Clinical Study Report SYNOPSIS
Clinical Trial XCEL-PSART-01
EudraCT: 2013-005025-23
August 05, 2020

Title of Study: A Phase IIa, Single Center, Prospective, Randomized, Parallel, Two-arms, Single-dose, Open-label With Blinded Assessor Pilot Clinical Trial to Assess ex Vivo Expanded Adult Autologous Mesenchymal Stromal Cells Fixed in Allogeneic Bone Tissue (XCEL-MT-OSTEO-ALPHA) in Non Hypertrophic Pseudoarthrosis of Long Bones.	
Principal Investigator: Dr. Fernando Granell Escobar	
Study center: Hospital ASEPEYO Sant Cugat (Barcelona)	
Publication (reference): None	
Studied period (years): 2014-2019	Phase of development**:** IIa

Objectives:

Primary

- To assess the efficacy of XCEL-MT-OSTEO-ALPHA in the treatment of non-hypertrophic pseudarthrosis of long bones by the Hounsfield unit's quantification though TC at month 12 posttreatment.

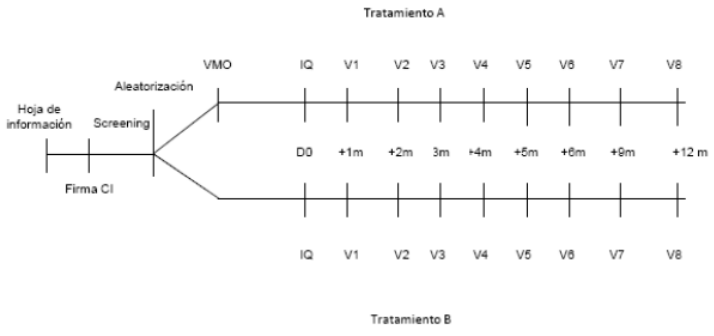
Secondary

- To assess the feasibility and safety of XCEL-MT-OSTEO-ALPHA in the treatment of non-hypertrophic pseudoarthrosis of long bones
- To assess the efficacy of XCEL-MT-OSTEO-ALPHA in the treatment of non-hypertrophic pseudoarthrosis of long bones through:

a) Characteristics of the callus by TC at month 6 posttreatment
b) Characteristics of the callus by standard x-ray
c) Quality of life by EUROQOL-5D test

Methodology:

This is a prospective, single-center, open-label, randomized, single-dose, phase IIa pilot study with blind evaluation of the results, in which 20 patients between 18 and 65 years of age affected with acquired metaphysodiaphyseal non-hypertrophic pseudoarthrosis of long bones were selected. These patients were randomized in a 1: 1 design to one of the 2 study treatment-arms. Treatment A: mechanical stabilization and XCEL-MT-OSTEO-ALPHA; treatment B: mechanical stabilization and autologous graft (current standard of care). After the application of the treatment, the patients were followed for a period of 12 months. During the follow-up period monthly control radiographs (Rx) were performed up to 6 months and subsequently, at 9 and 12 months and computed tomography (CT) at 6 and 12 months. In addition, quality of life was analyzed following the EUROQOL-5D questionnaire at 1, 3, 6, 9 and 12 months, and control tests were carried out at 1, 6 and 12 months. The patients completed participation in the study at 12 months of follow-up.



Number of patients (planned and analyzed):
Planned: 20
Randomized and treated: 20/19
Men/women: 17/3
Mean age (SD): 47.8 (8.9)
Analyzed for efficacy:
Full Analysis Set (FAS): 20
Analyzed for safety: 19

Diagnosis and main criteria for inclusion:
The diagnosis of pseudoarthrosis was made by conventional radiology and / or CT, classifying:
- Location: metaphyseal, diaphyseal or metaphyseal-diaphyseal
- Callus anatomy: atrophic or hypotrophic
- Severity and evolution: without loss of bone substance, with loss of bone substance ≤1 cm or with loss of bone substance> 1 cm.
- Time since the fracture, which should be greater than 6 months.

Patients had to meet the following criteria to be included in the study:
1- 18 to 85 years of age (male and female)
2- Atrophic or hypothrophic metaphyseal–diaphyseal pseudarthrosis of long bones, confirmed radiographically.
3- Signed Informed Consent Form
4- The patient is able to understand the nature of the study

Those patients who met any of the following criteria were excluded:
1-Suspicious of pseudarthrosis focus infection diagnosed by clinical inspection and blood analysis.
2-Positive serology for HIV (Anti-HIV I/II-Ac), Hepatitis B (HBsAg, HBcAc), Hepatitis C (Anti-HCV-Ac) or Syphilis (TP-Ac).
3-Significant abnormal laboratory tests that contraindicates patient's participation in the study.
4-Pregnant woman or without proper anticonceptive measures according to the investigator, or breath feeding
5-Smoker of more than 15 cigarettes a day
6-Congenital disorders of bones (hypophosphatemia), bone metabolic disorders associated to primary or secondary hypoparathyroidism.
7-Badly managed diabetes mellitus.
8-Patients diagnosed with peripheral arterial disorders
9-Previous therapeutic radiation (5 previous years) of the affected bone.
10-Neoplasia within the previous 5 years, or without remission
11-The patient is legally dependent
12-Participation in another clinical trial or treated with an investigational medicinal product the previous 30 days
13-Other pathologic conditions or circumstances that difficult participation in the study according to medical criteria
14-The patient does not accept to be followed-up for a period that could exceed the clinical trial length

Test product: dose, mode of administration and batch number
Product: XCEL-MT-OSTEO-ALPHA
- Dose: $3x10^5$ y $1x10^6$ mesenchymal stromal cells per cubic centimeter of bone
- Pharmaceutical form: Solid particles.
- Administration route: Surgically implanted
- Administration periodicity: Single dose.
- Batch number: Each product has a unique batch number (10 productions).

Reference therapy: dose, mode of administration and batch number
Mechanical stabilization and autologous graft (current standard of care).

Treatment duration:
After bone marrow aspiration and a 21-day of cell culture and bone particle colonization (XCEL-MT-OSTEO-ALPHA), the product was surgically implanted in a single dose. The duration of the patients' participation in the study was 1 year (1 day for the treatment and 12 months of follow-up).

Assessment criteria:
Principal variable:
Degree of consolidation by measuring Hounsfield Units by CT at 12 months post treatment.

Secondary variables:
Image
-By CT: Degree of consolidation by measuring Hounsfield Units at 6 months post treatment.
-Degree of consolidation according to the TUS scale (Tomographic Union Score) at 6 and 12 months after treatment
-By Radiography: Degree of consolidation according to the RUS scale (Radiographic Union Score) at 1, 2, 3, 4, 5, 6, 9 and 12 months after treatment.
Clinical criteria
Changes in the EUROQOL-5D quality of life test at 1, 3, 6, 9 and 12 months, compared to baseline
Safety
Safety was assessed by physical examination, vital signs, laboratory results (biochemistry, hematology), and adverse events.

Study population:
In general, tables with information on demographic variables and other relevant baseline characteristics are presented for all randomized patients. Efficacy analyzes are presented for the FAS population and safety analyzes for the safety population.
The following sets of patients will be considered:
Evaluated for selection
All patients initially considered for inclusion in the study, regardless of whether they were actually included or not.
Randomized patients
All patients assigned to one of the study treatments according to the randomization list.
Full Analysis Set (FAS)
All randomized patients who had the main variable in the baseline evaluation (percentage of consolidation in at least one of the four quadrants in the baseline visit).
Per protocol population (PP)
All those patients considered for the FAS population who did not present major protocol violations and have efficacy assessments (percentage of consolidation in at least one of the four quadrants) at baseline and 12 months.
Safety population
All patients who received treatment A, who underwent bone marrow aspiration and all patients who received treatment B, who underwent intervention.

Statistical methods:
Efficacy analysis was performed by intention to treat, using the FAS analysis set. Demographic, safety, and efficacy variables are listed and summarized using descriptive statistics. In general, all data is listed and ordered by treatment, center, patient and by number of visit or evaluation.

For the quantitative variables, we calculated: n (sample size without missing data), mean, standard deviation, 95% confidence interval for the mean, median, 25th and 75th percentiles, and minimum and maximum. For qualitative variables we calculate the number of subjects at each level (absolute frequency) and their respective percentage (relative frequency).

To compare groups of patients, we used parametric tests (Student's t or ANOVA) or non-parametric tests (Mann-Whitney or Kruskal-Wallis) for the quantitative variables, according to the characteristics of the variables under study and the number of groups to be compared. For qualitative variables we used Chi-square tests and Fisher's exact test.

All analyzes were performed using the SAS v9.3 statistical package.
In the event of significant protocol violations, the convenience of conducting sensitivity analyzes without imputation of missing data, or excluding such violations, was assessed.
For very obvious violations of the assumptions of the linear model (which were evaluated using graphical methods), a non-parametric analysis of change was performed using the Wilcoxon rank sum test.

Safety variables
Safety analyzes were performed with the available data, without using missing data imputation techniques.
The analysis techniques were descriptive, including graphs and individual data listings. The AE were described by means of lists of the AE, organized by treatment group and patient, which included the preferred terms (MedDRA), as well as the characteristics of the AE, especially the relationship with the treatment, severity and intensity.
Physical examination findings were described by listing the findings, organized by treatment group, patient, and visit. Vital signs were described by individual data listings, organized by treatment group, patient, and visit.
Laboratory analysis were described by individual data listings, organized by treatment group, visit, and patient, and by separate individual profile charts for each treatment group.

SUMMARY - CONCLUSIONS

Efficacy results:
The present study was carried out at the ASEPEYO Sant Cugat Hospital (Barcelona, Spain), and included 20 patients who presented non-hypertrophic pseudoarthrosis of long bones. The population was characterized by being mostly men (85%), with a mean age (SD) of 47.8 (8.9) years, with similar baseline demographic and clinical characteristics. 20 patients were randomized (10 in the Treatment A group treated with XCEL-MT-OSTEO-ALPHA and 10 in the Treatment B group treated with iliac crest autograft)

Efficacy analyzes were performed in the FAS population, which included 20 patients (n = 10 in each group).
The degree of consolidation of the pseudoarthrosis area was analyzed by measuring Hounsfield Units (HU) in CT at 12 months post treatment as the main efficacy variable. This analysis did not show significant differences between the two treatment groups (p = 0.4835), showing that the study product XCEL-MT-OSTEO-ALPHA has an efficacy level equal to that obtained with a current standard treatment that has been used as a comparator (application of cortical grafts obtained from the patient's iliac crest). The same result was obtained when analyzing the efficacy of the treatments at six months and when measuring the evolution of the response per visit. None statistically significant differences were found when analyzing the efficacy of both treatments using radiographic techniques. The analysis of the degree of consolidation using the RUS and TUS scales did not show significant differences between the treatment groups either at 6 months or 12 months after treatment. Similarly, no significant differences were found when analyzing the degree of consolidation using the RUS scale with respect to the TUS scale.
The quality of life analysis once again highlighted the equality between treatments.
Taking into account all data, the efficacy analysis reveals that the XCEL-MT-OSTEO-ALPHA has an efficacy level equal to that obtained with a current standard treatment that has been used as a comparator.

Safety results:
All randomized patients treated with one of the 2 treatments were included in the safety population.
In total, 36 AA were reported (21 in patients treated with XCEL-MT-OSTEO-ALPHA and 15 in patients treated with iliac crest graft), by 14 patients (6 in the XCEL-MT-OSTEO- ALPHA group and 8 in the iliac crest graft group). Most AEs were mild (20), 12 were moderate and 4 were severe.
Of the total AEs, 5 were serious. None of the AEs were related to the study treatment.
In most cases, AEs required administration of concomitant medication or non-pharmacological treatment. There were no reported deaths.

The most frequent AE corresponded to the System Organ Class (SOC) categories of musculoskeletal and connective tissue disorders, with a total of 13 events.
No clinically relevant changes in laboratory parameters were described at post-randomization visits.
In vital signs (heart rate, blood pressure), no clinically relevant changes were detected throughout the study in either group. Regarding the physical examination, the findings identified throughout the follow-up visits were comparable in both treatment groups.
The results obtained suggest that the procedures before, during and after the surgical application of XCEL-MT-OSTEO-ALPHA indicate that there have been no relevant safety issues, reveling a safety profile.
Therefore, it is concluded that the administration is safe and well tolerated at the dose evaluated in the present study.

Conclusions
Overall, it can be concluded that XCEL-MT-OSTEO-ALPHA is safe and facilitates the consolidation of long bones affected by pseudoarthrosis at 12 months posttreatment, although subsequent clinical trials with a larger number of patients are necessary to confirm and detail the conclusions obtained in this study.