were established as long-term follow-up.

Reference therapy: Not applicable (NA). Without reference treatment. Comparison with placebo.

Dose: NA
Mode of administration: intravenous
Duration of treatment: 2 days

The 2 doses were administered on day 1 (D1) and on D3, obtaining baseline follow-up data (prior to the 1st infusion) and on days 3, 5, 7, 14, 21 and 28. Once the study was completed, controls at 3 months, 6 months and 12 months were established as long-term follow-up.

Criteria for evaluation:

Principal variable:

- Number of patients who died at day 28, by treatment group

Secondary variables

- Safety was assessed by physical examination, vital signs, laboratory data, and adverse events throughout the study, by treatment group. The feasibility was evaluated by means of the time elapsed from the treatment request by the hospital until the delivery date and the number of patients that could be treated within 2 days of the treatment request.
- Number and percentage of patients who, after the start of treatment, required rescue medication on day +28, by treatment group.
- Number of days that the patient required invasive mechanical ventilation from the start of treatment to day +28, by treatment group.
- Post-treatment days in which the patient was alive and free from invasive mechanical ventilation, up to day +28, by treatment group.
- Variation of the oxygenation index (PaO2/FiO2 on days 3, 5, 7, 14, 21 and 28 after the start of treatment) with respect to the baseline value, by treatment group.
- Variation of the SOFA Index (Sepsis related Organ Failure Assessment) score on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group.
- Change in the APACHE II (Acute Physiology and Chronic Health disease Classification System II) score on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to baseline, by treatment group.
- Days of stay in the ICU / semi-critical-intermediate units from the day of admission until discharge to day 28, or date of death if earlier, by treatment group.
- Variation in the values of the disease progression markers on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group.
- Variation in the count and percentage of leukocytes and neutrophils on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group.

Statistical methods:
All the data collected in the case report form were provided in anonymized electronic format to the statistical analysis team, keeping the treatment masked. As it was a pilot study, there was no pre-calculated sample size and the hypothesis contrasts were carried out for illustrative purposes as the conditions for applying some statistical tests were not met. When applicable, a type I error of 0.05 was considered. Analyses were performed with Stata 15.1.

The qualitative variables have been presented as the absolute number of cases and percentage in each category. Quantitative variables have been presented as means (standard deviation (SD)), median (25th percentile (Q25), 75th percentile (Q75)) and minimum and maximum value.
In addition, for safety variables are presented in listings, coded using the Medical Dictionary for Regulatory Activities (MedDRA ™).
Statistical analyses were performed by intention to treat.

SUMMARY - CONCLUSIONS:

1. A total of 26 patients were randomized but one of them did not receive the treatment due to the worsening of his basal condition and requested the transfer to another hospital. The patient was withdrawn from the study. For this reason, the population analysed was 25 patients.

2. Main variable (number of patients deceased on day + 28, by treatment group): 2 deaths occurred, both in the placebo group, however, no statistically significant differences were found, as indicated by the p-value of the Fisher test greater than 5% (p=0.1833)

3. Regarding the secondary variables, the results observed were the following:

• Time elapsed from the treatment request to the delivery date and number of patients who could be treated within the 2 days following the treatment request:
- The average number of days from the medication request to the first dispensing was 0.57 days for the experimental group versus 0.73 days for the placebo group (p=0.4298). All patients in both groups could be treated within two days of requesting treatment.
- The average number of days from the medication request to the second dispensing was 2.36 days for the experimental group compared to 2.55 days for the placebo group (p=0.3562).
- 9 patients in the experimental group (64.3%) and 5 patients in the placebo group (45.5%) could be treated within two days of requesting treatment

• Number and percentage of patients who, after the start of treatment, required rescue medication on day +28, by treatment group: No patient required rescue medication.

• Number of days that the patient required invasive mechanical ventilation from the start of treatment to day +28, by treatment group: 10 patients in the experimental group (71.4%) required mechanical ventilation at some time vs. 5 patients in the placebo group (45.5%), p=0.2406.

• The average number of days on mechanical ventilation was 18.30 days for the experimental group compared to 10.60 days for the placebo group (p=0.0842).

• Days after treatment in which the patient remained alive and free of invasive mechanical ventilation, until day +28, by treatment group: The mean days free of mechanical ventilation until day 28 was 4.90 days for the experimental group compared to 8.40 days in the placebo group (p=0.4200).

• Variation of the oxygenation index (PaO2/FiO2 on days 3, 5, 7, 14, 21 and 28 post treatment start) with respect to the baseline value, by treatment group: No differences were found (p =0.4123).

• Variation of the SOFA index score on days 3, 5, 7, 14, 21 and 28 post-initiation of treatment with respect to the baseline value, by treatment group: No differences were found (p= 0.8893).

• Variation of the APACHE II score on days 3, 5, 7, 14, 21 and 28 post-start of treatment with respect to the baseline value, by treatment group: No differences were found (p=0.3552).

• Days of stay in the ICU/semi-critical-intermediate units from the day of admission to discharge on day 28, or date of death if earlier, by treatment group: The mean days of hospitalization in the ICU was 17.14 days in the experimental group versus 11.91 days in the placebo group (p=0.1096).

• Variation in the RT-PCR value on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group: No differences were found (p= 0.6140).

• Variation in the LDH value on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group: No differences were found (p=0.4875).

• Variation in the D-dimer value on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group: No differences were found (p=0.8554).

• Variation in the value of Ferritin on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group: Differences were found (p=0.0000) for the experimental group.

• Variation in the value of procalcitonin on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group: No differences were found (p=0.4940).

• Variation in the leukocyte count on days 3, 5, 7, 14, 21 and 28 after the start of treatment with respect to the baseline value, by treatment group: No differences were found (p=0.5908).

• Variation in the neutrophil count on days 3, 5, 7, 14, 21 and 28 post-initiation of treatment with respect to the baseline value, by treatment group: No differences were found (p=0.6127).

• Variation in the percentage of neutrophils on days 3, 5, 7, 14, 21 and 28 post-start of treatment with respect to the baseline value, by treatment group: No differences were found (p=0.4035).

4. Regarding safety, during the clinical trial, 76 adverse events were reported, 12 of which were serious. Of the total number of adverse events, 57 occurred in the experimental group and 19 in the placebo group. In the experimental group, 4 of the adverse events were considered related to the study medication by the investigator (hypersensitivity (allergic reaction), elevated fibrin D-dimer, increased liver function test, and occlusion of the medical device (withholding enteral nutrition)) and in the placebo group, none of the adverse events were considered treatment related by the investigator. 4 patients in the experimental group and 3 patients in the placebo group reported serious adverse events, one of which was related to the study medication (hypersensitivity (allergic reaction)). In both groups, the most frequently reported serious adverse events were related to infections and infestations disorders, followed by thoracic and mediastinal respiratory disorders.

5. Based on this information, it can be concluded that MSC,WJ is safe for patients with acute respiratory distress syndrome secondary to COVID-19 infection.

Date of report: 20 December 2022