Research Project:

Orthopedic randomized clinical trial with expanded bone marrow MSC and bioceramics versus autograft in long bone non-UNIONs

Introduction

Current orthopedic treatments permit spontaneous bone regeneration to unite and heal 90% bone injuries. Non-union associates pain and disability, often requiring biological enhancement. Regenerative medicine research suggests to the general public that alternative treatments based on advanced therapy medicinal products (ATMP) are already available. However, early clinical trials only explore its potential benefit. Underreported results and absence of early trial confirmation in adequately powered prospective randomized clinical trials (RCT) indicate that evidence is not available to transfer any technique into routine clinical application.

This ORTHOUNION Project was developed from FP7-Project (REBORNE). Its results confirmed 92% bone healing rate (Gómez-Barrena et al, 2016 submitted manuscript) with an autologous ATMP of GMP expanded bone marrow derived human MSC in non-unions, where the reported bone healing rate after surgery with standard bone autograft is 74%. Any further development requires adequately powered prospective RCTs. This will be the main aim of ORTHOUNION: to assess clinically relevant efficacy of an autologous ATMP with GMP multicentric production in a well-designed, randomized, controlled, three-arm clinical trial under GCP, versus bone autograft, gold-standard in fracture non-unions. A non-inferiority analysis will evaluate if cell dose can be lowered. ATMP has been authorized by the National Competent Authorities of the participating countries in 3 previous trials (REBORNE) and will be monitored by ECRIN-ERIC to ensure quality and credibility of RCT results.

Secondary aims include innovative strategies to increase manufacturing capacity and lower costs to pave translation into routine clinical treatments, biomaterial refinement to facilitate surgery, personalized medicine supportive instruments for patient selection and monitoring, and health economic evaluation. Results in this project may help define the future of bone regenerative medicine

Activity Title:

Analysis of potential models for an affordable and cost-effective implementation of ORTHOUNION therapy into medical practice in EU National Health Systems

Activity Description:

The analysis of a potential model for industrial production and implementation within Health Systems will take on board aspects about refining the clinical indication that would benefit from the therapy, the identification of subgroups with better response by means of predictive biomarkers, optimization of cell production, transport and supply issues, patient management, and other factors identified within the ORTHOUNION project. The regulatory pathway and
developments necessary to obtain either a marketing authorization or an authorization for use under a hospital exemption scheme will be defined.

**Activity Deliverable:**

Report on a potential model for industrial production of BM-MSC for bone regeneration that would be adequate for wide access to patients in medical practice at an affordable cost. The report is to be submitted by month #60 of the entire ORTHOUNION project.

**Plan of activities**

The activity will take a 2-year period to be completed and submitted as detailed below:

**Year 1:**
- Collection of relevant literature on the existing industrial model for BM-MSC in bone regeneration.
- Developing the conceptual framework for conducting a feasibility study or analysis of the existing industrial model for BM-MSC.
- Perform a feasibility analysis of an industrial model for BM-MSC in bone regeneration taking into account the different factors that could impact on the model.

**Year 2:**
- Prepare and submit a regulatory package for a Priority Medicine designation by the European Medicines Agency as first step in a marketing authorization strategy.
- Elaborate a report on the potential use under the hospital exemption scheme in the different MS and at an EU level, taking into account its role in case a marketed product is not possible.
- Elaborate a report on the comparison of costs with strategies of concentration of production of BM-MSC in a few centers per country vs involvement of a larger number of production centers per country or a scale economy process.