SYNOPSIS

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-M-ALPHA		
Name of Active Ingredient: Expanded autologous adult mesenchymal stem cells from bone marrow	Page: **Code No.:** EudraCT Nº 2011-006270-13	

Title of Study:

A Phase I-IIa Safety and Efficacy Pilot Clinical Trial of Intraarticular Administration of Autologous Mesenchymal Cells for Meniscus Injury

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Study centre: USP Institut Universitari Dexeus

Publication (reference): Not applicable

Studied period (years): 2014-2017 **date of first enrolment:** 31/01/2014 **date of last completed:** 04/03/2017	**Phase of development:** Pilot exploratory study. Phase I–IIa

Objetives:

Principal objective

- To assess the efficacy of intraarticular administration of XCEL-M-ALPHA by VAS for pain at 12 month follow-up

Secondary objectives

- To assess the safety of intraarticular administration of XCEL-M-ALPHA in degenerative meniscus injury.
- To assess the efficacy of intraarticular administration of XCEL-M-ALPHA in degenerative meniscus injury by dGEMRIC and T2 mapping at 6 and 12 month follow-up.
- To assess the efficacy of intraarticular administration of XCEL-M-ALPHA in cartilage injuries associated to degenerative meniscus injury by dGEMRIC and T2 mapping at 6 and 12 month follow-up.
- Overall rating of osteoarthritis (WORMS) at 6 and 12 months follow up. - To assess the efficacy of intraarticular administration of XCEL-M-ALPHA by VAS for pain at 1, 3 and 6 month follow-up.
- To assess the efficacy of intraarticular administration of XCEL-M-ALPHA in degenerative meniscus injury by IKDC, KOOS and Lysholm functionality test and SF-36 quality of life at 3, 6 and 12 month follow-up

Methodology:

Pilot exploratory phase I-IIa, single-center, prospective, open and parallel clinical trial of two treatment arms. 21 patients were included, 40 to 60 years of age, both sexes, diagnosed with a grade 3 degenerative meniscus lesion (Crues et al. classification) with the aim of exploring the efficacy and safety of XCEL-M-ALPHA by the VAS for pain, changes in the MRI (signal intensity and morphology of the meniscus, and qualitative and quantitative signal intensity in T2 mapping of the articular cartilage) and clinical efficacy according to the IKDC, KOOS, Lysholm functionality tests and the quality of life questionnaire (SF-36).

In the pre-inclusion visit, the meniscus injury was classified and the patients signed the informed consent. The 21 patients were randomized to one of the two treatment arms (11 patients in the rehabilitation arm; 10 patients in the XCEL arm). The experimental treatment was an intra-articular infiltration of XCEL-M-ALPHA (autologous bone marrow mesenchymal cells expanded ex vivo) and rehabilitation, while the control group followed conservative treatment

through the same rehabilitation program.

The patients assigned to the experimental treatment were scheduled for the previous extraction of BM and, after the days necessary for cell expansion, the mesenchymal cells were infiltrated in the knee by intra-articular puncture.

All patients were visited at 1, 3, 6 and 12 months post-treatment, undergoing a physical examination and the corresponding complementary tests (safety lab test, MRI, VAS for pain, and tests for functionality and quality of life).

Patients completed their participation in the study at 12 months of follow-up. However, those who had been infiltrated with cells had to follow a specific control until at least 5 years after the infiltration, in which they would be followed individually to obtain additional data on safety and long-term efficacy.

A meniscus biopsy was planned for histology in the event of knee intervention.

Number of patients (planned and analyzed):

No. evaluable patients planned:	20
No. randomized and treated:	21
male/female:	16/4
Mean age (SD)	48,5 (6,3)
No. analyzed for efficacya:	
Full Analysis Set (FAS)	20
No. analyzed for safety:	21

Diagnosis and main criteria for inclusion:

Patients had to meet the following criteria to be included in the study:

1. Patient between 40 and 60 years of age
2. Degenerative meniscus injury grade 3 (Crues et al.)
3. Indication of conservative treatment
4. Normal alignment of the knee (between 3º varus and 10 º valgus)
5. Patient is able to follow a rehabilitation program
6. Informed consent given by the patient in writing
7. Patient is able to understand the trial

Those patients who met any of the following criteria were excluded:

1. Traumatic meniscus injury
2. Surgical intervention to the affected knee
3. Local or systemic infection
4. Intraarticular treatment of the affected knee with steroids or hyaluronic acid within the past 3 months

5. Significant abnormal laboratory tests that contraindicates participation in the trial.

6. Pregnant women or intend to become pregnant within the subsequent 12 months after the signature of the informed consent or breast-feeding

7. Smoker of >5 cigarettes per day.

8. Neoplastic disease detected in the last five years or without complete remission

9. Legally dependent patient.

10. Simultaneous participation in another clinical trial or treatment with another investigational product in the 30 days prior to inclusion in the study.

11. The patient is wearing a pacemaker, allergy to contrast, severe renal insufficiency or any other condition that contraindicates the magnetic resonance using contrast.

12. Other pathologic conditions or circumstances that difficult participation in the study according to medical criteria

13. The patient does not accept to be followed-up for a period that could exceed the clinical trial length

Test product, dose and mode of administration, batch number:

XCEL-M-ALPHA

Dose: $40x10^6 \pm 10x10^6$ mesenchymal cells in approximately 6 ml suspension.

Pharmaceutical form: Suspension for intraarticular infiltration in a prefilled syringe

Administration route: Intraarticular

Treatment administration schedule: Single dose

Lot number: Autologous product with a unique lot number for each one of the 10 productions

Reference therapy, dose and mode of administration, batch number

Conservative treatment based on rehabilitation

Duration of treatment:

After BM aspiration and the process for obtaining XCEL-M-ALPHA, intra-articular infiltration was performed in a single dose. The duration of the patients' participation in the study was 1 year (1 day of treatment and 12 months of follow-up).

Criteria for evaluation:

(1) Efficacy:

Main variable:

Changes in the pain scale by VAS at 12 months after the XCEL-M-ALPHA infusion.

Secondary variables:

Efficacy was also assessed using imaging criteria (MRI, T2 mapping, and WORMS scale score) at 6 and 12 months, as well as clinical criteria (VAS at 1, 3, and 6 months and changes in the IKDC tests, KOOS and Lysholm at 3, 6 and 12 months), as well as the evolution of the quality of life observed by the SF-36 questionnaire at 3, 6 and 12 months.

In cases of knee surgery, samples would be taken for histological evaluation.

(2) Safety:

Safety was assessed by recording study treatment-related adverse events and the percentage of patients who experienced a related serious adverse event. It also included the physical examination, vital signs, and laboratory tests that were performed in the safety population.

Study population:

Full Analysis Set (FAS): all randomized patients with the main variable (pain assessment by VAS) at baseline. It constitutes the intention-to-treat (ITT) population in efficacy analyzes.

Safety population: all patients who have received study treatment.

Statistical methods:

Efficacy analysis was performed by intention to treat, using the FAS analysis set. In case of missing values (missings), these were replaced by the last available value (Last Observation Carried Forward or LOCF), even if this was the baseline. In this case, as well as in the case of important protocol violations, the convenience of conducting sensitivity analysis without imputation of missing data, or excluding said violations, was assessed.

The continuous efficacy variables for which a baseline evaluation was available (VAS, IKDC, KOOS and Lysholm, quality of life by the SF-36 questionnaire and quantitative variables of the imaging tests: T2 mapping cartigram), were analyzed using a linear model (ANCOVA), which included treatment as a fixed effect and baseline value as a covariate. The possible interaction between the treatment and the baseline value was evaluated using Wald tests, and the interaction term was removed from the model if it was not significant ($p > 0.05$), so that the main effect of the treatment was estimated at a model without interaction term. The degree of bilateral significance (p-value) of the treatment effect, the adjusted least-squared means of each treatment, as well as their difference and the 95% confidence interval of said difference were documented.

For very obvious violations of the assumptions of the linear model (which were evaluated by graphical methods), a nonparametric analysis of change was performed using the Wilcoxon rank sum test.

Qualitative efficacy variables (imaging tests: T2 mapping cartigram) were analyzed using Chi-square tests, using the Monte-Carlo method to calculate the degree of significance. Given the limited sample size, it was not possible to use models that allow adjustment for the baseline values of these variables.

All analyzes were performed using a significance level of 5%. Given the exploratory nature of the study, no adjustments were made for multiplicity.

Safety variables

Safety analyzes were performed with available data, without using missing data imputation techniques.

The analysis was descriptive, including graphs and individual data lists. AEs were described by AE lists organized by treatment group and patient, and by preferred terms, as well as the characteristics of AEs, especially the relationship with treatment, severity and intensity of the AE.

The 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 data 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 in patients with grade 3 meniscus injury, the majority men (80%), with a mean age (SD) of 48.5 (6.3) years, with similar baseline demographic and clinical characteristics between both treatment groups. 21 patients were randomized (10 in the XCEL group and 11 in the rehabilitation group).

Efficacy analyzes were performed in the FAS population, which included 20 patients (n = 10 in each group), while the safety analysis was performed in all patients (n = 21).

Premature study discontinuations were significantly more frequent in the rehabilitation group than in the XCEL group (7/10 vs 1/10 patients respectively, p = 0.022), most of them due to therapeutic ineffectiveness.

For the efficacy variables, greater percentage changes were observed in the group treated with XCEL-M-ALPHA than in the group that only received rehabilitation, although the differences were not statistically significant, which could be attributed to the low sample size, to the dispersion of results obtained or to the high number of missing data.

In the main variable for efficacy of changes in the VAS for pain at 12 months, the adjusted mean estimates (least-squares) showed a slightly greater percentage reduction in the XCEL group (-67.46) than in the rehabilitation group (-44.33), which represents a difference of 23.13 [-31.57; 77.84]. However, no statistically significant differences were detected between the two treatment groups (p = 0.3574).

There were also no statistically significant differences between the two treatment groups in the observed percentage changes (without substitution of missing data) in the pain VAS at 1 month (v1), at 3 months (v2) or at 6 months (v3). These results should be interpreted with caution due to the high number of missing data for this variable.

In the specific questionnaire to evaluate knee injuries, IKDC, the mean values of percentage change were higher in the XCEL group (23.7 vs 19.6 in v2; 53.1 vs 23.8 in v3 and 74, 5 vs 58.3 in v4).

In the KOOS questionnaire, which assesses knee injuries and their evolution, higher mean percentage changes were observed in the group treated with XCEL-M-ALPHA than in the rehabilitation group at visits 2 (25.9 vs -4.5), 3 (51.9 vs 8.3) and visit 4 (53.2 vs 32.5).

In the Lysholm questionnaire, which assesses knee ligament injuries, higher mean percentage changes were observed in the group treated with XCEL-M-ALPHA than in the rehabilitation group at visits 2 (20.5 vs 15.5) and visit 3 (28.1 vs 17.2).

In MRI evaluations, a greater change was observed in the XCEL group at visit 4 (2.7 vs -7.6) in the cartilage T2 mapping, while in the meniscus T2 mapping, greater changes were detected in the XCEL group in visits 3 (14.0 vs -12.3) and 4 (13.2 vs -11.4). In the WORMS scale, which assesses joint changes by MRI, a greater change was also observed in the XCEL group at visits 3 (12.9 vs -4.7) and visit 4 (9.9 vs -5, 8).

Regarding quality of life SF-36 questionnaire, higher mean percentage changes were observed in the XCEL group in all dimensions. For body pain, greater percentage changes were observed in visits 2 (7.8 vs -7.2) and 3 (39.4 vs 12.6) in the XCEL group, and similar values were observed between groups in visit 4. In the general health domain, greater changes were observed in the XCEL group than in the rehabilitation group at visit 3 (9.6 vs 4.2) and at visit 4 (8.7 vs 0.2). In the mental health domain, higher changes were observed in the XCEL group at visits 2 (2.1 vs 1.5) and 4 (9.4 vs 6.0). In the physical function domain, clearly higher mean percentage changes were obtained in the XCEL group in the three visits (29.0 vs -7.1 in v2; 46.8 vs 4.4 in v3; 58.3 vs 14, 2 in v4). Regarding the emotional role, clearly greater changes were also observed in the XCEL group in the three study visits (43.0 vs 13.3 in v2; 39.1 vs 8.8 in v3; 41.2 vs 5.0 in v4). In the physical role, higher changes were also observed in the XCEL group in the three visits (30.4 vs -11.1 in v2; 26.0 vs 19.6 in v3; 37.9 vs 22.2 in v4). In the social role, greater changes were observed in the XCEL group in visit 2 (11.4 vs -4.2) and in visit 4. Finally, in the vitality domain, the percentage change was clearly higher in the XCEL group in the three visits (49.4 vs -7.1 in v2; 47.9 vs 6.5 in v3 and 52.5 vs 7.2 in v4).

The main analysis did not allow to demonstrate differences between the two treatment groups, so it is only possible to see trends. Based on this, it can be concluded that the application of cell therapy with XCEL-M-ALPHA reduces pain in patients, improves knee injury, both by physical evaluation of the patients and by MRI, and produces improvements in the quality of life mainly in relevant aspects such as physical function.

Safety Results:

All randomized patients were included in the safety population. In total, 26 AEs were reported (8 in the rehabilitation group and 18 in the XCEL group) in 16 patients (7 in the rehabilitation group and 9 in the XCEL group). Most AEs were mild in intensity (16), 6 moderate and 3 severe.

Of the total AEs, 2 were serious, one in the rehabilitation group (mass in a muscle) and another in the XCEL group (neck pain). None of them were related to the treatment under study.

In most cases, AEs required administration of concomitant medication or non-pharmacological treatment. Only one patient required hospitalization (mass in a muscle, rehabilitation group). There were no deaths during the study.

The most frequent AEs corresponded to the System Organ Class (SOC) categories of musculoskeletal and connective tissue disorders, with a total of 18 disorders (including tendon pain (1), patellofemoral pain syndrome (4), mass in a muscle (1) , arthralgia (7), muscular atrophy (1), bursitis (1), back pain (2), cervicalgia (1)). Arthralgia was the most frequent AE, affecting 7 patients, 3 patients in the rehabilitation group and 4 in the XCEL group.

Other AEs included epicondylitis (1), ligament sprain (1), headache (1), pain associated with therapeutic procedure (3), joint pain at the application site (1), and abnormal blood cholesterol (1).

None of them were associated with the study medication.

Regarding intensity, 11 AEs were reported as mild, 4 as moderate and 3 as severe (neck pain and back pain in the XCEL group and muscle mass in the rehabilitation group).

The number of premature study interruptions was higher in the rehabilitation group than in the XCEL group ($p = 0.022$, Chi-square test), the most frequent reason being therapeutic ineffectiveness, which was recorded in 5 patients (4 in the group rehabilitation and 1 in the XCEL group). Two patients in the rehabilitation group withdrew their consent to continue in the study. These results could be correlated with the trend towards greater efficacy observed with the XCEL-M-ALPHA product compared to rehabilitation, both in the pain scale, specific questionnaires and quality of life.

No clinically relevant changes in laboratory parameters were described at post-randomization visits. Elevated cholesterol levels were only detected in one patient (XCEL group).

In vital signs (heart rate, SBP and DBP), no clinically relevant changes were detected throughout the study in either group. Regarding the physical examination, the findings identified in the different visits were comparable in both treatment groups.

The results obtained suggest that the procedures before, during and after the infusion of XCEL-M-ALPHA indicate that there have been no relevant safety issues, therefore the product has a good safety and tolerability profile.

It can be concluded that the administration of XCEL-M-ALPHA is safe and well tolerated at the dose evaluated in the present study.

Conclusion

XCEL-M-ALPHA presents a safe and viable profile, facilitating the regeneration of the affected areas of the meniscus at 12 months post-infusion, although subsequent clinical trials with a larger number of patients are necessary in order to confirm and detail the conclusions obtained in this pilot study.

Date of report

31 July 2018