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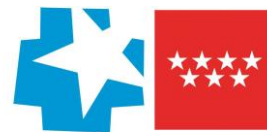


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The ORTHOpaedic treatment with ALLOgenic ATMP in long bone delayed UNION and non-union fractures

Cristina Avendaño-Solà

16/06/2025

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Ortho

Allo
Union

DATA SHEET



Project name: The **ORTHO**paedic treatment with **ALLO**genic ATMPs in long bone delayed **UNION** and non-union fractures

Acronym: Ortho-Allo-Union

Project number: 101137464

Call and topic: HORIZON-HLTH-2023-TOOL-05-01: Clinical trials of combined ATMPs (RIA)

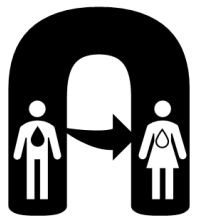
Granting Authority: European Health and Digital Executive Agency

Total grant: 9 993 416.25 EUR

Project start date: 1st December, 2023

Duration: 60 months

Project Coordinator: Cristina Avendaño Solá



Bone consolidation failure

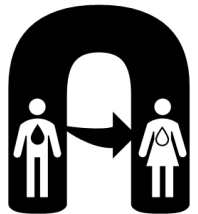
Delayed union and non-union fractures represent the **inability of bone to heal without further intervention**.

Identified based on **radiological, clinical, and temporal** criteria.

Patients show **pain** at the fracture site, inability to bear **weight**, and associated **disability**.

Definitions:

- *Delayed union has been defined as the absence of bone bridging and the presence of fracture line after three to six months, reaching the definition of non-union nine months after the original fracture with lack of progressive signs of bone healing over three consecutive months. However, **fractures with more than six months without consolidation are frequently considered non-union and have been identified as the preferred option for surgeons to intervene.**[Megas,2005, Ozkan 2019, Nicholson 2021]*
- *A well-accepted alternative and practical definition of non-union is a **fracture that in the opinion of the treating physician has no possibility of healing without additional intervention.**[Schmal 2020]*
- *Further, fractures that fail to heal after a first non-union therapeutic procedure are defined as **recalcitrant non-union.**[Wiss 2021]*

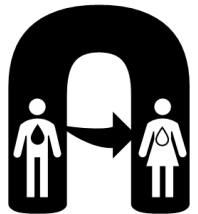
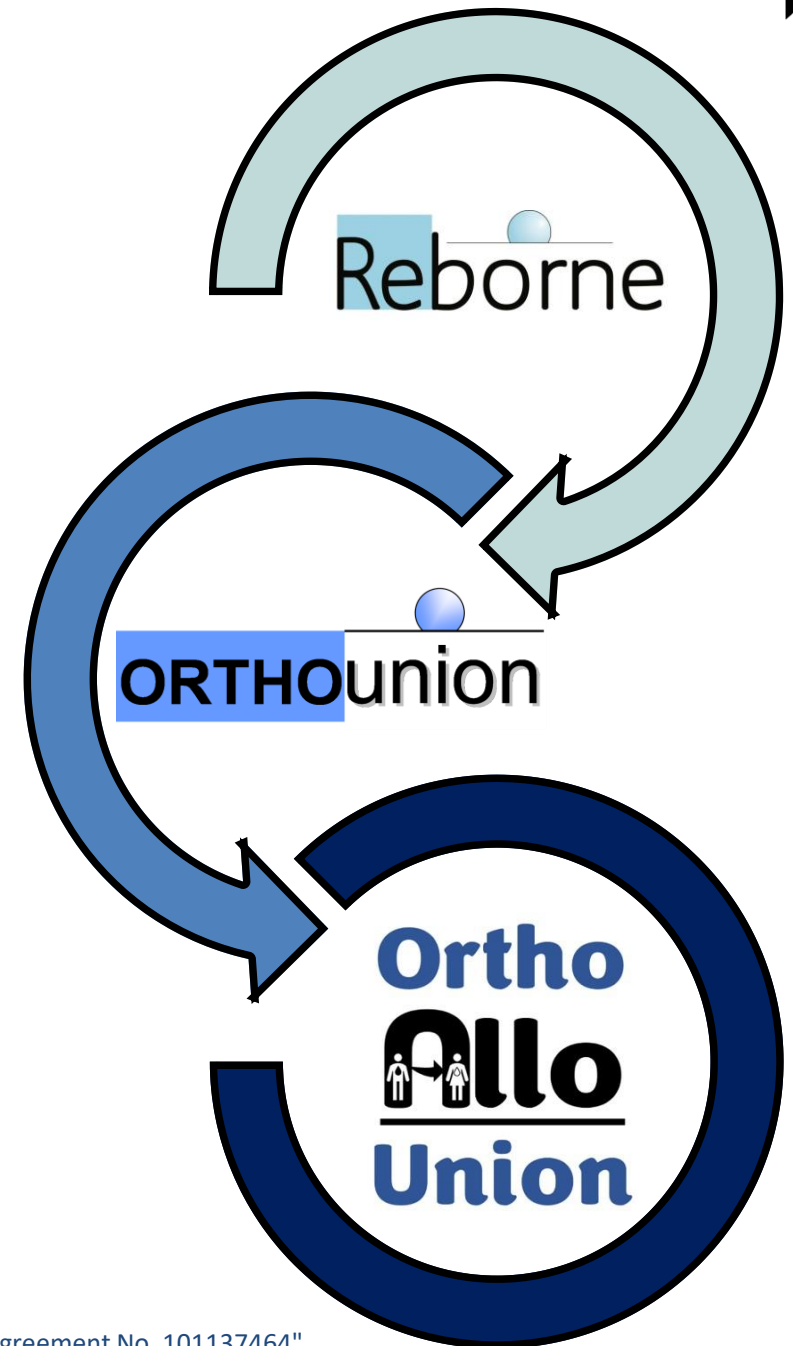


BACKGROUND

“**RE**generating **BO**ne defects using New biomedical Engineering approaches.”
FP7-HEALTH-2009-1.4-2 Large-scale integrating Project under G.A. 241879, 2010-2015. Coordinator: Pierre Layrolle (INSERM). Co-coordinator: Luc Sensebé (EFS).

“**ORTHO**paedic randomized clinical trial with expanded bone marrow MSC and bioceramics versus autograft in long bone non**UNIONS**.” **H2020**-SCI-PM-11-2016-17 Large-scale integrating Project under G.A. 733288, 2017-2022. Coordinator: Enrique Gómez Barrena (UAM). Co-coordinator: Cristina Avendaño (SERMAS-FIBHUPH).

The “**ORTHO**paedic treatment with **ALLO**genic ATMPs in long bone delayed **UNION** and non-union fractures”. HORIZON Research and Innovation Actions, in the topic **HORIZON**-HLTH-2023-TOOL-05-01: Clinical trials of combined ATMPs, G.A.: 101137464, 2023-2028. Coordinator: Cristina Avendaño-Solà (SERMAS).



Destination 5. Unlocking the full potential of new tools, technologies and digital solutions for a healthy society 145

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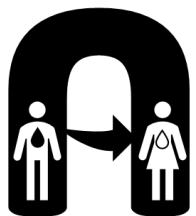
HORIZON-HLTH-2023-TOOL-05-03: Integrated, multi-scale computational models of patient patho-physiology ('virtual twins') for personalised disease management 151

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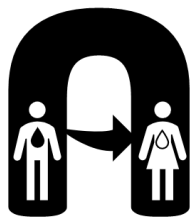
Destination 5. Unlocking the full potential of new tools, technologies and digital solutions for a healthy society

Calls for proposals under this destination are directed towards the Key Strategic Orientation KSO-A *'Promoting an open strategic autonomy by leading the development of key digital, enabling and emerging technologies, sectors and value chains'* of Horizon Europe's Strategic Plan 2021-2024. Research and innovation supported under this destination should contribute to the impact area *'High quality digital services for all'* and in particular to expected impact, set out in the Strategic Plan for the health cluster: *'Health tech tools and digital solutions are applied effectively thanks to their inclusive, secure development, delivery, integration and deployment in health policies and health systems'*. In addition, research and innovation supported under this destination contribute to the following impact areas: *'A competitive and secure digital economy', 'Industrial leadership in key and emerging technologies that work for people health and high-quality accessible health care'*.

Expected Impacts

Proposals for topics under this destination should set out a credible pathway towards unlocking the full potential of new tools, technologies and digital solutions for a healthy society, and more specifically to several of the following expected impacts:

- Europe's scientific and technological expertise and know-how, its capabilities for innovation in new tools, technologies and digital solutions, and its ability to take-up, scale-up and integrate innovation in health care is world-class.
- Citizens benefit from targeted and faster research resulting in safer, more sustainable, efficient, cost-effective and affordable tools, technologies and digital solutions for improved (personalised) disease prevention, diagnosis, treatment and monitoring for better patient outcome and well-being, in particular through increasingly shared health resources (interoperable data, infrastructure, expertise, citizen/patient driven co-creation)²³³.
- The EU gains high visibility and leadership in terms of health technology development, including through international cooperation.



HORIZON-HLTH-2023-TOOL-05-01: Clinical trials of combined Advanced Therapy Medicinal Products (ATMPs)

Expected Outcome: This topic aims at supporting activities that are enabling or contributing to one or several expected impacts of destination 5 “Unlocking the full potential of new tools, technologies and digital solutions for a healthy society”. To that end, proposals under this topic should aim for delivering results that are directed towards and contributing to several of the following Expected Outcomes:

- Healthcare providers increase their knowledge on the potential of combined ATMPs and get access to innovative treatment options with demonstrated health benefits for unmet medical needs;
- Developers and manufacturers of combined ATMPs obtain scientific evidence on the proposed therapeutic approach;
- Patients benefit from new advanced therapies delivered through the combined ATMPs;
- EU companies get a better market position in the field of combined ATMPs.

Scope: The subjects of this topic are combined ATMPs (Advanced Therapy Medicinal Products) according to the definition of the ATMP-regulation (EU 1394/2007, Article 2d). Such combined ATMPs are composed of an ATMP and one or more medical devices or one or more active implantable medical devices, and their cellular or tissue part must either contain viable cells or tissues, or non-viable cells or tissues liable for exerting the primary action on the human body.

The combined ATMPs should be more effective than current state-of-the-art solutions on the European market owing to improved features like personalisation, accuracy, reliability and usability and contribute to long-term sustainability (faster and affordable) of European health systems.

Research should focus on advanced stages of clinical development with regulatory work on the Medical Device part completed and safety studies of the combination product in an advanced stage.

Proposals should address all of the following activities:

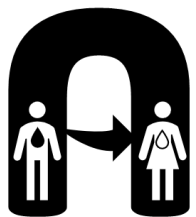
- Phase 2 clinical trials and above of combined ATMPs focussing on:
 - technologies ready to undergo interventional clinical trials in patients/end users assessing the usability and clinical performance, and/or
 - technologies that have demonstrable safety/performance profiles and should undergo clinical validation in view of their inclusion into guidelines for specific clinical pathways.
- Delivery of safe and clinically validated combined ATMPs that are compliant with current European regulatory requirements. The related regulatory work should be considered as an essential component and the proposed work should involve consultation/interaction with competent regulatory agencies such as the European

Medicines Agency (EMA) or national regulatory agency. Applicants are encouraged to seek regulatory and/or Health Technology Assessment (HTA) advice as appropriate.

The topic invites proposals that include innovative treatments for any medical condition excluding rare diseases that are ready to be assessed for clinical efficacy (performance and clinical benefit) in a specific indication on a big number of patient cohorts; already existing market solutions are not in the scope of this topic.

Sex and gender aspects, age, socio-economic, lifestyle and behavioural factors and any other non-health related individual attributes should be taken into consideration. SME participation is strongly encouraged.

Applicants envisaging to include clinical studies should provide details of their clinical studies in the dedicated annex using the template provided in the submission system. See definition of clinical studies in the introduction to this work programme part.



OBJECTIVES AND AMBITION

a) Towards a more accessible combined ATMP.

Switch to allogeneic. Off-the-shelf clinical doses with easier logistics

Need for a clinical trial to confirm efficacy

Extended indication

Sustainable access within Health Services

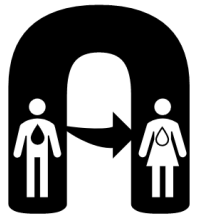
b) Towards a reliable and consistent ATMP

Creation of a MCB from selected donors

c) Further improvements of access and sustainability

New presentation with easier logistics.

Non-animal models to facilitate new developments



SPECIFIC OBJECTIVES

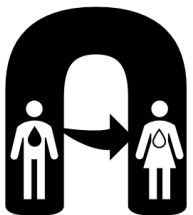
SO1: To develop a universal therapy for delayed union and non-union fractures of long bones.

To achieve this, an adaptive, open, multicentre, multinational clinical trial is designed to prove that allogeneic bone marrow mesenchymal cells (allo-BM-MSC) combined with a biomaterial is effective in healing delayed union and non-union long bone fractures one year after surgery.

SO2: To provide a ready-to-use and off-the-shelf allogenic combined ATMP (allo-BM-MSC plus biomaterial), with optimized production through the use of a potency-driven master cell bank obtained from a pool of healthy volunteer donors selected by their bone formation potential.

SO3: To provide a new therapy that improves the current outcome of non-healed fractures at an affordable cost for the EU Health Systems and in compliance with all regulatory requirements for approval.

SO4: To provide scientific information and laboratory models for assessing the potential for bone regeneration of different combined ATMP products, helping biomaterial companies to develop and get to the market with other new combined ATMP usable for the heterogeneous unmet medical need that exists in the bone regeneration field.



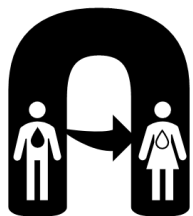
1. Excellence #@REL-EVA-RE@#**Background**

Delayed union and non-union fractures are well-defined medical conditions, that represent the inability of bone to heal without further intervention, which is usually identified based on radiological, clinical, and temporal criteria. The patients show pain at the fracture site, inability to bear weight and associated disability. *Delayed union* has been defined as the absence of bone bridging and the presence of fracture line after three to six months, reaching the definition of *non-union* nine months after the original fracture with lack of progressive signs of bone healing over three consecutive months.[1-3] However, fractures with more than six months without consolidation are frequently considered non-union and have been identified as the preferred option for surgeons to intervene.[4-6] A well-accepted alternative and practical definition of non-union is a fracture that in the opinion of the treating physician has no possibility of healing without additional intervention.[7] Further, fractures that fail to heal after a first non-union therapeutic procedure are defined as *recalcitrant non-union*. [8]

The reported frequency of non-union after acute long bone fractures is highly variable, classically reported between 5% -10% of total long bone fractures. Their occurrence is more likely depending on factors such as the anatomical site (e.g. tibia), fracture types (e.g., open tibia fractures, bone loss, high energy trauma with comminution) or the presence of local infection. Patients' habits (smoking/alcohol abuse), medications (e.g., bisphosphonates, chronic NSAIDs) or the presence of certain conditions (e.g. diabetes, peripheral vascular disease, obesity) can also increase the likelihood of non-union after fracture.[9-13] A large study using the Victorian Orthopaedic Trauma Outcomes Registry of Australia determined the rate of failure non-unions according to the type of bone fracture, finding 2.3% of failures in the proximal humerus, 7.8% in the humerus shaft, 4.2% in the subtrochanteric fracture, 13.5% in the femur shaft, 8.4% in the distal femur, and 11.7% in the tibia shaft.[14] Mills et al.[12] reported an annual prevalence of non-union per acute fracture in the Scottish population of 1.9% with a risk up to 9% for certain fractures in specific age groups.[15] A 2-10% percentage of long bone fractures evolving to non-union means a very substantial number of patients due to the incidence of long bone fractures. Results from a Spanish study suggest that the rate of non-union fractures remains mostly stable over time, from 3.7/100000 inhabitants in 2000 to 4.8/100000 inhabitants in 2015,[16] strengthening the hypothesis of the current lack of an effective treatment.

The unmet medical need.

To heal delayed union or non-union fractures, in addition to an adequate mechanical environment with stabilization of the fracture, a local biological stimulus for bone formation is considered necessary. The most accepted standard treatment is autologous bone grafting, obtained from the same patient in a different surgical site (i.e from the iliac crest) and transplanted to the reconstruction site. Its major advantage is to provide extracellular matrix (for osteoconduction), growth factors (modulating bone healing as per osteoinduction), and patient's cells (leading to local osteogenesis). These factors are considered to guide bone regeneration and thus to heal the bone injury. However, autologous bone graft has drawbacks due to the bone collection such as persistent pain, patient refusal, scar, late recovery, limping and gait abnormality associated with pain, and limited amount of bone, and all these with limited radiological consolidation results (reported rate of failure up to 26%).[17] Other invasive surgical options that can be used in particular cases are bone transport, vascularized bone graft or a free flap (vascularity).



Ambition

The OAU Consortium proposes the development of a universal, standardized and cost-effective therapy for fractures with delay or failure to heal, with a ready to use combined product that is affordable for Health Systems and suitable for use in a broad number of patients.

Rather than considering combined ATMP only as a last solution in recalcitrant non-unions, this project advocates that the indication should be moved to an earlier point in the clinical management of bone healing. The combined ATMP will be developed as a solution to be used as soon as the need for reoperation is identified due to delayed healing, with or without an added infectious component, with the aim of avoiding long-term suffering from the patient, heavy social and economic costs, and secondary complications such as permanent disability.

This approach responds better to the real patients' needs and fits with the usual clinical practice, in which reoperation is very frequently performed at 3-6 months, in an attempt to accelerate healing and avoid the progression to severe established non-unions.

This expanded and ambitious therapeutic approach with ATMP relies on several novel concepts that are detailed below and will be brought forward with the project activities.

a) Towards a more accessible combined ATMP. From autologous to allogeneic BM-MSC

Our previous ORTHOUNION project demonstrates efficacy of the combined autologous ATMP and, at the same time, delivered as important non-clinical results, several in vitro tests to predict the in-vivo bone forming capacity of MSC. However, the use of autologous MSC is a limitation for providing patient's access and the switch to allogeneic MSC has several advantages:

- Provides an off-the-shelf product suitable for all patients, including those with potentially compromised cell quality or inability to donate bone marrow.
- Allows the selection of well-characterized allogeneic donors with the best-performing BM-MSC in terms of in vitro bone regeneration potential.
- Provides a standardized ATMP since MSC could be expanded from a cell bank which reduces donor-dependent batch-to-batch variability.
- Makes the manufacturing process more reliable and faster, simplify the logistics, thus reducing the costs of the ATMP, a crucial issue for delivering wide access across the EU Health Systems.

The switch to allogeneic is therefore considered a necessary step, although it raises the concern of possible alloreactivity of the recipient immune system against the donor cells.

Expanded human MSC lack of MHC II molecule expression and express a very low level of MHC I.[23] Additionally, stimulatory molecules such as CD86, CD40, or CD40L are not detectable in MSCs and therefore not recognised by alloreactive T cells. As a result, donor MSCs can go undetected by the host immune system in allogeneic therapies.

d) Towards an accessible and cost-effective combined ATMP

The costs of production, quality controls and transportation of autologous MSCs as clinical grade ATMP by GMP facilities are around 25-35 k€ per patient, as calculated in our previous ORTHOUNION project, which included a detailed cost collection of the production process. The establishment of an allogeneic CMB will considerably lower the costs to a target of around 10k to 15k€ per patient or less (after introduction to routine large-scale manufacturing). The costs may further decrease with the use of automated closed systems bioreactors and process predictability. The potential costs savings with the use of three different bioreactors was studied and it was concluded that bioreactors could be the preferable option in case of scaling up the production and for manufacturing clinical doses from a master cell bank in allogeneic production. Our study identified the prices of the consumables of the bioreactors as a challenge to solve, they are more expensive than standard consumables because they are specific for each bioreactor and this limits market competence.

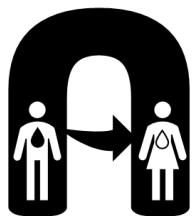
The autologous approach has also drawbacks related to the logistics in handling and transportation fresh bone marrow donation and MSC clinical dose 2 weeks later, two surgeries at a fixed strict interval with eventual failures to obtain adequate cell dose that are suddenly known at the time of scheduled surgery. The logistics of allogeneic clinical doses are eased by the frozen allogeneic intermediate products, and there is also a clear additional value by facilitating patient's surgery planning with the use of an off-the-shelf product.

Moreover, a major step towards a widely accessible and affordable product for the Health Systems would be a combined ATMP that could be sent to hospitals as a frozen product. A final step of preparation has then to be performed at the point of care. This innovative development will be explored, either the possible use directly after thawing the frozen product or, alternatively, with a final step to be performed in a closed automated system.

e) Combined ATMP final characterization and pathway for new biomaterials development

The OAU project will provide the scientific evidence and regulatory information that will allow a submission for approval of the combined ATMP (allogeneic BM-MSC combined with biphasic calcium phosphate granules (MBCP®+, CE-Marked), in a ready-to-use presentation. For that end, the clinical study results are crucial but also some additional work to characterize the final product, to develop a feasible quality control procedure and validation for transport specifications suitable for a wide use and marketing authorization.

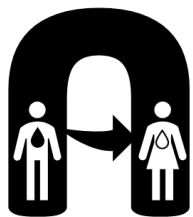
On the 9th of February of 2023, the consortium consulted one of the involved National Competent Authorities (AEMPS-Spanish Agency for Medicines and Medical Devices). Supported by their written advice on the requirements to assess different biomaterials for combination with MSC, in which the AEMPS stated that "if a different CE-marked biomaterial is to be used, it would be sufficient to provide in vitro data to show cell viability and bone differentiation with no need to conduct animal studies," we commit to deliver a 3D validated model to fulfil the preclinical regulatory requirements for bone regeneration. This will be useful to biomaterials companies to assess



Relation to the Work Programme

The objectives before mentioned will match the scope of the topic.

Table 2: Relationship between the Scope of the work programme topic and the OAU project	
Scope of the Work Programme topic	OAU indicators
<i>Scope I</i>	
"Technologies ready to undergo interventional clinical trials in patients/end users assessing the usability and clinical performance"	Combined ATMP which is ready to demonstrate efficacy and safety in a phase III clinical study.
"Technologies that have demonstrable safety/performance profiles and should undergo clinical validation in view of their inclusion into guidelines for specific clinical pathways."	Combined ATMP which has demonstrated efficacy and safety in the autologous setting (ORTHOUNION) and goes to clinical validation in the allogeneic setting in this project, also aiming to expanded indications
<i>Scope II</i>	
"Combined ATMP should be more effective than current state-of-the-art solutions on the European market"	The combined ATMP is expected to be less invasive and more effective (>90%) than the current standard (autograft, reported efficacy 74%).
"...owing to improved features like personalisation, accuracy, reliability and usability and contribute to long-term sustainability (faster and affordable) of European health systems"	The allogeneic combined ATMP shows improved features in terms of reliability and usability as compared to autologous. It will contribute to long term sustainability due to decreased production cost of the new product
"ATMPs compliant with current EU regulatory requirements. The related regulatory work (..) as an essential component and (..) involve consultation/interaction with competent regulatory agencies such as the EMA or NCA"	The regulatory development and approval of the combined ATMP is part of the project with a specific WP6 and involves interaction with regulatory agencies.
"Applicants are encouraged to seek regulatory and/or Health Technology Assessment (HTA) advice as appropriate"	Interaction with HTA agencies and reimbursement bodies is also part of the project, including a possible Joint Clinical Consultation according to the new HTA EU Regulation



1.2 Methodology #@CON-MET-CM@# #@COM-PL-CP@#

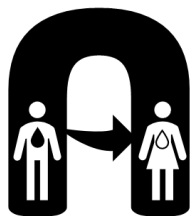
The project addresses the demonstration of the clinical efficacy, safety and usability of a combined ATMP composed by allogeneic MSC+MCBP granules in a clinical trial performed in an extensive cohort of patients with delayed union or non-union after long bone fracture. After demonstration of clinical efficacy of autologous MSC in a previous controlled clinical trial performed by our Consortium in a restricted population, the confirmation of the clinical efficacy with a combined allogeneic ATMP with improved features in a big cohort is a major step forward to an effective and affordable universal ATMP treatment for fractures with bone consolidation failure. In addition, the development of the OAU combined ATMP should deliver a product approvable by the Regulatory Agencies and affordable for the EU Health Systems. Moreover, the public deliverables of this project have to pave the way for the development of other combined ATMP products for bone regeneration, fostering versatile combinations that could provide new solutions for the heterogeneous medical conditions where failure to regenerate bone causes relevant suffering and disability.

This ambitious concept entails some methodological and regulatory challenges that will be addressed in the project.

1.2.1. An expanded indication to better respond to the patients' and society needs and improve the current state-of-the art.

The non-randomized design is justified because it is not feasible to randomize delayed unions to ATMP or ICAG (see clinical trial annex) and we propose an adaptative single-arm clinical trial to demonstrate efficacy of the combined ATMP (allogeneic BM-MSC combined with MCBP+) in patients with long-bone traumatic fracture with delayed union or non-union, either aseptic or septic cases, as long as the infection is not acute or requiring debridement. We are confident that this trial may provide a robust proof of efficacy, acceptable for a regulatory purpose with the incorporation of the following methodological features:

- A well-defined and restrictive criteria for delayed union (4 months or more since fracture), with a strata of at least 40 patients affected by the more severe condition, non-union after 9 months or more since fracture.
- An objective and ambitious end point for efficacy (clinical and radiological consolidation with no additional surgeries), with outcomes assigned by an independent Adjudication Committee. Radiological consolidation will be assessed on the validated REBORNE score for long bone non-unions (bone consolidation considered with a score ≥ 0.6875) with a good CT reliability of 88%.[42] The estimand for efficacy with identification of possible intercurrent events will be carefully defined a priori.
- An ambitious target efficacy rate of $>90\%$, which is higher than data shown in relevant published series and similar to the results of the ORTHOUNION autologous arm in the controlled clinical trial.
- A register will be established to documenting the lack of bias of selection. All participating centres will register all identified patients with delayed/non-union that come to the clinic during the period of recruitment. A complete register of reasons for not offering trial participation and all screening failures will be established and monitored following the ICH-GCP procedures.
- The establishment of an external cohort for comparison purposes. This cohort will be open to all participating centres and will include retrospective patients, with same selection criteria than those established in the trial. The protocol and analysis plan for the external cohort will be finalized before initiating the data collection, and all sources of bias will be controlled as much as possible: procedure for selection of patients, definition of suitable study data sources, baseline eligibility (inclusion and exclusion) criteria, treatments, measure of confounding factors influencing outcomes, appropriate exposure definitions and windows, definition of outcomes, intercurrent events and missing data, analytical approach, etc.
- The use of 3-D reconstruction using Osirix Software® - Region of Interest application. We estimated the volume of non-union, the cortical volume, and combined ATMP treatment in a sample of 19 ORTHOUNION patients with completed CT and efficacy follow-up time at 12 months. Analysis shows a decrease in bone defect volume and an increment in cortical bone volume. Considering a 10cm^3 cylinder bone the 100% area, the mean basal non-union volume changed from $8.9\% \pm 6.3\%$ to $1.7\% \pm 2.3\%$ after 12 months FU; the basal mean cortical volume changed from $91.7\% \pm 6.7\%$ to $101.1\% \pm 10.8\%$, and the treatment volume changed from $12.4\% \pm 7.7\%$ at six-months after surgery to $7.3\% \pm 5.4\%$ at 12 months FU. This technique will allow us to compare final results with



1.2.2 The switch from autologous to allogeneic MSC

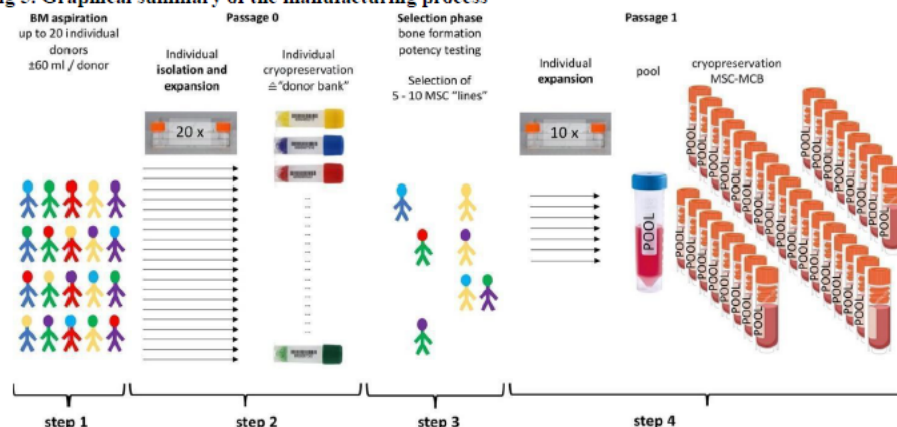
The potential negative consequences of alloreactivity of the recipient against the administered MSC on safety or efficacy must be carefully assessed. Although from a safety point of view, the possible alloreactivity does not raise major concerns, as a safety safeguard, the clinical protocol envisages a first cohort of patients with a sequential recruitment to guarantee that the possible side effects are sufficiently investigated, and that safety shown in this first cohort is endorsed by the independent DSMB before entering into the main phase of the study. From the efficacy point of view, the planned clinical study is the tool to confirm if allogeneic MSC retains the efficacy of autologous MSC. It should be mentioned that the project plans the use of allogeneic MSC from a pool of up to 10 donors and this allows to minimize the potential effect on efficacy of eventual baseline anti HLA antibodies of the patient, as different HLA donor profiles will be administered.

Complementary biological studies will be performed to better understand possible issues in the interaction of allogeneic MSC with the recipient by means of 1) analysis of donor-specific antibodies levels in patients at baseline and after treatment, using sensitive methods, by determination of antigen specificity and correlation with tolerability and efficacy of treatment and possible predictive factors for alloimmunization, 2) change in patients' peripheral blood distribution of circulating monocyte into the three main populations; classical (CD14+CD16-), non-classical (CD14dimCD16+), and intermediate (CD14+CD16+), as a systemic marker of allogeneic effects on the bone fracture microenvironment, circulating B and T lymphocyte subset proportion and phenotype change, serum level of pro-inflammatory and anti-inflammatory cytokines.

1.2.3. A combined ATMP with improved features

To ensure a safe and reliable production of the IMP, i.e., a combined ATMP consisting of allogeneic, selectively pooled bone marrow-MSC on a biomaterial, MSC from up to 20 donors will be isolated, expanded, cryopreserved and tested individually for their ability of bone formation and immune modulatory potency in an allogeneic setting. MSC from the 5 – 10 most suitable donors (i.e., with highest bone formation capacity) will be selected to generate a pooled allogeneic MSC bank.

Fig 5. Graphical summary of the manufacturing process



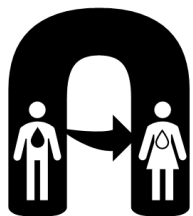
1.2.8 Gender Dimension

The efficacy of ATMP treatment on delayed union and non-union fractures of long bones should be assessed disaggregated by gender, as females have a higher incidence of fractures, but a better fracture healing rates than males.[43] The mechanisms behind these differences may include the originating trauma, besides hormonal, genetic, and lifestyle factors. Up to 2/3 of fractures in women are associated with fragility vs only 1/3 in men, with a higher rate of high impact trauma fractures in men. Regarding non-union, observational studies show a similar rate in male and females although some clinical trials have a higher representation of males. We will take measures to avoid the underrepresentation of women in our clinical trial, as this has with implications for understanding gender-specific differences in disease presentation, treatment response, and outcomes.[44] Our study avoids the upper age limitation (which reinforce the participation of female patients) and the inclusion of women with child-bearing potential will not be hampered with unnecessary restrictions in the trial design and selection criteria, allowing standard contraceptive measures and recommendations for avoidance of pregnancy. Gender-sensitive measures have been put

1.2.9 Open Science

The open science approach in this proposal is based on open, cooperative work and systematic sharing of knowledge and tools as early and widely as possible in the process. Open science practices within the project will include:

- Early register of the OAU clinical trial in public registers: European register of clinical trials (www.clinicaltrialsregister.eu/) and also in the WHO International clinical trials registry platform (www.who.int/clinical-trials-registry-platform) and in ClinicalTrials.gov.
- Open access publication of the full clinical trial protocol as soon as approved by the National Competent Authorities.
- Establishment of two patient focus groups (two different participating countries) to understand the benefits



Proposal Evaluation Form

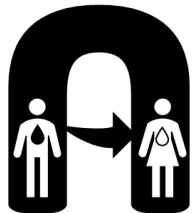
	EUROPEAN COMMISSION Horizon Europe (HORIZON)	Evaluation Summary Report - Research and innovation actions
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Call: HORIZON-HLTH-2023-TOOL-05
Type of action: HORIZON-RIA
Proposal number: 101137464
Proposal acronym: ORTHO-ALLO-UNION
Duration (months): 60
Proposal title: ORTHOpaedic treatment with ALLOgenic combined ATMP in long bone fracture delayed UNION and non-union (ORTHO-ALLO-UNION).
Activity: HORIZON-HLTH-2023-TOOL-05-01

Evaluation Summary Report

Evaluation Result

Total score: 13.50 (Threshold: 12)



Score: **5.00** (Threshold: 4 / 5.00 , Weight: -)

The project objectives are relevant for improving the management of bone fractures that are hard to heal, with high potential positive health impact on the patients. In this regard, the proposal addresses an area of clinical research with high demand for improvements. The proposal presents an excellent range of objectives that are highly relevant to the specific topic of the work programme, including a combined ATMP and a scaffold ready to be tested for efficacy in a Phase III clinical trial.

The device-ATMP combination convincingly brings the technology beyond the state-of-the-art, as currently only cell-based products without a scaffold are approved and available. Other therapies like biomaterials alone, and growth factors, have not provided sufficient clinical efficacies and 2-10% of long bone fractures remain unhealed and result in non-unions.

The R&I level of the proposed technology is well documented. The ATMP is convincingly at a TRL8 as the autologous version has been approved for clinical trials by multiple EU agencies. In turn, the scaffold is also convincingly classified at TRL9. Regulatory issues have properly been taken into consideration when designing the R&I programme.

The methodology is sound, based on already known and repeatedly validated concept of enhancing osteogenic potential of MSCs with mineralized granules. The methodology robustness is enhanced by a cell bank proposal, which would enable to produce the ATMP with higher quality and the most desired consistency. The intended move from an autologous to an allogeneic strategy is logically and effectively supported.

A minor shortcoming is that ways to prevent potential elimination/apoptosis of the allogeneic MSCs after transplantation into the host organism are not discussed.

The inter-disciplinary approach is present and consistent with the aimed goals. The consortium has already proved its ability to work across disciplines in previous projects, including in the scope of a large-scale clinical trial.

The integration of social sciences and humanities is not sufficiently addressed in the proposal, which is considered a very minor shortcoming in this context.

The gender dimension and the epidemiology of the indication have been adequately addressed and have been well-taken into account for the study design.

The open science practices are adequately addressed. The project adheres to the Open Science principles that enable a full range of stakeholders to retain a sense of awareness and involvement.

The research data management plan is in place and evolves around the FAIR principles and the relevant EU Guideline.

2. Impact #@IMP-ACT-IA@#

2.1 Project's pathways towards impact

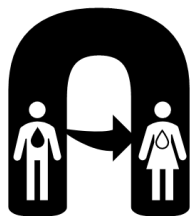
ORTHO-ALLO-UNION will contribute to all the Expected Outcomes of the topic **HORIZON-HLTH-2023-TOOL-05-03** and to all 6 expected impacts of Destination 5:

2.1.1 Expected outcomes.

Table 4. Contribution to the expected outcomes

Expected outcome 1. Healthcare providers increase their knowledge on the potential of combined ATMPs and get access to innovative treatment options with demonstrated health benefits for unmet medical needs.	OAU results, added to previous results from REBORNE and ORTHO-UNION projects, will provide definite scientific evidence about the clinical efficacy of a combined allogeneic ATMP to heal long bone fractures with failure to consolidate. The new combined ATMP will be a therapy to be used in long bone fractures with delayed healing, as soon as the need for reoperation is identified -i.e., up to 5% of long bone fractures-, with the objective of preventing the patient's prolonged suffering as well as high associated medical, social, and economic cost. The new combined ATMP will achieve more than 90% bone healing after first surgery for delayed union or non-union, with no need for further surgeries and medical care. An affordable access for healthcare providers will derive from its improved cost-effectiveness, through its decreased production costs and a more reliable and consistent potency of the product.
Expected outcome 2. Developers and manufacturers of combined ATMPs obtain scientific evidence on the proposed therapeutic approach	The Global Advanced Therapy Medicinal Product (ATMP) Manufacturing Market is projected to grow from USD 9.37 billion in 2022 to USD 22.48 billion from 2022 to 2027. OAU project will provide clinical evidence of improved bone consolidation with the use of an ATMP composed of allogeneic BM-MSC combined with biphasic calcium phosphate granules (MBCP+ ^{CE} and possibly also FDBS) together with a wide portfolio of useful preclinical studies and models and optimized production procedures and quality controls. As a result, the combined products assessed in OAU, may reach the market in a ready-to-use presentation as soon as one year after the end of the project. And other combined products may use the OAU evidence to shorten their preclinical developments avoiding the need of animal studies and getting earlier to the market.
Expected outcome 3. Patients benefit from new advanced therapies delivered through the combined ATMPs	Results from ORTHO-UNION and OAU clinical trials will give robust evidence on the effectiveness of the combined ATMP as compared to standard therapies for patients with delayed union or non-union after long bone fractures. Patients will benefit from a treatment less invasive than autograft and more reliable for clinical efficacy, suitable for all patients, including those with potentially compromised cell quality or inability to donate tissue, increasing equity in the access to this effective therapy. It is expected to achieve more than 90% success after first surgery and clinical and radiological healing could be obtained in 70% of patients already at 6 months. Avoidance of further new surgeries and reduced time of sick leave, absenteeism, and disability is a benefit to a patients otherwise healthy at a crucial age in personal, family, social and working life.
Expected outcome 4. EU companies get a	With OAU we expect to contribute with at least one new and effective combined ATMP ready to get approvals for its use in regular clinical practice. Other interested EU

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2.1.3 Impact assessment

To describe the potential impacts of OAU, the CAHS-ROI model will be used (task 1.4). This will be assessed on a timely basis during the project and included in partial and final reports.

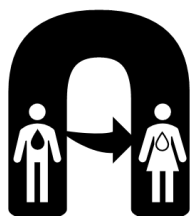
2.1.4. Barriers

Some of the barriers hampering OAU impact as well as mitigation measures are identified in the following table:

Table 6. Barriers hampering ORTHO-ALLO-UNION impacts and mitigation measures and solutions		
Type	Barriers	Mitigation measures
Social	Different ethical, social, and political views on the use of altruistic donation of bone marrow for manufacturing a combined ATMP which is finally supplied with a price. The non-for-profit production (still with a cost) or the industrial production by a Pharmaceutical Company as an issue to consider.	The consortium supports a comprehensive, all-inclusive strategy for stakeholder involvement in the product development, including regulators, patients, and healthcare professionals in the process to ensure that their viewpoint is taken into account at every stage.
Technical/ Legal	Adaptation of the product to the business plans of pharmaceutical companies in a scenario of necessary cooperation with biomaterials companies and possible parallel production through the hospital exemption pathway. The scarce regulatory precedents on combined ATMP adds uncertainties to the approval process.	the consortium will study the regulatory and exploitation pathways with regulators, providers and interested companies along the project, in order to come up with the most feasible plan to ensure wide access to an effective product (T6.5 and T6.6)
Economical	Difficulties to end with a cost-effective and affordable product for the different Health Systems.	Cell producers will work to decrease costs as much as possible and interactions with HTA and reimbursement bodies will be held along the project, to explore and proposed any innovative model of payment (T6.6)

2.2 Measures to maximise impact - Dissemination, exploitation and communication. #@COM-DIS-VIS-CDV@#

A detailed internal and external dissemination, exploitation, and communication strategic Plan (DECP) will be prepared to ensure adequate internal communication between the project partners and external communication to raise awareness and facilitate final market access. The consortium will establish the Dissemination and Exploitation and Communication Committee (DEC) which coordinates the (I) Dissemination and Outreach Activities; (II) IPR



Proposal Evaluation Form		
EUROPEAN COMMISSION Horizon Europe (HORIZON)		Evaluation Summary
		Report - Research and innovation actions

HORIZON-HLTH-2023-TOOL-05

Criterion 2 - Impact

Score: **4.50** (Threshold: 4 / 5.00 , Weight: -)

The following aspects will be taken into account, to the extent that the proposed work corresponds to the description in the work programme:

- Credibility of the pathways to achieve the expected outcomes and impacts specified in the work programme, and the likely scale and significance of the contributions from the project.
- Suitability and quality of the measures to maximise expected outcomes and impacts, as set out in the dissemination and exploitation plan, including communication activities.

The credibility of the pathways to achieve the expected outcomes and impacts is high. The project is expected to provide access to a novel, more affordable therapy for non-union bone fractures that currently represent significant challenges for health practitioners and cause a high burden for the health and social systems. Furthermore, the outcomes could pave the way for further clinical developments of similar combined products for different indications (the development of in vitro / ex vivo bone formation assays will have a significant impact and can help / boost further therapy developments). Finally, a novel business area could be generated for EU industrial partners to become more competitive in the global market.

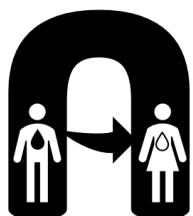
The scale and significance of the project's contribution to the expected outcomes and impacts is well addressed, with high-level quantifications of global targeted markets, but lacking some specification and quantification against more addressable areas relevant to the cATMP in question, e.g. orthopaedics.

Major potential social, economic, and legal barriers to the expected outcomes and impacts have been convincingly identified and addressed. The proposed mitigation measures are overall very good.

The dissemination plan is overall efficacious based on traditional means but lacking some degree of innovative reach. The establishment of a Dissemination Committee for coordinating and monitoring the different dissemination activities is considered a very good measure. The proposed communication plan also contains the traditional route, but improved by the inclusion of relevant target stakeholders, such as regulators, reimbursement/commissioners, policy makers, patient focus groups, and industry.

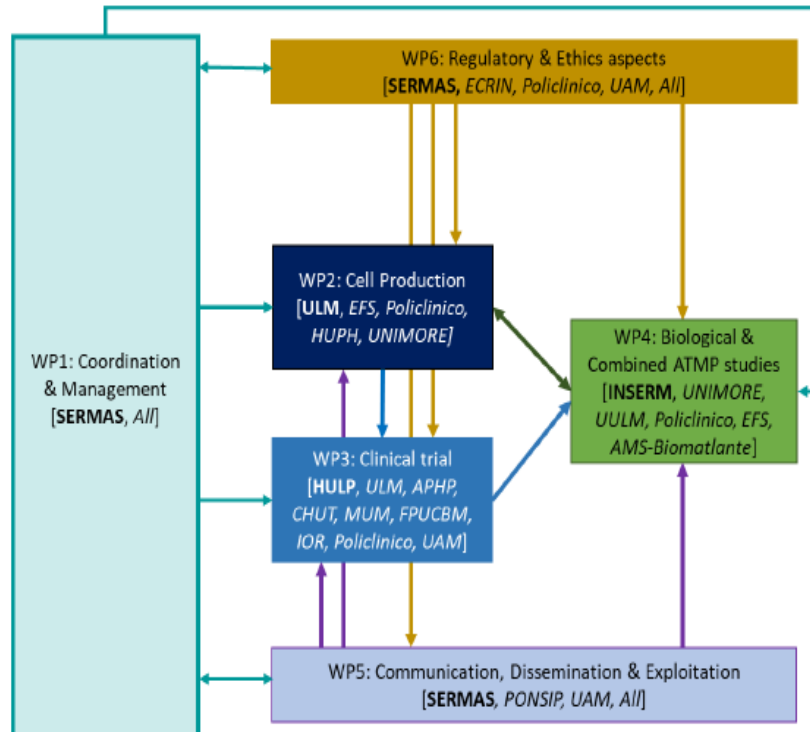
Exploitation of project results is convincingly addressed. A clear approach for exploitation is presented which involves a good identification of translational assets and agreement among the partners on what role they wish to play in commercialization. In case of failing successful exploitation, the consortium is willing to put the results on the Horizon Result Exploitation platform.

The plan for managing intellectual property issues is convincingly presented.

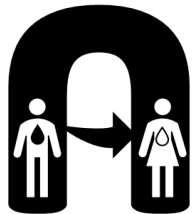
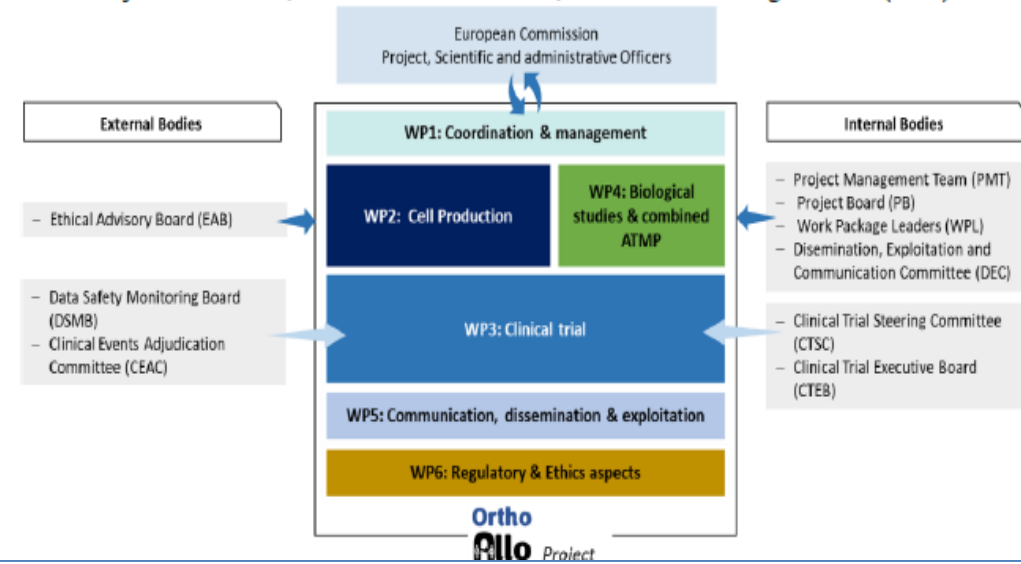


3. Quality and efficiency of the implementation @@QUA-LIT-QL@@ @@WRK-PLA-WP@@

The OAU consortium includes eighteen partner (three affiliated entities under article 8), from France, Germany, Italy, and Spain. The consortium is organised in six inter-related work packages (WP).



The management structure of the project includes individuals, internal and external bodies which would be responsible for the management decisions and the implementation of actions. Management will rely on three key functions: the Project Coordinator, the Scientific Coordinator, and the Work Package Leaders (WPL).



Work package number	2
Work package title	Production of the combined ATMP
Objectives To produce and release under Good Manufacturing Procedures (GMP) the combined ATMP. The product is composed of allogeneic, pooled expanded Mesenchymal Stromal/Stem Cells from donor bone marrow (allo-BM-MSC) combined with biomaterial as an integral part of the product. Specific objectives in a stepwise approach: 1. To enrol healthy, volunteer allogeneic MSC donors for collection of bone marrow aspirate for isolation and expansion of allogeneic BM-MSC (step 1) 2. To isolate and expand cells from these donors in a first passage (passage 0 [p0]) and perform quality controls of MSC established in p0 (safety assessment, proficiency testing for bone formation capacity and immune modulation)(step 2a) in cooperation with WP4 and WP5. 3. To optimize established cryopreservation and thawing protocols for MSC (step 2b). 4. To select MSC lines from step 2 who are fulfilling pre-specified criteria and pool aliquots of p0 of selected allogeneic donors (allogeneic pooled cell bank) for further expansion (step 3). 5. To expand MSC of selected, pooled, allogeneic MSC lines in passage 1 (p1) and transport cryopreserved aliquots of these p1 harvest to all involved manufacturing centers for preparation of clinical doses (step 4) 6. To expand aliquots of p1 in a further expansion step (p2) of the selectively pooled, allogeneic MSC line to generate sufficient of-the-shelf products available as clinical dose and cryopreserve these aliquots (step 5) 7. To establish a protocol for thawing, short term culture and adhesion protocol to generate the final product, i.e., allogeneic, pooled, <i>ex vivo</i> expanded bone marrow-MSC attached to biomaterial (step 6). 8. To establish a set of in-process controls and release controls which allows immediate release of a fresh combined ATMP available within short period after enrolment of a patient into the clinical trial OAU (this happens as part of steps 1-6). 9. To develop a cryopreserved, combined ATMP which is available off-the-shelf (step 7) To closely interact with WP3 (supply of the IMP); WP4 (proficiency testing) and WP6 (regulatory aspects).	
Description of work Lead: UULM#4. Participants: EFS#6, Policlinico#5, HUPH#2, AMS-Biomatlante#15, UNIMORE#7. This work package will ensure safe and reliable production of the investigational medicinal product (IMP), i.e., a combined ATMP consisting of allogeneic, selectively pooled bone marrow-MSC on a biomaterial. The production process is performed in compliance with GMP standards in production sites authorized to the production of ATMPs in the respective Countries (Authorization number: "ES/0961/19" for Cell Production Unit-HUPH#2; "ETI/14/M/005// ETI/14/M/003//HPF/FR/207/2014" for EFS#6, "DE_BW_01_MIA_2023_0018/DE_BW_01_IKT Ulm" for UULM #4, and "aM-51/2018" for POLICLINICO #5). Protocols for isolation and expansion of autologous GMP grade bone marrow-MSC are established in all production centres. Among other projects, this experience is based on manufacturing of MSC for clinical trials performed in REBORNE: ORTHO1 (EudraCT 2011-005441-13), ORTHO2 (EudraCT 2012-002010-39), MAXILLO1	

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donor). Also, the donor centre, which is responsible for the donor, must agree to the procedure. With this procedure, bone marrow aspiration would be performed anyway because of allogeneic hematopoietic stem cell transplantation, and the potential additional burden to donors by providing an additional small volume of bone marrow aspirate is low.

b) Healthy, volunteer donors should be asked if they agree to bone marrow aspiration with collection of about 60 ml of bone marrow aspirate. This procedure is usually performed under local anaesthesia by aspiration at the dorsal superior iliac spine. This procedure of bone marrow aspiration will be the same as in the in the previous trials.

Task 2.2: Initial expansion of bone marrow MSC and selection of those MSC cell lines to be pooled in the allogeneic MSC cell bank (Lead: UULM#4; Participants: UNIMORE#7)

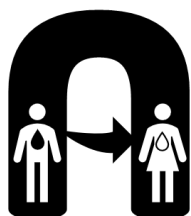
In detail, this task includes the steps 2 to 4:

- Starting material (bone marrow aspirate) of up to 20 individual allogeneic donors will be separately expanded in p0 (14 ± 2 days) by the established protocols (cultures in CellStacks in αMEM medium with human platelet lysate as growth factor cocktail to promote MSC growth). We expect a median p0 harvest of 1.5x10⁸ MSC per donor. Aliquots of these harvest will be used for in-process control for p0 MSC and proficiency tests, in particular for bone forming potential (see Task 4.1 in WP4) (step 2).
- MSC from several donors (n=5 to n=10) will be selected for further expansion (step 3). Selection criteria are detailed in task 4.1 and include (a) bone forming potential and gene expression above a pre-specified threshold, (b) accomplishment of all in-process requirements and (c) harvest of at least 1x10⁸ MSC from passage 0. If MSC from more donors fulfil these criteria, those with the highest bone forming potential will be preferred.
- Cryopreserved aliquots of p0 of the selected MSC lines will be thawed and pooled and expanded in large-scale p1 expansion (step 4). Aliquots of p0 shall be sufficient to perform up to ten p1 expansion runs (each) (5-7 days) with an expected median harvest of 5.6x10⁸ MSC each. This in total will provide the OAU MSC cell bank (MCB) of pooled allogeneic cells ready for distribution to manufacturing centers for further expansion (passage 2; manufacturing of the combined ATMP) and to UNIMORE to further confirm the selection of MSC lots.

Task 2.3: Expansion of MSC for the OAU MCB (Lead: UULM#4; Participants: EFS#6, Policlinico#5, HUPH#2, AMS-Biomatlante#15, UNIMORE#7)

This task includes step 5. This task will involve all manufacturing centres.

- Cryopreserved aliquots of the OAU MCB will be shipped to the manufacturing centres on request (based on the requested number of clinical doses according to the projected patient enrolment in the clinical trial centres in the respective country).
- Aliquots of the OAU MCB will be expanded by the established expansion method in p2 over 5-7 days to generate the cellular component of the final combined ATMP. The p2 runs shall provide a median harvest of about 5.6 x10⁸ MSC each, i.e., sufficient for two clinical doses from each p2 expansions step. Based on the numbers of MCB aliquots generated in step 4 (see task 2.2) and the expected harvest the MCB shall allow to generate about 120 clinical doses, i.e., sufficient to cover the clinical trial (including second treatment of patients with insufficient response). Loss of cells by freezing/thawing and material required for quality control assays was taken into account.
- The manufacturing centre shall serve the assigned clinical trial centres in the participating countries:
- HUPH#2 will produce cells for the clinical centres in Spain.
- EFS#6 will produce cells for the clinical centres in France.
- UULM/IKT#4 will produce cells for the clinical centres in Germany.
- POLICLINICO#5 will produce cells for the clinical centres in Italy.





"Funded by the European Union, HORIZON Research and Innovation Actions under grant agreement No. 101137464"

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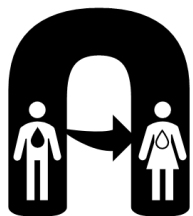
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	C	D	E	F	G	H	I	J	K	L	M	N
	Short Name	Direct Personnel Costs (A1 - A4)	Subcontracting Costs	Purchase costs - Travel and subsistence (C1)	Purchase costs - Equipment (C2)	Purchase costs - Other goods, works and service (C3)	Internally invoiced goods and services/€ (Unit costs-usual accounting practices) (D)	Internally invoiced goods and services/€ (third party giving in kind contribution) (D2)	Indirect Costs = 25% * (A + C)	Total eligible costs (A + B + C + D + E)	Total cost per beneficiary	% total budget
1		(A)	(B)	(C1)		(C3)		(D2)	(E)	(H)		
2	SERMAS	539.700,00 €	- €	- €		5.000,00 €			136.175,00 €	680.875,00 €	2.856.556,50 €	29%
3	FIBHUPMH	687.854,20 €	48.000,00 €	67.200,00 €		552.691,00 €			326.936,30 €	1.682.681,50 €		
4	FIBHULP	349.800,00 €	- €	18.600,00 €		26.000,00 €			98.600,00 €	493.000,00 €		
5	UULM	473.449,29 €	70.000,00 €	17.000,00 €		617.130,00 €	266.480,00 €		276.894,82 €	1.720.954,11 €	1.720.954,11 €	17%
6	Policlinico	288.637,46 €	- €	17.400,00 €		263.500,00 €			142.384,37 €	711.921,83 €	711.921,83 €	7%
7	EFS	205.656,00 €	142.248,00 €	10.000,00 €		362.579,00 €	13.519,00 €	55.000,00 €	144.558,75 €	933.560,75 €	933.560,75 €	9%
8	UNIMORE	279.750,00 €	- €	17.000,00 €	53.000,00 €	145.000,00 €			123.687,50 €	618.437,50 €	618.437,50 €	6%
9	INSERM	336.169,80 €	- €	15.000,00 €		105.000,00 €			114.042,45 €	570.212,25 €	570.212,25 €	6%
10	UAM	343.200,00 €	- €	6.600,00 €		32.000,00 €			95.450,00 €	477.250,00 €	477.250,00 €	5%
11	AP-HP	308.603,70 €	- €	10.000,00 €		23.000,00 €			85.400,93 €	427.004,63 €	427.004,63 €	4%
12	CHUT	96.000,00 €	- €	5.000,00 €		6.000,00 €			26.750,00 €	133.750,00 €	133.750,00 €	1%
13	MUM	169.200,00 €	- €	6.800,00 €		9.000,00 €			46.250,00 €	231.250,00 €	231.250,00 €	2%
14	IOR	185.723,70 €	- €	15.750,00 €		53.400,00 €			63.718,43 €	318.592,13 €	318.592,13 €	3%
15	CAMPUS	110.400,00 €	- €	10.000,00 €		6.000,00 €	24.000,00 €		31.600,00 €	182.000,00 €	182.000,00 €	2%
16	BIOMATLANTE	110.130,62 €	28.974,75 €	18.000,00 €		20.850,00 €			37.245,16 €	215.200,53 €	215.200,53 €	2%
17	PONSIP	93.600,00 €	- €	4.000,00 €		- €			24.400,00 €	122.000,00 €	122.000,00 €	1%
18	ECRIN	21.000,00 €	391.913,00 €	- €		5.000,00 €			6.500,00 €	424.413,00 €	474.725,50 €	5%
19	FIMABIS	35.000,00 €	- €	5.250,00 €		- €			10.062,50 €	50.312,50 €		
20	TOTAL	4.633.874,77 €	681.135,75 €	243.600,00 €	53.000,00 €	2.232.150,00 €	303.999,00 €	55.000,00 €	1.790.656,19 €	9.993.415,72 €	9.993.415,72 €	
21	% total budget	46%	7%	2%	1%	22%	3%	1%	18%			
22												
23						2.591.149,00 €						
24						26%						

...	OAU-BUDGET	1 SERMAS	2 FIBHUPH	3 FIBHULP	4 ULM	5 POLICLINICO	6 EFS	7 UNIMORE	8 INSERM	9 UAM	10 APHP	11 CHUT	12 MUM	13 IOR	14 FPCBM-R	1 ... + :
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Actualizado: 01/06/2025

Presupuesto: 01/06/2025

Presupuesto: 01/06/2025



#§RSK-MGT-RM§#

Table 3.1f: Summary of staff effort

Please indicate the number of person/months over the whole duration of the planned work, for each work package, for each participant. Identify the work-package leader for each WP by showing the relevant person-month figure in bold.

Short Name	WP1	WP2	WP3	WP4	WP5	WP6	Total Person-Months per Participant
SERMAS#1	15.00	16.80	20.40	0.00	3.00	48.00	103.20
HUPH#2	6.00	43.20	0.00	0.00	0.00	174.00	223.20
HULP#3	0.00	0.00	120.00	0.00	0.00	0.00	120.00
UULM#4	0.50	74.50	17.40	0.00			92.40
Policlinico#5	0.00	47.40	27.00	0.00	2.00	4.00	80.40
EFS#6	0.00	31.92	0.00	12.00		0.00	43.92
UNIMORE#7	0.00	2.00	0.00	92.00	2.00	0.00	96.00
INSERM#8	0.50	0.00	0.00	75.10	0.00	0.00	75.60
UAM#9	20.00	0.00	56.60	0.00	10.00	10.00	96.60
APHP#10	0.00	0.00	77.10	0.00	0.00	0.00	77.10
CHUT#11	0.00	0.00	24.00	0.00	0.00	0.00	24.00
MUM#12	0.00	0.00	42.00	0.00	0.00	0.00	42.00
IOR#13	0.00	0.00	50.40	0.00	0.00	0.00	50.40
FPCBM#14	0.00	0.00	27.00	0.00	0.00	0.00	27.00
AMS-BIOMATLANTE#15	0.00	0.00	0.00	19.08	0.00	0.00	19.08
PONSIP#16	0.00	0.00	0.00	0.00	24.00	0.00	24.00
ECRIN#17	0.00	0.00	3.00	0.00	0.00	0.00	3.00
FIMABIS#18	0.00	0.00	7.00	0.00	0.00	0.00	7.00
Total Person Months	45.00	215.82	471.90	198.18	38.00	236.00	1204.90

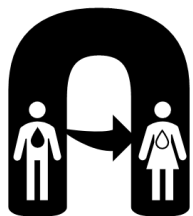
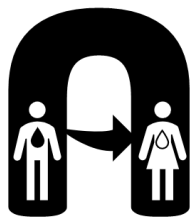


Table 3.1e: Critical risks for implementation #@RSK-MGT-RM@#

Description of risk (indicate level of (i) likelihood, and (ii) severity: Low/Medium/High)	Work package(s) involved	Proposed risk-mitigation measures
Low recruitment of BM donors in ULM (low, high)	WP2	Strategies to foster donation in Ulm, nationally acceptable back-up initiatives planned in the rest of participating member states since the start of the project
Failure to use the new signature to select good donors (low, low)	WP2-WP4	Selection of donors based on the best available clinical and laboratory parameters
Delays in setting up the master cell bank (low, high)	WP 2	Back-up initiatives planned in the rest of cell production units as soon as first issue appears
The combined final product validations suffers delays and not ready at the time to start the trial. (low, medium)	WP2-WP4	Validations test can start with excedents cell samples from ORTHOUNION project. The clinical trial to be performed (start) with manual mixture in the surgical room, as per ORTHOUNION procedure. Final validations will be a project deliverable, still complying with regulatory requirements for approval or an amendment to the IMPD after clinical trial approval.
The combined final product validations fail on favour to continue mixing both products in the surgical room.(low, low)	WP2-WP4	The clinical trial to be performed with manual mixture in the surgical room (as per ORTHOUNION procedure). Prepare an alternative process easily transferable to normal operation in hospitals, i.e. validation of a closed device for easy obtention of a ready to use combined ATMP product at the point of care
Patients reject to receive allogeneic product due to safety concerns. (low, medium)	WP3	Revision of informed consent providing additional information and further expand clinicians' knowledge about safety safeguards with allogeneic products and low impact on further needs for blood transfusions or transplantations – including regular update of published evidence of the safety of allogeneic MSC therapy.
Patients reject receive the second rescue injection of allo-BM-MSC when clinical signs indicated poor regeneration or no regeneration. (low, low)	WP3	Patients will continue the follow-up visits until the end of his/her participation in the clinical trial but will be analysed as ITT



Proposal Evaluation Form		Evaluation Summary Report - Research and innovation actions
		EUROPEAN COMMISSION Horizon Europe (HORIZON)
		HORIZON-HLTH-2023-TOOL-05

Criterion 3 - Quality and efficiency of the implementation

Score: **4.00** (Threshold: 3 / 5.00 , Weight: -)

The following aspects will be taken into account, to the extent that the proposed work corresponds to the description in the work programme:

- Quality and effectiveness of the work plan, assessment of risks, and appropriateness of the effort assigned to work packages, and the resources overall.
- Capacity and role of each participant, and the extent to which the consortium as a whole brings together the necessary expertise.

The workplan is overall very good, with a clear and coherent interconnection of logically established work packages and management plan. Responsibilities are clearly assigned, and the work plan suggests a good flow of proficiently defined deliverables and milestones. The proposed project duration is well-aligned with the duration of the intended clinical study. Nevertheless, some specific shortcomings have been identified:

- i) In WP2 the time for collection and expansion of MSCs is underestimated, leaving no buffer in case of any relevant problems,
- ii) the cell banking / production is to be established in 4 different sites. This seems to be inefficient as one centralized site could provide the MSCs for all clinical partners. This is especially relevant as one of the aims of the project is to provide an easy to access, of-the-shelf, product, which would also confer manufacturing /process reproducibility - one of the main cell-based therapy bottlenecks this project could contribute to overcome. The multiple manufacturing site also lacks justification with respect the allogeneic nature of cells and scale for the desired clinical study,
- iii) the exploitation activities in the work plan are limited. More detailed attention to future commercialization would be expected.

The allocated human resources are overall appropriate to reach the desired goals. In turn, a more rational spending of the financial resources allocated could be achieved if manufacturing would be concentrated in one single site.

Overall, the identified risks are relevant and the described mitigation measures are adequate. A minor shortcoming is the lack of managerial mitigation when dealing with the involvement of 18 partners; being quite diluted the roles and responsibilities are not always easy to track down and reaffirm.

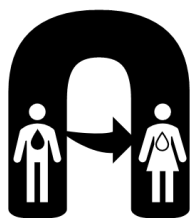
The consortium is properly multidisciplinary. It is acknowledged that public, private industry, and academic partners intend to work together to the benefit of patients. The different partners bring most of the necessary expertise into the project, with exception of significant industrial and project management expertise in the cATMP translation area.

Partners congregate very good quality infrastructures to endeavor the proposed tasks.

Scope of the application

Status: **Yes**

Comments (in case the proposal is out of scope)
Not provided



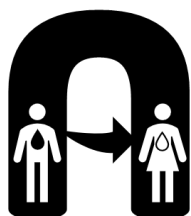


Kick-off meeting. 7-8 March 2024





Annual meeting. 6-7 March 2025





Thank you!



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