ORTHOpedic randomized clinical trial with expanded bone marrow MSC and bioceramics versus autograft in long bone nonUNIONs

Rapports

Informations projet

ORTHOUNION

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Periodic Reporting for period 4 - ORTHOUNION (ORTHOpedic randomized clinical trial with expanded bone marrow MSC and bioceramics versus autograft in long bone nonUNIONs)

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Résumé du contexte et des objectifs généraux du projet

Bone injuries represent an important world medical problem producing significant healthcare and societal expenditure. While most bone injuries are not severe and capable of healing through bone regeneration by natural callus formation with standard treatments, severe bone injuries may not heal, becoming a critical unmet clinical need. Severe bone injuries may associate with soft tissue injuries and impaired biological scenarios, frequently leading to consolidation problems after a fracture and eventually to recalcitrant non-unions. Functional capacity and quality of life in survivors of severe injuries often do not return to normal, even one year after trauma. Therefore, this proposal is oriented to prove the added value of bone regenerative medicine to heal bones with consolidation problems.
Non-unions, also known as pseudarthrosis, may occur in 5% of long-bone fractures that cannot heal properly after more than six months, with morbidity, prolonged hospitalization, and increased expenses. The most accepted standard augmentation to procure fracture and non-union healing consists of autologous bone grafting frequently obtained from the iliac crest (ICAG). ICAG is the best available biological option because it provides factors that are considered to guide bone regeneration and thus heal bone injuries, such as extracellular matrix (for osteoconduction), growth factors (modulating bone healing as per osteoinduction), and patient's cells (leading to local osteogenesis). ICAG has drawbacks due to persistent pain, patient refusal, scar, late recovery, limping and gait abnormality associated with pain, and a limited amount of bone, all with a limited regeneration efficacy (success rate of about 74%) and high societal cost. Culture-expanded autologous MSCs combined with biphasic calcium phosphate (BCP) biomaterial granules have been claimed as a solid regenerative medicine alternative to autologous bone grafting in non-unions, although current data are limited.
The primary aim of ORTHOUNION is to prove the efficacy of an advanced therapy medicinal product (ATMP) in long bone non-unions developed after a bone fracture in a comparative, multicentre, multinational, randomized clinical trial (RCT). This advanced RCT may confirm previous encouraging results and provide high-level evidence. The importance of an evidence-based positive confirmation would be translating this ATMP towards clinical application as an efficacious therapeutic strategy for unmet clinical needs of significant complexity, such as unhealed severe traumatic injuries, while decreasing disability and improving quality of life in patients.
The secondary aim of the project is to pave the way for future clinical translation by defining exploitation strategies based on objective economic evaluations. This is reinforced by associated innovation to facilitate personalized medicine approaches with safe and efficacious but variable autologous cells.
The overall objective of ORTHOUNION is to obtain evidence on the efficacy of an ATMP for bone regeneration. In case of positive results, these would support the progress of bone regenerative medicine towards clinical application. In case of negative outcomes, these would inform the limitations of obtaining clinical benefits from this technology. Either positive or negative results may be highly valuable to define the future of the field.

Travail effectué depuis le début du projet jusqu'à la fin de la période considérée dans le rapport et principaux résultats atteints jusqu'à présent

For the conduction of the ORTHOUNION clinical trial, all regulatory approvals were obtained in the four Member States of the EU (Spain, Italy, Germany and France). Fifty-one patients were included; 42 were finally treated (31 with the BM-MSC investigational product, and 11 patients were treated with ICAG).
As of May 2022, 50% of treated patients completed their participation in the study, and 81% had completed one-year follow-ups. From preliminary safety results, no related Serious Adverse Events have been reported, and no new or concerning safety issues have been observed by the researchers or by the Data Safety Monitoring Board.
Final exploitable efficacy and economic study results will not be available until the end of the clinical trial (Dec 2023). The preparatory activities required to conduct the statistical and pharmacoeconomic analyses have been developed and completed.
After the briefing meeting with European Medicine Agency (EMA) Innovation Task Force, the consortium can report advances on the strategic business plan for ATMPs in bone regeneration. The ORTHOUNION team believes that in the current scenario of widely spread MSC production by academic centres and hospitals, an autologous product better fits the Hospital Exemption model for use in several hospitals throughout the EU that have these types of specific patients.
Regarding innovation activities, the studies progressed to obtain significant outcomes in line with achieving the personalized medicine objectives planned:
• Partners established an ex vivo potency assay to measure osteogenic medium-induced gene expression.
• MSC engraftment on the different materials and their progressive clearance in host mice were confirmed.
• On the optimization of MSC expansion costs, ORTHOUNION reports that bioreactors allow a more efficiently use of human resources.
• Partners tested biomarker patterns to understand the individual patient evolution.
• Partners show the high potential of FDBS to be used as a platform for bone tissue engineering strategy.
Finally, up to June 2022, 81% of the project tasks were executed, 100% of deliverables were submitted, and 96% of milestones were achieved.

Progrès au-delà de l'état des connaissances et impact potentiel prévu (y compris l'impact socio-économique et les conséquences sociétales plus larges du projet jusqu'à présent)

The clinical trial results will not be available until the end of the trial (Q4 2023), but the project has obtained results beyond the state-of-the-art in some aspects.
(1)The non-union radiological bone healing scale (REBORNE scale) has been validated. The REBORNE scale was defined as a more detailed evaluation of long bone consolidation from radiographs and Computer Tomographies (CT). The REBORNE-scale measured with radiographs

proved to be valid in assessing consolidation against CT measurements. Measures with CT or radiographic were found reliable among 3 raters at a follow-up time above 6 months for long bone non-union fractures, based on the clinical cases from the ORTHO1 pivotal trial. These results increased the robustness of the ORTHOUNION clinical trial efficacy endpoint assessment.
(2) The international multicentric approval of the clinical trial was completed in all the participating countries. This is beyond the state-of-the-art achievement because many new hurdles appeared, even in the case of the previously approved investigational medicinal product, associated with continuous changes in the regulatory approach of the participating member states.
(3) Studies to optimize the cell expansion cost shows the viability of cells obtained from any bioreactor system tested above 90%, which is the release criterium for MSC in the project.
(4) The major impact of the project is to provide information about the feasibility of multicentric, multinational clinical trials on bone regenerative medicine in EU member states, confirming safety, complex logistics (including regulatory hurdles) and efficacy approaches. This will undoubtedly impact future clinical trials, helping hospitals and companies to orient further strategies towards success.

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