OSTEOGROW Report Summary

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Final Report Summary - OSTEOGROW (Novel Bone Morphogenetic Protein-6 Biocompatible Carrier Device for Bone Regeneration)

Executive Summary:
The main objective of the OSTEOGROW project was timely and highly relevant. It was aimed to develop a novel bone repair therapy and provide an efficacious therapeutic option for patients with bone defects. As there are more than 6 million fractures registered yearly in the EU which are projected to double by 2050 and since 5–11% result in delayed/impaired healing with well-known complications and healthcare burden, the development of a safe and cost-effective therapy is also of high socio-economic importance.

The novel therapy called OSTEOGROW is composed of an autologous blood coagulum (ABC) obtained from the patient's own blood and a biologically active ingredient recombinant human morphogenetic protein 6 (rhBMP6). OSTEOGROW is used to accelerate and enhance bone repair following fracture and it represents an original therapeutic solution for bone regeneration improved over currently available options. The biocompatible carrier ensures less inflammatory reactions and related side effects while rhBMP6 permits superior stimulation of bone formation. The main advantages of OSTEOGROW include its biocompatibility, safety and bone enhancement properties.

The multidisciplinary project consortium consists of 11 partners from 7 EU countries coming from both, academic and private sector. Main activities included production of the clinical grade rhBMP6, design and supply of the final formulation and manufacturing of the OSTEOGROW kit. Additionally, the project generated sufficient pre-clinical testing data and obtained all necessary ethics, as well as regulatory approvals for the planned clinical trials. Although at the start project experienced some delays in production of the necessary quantities of rhBMP6, resulting in the postponement of the downstream pre-clinical and clinical testing, the initial hurdles were overcome and production of sufficient amounts of protein allowed the necessary tasks to be accomplished. The protein was characterised and analysed according to the regulatory requirements and generated data supported completion of the Investigational Medicinal Product Dossier (IMPD) file. The obtained results of the animal safety testing and information on the final formulation and preparation; completed the data set required for the clinical trial applications. The expertise of the involved partners facilitated the progression of the initial idea into pre-clinical studies and the obtained results supported approvals of the clinical trials in bone healing indications. The progression of the project towards Phase I/II clinical trials in distal radius fractures (DRF) and high tibial osteotomy (HTO) was the main achievement of the project. The HTO clinical trial recruited and treated all patients planned (20/20), while the enrolment into Phase I of the DRF study is nearly completed (30/36). The absence of serious adverse events for both studies indicates that OSTEOGROW is a safe therapeutic option for bone fracture repair.

Project Context and Objectives:
Fractures in elderly lead to an excessive and often irreversible loss of quality of life. Associated complications that appear during prolonged bone fracture healing often result in a serious disability and could finally lead to an increase in mortality. Pain and immobility after osteoporotic fractures may also increase potentially irreversible frailty. The longer the healing time, the more of these problems will occur and many patients with osteoporotic fractures cannot tolerate load bearing even after...
surgery. The rate of secondary interventions after a fracture can reach 10% thus representing a significant burden for national health insurances with annual costs exceeding 10 billion €. The prevalence of bone fractures in the EU, in particular in osteoporotic patients, is around 6 million, 8 million in the U.S. and another 30 million are registered elsewhere. As the population ages, it is predicted that this number will double by 2050. Developing the novel therapies to enhance bone regeneration, which shortens the healing time and prevents non-unions, represent an urgent (yet unmet) medical need.

Standard therapy to treat bone fractures includes mechanical support either by plaster and/or mechanical devices (e.g. nails, plates and screws) and attempts to biologically support fracture healing are based on the use of either bone morphogenetic protein 2 (BMP2) or bone morphogenetic protein 7 (BMP7). These bone morphogenetic proteins are signalling molecules that initiate and accelerate bone formation, but which need to be combined with bovine collagen carrier. When bovine collagen is used with large amounts of these recombinant BMPs immunogenic and inflammatory reactions occur and cause major side effects. In addition, although BMP2 and BMP7 may be efficacious in long bone fractures (such as in the indication of a broken lower leg) they do not promote bone formation inside the cancellous bone, i.e. the type of bone that is broken most commonly, such as hip or wrist fractures.

The OSTEOGROW concept included the use of BMP6 which appeared efficacious in cancellous bone, had 2 orders of magnitude stronger effects than the “older” BMPs and was more specific in its ability to convert stem cells to bone-forming cells, suggesting a more advantageous relation between the desired effects and side effects than for BMP2 or BMP7. Another innovation of OSTEOGROW was the replacement of bovine collagen carrier with the patient’s peripheral blood coagulum as a carrier for BMP6. The goal for OSTEOGROW partners was to develop a novel osteogenic medicinal product named OSTEOGROW that is composed of a small amount of rhBMP6 added to a biologically compatible autologous carrier, used for acceleration and enhancement of bone formation following bone fracture. The expertise of the OSTEOGROW project consortium lay in pioneering contributions in the field of BMPs, with special reference to the discovery of novel BMP family members and their function in bone regeneration, as well as in the technology and the know-how in drug discovery and development. The capability of the partners included GMP production of rhBMP6, expertise in the drug formulation and design and finally, supply of the OSTEOGROW kit. The project team had the experience and generated sufficient pre-clinical data to obtain all the necessary ethics and regulatory approvals for conducting originally planned clinical trials. The indications investigated in the OSTEOGROW project were acute distal radius fractures (DRF) and high tibial osteotomy (HTO) preventing development and progress of osteoarthritis.

The project work plan divided into 8 work packages (WPs) was implemented by 11 partners from 7 EU countries coming from both the academic and the private sector. The main objectives of the WPs were:

WP1 – Process development and production of BMP6 – to finalise the rhBMP6 process development and ensure the continuous production of rhBMP6 GMP batches as well as to characterise the protein and demonstrate the efficacy and stability of rhBMP6

WP2 – Toxicology testing – to perform rigorous safety assessment of rhBMP6 and the autologous blood coagulum carrier

WP3 – Optimisation of final formulation – to optimise OSTEOGROW formulations for clinical trials and develop kit for commercial use

WP4 – Preparation for IMPD and CTA, design and performance of Phase I clinical trial – to obtain scientific advice from a respected regulatory agency on individual components and clinical trials in patients with fractures of the radius and in patients with the tibial osteotomy before submission of IMPD

WP5 – Healing of distal radial fractures and WP6 - High tibial opening wedge osteotomy (HTO) prospective randomized clinical trial – to develop protocols and documents for monitoring and analysing clinical study results, to obtain national ethics committee’s and related health authority’s clinical trial approvals, to organise stringent clinical trial monitoring and coordination in participating medical institutions to ensure most efficacious recruitment of patients

WP7 – Innovation-related activities - to effectively communicate and disseminate project results and find a partner for Phase III
clinical trial and PMA

WP8 – Project management - to ensure technical and administrative coordination, quality control of OSTEOGROW results and risk management of the project as a whole, to provide timely and efficient administrative and financial coordination of the project

The main tasks included finalisation of rhBMP6 protein production process development, its manufacturing and protein quality testing, quality assurance, as well as stability testing by partner Genera Research (GEN) (Zagreb, Croatia). Extensive testing of the cell line used, as well as the final protein, was performed by the partner Vitrology/SGS (VITR) (Dunbartonshire, UK). Safety evaluation testing on animal models was carried out by MediTox (MT) (Prague, Czech Republic) with input from University of Zagreb School of Medicine (UZSM) (Zagreb, Croatia). The OSTEOGROW kit with all components for use in clinical testing was developed by GEN and UZSM. Continuous consulting and guidance on regulatory adherence were provided by Paul Regulatory Services (PRS) (Cardiff, UK) comprising also the scientific advice requested and obtained from the Medicines and Healthcare products Regulatory Agency (MHRA), UK. Development of clinical study protocols and establishment of other required documents for executing and monitoring the clinical trials was performed by University of Zagreb School of Medicine (UZSM), 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 Centre (USCC) and Clinical Hospital Centre Sisters of Mercy (KBCSM). Upon obtaining the approvals from the national ethics committee and the regulatory agencies, implementation of Phase I/II clinical trials was initiated at MUW, USCC and KBCSM with constant coordination by UZSM and monitoring by SMED and PRS. The project coordinator (UZSM) was supported by the European Research and Project Office GmbH (EUR) (Saarbruecken, Germany) in monitoring and administrating OSTEOGROW.

The new medicinal product OSTEOGROW is expected to find a wide use in human and veterinary medicine.

Project Results:
The implementation of the project was accomplished by dividing the work into 8 distinct work packages. The main scientific and technological results including the project foregrounds are presented below.

WP1 – Process development and production of BMP6
The main result of WP1 is the production of rhBMP6 protein at large scale. For this to be achieved a robust production process was developed by using a cell line with high genetic stability, establishing a fully serum-free suspension culture in a closed production system and accomplishing high production capacity for commercial manufacturing. The pre-master cell bank (pre-MCB) was tested for sterility and stability, with special reference to viral safety. The developed rhBMP6 purification process is effective, economical and time efficient. The purified rhBMP6 protein was found to be stable in lyophilized form, biologically active and free of host cell contaminants and other tested impurities. In the beginning, the project experienced some delays during the scale-up optimisation, which delayed the production of the necessary rhBMP6 quantities. After the initial hurdles were overcome, the production of sufficient amounts of protein allowed the subsequent tasks to be accomplished. The production of gram quantities of rhBMP6 was finalised and the productivity of the producer cell line in continuous culture was found stable over several months of follow-up. Several analytical methods and bioassays have been introduced and validated to test rhBMP6, including liquid chromatography mass spectrometry, MALDI-TOF mass spectrometry, N-terminal sequencing, isoelectric focusing, protein concentration methods, SDS-PAGE, ELISA, proximity extension assay (PEA) and custom made C2C12 bioassay, enabling the sensitive and specific determination of rhBMP6 activity in vitro. The obtained pre-clinical and clinical batches of rhBMP6 protein were impurities-free, soluble and stable in formulated lyophilised form and their biological activity was preserved. The continued evaluation of rhBMP6 stability was performed according to the stability study plan of multiple batches at recommended storage temperatures, as well as accelerated and stress storage conditions providing useful data for establishing the shelf life of the final product. Analytical stability testing evaluated physical appearance, potency and purity of the drug substance and drug product at numerous time points, under defined storage conditions of temperature and humidity. All obtained data is being used for the extension of the expiration date, thus ensuring OSTEOGROW kit use in clinical trials.
WP2 - Toxicology testing
The main objectives of WP2 were to test the safety of rhBMP6, as well as of rhBMP6 in autologous blood coagulum (OSTEOGROW) in an in vitro and in vivo setting. The in vitro safety profile of rhBMP6 has been tested in human tumour cell lines and no cytotoxic effects have been displayed. Additionally, pharmacokinetic (PK) studies with GLP batches of rhBMP6 showed that the protein is rapidly cleared from the blood after systemic injection in mice, rats and rabbits. The PK studies of rhBMP6 released from coagulum implanted into the fractured femur demonstrated that only a very small amount was released into the systemic circulation and confirmed its retention at the implantation site.

The initial in vivo safety assessment plan for the OSTEOGROW project was revised in 2014 after receiving the MHRA scientific advice supportive of the reduced toxicology programme. Biocompatibility studies in rabbits have been performed by testing the local tolerance of paraosseally and intraosseally administered rhBMP6 and no issues have been detected. The safety of OSTEOGROW was also confirmed in acute and repeated dose toxicology studies in rats and rabbits which included general tolerability and immunogenicity assessment.

All the gathered information was thoroughly analysed by the animal toxicology experts and included in the documentation presented to the ethics and regulatory authorities.

WP3 - Optimisation of final formulation
The WP3 activities were crucial for establishing final formulation of rhBMP6 protein that would enable its stability and long shelf-life. Additionally, an OSTEOGROW kit was designed to ensure a convenient and easy product use for clinical testing. The final OSTEOGROW product is composed of the autologous blood coagulum containing rhBMP6 and is optimised to be used as an injectable implant. The evaluation of OSTEOGROW included: characterisation of the blood coagulum carrier, rhBMP6 binding to blood coagulum, rhBMP6 release from the carrier, carrier biomechanics, microbial purity and in-use stability. The results indicated that >90% of rhBMP6 added to the full blood remains in the blood clot, bound mainly to its extracellular matrix component. In vivo this formulation of OSTEOGROW showed significant osteoinductive activity in the rat and mouse model of ectopic bone formation and full absence of inflammation and swelling at the implantation site. The kit for using OSTEOGROW in clinical studies has been designed: its single components have been defined and it has been manufactured according to GMP requirements. The OSTEOGROW kit was supplied in sufficient quantities and with appropriate instructions for use and randomisation scheme to clinical sites. Clinical personnel was properly educated and trained in the preparation and use of the OSTEOGROW product making sure that the application is performed in a safe and reproducible manner.

WP4 - Preparation for IMPD and CTA, design and performance of Phase I clinical trial
The main objective of WP4 was to provide regulatory support to OSTEOGROW and ensure its regulatory compliance with respect to EU and national requirements. Specifically, one of the main tasks was to obtain scientific advice related to the pre-clinical and clinical development plan from a regulatory agency, as well as to prepare IMPD and Clinical Trial Application (CTA) documents to be submitted to the regulatory authorities in countries where the trials will be conducted. The OSTEOGROW partners performed the re-evaluation of all planned studies, generating detailed study plans and presenting the pre-clinical and clinical development plan to MHRA (Medicines and Health Care Regulatory Agency, UK). The MHRA scientific advice was very positive and in general fully supportive of the entire programme. Continuous work on the Investigational Medicinal Product Dossier (IMPD) and Investigator Brochure (IB) warranted the timely and suitable collection of the necessary data. All data regarding chemistry, manufacturing, control, pharmacology, toxicology and safety generated throughout the project was collected and evaluated by all participants. Clinical protocols for Phase I and Phase II studies have been designed by the consortium’s clinical partners lead by UZSM. The project experienced some delays primarily due to rhBMP6 production hurdles and related pre-clinical data availability. Also obtaining the necessary regulatory approvals took longer than originally planned, because additional technical requirements were requested. This led to a postponement of the clinical trials by 5-15 months. The clinical trial protocols for the two clinical studies were prepared according to GCP regulations and were also submitted to the CTA. The items that were prepared for the CTA included: IMPD, Investigators Brochure, EudraCT form, local application
forms and patient informed consent. Clinical Trial Applications were submitted to Croatia, Bosnia and Herzegovina and Austria and the required ethical and regulatory approvals were obtained from 2014 to 2016. Protocol amendments of both DRF and HTO clinical trials have been obtained, and the technical requirements requested by the Regulatory Austrian Agency (AGES) have been fulfilled.

**WP5 – Healing of distal radial fractures**

The clinical trial investigating OSTEOGROW in distal radius fractures (DRF) is titled: “Safety, tolerability, systemic pharmacokinetics and efficacy of a single dose of OSTEOGROW (rhBMP6 in autologous Whole Blood Coagulum Derived [WBCD] carrier) delivered locally to the fracture site in adult patients with a closed distal radius fracture (DRF)”, protocol number GR-OG-279239-01 (EudraCT number: 2014-005101-21). The trial is being conducted in two counties: Croatia and Bosnia and Herzegovina. It was the first trial of OSTEOGROW in humans. It is two-stage, one dose-level, placebo (PBO) and no-treatment controlled randomised trial. Eligible patients receive the standard of care (SoC): fracture reduction, baseline radiological evaluation, fixation with Kirschner wires and temporary immobilisation (first 5 weeks). In respect to locally delivered treatments, they are randomised (overall, 1:1:1) to:

- No-treatment control (SoC)
- PBO (SoC + WBCD- excipients, 1.0 mL)
- OSTEOGROW (SoC+WBCD-rhBMP6 250μg, 1.0 mL)

Primary objectives of the study are:

- Evaluate safety and tolerability of a single dose of OSTEOGROW delivered locally to the closed distal radius fracture site
- Evaluate systemic pharmacokinetics (PK) of rhBMP6 after single dose of OSTEOGROW delivered locally to the distal radius fracture site

Secondary objectives are:

- Explore relationship between systemic PK and systemic safety/tolerability
- Explore efficacy of a single dose of OSTEOGROW delivered locally to the distal radius fracture site in acceleration of bone healing.

Patients meeting all of the following criteria at screening are eligible for participation in the study:

1. Willing and able to provide informed consent. A signed informed consent form must be provided before any study assessments are done. Patients must be fluent in the language that is spoken by the investigator and the trial staff and in which the informed consent is written.
2. Male or female, age ≥18 years.
3. Current diagnosis of unilateral dorsally angulated closed fracture of the distal radius within the past 72 hours needing reduction and stabilisation by Kirschner wires, but no open surgery.
4. Otherwise healthy as defined by an absence of clinically relevant abnormalities identified by a detailed medical history, full physical examination (including vital signs), 12-lead ECG, and clinical laboratory tests.
5. Willing and able to be confined to the hospital/inpatient unit for at least 48h postoperatively and to comply with all other follow-up procedures according to protocol.

Patients meeting any of the following criteria at screening are not eligible for participation in the study:

1. Previous fracture or bone surgery in the currently fractured distal forearm.
2. Joint diseases that affect the function of the wrist and/or hand of the injured arm.
3. Previous treatment with bone morphogenic proteins (e.g. Ossigraft).
4. Evidence or history of the clinically significant hepatic disease (>3 x ULN for AST/ALT and total bilirubin) or other abnormalities in screening laboratory tests, which in the judgment of the investigator, would interfere with the patient’s participation in the study.
5. Presence or history of an uncontrolled, unstable, clinically significant medical condition (renal, endocrine, hepatic, respiratory, cardiovascular, hematologic, immunologic or cerebrovascular disease or malignancy) that in the judgment of the investigator may interfere with the interpretation of safety and PK evaluations.
6. Other clinically significant systemic or bone metabolic disease
7. History of symptomatic nephro- or urolithiasis within two years.
8. Diabetes mellitus.
9. Treatment with an investigational drug within 6 months or 5 half-lives (whichever is longer) preceding the first dose of study medication.
10. Screening 12-lead ECG demonstrating at least 1 of the following: Heart rate >100 bpm, QRS >120 msec, QTc > 430 msec (males), QTc >450 msec (females), or PR interval >220 msec.
11. Breastfeeding a child or planning to become pregnant within 6 months.
12. Use within 7 days prior to surgery and postoperative for the duration of the study of the following medications: NSAIDs (paracetamol accepted), corticosteroids.
13. Known serological evidence of human immunodeficiency virus (HIV) antibody.
14. History of hepatitis B infection within the past year or history of inadequately treated hepatitis C infection.
15. Known drug or alcohol abuse.
16. Donation of blood in excess of 500 mL within 56 days prior to and 1 month following surgery.
17. Current participation in any other clinical trial.

Upon obtaining necessary ethics and regulatory approvals, DRF clinical trial began in Zagreb, Croatia in December 2015 following IMP delivery to the site (KBCSM) and official site initiation. Consequently, in September 2016, following national Ethical Committee (EC) and regulatory approval in Bosnia and Herzegovina, Sarajevo clinical site joined the trial. Amendments have been submitted to the initial protocol and these amendments were then approved by the Ethics bodies and regulatory agencies in both Croatia and Bosnia and Herzegovina. To support the achievement of the OSTEOGROW project as well as WP5 objectives, the extension of the project was requested from European Commission representatives and subsequent approval enabled the continuation of the planned activities within this WP as well as further recruitment, treatment and follow-up of patients in the DRF trial. Phase IA of the trial was finalised in February 2017 (19/19 patients recruited and treated). The Independent Data Safety Monitoring Board (IDSMB) evaluated the available data and approved the study progression to stage 1B. Until the end of January 2018, 30 patients have been recruited and treated according to the study protocol: 23 patients completed 26 weeks follow up; 2 patients completed 13 weeks; 2 patients completed 9 weeks; 1 patient completed 7 weeks, and 2 patients completed week 3. The safety and tolerability data indicate no risks for OSTEOGROW in DRF indication since no adverse reactions (serious or non-serious) were reported for the DRF trial and there was no significant safety information available from any of the sites included in the trial as reported by PIs, study monitor and official Pharmacovigilance company. Preliminary radiography assessment of the fracture affected limb is being performed by four independent evaluators and the analysis of the obtained results is pending. Phase I b clinical study will be completed by joint efforts of UZSM, GENERA and KBCSM during 2018 and results will be unblinded following 13 weeks of the final patient enrolment.

WP6 - High tibial opening wedge osteotomy (HTO) prospective randomised clinical trial
The clinical trial investigating OSTEOGROW in high tibial osteotomy (HTO) is titled: “Safety, tolerability, rhBMP6 pharmacokinetics and bone healing effect of a single dose of Osteogrow (rhBMP6 in autologous Whole Blood Coagulum Derived [WBCD] carrier) in adult patients treated by high tibial wedge osteotomy (HTO) for varus deformity of the knee”, (study protocol GR-OG-279239-02, EudraCT Number: 2015-001691-21. It is a randomized, double-blind, placebo (PBO)-controlled trial conducted in 2 stages to address Phase I-II clinical development. It is being conducted at one centre in Vienna, Austria.

All enrolled patients (N=20) receive the standard of care (SoC) and are followed-up for 24 weeks with a post-trial follow-up at 18 months after the surgery (SoC time of removal of osteosynthetic elements). They are being randomised (1:1 assignment) in respect to locally administered treatment:
• PBO (SoC + WBCD with excipients); volume = 10 mL
• OSTEOGROW (SoC + 1 mg rhBMP6 in WBCD); volume = 10 mL (0.10 mg rhBMP6/mL of WBCD).

Primary objectives of the study are:
• Evaluate safety and tolerability of a single dose of OSTEOGROW delivered locally into the osteotomy site
• Evaluate systemic pharmacokinetics (PK) of rhBMP6 after single dose of OSTEOGROW delivered locally into the osteotomy site

Secondary objectives are:
• Evaluate the bone-healing acceleration effect of a single dose of OSTEOGROW delivered locally into the osteotomy site.
• Explore the relationship between systemic PK and systemic safety/tolerability.

After earning the required ethics and regulatory approvals, the HTO clinical trial began in Austria in June 2016 following IMP delivery to the Vienna site and official site initiation. To support the achievement of the OSTEOGROW project, as well as WP6 objectives, the extension of the project was requested from European Commission bodies/officers and subsequent approval enabled the continuation of the planned activities within this WP as well as further recruitment, treatment and follow-up of patients in the HTO trial. The enrolment and necessary follow-up of 6 patients into Phase I was completed in October 2016 and Independent Data Safety Monitoring Board (IDSMB) approved the study progress into Phase II in December 2016 after positive assessment of safety and tolerability. By the end of 2017, 22 patients have been included in the trial: 20 patients were treated, 17 patients completed 24 weeks follow-up; 1 patient completed 18 weeks and 2 patients completed week 3. The collected safety data indicate that there are no clinical safety concerns since no serious adverse events related to the therapy were reported. Preliminary radiography assessment is being performed by four independent evaluators and the analysis of the obtained results is pending. The x-ray evaluation results will be unblended in May 2018, following 24 weeks of the final patient enrolment.

Potential Impact:
The high prevalence of acute bone fractures in the EU, in particular in osteoporotic patients, often with delayed/impaired healing and well-known complications poses a significant socio-economic burden. Currently, with no adequate therapy for the treatment of complicated bone fractures and non-unions available, medical interventions and healing rely on expensive and side-effects associated bone devices. Through the development of a more efficient, cost-effective osteogenic medicinal product, with therapeutic efficacy and minimal side effects OSTEOGROW has contributed to finding a solution to this major medical problem. OSTEOGROW concept demonstrated the improvement of bone repair by utilizing autologous blood coagulum and minimal quantities of rhBMP6 following application directly in the fracture site. The originality of OSTEOGROW approach rests on the innovative formulation and carrier design. The new therapy works by using the patient’s own blood in order to create a clot when in the operating theatre. The implant is then injected with rhBMP6 and placed between broken bones’ ends thus stimulating the formation of a new bone where needed. The therapy also has the advantage of reducing inflammatory reactions common after application of currently-used bone devices. Within several months, the new bone is created, taking only millilitres of blood to create the needed autologous blood clot.

The development and manufacture of the OSTEOGROW kit supported the application of the concept in the clinical setting. Research indicators in the form of new and innovative clinical trial protocols and observations introduced the novel investigative procedures and enhanced the level of orthopaedic trauma surgery evidence-based medicine. The national authorities of Croatia, Bosnia and Herzegovina and Austria supported the initiation of the planned Phase I/II clinical trials in DRF and HTO indications. Clinical teams in DRF and HTO study enrolled a total of 30 and 20 patients, respectively, and provided treatment with this pioneering new therapy. Safety indicators demonstrated superior safety and tolerability of the applied OSTEOGROW product. HTO trial concluded recruitment of the needed number of patients while several more are needed to conclude Phase I in DRF study. This achievement ensured that the patients in need of a bone enhancing therapy have the access to this new and safe therapeutic option. Although, currently only a smaller number of patients from three EU countries have the possibility to participate in the studies, upon conclusion of data analyses the clinical investigation might be extended to include a larger number of patients in more countries.

Additionally, the results of the project enabled the development of the product towards new indications providing the patients with the lower back pain and in a need for spinal fusion surgery the access to this novel therapeutic option of high medical and commercial impact.
Millions of people worldwide suffer from chronic lumbar back pain, which is most often caused by degenerative spine disorders (DSD). This chronic condition has a devastating effect on the quality of life as it impairs the patient’s physical, psychological and social functioning. Due to its high incidence (lumbar back pain is the second most common medical condition after common cold) and chronic nature, lumbar back pain drains healthcare resources and, as a frequent cause of absenteeism, has a direct impact on the economy. Two and a half million patients in EU and US are annually treated for chronic back pain by spinal fusion surgery following exhaustion of conservative options to control pain. The current surgical procedures (spinal fusion), however, have a modest long-term success rate of approximately 35%. Thus a new therapy to (re)generate bone tissue for stabilizing lumbar vertebral segments would be a major advance. The new Horizon 2020 project OSTEOproSPINE (“Novel Bone Regeneration Drug Osteogrow: Therapeutic Solution for Lumbar Back Pain”, GA no. 779340) represents a successful continuation and significant upgrade of OSTEOGROW. Its aim is to obtain first clinical evidence of the efficacy and safety of two OSTEOGROW doses for posterolateral lumbar interbody fusion (PLIF), implanted in combination with bone allograft (OSTEOproSPINE), in comparison with autologous bone grafting. There have been many attempts over years in using biological posterolateral approach to treat spinal fusion conditions in man but without a long term success in achieving high rates of fusion and patients still await safe therapeutic option to restore the weight function of the spine and minimize or eliminate the back and leg pain due to compression of the spinal nerves. A positive outcome of the OSTEOproSPINE trial will pave a way for further clinical development of OSTEOGROW regeneration therapy as a bone autograft equivalent for spinal fusion. This eventually; a) could eliminate the need for autologous bone and related iliac bone injury during PLIF, and b) provide an unlimited amount of safe implant with at least similar osteogenic capacity as the autograft. This would significantly advance the treatment of a wide spectrum of lumbar spine diseases, which are treated by lumbar spine fusion. The OSTEOGROW team expects that knowledge and experience in successfully implementing all the planned activities within OSTEOGROW project will have a significant impact on the success of the new OSTEOproSPINE undertaking.

Furthermore, the project is enabling further development of participating SMEs, their R&D capacities and contributes to the new Commission’s emphasis, outlined in the Europe 2020 strategy for smart, sustainable and inclusive growth. As the first Croatian biotech, GEN promotes innovation and innovative products supporting better and faster integration of Croatian industrial/biotech sector into EU, leveraging it with European standards and adding value to the EU health research area and industry. Through the partnership within this project, SMEs involved covering the whole drug development process from innovation and production through pre-clinical development to the clinical trials already created a basis for extending the collaboration in the spinal fusion indication including even more SMEs on board in this new innovative project.

Another important achievement of OSTEOGROW is the education of young scientists through not only advanced research opportunities and hands-on training but also scientific meetings and international exposure fostering their own careers as well as institutional excellence and the long-term scientific progress in the EU.

OSTEOGROW demonstrated that the concept of an inexpensive production of a new biological entity (rhBMP6) and a pre-clinical and clinical development of a novel biocompatible therapeutic option is feasible in a short time frame and can be successfully implemented through an EU funded project. As we believe that OSTEOGROW device is superior and safer to currently used biological bone regeneration procedures, it might become an affordable new therapeutic solution for the enhancement of bone healing and prevention of bone non-unions with a very promising market potential. Last but not least, several big pharma companies have expressed their interest in the product and discussions have already started. Next round of negotiations is planned after all the results of phase I/II clinical trial will be available.

Dissemination activities
Communication and dissemination related activities resulted in increased visibility of OSTEOGROW project achievements and exploited 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. 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.
In addition to a number of peer-reviewed publications, press-releases, interviews and regular participation at scientific conferences and events, where OSTEOGROW was presented, here are a number of dissemination activities that should be mentioned in particular:

Awareness-raising of scientific and general public
• OSTEOGROW website (http://www.osteogrow.eu/)
• Creation of a number of dissemination materials including brochures, postcards, bags and pens.
• Repeated participation of the OSTEOGROW consortium at the Croatian Conference on Osteoporosis and the European Calcified Tissue Society Annual Conference.
• Researchers’ Night on September 27, 2013 in Zagreb. The researchers presented OSTEOGROWs objectives by hosting a scientific booth called “Little Bone Clinic”.
• Main achievement of the OSTEOGROW project is entering into the clinical trials with two indications, distal radial fractures and high tibial osteotomy, in 3 EU countries.
• OSTEOGROW project results were presented at the prestigious 7th International Workshop on Advances in the Molecular Pharmacology and Therapeutics of Bone and Other Musculoskeletal Diseases held in Oxford in July, 2016, where top experts in the field were very interested and positive regarding the project outcomes.
• Presentation of OSTEOGROW project results at 11th International BMP Conference held in Boston, October 2016.
• In September 2016 OSTEOGROW was widely covered in Croatian media. The project made front page in the daily newspaper Jutarnji List followed by a three page article. It was also featured on Croatian TV news and the national TV (HRT) documentary “Labirint”.
• Reporting in the EU Research magazine, issue 52 from February 2017 presented on the cover-page and described on the entire page 13. It is worth mentioning that the EU Research magazine is the World leading open access publication for scientific research and dissemination.

Networks and collaborations
• OSTEOGROW was presented at the annual meeting (December 2016/January 2017) of the FP7 large scale integrated project REBORNE.
• The coordinator, Prof. Slobodan Vukicevic (UZSM, P1) successfully applied and received the grant for the project “A novel anabolic targeted therapy for osteoporosis: BONE6-BIS” from the Croatian Science Foundation that expands the research of OSTEOGROW towards osteoporosis investigation and introduced new ideas to combine the BMP-6 protein with the know drugs (bisphosphonates) as a novel anabolic therapy for osteoporosis.

List of Websites:
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