1 Publishable Summary

This section will be edited by the Commission as such. This summary report has to be updated at the end of each reporting period.

Project Acronym:	OSTEOGROW
Project full title:	Novel Bone Morphogenetic Protein-6 Biocompatible Carrier Device for Bone Regeneration
Grant Agreement no:	279239
Project website:	www.osteogrow.eu
Project logo:	

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Summary description of the project context and the main objectives

The main objective of the Osteogrow project was to develop a novel device for bone repair that is safe and cost-effective limiting the need for secondary interventions. In a time period of 60 months Osteogrow partners developed the novel osteogenic device named Osteogrow which contains biologically compatible autologous carrier made from the peripheral blood (whole blood containing device, WBCD) that significantly limits inflammatory processes common in the BMP2 based commercial bone device. A small amount of rhBMP6 is added to Osteogrow for acceleration and enhancement of bone formation, which has been confirmed in preclinical studies.

We confirmed that this simple method of “translating blood to bone” is the best approach in substituting the use of patients’ iliac crest autologous bone graft that is today available in very limited amounts. Ongoing clinical studies of Osteogrow include patients with an acute distal radius fracture (DRF) and high tibial osteotomy (HTO). In both indications Osteogrow was injected into the metaphyseal bone which has a different regenerative pathway than the diaphysis of long bones. Confirmation of metaphyseal bone regeneration safety with Osteogrow will ensure its applicability in other indications of skeletal bone defects. In this time period finalization of rhBMP6 process development and clinical batch drug substance was performed by project partner Genera Research (GEN) (Zagreb, Croatia) and BMP6 protein validation by partner Vitrology/SGS (VITR) (Dunbartonshire, UK), including sterility

testing, virus contamination and protein quality analyses. Protein stability of GLP batches and toxicology testing were conducted by MediTox (MT) (Prague, Czech Republic) and University of Zagreb School of Medicine (UZSM) (Zagreb, Croatia). Documents required for clinical study approvals were developed by Paul Regulatory Services (PRS) (Cardiff, UK), Linkoping University (LIU) (Linkoping, Sweden), Smart-Medico (SMED) (Zagreb, Croatia), Medical University of Vienna (MUW) (Wien, Austria), University of Sarajevo Clinical Center (USCC) and Clinical Hospital Centre Sisters of Mercy (KBCSM). Finally, approvals from national Ethics Committees (Croatia, Austria and Bosnia and Herzegovina), Ministry of Health in Croatia and AGES in Austria were obtained for conducting Phase I/II clinical trials at KBCSM, MUW and USCC. Interest has been expressed by leading pharmaceutical companies to participate and support the continuation of further clinical development, which might lead to the wide use of Osteogrow in human and veterinary medicine.

Description of work performed since the beginning of the project and main results achieved so far

Management and dissemination resulted in increased visibility of Osteogrow achievements and its potential for clinical use in patients with bone defects, for technology transfer and project sustainability through novel commercial opportunities and additional funding towards pre-marketing approval. Clinical part of the project has been successfully initiated and all prerequisites were assured for the appropriate conducting of this technically complex, challenging and highly innovative **First Time in Man (FTIM)** trials fully aligned with regulatory requirements and standards. Clinical trial protocols (including Informed Consent and Case Report Form) have been approved for DRF trial - GR-OG-279239-01, with amendments 1-5 by national authorities in Croatia and Bosnia and Herzegovina and HTO trial - GR-OG-279239-02, with amendments 1-3 by national authorities in Austria. IMPD (Investigational Medicinal Product Dossier) has been approved by national authorities in two versions for two indications: IMPD for distal radius fracture (submitted in Croatia and Bosnia and Herzegovina) and IMPD for high tibial osteotomy (submitted in Austria). Investigator's brochure was submitted in Austria, Croatia and Bosnia and Herzegovina together with the clinical trial protocols and IMPD and approved by national authorities. Investigational drug product (Osteogrow kit) was delivered to sites and expiration date regularly extended according to continuous incoming drug product stability results. Technical requirements like safety cabinet instalments (Austrian national agency - AGES requirement to handle Osteogrow preparation in the surgery ward according to GMP, thus transferring its preparation into a sterile laminar cabinet to prevent potential contamination), study staff personnel education and continuous monitoring of clinical trial results were fulfilled.

Presently, both studies are actively recruiting patients and the current status of the trials is summarised below:

- GR-OG-279239-01 (DRF) – Phase 1A clinical study has been completed and the report for the Independent Data Safety Monitoring Board (IDSMB) is in preparation.

Further plan includes Phase 1B (17 patients) and Phase 2 (39 patients). In Croatia – 15 patients have been recruited, 13 completed 13 weeks follow up without reported serious side effects by the PI to pharmacovigilance CRO. In Bosnia and Herzegovina – 4 patients have been recruited.

- GR-OG-279239-02 (HTO) – Phase I clinical study has been completed in which 6 out of 6 planned patients enrolled and followed for 3 to 16 weeks. IDSMB concluded that "the available safety data supports the continuation of the trial". In the Phase II clinical study active recruitment is ongoing.

Due to justified unforeseen time for obtaining necessary approvals suggesting additional technical requirements, beginning of clinical trials was delayed for 15 months in Austria, 12 months in Croatia and 5 months in Bosnia and Herzegovina. Protocol amendments of both DRF and HTO clinical trials have been obtained, and technical requirements requested by regulatory Austrian agency fulfilled. Osteogrow partners and team members are grateful to EU Commission for allowing the study extension for 12 months when all patients will be enrolled into the clinical trials and results analysed.

Expected final results and their potential impact and use (includind socio-economic impact and the wider societal implications of the project so far)

Currently there is no adequate therapy available that can accelerate long bone fractures and promote healing. Present solutions in this therapeutic area rely on expensive and side effects associated bone devices. The Osteogrow project has developed an entirely new therapy that promises to be safe and cost-effective and will decrease the need for secondary interventions.

The new therapy works by using the patient's own blood in order to create a clot when in the operating theatre. The blood is then injected with rhBMP6 and placed in the spot where new bone is needed to be created. The therapy also has the advantage of reducing inflammatory reactions which are common as a result of employing currently-used bone devices.

Within several months, the new bone piece is created, taking only millilitres of blood to create the needed clot. Beyond currently tested clinical indications, this therapy would also be employed to treat other common causes of serious pain, degenerative changes in the spinal cord, recalcitrant non-unions of the tibia, atypical fractures of the femur in patients with osteoporosis and long-time using bisphosphonates.

Phase 2 clinical trials are taking place in Zagreb, Croatia (where the project is coordinated), Sarajevo and Vienna. 19 patients underwent the pioneering new therapy at the Sisters of Charity Hospital in Zagreb, which resulted in no complications or toxic effects. In Vienna, surgeons are using the new therapy to treat patients with high tibial osteotomy to correct various deformities for preventing knee osteotomy. By the end of the trials, 95 patients will have undergone treatment with the new Osteogrow device.

The research team is also particularly proud of the fact that Osteogrow is the first major international collaborative project to develop an entirely new medical treatment led and

coordinated by clinicians in Croatia. For the first time the European Commission confided the project coordination to a Croatian medical institution, with 11 European partners from six states. They all helped, but the innovation and originality come from Zagreb, while partners enabled to do preclinical trials and move the project to clinical trials.

As the project enters its final months and clinical trials have thus far proved extremely promising, the research team is now concentrating on the commercial prospects of the new therapy. Acute bone fractures are prevalent in the EU and it is estimated that by 2050, due in part to an ageing population, 12 million bone fractures will occur on an annual basis and more than 4 million bone grafts will be needed. As such, new therapies to enhance bone formation, substitute patients' own autologous bone graft, shorten healing time and prevent non-unions will become an increasing medical requirement.

It is expected that the new therapy pioneered by Osteogrow will be market-ready within the next two to three years.