OSTEOPROSPINE

Newsletter Issue 4 - April 2023

www.osteoprospine.eu

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Introduction

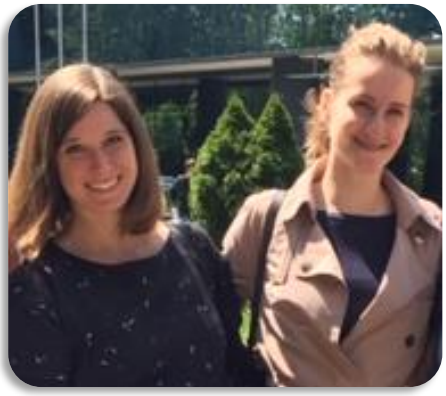
Dear colleagues and followers of the OSTEOproSPINE Newsletters,

On behalf of the project consortium, we are pleased to introduce the 4th Issue of the OSTEOproSPINE Newsletter!

We have reached the final, 6th year of the project implementation. After a successful start in 2018, we faced a lot of challenges, mostly due to the COVID-19 pandemic. Suddenly, there were many restrictions and a lot of management and administrative efforts have been invested to ensure the conduction of the OSTEOproSPINE clinical trial. Also, in 2020 the earthquake hit Zagreb and damaged buildings of the University of Zagreb School of Medicine which put another challenge in front of the project coordination team. No matter what, we have achieved all major milestones and the recruitment of required patients was finalized.

In this Issue we would like to present our important, non-clinical partners who ensure that the work in our project runs smoothly and with minimal difficulties. Also, after two years of postponing, the 13th International BMP conference was successfully hosted by the project coordinator, University of Zagreb School of Medicine in Dubrovnik, Croatia – you can find a short recap on it in this issue. We hope that you will enjoy reading it.

Lucija Rogina and Michaela Scheid
OSTEOproSPINE management team



Michaela Scheid (Eurice) and Lucija Rogina (UZSM), both part of the OSTEoproSPINE Management Team

Who we are: OSTEOproSPINE non-clinical partners

Clinres Farmacija research d.o.o., Slovenia

Clinres Farmacija research d.o.o., is a Slovenian CRO company led by Dr. Dunja Vujić-Podlipec, mag. farm., which provides all the services related to the clinical development of new medicines and medical devices and covers all aspects of services related to the registration process of medical products including global and local pharmacovigilance services in postauthorisation phase and safety in clinical trials.

Clinres Farmacija has strong references in the field of clinical trials with more than 20 years of experience. Our team of experts and proven track record make us a trusted partner in the field of Clinical Trials: legal representation, data management and biostatistics, strategic solutions, feasibility studies, site activation, clinical monitoring, site management, international project management, clinical trial application, CRF and eCRF design, medical writing and pharmacovigilance. Clinres Farmacija's involvement in the OSTEOproSPINE project includes project management, pharmacovigilance and quality assurance activities.

Our project manager coordinates the activities and discussions between all partner's representatives with regard to the clinical trial. It is crucial to ensure all processes and steps for efficient initiation of sites. It is also important to ensure operative efficiency throughout the course of the trial until final report. In the OSTEOproSPINE project, three clinical centres performed the enrolment of patients, surgeries and patient visits. All procedures have to be consistent across study sites to enable analysis of obtained results. Following our Standard Operating Procedures (SOP) for clinical trials, Investigator Site Files with study specific forms and training materials are delivered to the study sites. All activities are regularly checked by review of electronic case report form (eCRF) data, opening queries and monitoring reports. All protocol deviations are recorded and discussed in meetings, preventive and corrective measures are implemented.

The person responsible for Pharmacovigilance (PV) performs the registration of the sponsor within EudraVigilance database and registration of the IMP in the extended EudraVigilance medicinal product dictionary (XEVMPD) database.


Organisation being modified: ORG-100010339 - Genera Research d.o.o. - GENRESLTD

Organisation EudraVigilance Information

> Organisation Information

Organisation Identifier	GENRESLTD
Organisation Name	Genera Research d.o.o.
Location	LOC-100016700
	OMS Location address needs updating, please press update.
Street	Svetonedeljska Cesta 2 Kalinovica
City	Sveta Nedelja
Postal Code	10436
State	Zagrebacka Zupanija
Country	Croatia
Organisation Category	Commercial Sponsor
Gateway profile	WebTrader
Sending products	Enabled
Posting Reports	Not Authorised

The PV person shall ensure that the investigator(s) monitors all of the patients included in the clinical trial and records detailed information about all of the adverse events, in all treatment groups, regardless of suspected causal relationship to IMP. Management of cases and case processing (SAE), SAE medical review, MedDRA coding, safety data reconciliation with all sites in the OSTEOproSPINE project are part of our daily activities in the PV process. In case of Suspected Unexpected Serious Adverse Reactions (SUSARS) expedited reporting is performed. Annual safety reports containing all relevant safety information according to the corresponding guidelines are prepared and submitted to Regulatory Authorities and Ethics Committees as appropriate.

Due to quality assurance activities, audits and double visits to all three sites during last five years have been performed. In case of some discrepancies and different opinions, the Quality Assurance staff was consolidated for making a final decision.

The OSTEOproSPINE study has been going on for more than five years. During this time several changes to study protocol and protocol related documents had to be performed.
For example, due to COVID-19 pandemic and related restrictions safety measures had to be implemented and study activities had to be changed:

	Vienna	Linz	Graz
Safety measures implemented	17-MAR	17-MAR	17-MAR
On-site patient visits resumed	11-MAY	28-MAY	11-MAY
Elective surgeries resumed - Safety measures retired	27-MAY	28-MAY	27-MAY
Re-training completed & Stage 3 initiated	2-JUN	26-JUN	23-JUN

Consequently, an adjustment of the patient enrolment plan had to be made, Stage 3 started 3 months behind the plan.

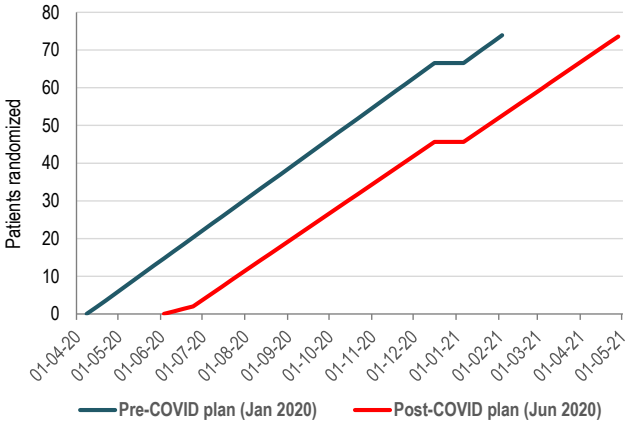


Figure: Adjustment of Stage 3 enrolment plan

Regulatory Agencies and Ethics Committees were informed and study activities, forms and records were changed. Project management ensured that all changes are communicated, documented and reported in line with principles of good clinical practice and applicable regulatory requirements. Weekly teleconferences lead by Clinres Clinical Trial Project Manager are performed with representatives of all clinical sites and partners of OSTEOproSPINE project.

Study documentation, communications, meeting's minutes are continuously stored in Trial master file.

In this final part of the study, a review of all study data and statistical evaluation will be done. All documentation will be reviewed. Detailed observation of all activities and regular communication between all project team members will be performed to ensure the finalisation of OSTEOproSPINE clinical trial on time.

QBEX – Quality by Experts, Austria

Qbex is an Austrian-based clinical development organisation with an excellent reputation for conducting complex clinical trials. Founded in 2014 by DDr. Alexander Hönel (former Head of Surveillance for Medicines and medical devices of the competent authority in Austria) with a special focus on regulatory consulting and planning of clinical studies for pharmaceutical companies of all sizes, the services have been widely expanded over the years. Today, the QBEX team can draw on more than 80 years of combined experience in the conduct of clinical trials. Our experience saves our clients valuable time and budget, allowing them to focus on what they do best. QBEX is an organisation that is tailored to the individual needs of each client, from pre-clinical to all phases of clinical development for pharmaceutical, biotech and medical device companies. Qbex's services include scientific consulting planning, development consulting, feasibility studies and the full range of clinical operations including data management, biostatistics,

pharmacovigilance, quality management and medical writing. We are dedicated to assist our clients with the development of their products with a single, unified vision: the faster the clinical development stage is accomplished, the quicker novel treatments reach those who need them – the patients.

QBEX is mainly involved in the OSTEOproSpine project in the work package related to regulatory requirements. This includes obtaining and maintaining the necessary approvals for the clinical trial as well as the coordination of local and EMA Scientific advice activities.

It is a great pleasure for us to be part of this professional and experienced consortium and we hope to contribute to making OsteoGrow available to patients as soon as possible.

2KMM, Poland

2KMM is a full service, technology driven CRO with particular focus on Data Management and Biostatistics which are also key 2KMM's responsibilities in the OSTEOproSPINE project. To ensure high quality of data collected during the clinical trial, data collection is performed using individually designed electronic Case Report Forms (eCRF) prepared on the GoResearch™ platform, a web-based, validated, electronic data capture platform created by 2KMM for clinical research.

OSTEOproSPINE is one of the most challenging and complex studies supported by 2KMM so far. Over the course of the project around 10 people have been engaged in different activities which resulted in over than 1500 working hours altogether.

The eCRF itself scored a few top-level complexity metrics such as:

- 1 138 single (unique) collected data points per patient observation
- 3 322 implemented (coded) edit checks
- 79 automatic data queries,
- 11 502 eCRF forms have been filled out for 162 registered in the system patients (as of beginning of March 2023).

Other challenges come from the perspective of both planning and conducting the statistical analysis. It is a multifaceted topic. The richness of the research questions expressed in multiple endpoints, part of which form the compound primary endpoint, analyzed in a variety of ways at several timepoints, require the statistician to both propose a flexible toolset (helpful in case of potential obstacles) and effectively control the trial-level probability of making false discoveries. The nature of early-

phase trials, reflected by a relatively small number of available patients, overlaps with inevitable losses of patients' data caused by both intermittent absences and permanent study dropouts. Addressing only this very topic poses a substantial challenge, also in terms of availability of the ready-to-use statistical tools. The need for sensitivity analyses accompanying selected assessments contribute to the overall complexity.

The core team of 2KMM working on OSTEOproSPINE:

Michał Korzekwiński – Lead Data Manager, Certified Clinical Data Manager (CCDM® by Society for Clinical Data Management, scdm.org)

Jakub Domaszewicz – Data Manager, eCRF Developer, Microsoft Certified Solutions Associate (MCSA)

Adrian Olszewski – Biostatistician

Eurice – European Research and Project Office, Germany

Founded in the year 2000, Eurice - European Research and Project Office GmbH – is a leading European consultancy firm offering knowledge-intensive business services mainly related to R&I Project Design/Management, Collaborative Innovation Management and Communication & Training.

Eurice provides comprehensive support services for the planning, initiation, and implementation of large international innovation collaborative projects – with a strong involvement in EU Framework programmes such as Horizon 2020 (54 participations) and Horizon Europe (32 participations until now). Eurice is among Europe's largest R&I project management offices, with a dedicated team of more than 70 staff members across three locations in Germany and Croatia. In addition to classical project management, Eurice helps to develop and implement coherent IP strategies and supports

consortia through communication, dissemination, networking, training, as well as capacity building and sustainability planning activities.

Moreover, Eurice is the co-ordinator of two European-wide IP-flagship initiatives: the European IP Helpdesk and Horizon IP Scan. As a major training provider in the field of IP management, Eurice welcomed over 20,000 participants in its training courses in 2021/22.

Having already been a partner in the OSTEOGROW project, Eurice happily joined the OSTEOproSPINE consortium already at proposal stage. Eurice's main tasks in the project are project communication, IP management and project management support. As leader of 'WP6 Innovation Management: Communication, Dissemination and Project Sustainability', Eurice implemented a variety of communication measures (e.g., website, newsletter, media campaigns) and organized several "Exploitation Workshops" to define pathways for the commercialization of project results – going beyond the project duration.

As part of the OSTEOproSPINE Management Team, Eurice supports the coordinator UZSM in the overall project progress monitoring, financial monitoring, reporting processes, and meeting organization.

As the project is about to close in a couple of weeks, we want to express our thanks to the co-ordinator and the whole consortium for a successful and pleasant collaboration over the last years. We are happy to see that the ambitious objectives of OSTEOproSPINE have been realized – despite unexpected challenges, such as COVID-19, and promising outcomes will be translated into benefits for patients and the society as a whole.

Eurice Headquarter in St.Ingbert, Office facilities in Berlin and Office in Zagreb

Participants of the 13th International Bone Morphogenetic Protein Conference in Dubrovnik

OSTEOproSPINE – Events & Meetings Recap

13th International Bone Morphogenetic Protein Conference in Dubrovnik

We are very happy that, after postponing due to the COVID-19 pandemic, we successfully hosted the 13th International BMP Conference in Dubrovnik, Croatia from 8th to 12th of October 2022. The conference was organized by University of Zagreb School of Medicine, the Croatian Academy of Sciences and Arts, and the Scientific Centre of Excellence for Reproductive and Regenerative Medicine. The BMP field is very broad: it covers everything from basic research to translational and clinical studies with the goal to bring BMP-based therapies to patients, which is the purpose of our OSTEOproSPINE project.

Table 1. Awarded Laureates at the 13th International BMP Conference

EMBO Keynote Lecture	Carl-Henrik Heldin
Marshall R. Urist Lecture	Peter ten Dijke
Charles Huggins Lecture	Eileen Shore
BMP Scientist Appreciation Award	A. Harri Reddi Petra Knaus An Zwijsen Slobodan Vukicevic
Young Investigator Award	Tim Herpelinck Gonzalo Sanchez-Duffhues Nikola Stokovic Johanna Bolander
Best Poster Award	Wouter Dheedene Martina Rossi Viktorija Rumenović

To exchange knowledge and connect the BMP community, in 1994, A. Hari Reddi organized first International BMP conference in Baltimore, USA. This was the starting point for a series of regular BMP Conferences organised in many different international venues until today (USA, Japan, Croatia, Belgium, Germany). This one, held in Dubrovnik, was attended by more than 240 participants from North America, Europe, Asia, and Australia who got an insight into the latest achievements in basic,

translational and clinical research of BMP molecules through 75 lectures categorized into several scientific sections.

Some of presenters were awarded for their contribution to the BMP field (**Table 1**.). We are especially proud that one of the youngest OSTEOproSPINE team members, Nikola Stokovic from University of Zagreb School of Medicine, Laboratory for mineralized tissues, received a Young Investigators Award and presented the part of the laboratory work which is dedicated to the project. Also, another member of the Laboratory for mineralized tissues, Viktorija Rumenovic, was awarded for the Best Poster Award in Section 3.

Mihaela Peric from University of Zagreb School of Medicine giving a lecture

Between numerous high-quality lectures, it should be mentioned that the PI at the OSTEOproSPINE partner institution Medical University of Vienna, Univ. Prof. Dr. Reinhard Windhager presented the main results of our project in his lecture "*Clinical testing of OSTEOGROW family members in patients with long bone fractures, fracture nonunions and posterolateral spinal fusion*". Also, Mihaela Peric, PhD, one of the most important team members, presented "*Translational aspects of rhBMP6-based drug development*". Our partners from Triadelta Partners Ltd., Katarina Oreskovic, MD, PhD and Radan Spaventi, MD, PhD and Hermann Oppermann, MD from Genera Research Ltd. were part of the round table – "*Translational medicine and clinical study testing of novel drugs for rare bone diseases*".

Round table with OSTEOproSPINE partners among others. Left to right: Herman Oppermann, Radan Spaventi, Katarina Oreskovic, Susan Rhee and Jenn Lachey.

In order to connect the participants, social events as a visit to the arboretum Trsteno and a guided sightseeing tour of the old town Dubrovnik were organized in the course of the conference. They were very well attended.

The next BMP conference is planned for 2024 in the United States in 2024. We are looking forward to it!

More impressions from the BMP Conference:

Visiting arboretum Trsteno: A renaissance Dubrovnik garden owned by Croatian academy of Science and Arts.

Closing remarks and announcement of the next BMP conference by Prof. Slobodan Vukicevic, OSTEOproSPINE coordinator

5th and Final Progress Meeting

Right after the 13th International BMP conference, it was time to hold the 5th OSTEOproSPINE progress meeting. Those partners who didn't participate in the conference arrived on 12th October for the two-day meeting. As this was not only the first in-person meeting after the Corona pandemic but also the last one for the OSTEOproSPINE project, the consortium was very happy for this opportunity to discuss and prepare the final months in the project in the beautiful setting of Dubrovnik autumn season.

The OSTEOproSPINE partners at the Meeting Venue

The first meeting day was all about a recap of the conference as well as IP, dissemination, communication (WP6) and management (WP7) topics. The Eurice team gladly took the opportunity to discuss the successful review meeting that had just taken place two weeks earlier. Afterwards, the partners had a chance to learn more about the history of Dubrovnik in a guided walk around the old time and used the joint dinner for more discussions on the results of OSTEOproSPINE.

The second meeting day focused on science and sustainability: clinical as well as research activities and sustainability planning. All scientific work packages were presented by the WP leaders and the partners discussed open questions regarding the study protocols, data management and clinical trial management. Professor Windhager (MUW) presented the latest developments in the clinical trial, while Hermann Oppermann (GEN) gave a status update on the medicinal product supply. The consortium discussed the sustainability of the project in the plenary, exploring opportunities to carry on the work even after the end of OSTEOproSPINE. Mihaela Peric (UZSM) and Bernhard Liegl (QBEX) gave an overview on ethics and regulatory issues.

In the afternoon, the partners formed different working groups for in-depth discussions on the clinical trial, regulatory and ethical questions as well as data management issues. The meeting ended with more in-depth discussions during a second joint dinner in the evening.

More Impressions from our Progress Meeting in Dubrovnik:

Presentation to OSTEOproSPINE consortium partners by prof. Reinhard Windhager

Partners and experts in OSTEOproSPINE

The OSTEOproSPINE consortium brings together internationally renowned scientists with many years of experience in orthopedics, orthopedic surgeries, BMP6 research, and clinical trial management.