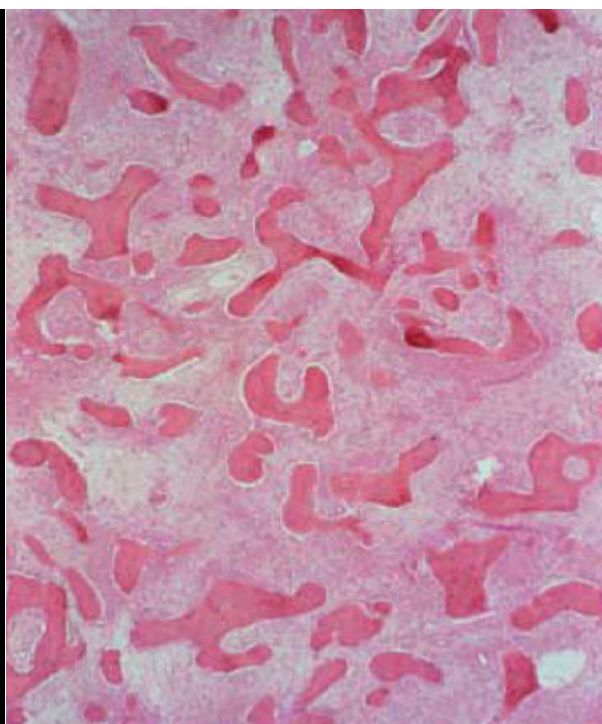


ESF EUROCORES Programme

Pan-European Clinical Trials (ECT)

Final Report



European Science Foundation (ESF)

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EUROCORES (European Collaborative Research)

The European Collaborative Research (EUROCORES) Scheme enables researchers in different European countries to develop collaboration and scientific synergy in areas where international scale and scope are required for top class science in a global context. The scheme provides a flexible framework for national basic research funding and performing organisations to join forces in supporting forefront European research in and across all scientific areas.

Until the end of 2008, scientific coordination and networking was funded through the EC FP6 Programme, under contract no. ERASCT- 2003-980409. As of 2009, the national organisations support all aspects including scientific coordination, networking and research funding.

Cover pictures:

Top: Osteosarcoma of the left knee visualised by Magnetic Resonance Imaging (MRI), and histological section.

Courtesy Professor S. Bielack

Bottom: Fibrous dysplasia of the femur before and after a 4-year bisphosphonate treatment, and histological section.

Courtesy Professor P. Orcel and Dr A. Quillard

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1. Introduction



The European Collaborative Research (EUROCORES) Scheme enshrines the goals of the European Science Foundation (ESF) of enhancing synergy at a pan-European level by providing a framework to bring together national research funding organisations and supporting interdisciplinary research in non-traditional areas, thereby opening new horizons in science. EUROCORES programmes are broad and complex in nature, with topics chosen by researchers and funded by national member organisations in an opt-in manner.

ESF oversees EUROCORES programmes from start-to-finish, which includes launching an open call for themes, assembling an international peer review panel that will select the best proposals based on scientific excellence, and establishing a ranking for organisations to choose what programmes they will finance. ESF also provides scientific and administrative support in managing the research networking and dissemination activities that ensue once that programmes are funded and launched.

The aim of the EUROCORES Scheme is to enable researchers in different European countries to develop collaboration and scientific synergies in areas where European scale and scope are required to reach the critical mass necessary for delivering top-class science that adds value in a global context. The scheme allows research organisations to jointly support networking and dissemination activities of excellent European research programmes, while maintaining the funding for research itself within their respective national borders.

The ESF provided the aforementioned scientific coordination and support for networking and dissemination activities, initially through the European Commission FP6 Programme (under contract ERASCT-2003-980409, until the end of

2008) and later through funding provided directly by participating national funding organisations. This Report features the final assessment of the Pan-European Clinical Trials (ECT) EUROCORES Programme. This EUROCORES programme was managed by the ESF Biomedical Sciences Unit under the European Medical Research Councils (EMRC). ECT was launched in January 2005 and features only two Collaborative Research Projects that are investigator-driven clinical trials (IDCTs) on rare childhood diseases: EURAMOS and PROFIDYS.

ECT is a unique programme that coordinates funding for pan-European, non-commercial, investigator-driven clinical trials addressing questions that have a strong impact on the quality of life, morbidity and mortality of the European population. The ECT programme provides a framework for the implementation of pan-European clinical trials in compliance with Good Clinical Practice (GCP) and current national legislation and European regulations. By promoting and supporting networking, the ECT programme fosters synergies with other European and international initiatives.

Training activities have contributed to the development of the necessary expertise for the implementation and management of multi-centre, pan-European academic clinical trials, ensuring patient safety in compliance with current legislation. Dissemination activities have brought together clinicians, ethicists, legal experts, policy makers, charities and funding bodies, representatives from regulatory agencies, professional associations and patient organisations to promote the best evidence-based approach for new treatments and also discuss current regulatory and ethical issues to ensure patient safety in the conduct of academic clinical trials.

The following national funding organisations have supported the ECT Programme:

- Fonds de la Recherche Scientifique (FNRS), *National Fund for Scientific Research*, Belgium
- Fonds voor Wetenschappelijk Onderzoek (FWO), *Research Foundation Flanders*, Belgium
- Forskningsstyrelsen, *Danish Research Agency*, Denmark
- Suomen Akatemia / Finlands Akademi, *Research Council for Health at the Academy of Finland*, Finland
- Institut National de la Santé et de la Recherche Médicale (Inserm), *National Institute for Health and Medical Research*, France
- Deutsche Forschungsgemeinschaft (DFG), *German Research Foundation*, Germany
- Norges Forskningsråd (NFR), *Research Council of Norway*, Norway
- ZonMw, *The Netherlands Organisation for Health Research and Development*, The Netherlands
- Medical Research Council (MRC), UK
- Assistance Publique-Hôpitaux de Paris (AP-HP), France

Details of the composition of the ECT Management Committee, the Review Panel, and the ESF-EMRC staff members involved in managing and administering this programme can be found in Annexes 1 to 3.

2.

Structure and governing bodies of ECT: EURAMOS and PROFIDYS



Management Committee:

This oversight body was integrated by representatives of each of the participating national funding agencies and the EUROCORES Programme Coordinator in Biomedical Sciences. See Annex 1 for a list of participants.

Scientific Committee:

This advisory body consists of all Project Leaders and the EUROCORES Programme Coordinator, and is responsible for proposing and agreeing on the networking and dissemination activities and for reporting to the Management Committee.

Review Panel:

This independent assessment body was formed by leading experts in the field, with a mandate from the funding agencies, who would oversee the scientific aspects of the programme and assess the final output. See Annex 2 for a list of members.

EMRC and ESF Biomedical Sciences Unit:

A Science Officer and an Administrator were permanently managing this Programme. See Annex 3 for staff in charge.

3.

Features and participants of the ECT Collaborative Research Projects



The Pan-European Clinical Trials (ECT) EURO-CORES Programme features only two Collaborative Research Projects (CRPs): EURAMOS and PROFIDYS. The information below contains data from ESF-EMRC plus data reported by both project leaders in their final reports.

3.1 EURAMOS

EURAMOS ('Maintenance treatment with interferon-alpha following intensive multi-agent chemotherapy and surgery for high-grade osteosarcoma') addresses questions evaluating therapeutic strategies in a rare disease, including the use of old drugs in a new indication. Patients with osteosarcoma, a rare bone cancer of primarily young people, are being evaluated for risk-based treatment strategies adapted to the response of the primary tumour to preoperative induction chemotherapy. This is being done in an international setting, as the rarity of the disease would otherwise preclude obtaining meaningful results.

EURAMOS is led by Professor Stefan Bielack (DE) and features 13 associated partners. This programme embodies a unique collaboration between the European and the American Osteosarcoma Study Groups. EURAMOS officially started in January 2005 and ended in May 2012, with an extension granted of 1 additional year. EURAMOS involved over 300 clinical centres in 20 countries worldwide (13 European countries, the USA, Australia, New Zealand, Bahamas, Puerto Rico, Guatemala and Canada), and at the time of reporting had recruited 2,260 patients, which is far above any other previous osteosarcoma clinical study in the world. More details may be

retrieved online, searching under the official registration number on clinicaltrials.gov website: NCT00134030. Other registry numbers that also apply: CDR0000438714, COG-AOST0331, ISRCTN67613327, EU-20530, MRC-EURAMOS1, MRC-BO08, EUDRACT-2004-000242-20, Deutsches Krebsstudienregister no. 377.

EURAMOS participants:

- **Professor Stefan Bielack (Project Leader)**
Klinikum Stuttgart – Olgahospital, Germany
- **Dr Jakob Anninga**
Leiden University Medical Centre,
The Netherlands
- **Professor Mark Lawrence Bernstein**
University of Nova Scotia / Dalhousie University,
Canada
- **Dr Catharina Dhooge**
Ghent University Hospital, Belgium
- **Dr Mikael Eriksson**
Lund University Hospital, Sweden
- **Dr Hans Gelderblom**
Leiden University Medical Centre,
The Netherlands
- **Dr Oskar Johannsson**
University Hospital of Iceland, Iceland
- **Dr Leo Kager**
Medical University of Vienna, Austria
- **Professor Thomas Kühne**
Universitätskinderspital beider Basel,
Switzerland
- **Dr Neyssa Marina**
Lucile Packard Children's Hospital at Stanford,
USA
- **Dr Zsuzsanna Papai**
Military Hospital, Budapest, Hungary
- **Professor Sigbjørn Smeland**



The junior investigators, study nurses, and data managers along with several (teaching) members of the EURAMOS Trial Management Committee taken at the third of the training courses 'Pan European Clinical Trials under current EU regulations'.

Scandinavian Sarcoma Group, Oslo University Hospital, Norway

- **Professor Ole Steen Nielsen**
Aarhus University Hospital, Denmark
- **Professor Maija Tarkkanen**
Laboratory of Cytomolecular Genetics,
University of Helsinki, Finland
- **Dr Jeremy Whelan**
European Osteosarcoma Intergroup, University
College London, United Kingdom

The 17 participating countries collaborated through three European (SSG, EOI, COSS) and one non-European (COG) osteosarcoma groups.

The Cooperative Osteosarcoma Study Group (COSS) attracted patients' data from Germany, Austria, Switzerland and Hungary. The COSS Data Centre was situated in Münster, Germany, until 2005 and is now in Stuttgart, Germany. It collected and controlled for quality the data for patients not only from Germany, but also from Austria, Switzerland, Hungary, and the Czech Republic.

The European Osteosarcoma Intergroup (EOI) grouped The Netherlands, Belgium and the UK.

The Scandinavian Sarcoma Group (SSG) gathered patients' data from Norway, Denmark, Finland and Sweden. The SSG Data Centre is situated in Lund, Sweden.

The Children's Oncology Group (COG) managed patients data from Canada and the USA. The COG Data Centre is situated in Arcadia, California, USA. It collected and curated the data from patients

from not only the USA, but also Canada, Australia, New Zealand, and selected institutions from other countries. COG, a USA National Cancer Institute-supported clinical trials group, is the world's largest organisation devoted exclusively to childhood and adolescent cancer research. The COG unites more than 7,500 experts in childhood cancer at more than 200 leading children's hospitals, universities, and cancer centres across North America, Australia, New Zealand and Europe in the fight against childhood cancer. The Children's Oncology Group has nearly 100 active clinical trials open at any given time. These trials include front-line treatment for many types of childhood cancers, studies aimed at determining the underlying biology of these diseases, and trials involving new and emerging treatments, supportive care, and survival.

Germany participated in the EURAMOS-1 trial through COSS. In addition, Germany was home to the EURAMOS Intergroup Safety Desk (EISD), responsible for global pharmacovigilance and the development of a monitoring standard operating procedure (SOP) at the Zentrum für Klinische Studien, University of Münster, and to the EURAMOS Quality of Life Data Centre (Düsseldorf, Germany, since 2008: Münster, Germany). In total, 101 COSS institutions (69.2% of 146 participating European institutions; 31.0% of total number of 326 participating institutions) registered 520 patients (46.9% of European recruitment, 23.0% of global recruitment of 2,260 patients). The

first German patient entered the trial on 14 April 2005, the last on 30 June 2011. A total of 85 German institutions participated in the trial, corresponding to 58.2% of 146 participating European institutions or 26.1% of the total number of 326 participating institutions. These German institutions registered 432 patients, corresponding to 39.0% of European recruitment or 19.1% of global recruitment. Two hundred-ninety eight of the 432 German patients were randomised for a randomisation rate of 69%.

EIDS was located at the Centre for Clinical Trials (ZKS, formerly known as Coordinating Centre for Clinical Trials, KKS) in Münster, Germany and charged with pharmacovigilance responsibilities. EISD received incoming Serious Adverse Event (SAE) reports from all participating institutions. An SAE-SOP specifically developed for this Pan-European and trans-Atlantic trial guided interactions between the Safety Desk and participating institutions, National Coordinators, Coordinating Data Centre, and – where applicable – competent authorities and Ethics Committees. Yearly safety reports were distributed to all involved bodies and to all investigators. At the time of the last safety report on September 2011, there had been 376 SAEs incl. 19 SUSARs (suspected unexpected serious adverse reactions). Until the end of April 2012, there had been 397 SAE incl. 19 SUSARs, none having had a prohibitive impact on the conduct of the trial. EISD was an important central structure to comply with pharmacovigilance reporting obligations for clinical trials as applicable since 2004. Such a structure did not exist for large multinational investigator-initiated trials and had to be newly established when EURAMOS-1 started. The central and timely overview of SAEs from all countries permits early identification of arising safety issues.

For assuring the quality management concerning the conduction of the trial in the institutions and data centres, a minimum standard for monitoring and auditing was established, as defined in manuals based on SOPs and procedures for the EURAMOS-1 trial. These demands are met under the responsibility of the National Coordinator by all participating countries. More than 90 on-site visits were performed in 11 countries and each Data Centre was audited. Findings could be clarified in cooperation with the institutions and the investigators accepted the support very well. This way of proceeding has proven feasible for an investigator-initiated trial in this range and now serves as a model for further projects.

Quality of Life (QoL) data are collected separately by an intergroup QoL Data Center at the

University of Münster, Germany, again based on a written and signed collaboration agreement. QoL is assessed at four time points during treatment and follow-up. As of end of 2011, 83.4% of all registered patients agreed to take part in the QoL evaluation. To this date, 1,406 complete QoL-Forms were available for time-point E1 (75% of all patients who had agreed initially), 885 (47%) for time point E2, 752 (40%) for time point E3 and 242 (13%) for time point E4. The decrease of numbers is mainly due to the fact that many patients have not yet reached the follow-up time points, especially E4. In addition, the non-randomised patients of COG were no longer part of the follow-up. Reduction because of non-compliance is estimated at 5-10% at every time point.

The Netherlands participated in the EURAMOS-1 trial through EOI. The first Dutch patient entered the trial on 13 October 2005, the last on 30 June 2011. A total of four Dutch institutions participated in the trial, corresponding to 2.7% of participating European institutions or 1.2% of the total participating institutions. These Dutch institutions registered 101 patients, corresponding to 9.1% of European recruitment or 4.5% of global recruitment. 65 of the 101 Dutch patients were randomised for a randomisation rate of 64%.

Belgium participated in the EURAMOS-1 trial through EOI. The first Belgian patient entered the trial on 17 November 2005, the last on 20 June 2011. A total of six Belgian institutions participated in the trial, corresponding to 4.1% of participating European institutions or 1.8% of the total participating institutions. These Belgian institutions registered 52 patients, corresponding to 4.7% of European recruitment or 2.3% of global recruitment. 44 of the 52 Belgian patients were randomised for a randomisation rate of 84%.

Norway participated in the EURAMOS-1 trial through SSG. The first patient from Norway entered the trial on 19 May 2005, the last on 8 April 2011. Three Norwegian institutions participated in the trial, corresponding to 2.1% of participating European institutions or 0.9% of the total participating institutions. These three institutions registered 41 patients, corresponding to 3.7% of European recruitment or 1.8% of global recruitment. Thirty-four of the 41 Norwegian patients were randomised for a randomisation rate of 83%.

Denmark participated in the EURAMOS-1 trial through SSG. The first patient from Denmark

entered the trial on 9 June 2006, the last on 7 June 2011. Two Danish institutions participated in the trial, corresponding to 1.4% of participating European institutions or 0.6% of the total participating institutions. These two institutions registered 27 patients, corresponding to 2.4% of European recruitment or 1.2% of global recruitment. Twelve of the 27 Danish patients were randomised for a randomisation rate of 44%.

Finland participated in the EURAMOS-1 trial through SSG. The first patient from Finland entered the trial on 19 December 2007, the last on 29 December 2008. One Finnish institution participated in the trial, corresponding to 0.7% of participating European institutions or 0.3% of the total participating institutions. This institution registered three patients, corresponding to 0.3% of European recruitment or 0.1% of global recruitment. All three Finnish patients were randomised.

The UK participated in the EURAMOS-1 trial through EOI. The British Medical Research Council (MRC) is the clinical trial sponsor of EURAMOS-1 within Europe and, specifically, the Medical Research Council Clinical Trials Unit (MRC CTU) is the Co-ordinating Data Centre (CDC) for the trial, as well as being the Data Centre for EOI trial sites. In its role as the CDC, the CTU has been responsible for overall trial management and will be responsible for conducting the trial analyses. It collected and quality-controlled the data for patients from not only the UK, but also Belgium, The Netherlands and Ireland. MRC CTU is a centre of excellence for the conduct of clinical trials, meta-analyses and epidemiological studies which is committed to strengthening and expanding the evidence-base for healthcare nationally in the UK and internationally. Key areas of research for the unit include cancer, infections and clinical trial methodology. The CTU is renowned for conducting high-impact clinical trials that focus on answering internationally important clinical questions through challenging and innovative studies. The CTU has a proven track record of osteosarcoma research and has been leading clinical trials in this rare cancer for over 25 years. It has been a key participant in the EURAMOS group since its inception. In total, 34 EOI institutions (23.3% of participating European institutions, that is, 10.4% of total participating institutions) registered 457 patients (41.2% of European recruitment, 20.2% of global recruitment of 2,260 patients). The first UK patient entered the trial on 19 September 2005, the

last on 25 May 2011. A total of 24 UK institutions participated in the trial, corresponding to 16.4% of participating European institutions or 7.3% of total participating institutions. These UK institutions registered 298 patients, corresponding to 26.9% of European recruitment or 13.2% of global recruitment. 168 of the 298 UK patients were randomised for a randomisation rate of 56%.

Canada participated in the EURAMOS-1 trial through the COG. The first Canadian patient entered the trial on 1 May 2006, the last on 12 May 2011. A total of 15 Canadian institutions participated in the trial, corresponding to 4.6% of the total participating institutions. These Canadian institutions registered 82 patients, corresponding to 3.6% of global recruitment. 46 of the 82 Canadian patients were randomised for a randomisation rate of 56%.

Sweden participated in the EURAMOS-1 trial through SSG. In total, 12 SSG institutions (8.2% of 146 participating European institutions; 3.7% of total number of 326 participating institutions) registered 119 patients (10.7% of European recruitment, 5.3% of global recruitment). The first Swedish patient entered the trial on 20 April 2005, the last on 1 April 2011. A total of six Swedish institutions participated in the trial, corresponding to 4.1% of participating European institutions or 1.8% of the total participating institutions. These Swedish institutions registered 48 patients, corresponding to 4.3% of European recruitment or 2.1% of global recruitment. 33 of the 48 Swedish patients were randomised for a randomisation rate of 69%.

Austria participated in the EURAMOS-1 trial through COSS. The first Austrian patient entered the trial on 27 February 2008, the last on 21 June 2011. A total of five Austrian institutions participated in the trial, corresponding to 3.4% of participating European institutions or 1.5% of the total participating institutions. These Austrian institutions registered 28 patients, corresponding to 2.5% of European recruitment or 1.2% of global recruitment. 20 of the 28 Austrian patients were randomised for a randomisation rate of 71%.

Switzerland participated in the EURAMOS-1 trial through COSS. One Swiss centre participated through the Children's Oncology Group. The first Swiss patient entered the trial on 16 June 2005, the last on 2 May 2011. A total of eight Swiss institutions participated in the trial, corresponding to 5.5% of participating European institutions or 2.5% of the

total participating institutions. These Swiss institutions registered 38 patients, corresponding to 3.4% of European recruitment or 1.7% of global recruitment. 24 of the 38 Swiss patients were randomised for a randomisation rate of 63%.

The USA participated in the EURAMOS-1 trial through COG. In total, 180 COG institutions (55.2% of total number of 326 participating institutions) registered 1,164 patients into EURAMOS-1 (51.5% of global recruitment of 2,260 patients). The first USA patient entered the trial on 6 December 2005, the last on 30 June 2011. A total of 153 centres from the USA (including Puerto Rico) institutions participated in the trial, corresponding to 46.9% of the total participating institutions. These USA institutions registered 1,025 patients, corresponding to 45.4% of global recruitment. 541 of the 1,025 USA patients were randomised for a randomisation rate of 53%.

Hungary participated in the EURAMOS-1 trial through COSS. The first Hungarian patient entered the trial on 27 June 2006, the last on 11 January 2011. A total of two Hungarian institutions participated in the trial, corresponding to 1.4% of participating European institutions or 0.6% of the total participating institutions. These Hungarian institutions registered 24 patients, corresponding to 2.2% of European recruitment or 1.1% of global recruitment. Nineteen of the 24 Hungarian patients were randomised for a randomisation rate of 79%.

3.2 PROFIDYS

PROFIDYS ('Prevention of bone morbidity using a bisphosphonate in fibrous dysplasia of bone') is a randomised placebo-controlled trial designed to assess the safety, tolerability and efficacy of an oral bisphosphonate in the reduction of bone pain and osteolytic lesions in patients with fibrous dysplasia of the bone, a rare congenital bone disease characterised by replacement of normal bone by fibrous tissue.

PROFIDYS is led by Professor Philippe Orcel (FR) and involves 5 clinical centres in 3 European countries (France, Belgium and The Netherlands). The PROFIDYS final report was submitted in the form of a progress report, since the Project Leader intends to recruit patients until the end of 2014. More details may be retrieved online, searching under the official identifier number on clinicaltrials.gov website: NCT00445575.

PROFIDYS participants:

- **Professor Philippe Orcel (Project Leader)**
Assistance Publique Hôpitaux de Paris, France
- **Professor Roland Chapurlat**
Hôpital Edouard Herriot, France
- **Professor Jean-Pierre Devogelaer**
Cliniques Universitaires Saint-Luc, Belgium
- **Dr Neveen A.T. Hamdy**
Leiden University Medical Centre,
The Netherlands
- **Professor Socrates E. Papapoulos**
Leiden University Medical Centre,
The Netherlands

Through the involvement of four Principal Investigators and their associated team members, PROFIDYS has yielded the following outputs:

- Website development and translation into English, Dutch and German.
- Elaboration of recommendations for clinical management and treatment of patients, currently processed for validation by the Haute Autorité de Santé in France (<http://www.has-sante.fr>).
- Establishment of "Reference Centres" for improving access to better care and networking with secondary care centres called "Competence Centres".
- Organisation of patients' meetings on three occasions (2008 and two in 2011), funded by a grant from the ESF and supported by the very active involvement of the French patients' association ASSYMCAL (<http://www.assymcal.org>).
- Submission of two grant applications to the French national hospital research program (PHRC): TEPFIDYS and TOCIDYS. The first one, TEPFIDYS, aimed at evaluating the potential interest of PET-imaging in fibrous dysplasia (diagnostic value, evaluation of the therapeutic response); unfortunately the proposal was not funded. The second, TOCIDYS, is a proof-of-concept clinical trial to evaluate the ability of an anti-interleukin-6 drug, tocilizumab, to decrease bone turnover in patients with bisphosphonate-resistant fibrous dysplasia and high bone turnover. It has been successfully evaluated and will start in late 2012.

4.

Progress of ECT Collaborative Research Projects



4.1 EURAMOS

As stated above, EURAMOS-1 is a prospective, multinational, randomised controlled clinical trial jointly run by three European (SSG, EOI and COSS) and one non-European (COG) osteosarcoma groups representing 17 countries. The ‘Individual Project (IP)/Associated Project (AP)’ model of the typical CRP does not really seem to fit such a project, as the work undertaken and the contribution of each IP and AP cannot really be ‘individual’ or ‘associated’, but might best be described as ‘joint’ or ‘integrated’.

IPs and APs worked closely together in organising a well-defined international framework for multinational recruitment in a prospective, randomised clinical trial focusing on an orphan disease, osteosarcoma, which is the most frequent bone cancer in children, adolescents, and young adults. This cancer arises in no more than 2-3 patients per million inhabitants per year, and no more than approximately half of these will be eligible for prospective trials with intensive chemotherapy and surgery. EURAMOS set out to register what amounted to be more than 2,000 patients from 17 countries, representing 600,000,000 people or almost 9% of the world population.

In order to organise and run an osteosarcoma trial on such an unprecedented scale, EURAMOS partners formed several transnational structures: a Trial Management Group (TMG) composed of investigators and data centre representatives, which handles the day-to-day running of the trial. Trial oversight is provided by an Independent Data Monitoring Committee (IDMC), composed of only independent members, and by a Trial Steering Committee (TSC), composed of independent members and representatives from the TMG. Both meet

regularly in person or via teleconference. Their respective roles are defined by charters which were developed specifically for EURAMOS-1 and which guide all procedures and decisions.

Legally, the UK MRC acts as sponsor for Europe. Parts of the sponsor’s responsibilities (such as applications and reporting to National Competent Authorities and Ethics Committees, obtaining proband insurance and sufficient national funds) were delegated to national bodies in the participating countries via a framework agreement signed by the National Coordinators (corresponding to the Principal Investigators of each IP or AP according to EUROCORES definitions) and their respective institutions.

A Coordinating Data Centre (CDC) was established at the MRC CTU. Trial data are collected and coded at each group’s Data Centre, according to a predefined Common Data Set, with each collaborating group assuming responsibility for its original member countries, and then forwarded to the CDC at regular intervals, where it is amalgamated and stored for analyses. CDC and the COG, COSS, EOI, and SSG Data Centres work closely together in assuring data accuracy and consistency and timeliness of reporting.

In addition to the infrastructure details defined previously, on-site monitoring is performed according to criteria predefined in the protocol and further specified in a Monitoring SOP. The Data Centres mentioned above audited each other on the basis of an Auditing SOP.

In order to further increase the knowledge about the trial and the regulatory framework within which it is performed, as well as to increase compliance and ‘corporate identity’, the EURAMOS group, within the EUROCORES Programme

ECT and supported by funds from the EC Sixth Framework Programme, under Contract no: ERAS-CT-2003-980409, organised three 'training courses on pan-European clinical trials' for (junior) physicians and data managers involved in the trial on a local level.

4.2 PROFIDYS

The submission of the research proposal to the ESF and to the national research institutions triggered very enthusiastic discussions between researchers. As reported in the 2009 mid-term report, challenges occurred later such as the withdrawal of the Italian partners, leading to a redistribution of efforts to maintain the project as a European multinational collaborative project.

Not all strategies were successful. Professor Jean-Pierre Devogelaer (BE) was very active and managed to start the trial in his centre at about the same time as in the French centres, that is, around mid-July 2007. In 2010, researchers from The Netherlands managed to start recruiting patients, too. By that time, however, a number of patients with fibrous dysplasia who had been waiting sometimes for several months to start the study had to be offered active treatment, which decreased the projected number of Dutch participants in the PROFIDYS study.

Two other major countries withdrew from participating in the PROFIDYS project, UK in 2010 and Germany in 2011, the main reason being the lack of support for implementation of regulatory procedures that affected the applications for funding, applications to the local or national ethics committee, and authorisation requests to the national regulatory authorities. The German Principal Investigator, who did proceed with these applications in 2010, had critical reviews from the German regulatory authority and from the German Ethics Committee, with requests for major protocol amendments which, if agreed to, would have jeopardised the whole project. German investigators had consequently no choice but to withdraw altogether from the project.

Considering the initial objectives, the European scope and interest of this collaborative project, the results may appear rather limited. However, the main scientific question of this project is still highly valid, as it remains as yet largely unanswered. Researchers therefore still have high hopes to be able to provide the scientific community with important answers regarding the management of patients with fibrous dysplasia.

Regarding the collaborative effort that PROFIDYS entailed and its derived actions in France, researchers reported that the scientific communication generated, triggered important and successful networking, stimulated a closer relationship of specialists in the field with the very active French fibrous dysplasia patients' association, ASSYMCAL, and stimulated this community to develop recommendations for the clinical management of patients with this bone disorder. The PROFIDYS project has fostered grant applications to the call for proposals for the establishment of reference centres in the context of the French government 'Rare diseases plan' in 2004. Two reference centres have been established in France: the reference centre Constitutive Bone Diseases was first created in Paris (featuring Dr Le Merrer and Professor Orcel as reference investigators on fibrous dysplasia), followed by a second reference centre for Fibrous dysplasia of bone and McCune-Albright syndrome in Lyon (featuring Professor Chapurlat). These two centres work closely with a third reference centre for Rare Endocrine Diseases of Growth, with additional special emphasis on the pediatric and endocrine care of these patients.

5.

Scientific highlights of ECT Collaborative Research Projects



5.1 EURAMOS

The trial recruited subjects from April 2005 until June 2011, during which 326 collaborating institutions from 17 countries (13 Europe – A, BE, CH, CZ, DE, DK, FIN, HUN, NL, NOR, SWE, UK; 4 overseas – AUS, CDN, NZL, USA) registered 2,260 patients (1,108 Europe, 1,152 overseas), of whom 1,332 went on to be randomised after 10 weeks of preoperative chemotherapy. This compares to less than 700 patients recruited into the largest previous prospective osteosarcoma study performed anywhere in the world. The European collaborators contributed 1,108 patients, corresponding to 49% of global recruitment. The average number of patients recruited per institution was seven, and five centres, four of them from Europe, managed to recruit more than 25 patients during the six years in which the trial recruited. The top ten recruiters accounted for 15% of total recruitment. These figures show that no single institution, and not even a group of large centres, could have managed to successfully perform such a study and exemplify the need for collaboration across a wide variety of countries and institutions.

The EURAMOS trial coincided and collided with the implementation of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of GCP in the conduct of clinical trials on medicinal products for human use. During the early years of the Directive, the number of new investigator-initiated trials in Europe dropped dramatically. Through the infrastructures described above, the EURAMOS collaborators managed to activate a very challenging project in particularly chal-

lenging circumstances. Through networking and dissemination activities, they were also able to both draw attention to the problems caused by the new European regulations (see for example ‘Clinical Trials Directive slows registration of pediatric studies’. *Lancet Oncology* 2007; 8:10) and to work together with others to develop solutions (see for example ‘Pan-European Sarcoma Trials: Moving Forward in a Climate of Increasing Economic and Regulatory Pressure’. *Sarcoma*, vol. 2007, Article ID 76405, 2007. doi:10.1155/2007/76405).

The EURAMOS trial is poised to answer a question which has intrigued investigators ever since the early 1980s, when the very strong prognostic importance of tumour response to preoperative induction chemotherapy was first described (almost three quarters of all patients with a good response, defined as less than 10% viable tumour in the resected specimen, but far less than half of all patients with a poorer response will survive their cancer): should postoperative treatment be adapted according to response and will patients benefit from such risk-adapted treatment modifications? The study is still ongoing, treatment of the last patient is scheduled to end in June 2013, so that there cannot yet be analyses or publications regarding final trial results. Results from the good responder randomisation are expected in 2013-2014, those from the poor responder randomisation in 2015-2017, depending on the number of observed events. However, lessons learned from the infrastructural and recruitment issues have already been presented at several national and international conferences.

As mentioned above, the trial is still ongoing. A publication plan with timelines has been put together by the TMG. Meanwhile, the collaborators have already published on topics such as the

measures taken to make the intergroup trial feasible on a multinational level (Marina *et al.*), on workshops and conferences (Carrle *et al.*, Thomas *et al.*) and have provided intergroup statements regarding various issues related to osteosarcoma therapy (e.g. Bielack *et al.*, Whelan *et al.*, Schwarz *et al.*)¹.

Meeting Report with co-authors from only one IP, but contributors from most IPs and APs: Carrle D, Dantonello T, Bielack S: Pan-European Sarcoma Trials: Moving Forward in a Climate of Increasing Economic and Regulatory Pressure. *Sarcoma*, vol. 2007, Article ID 76405, 2007. doi:10.1155/2007/76405

5.2 PROFIDYS

The project is still ongoing and is projected to recruit patients until the end of 2014. The final analysis is scheduled for 2017 (3 years in the protocol for patients included in the second arm of the trial).

No interim analysis has been planned and there are therefore no study results to report as yet. Researchers report that this is not an uncommon state of affairs in the field of clinical trials in rare diseases, because of the limited pool of available patients to study and the limitations attached to the premature reporting of results in small numbers of patients.

1. Marina N, Bielack S, Whelan J, Smeland S, Krailo M, Sydes MR, Butterfass-Bahloul T, Calaminus G, Bernstein M. International Collaboration is Feasible in Trials for Rare Conditions: The EURAMOS Experience. *Cancer Treat Res* 152: 339-353, 2010

2. Thomas DM, Wilhelm M, Cleton-Jansen AM, Dirksen U, Entz-Werlé N, Gelderblom H, Hassan B, Jürgens H, Koster J, Kovar H, Lankester AC, Lewis IJ, Myklebost O, Nathrath MHM, Picci P, Whelan JS, Hogendoorn PCW, Bielack S: Workshop Report on the European Bone Sarcoma Networking Meeting: Integration of Clinical Trials with Tumor Biology. *Journal of Adolescent and Young Adult Oncology*. September 2011, 1(3): 118-123

3. Bielack S, Marina N, Ferrari S, Helman LJ, Smeland S, Whelan JS, Reaman GH. Osteosarcoma: The same old drugs or more? (letter to: Meyers *et al* - Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival--a report from the Children's Oncology Group.) *J Clin Oncol* 26: 3102-3103, 2008

4. Whelan J, Patterson D, Perisoglou M, Bielack S, Marina N, Smeland S, Bernstein M. The Role of Interferons in the Treatment of Osteosarcoma. *Pediatr Blood Cancer* 54: 350-354, 2010

5. Schwarz R, Bruland O, Cassoni A, Schomberg P, Bielack S. The role of radiotherapy in osteosarcoma. *Cancer Treat Res*. 152:147-64, 2009.

6.

Integration of the Collaborative Research Projects into the ECT Programme



6.1 EURAMOS

EURAMOS was the first clinical trial to be run within the EUROCORES Programme. As a clinical trial, the infrastructures and needs differed considerably from those observed in other EUROCORES programmes. Most notably, the partners did not come in with varying areas of expertise and available technologies which were then combined into a single, synergistic project, as would be the case for most EUROCORES programmes. Rather, all partners contributed in an identical fashion, meaning they all recruited patients into a common trial. The ECT-EUROCORES then helped to build the transnational infrastructure required to perform the project.

The links to the EUROCORES programme mainly originated from very close interactions with the programme coordinators at ESF. These interactions as well as practical support by the programme coordinators were very intensive and frequent during the first several years of the ECT-EUROCORES. The Project Leader reported that they were crucial in helping them obtain support from ESF's Member Organisations (MOs).

EURAMOS and PROFIDYS came from different backgrounds. EURAMOS was developed as a joint project of four multinational trial groups representing several hundred individual institutions in Europe and abroad, all groups having already had a long-standing history of successfully running clinical trials in the disease in question, while PROFIDYS was organised from a different background and had a different scope. Interaction between EURAMOS and PROFIDYS mainly occurred at networking and dissemination events.

The intensity of interaction was modest, as not only the background, but also the type of interaction within the individual CRPs, the timelines from protocol development to trial activation, the scientific questions targeted by the two CRPs and the collaboration within the CRPs varied considerably between the two. Nevertheless, investigators from both trials interacted very closely during several training courses organised by EURAMOS with input from and participation by PROFIDYS.

When the ECT-EUROCORES call was made, there was an otherwise near total lack of cross-border funding opportunities for Pan-European clinical trials in rare diseases. Only through becoming part of the ECT-EUROCORES programme could EURAMOS be run on the appropriate scale, large enough to address its scientific questions. The ECT-EUROCORES then provided a unique platform which allowed establishing a professional infrastructure able to deal with the tremendous challenges to investigator-initiated clinical trials posed by the newly adopted EU Clinical Trials Directive 2010/20/EC. Another major advantage of EURAMOS being part of the EUROCORES programme was that this presented the collaborating European groups and IPs with the essential opportunities to meet and interact with each other and with associated partners from North America.

A curriculum for training courses for data managers and junior researchers which touched GCP and trial-specific issues was developed and three training courses were organised, which greatly helped to streamline trial activities across the multiple participating European sites and to form a sense of 'corporate identity' across borders. Another very important aspect of being part of the EUROCORES

programme was the increased visibility, which led to EURAMOS's success in implementing a Pan-European Investigator Initiated Trial soon after EU Directive 2001/20/EC attracted attention not only within the bone sarcoma community, but also far beyond. This is maybe best exemplified by several invitations to present on the clinical trial situation in Europe based on the EURAMOS experience. Opportunities to report to European legislative and regulatory bodies include oral presentations at the 2007 European Commission – European Medicines Agency (EMA) Conference on the Operation of the Clinical Trials Directive (Directive 2001/20/EC) and Perspectives for the Future, London, UK, or at the EU Parliament in Brussels at the occasion of the International Childhood Cancer Awareness Day 2011. Being able to contribute to the European Science Foundation's Forward Look 'Investigator-Driven Clinical Trials' (IDCTs) allowed to introduce the experience gained through EURAMOS into a structured process aimed at making clinical trials regulation in Europe better suited to the needs of IDCTs.

In summary, being part of the EUROCORES programme has allowed the EURAMOS collaborators to construct, implement and run a truly multinational trial in an orphan disease with a considerable amount of visibility, thereby being able to not only do research, but also to impact on science policy.

6.2 PROFIDYS

The integration into the EUROCORES Programme was limited, against the expectations of the Project Leader at the start of the project in 2002. The Project Leader found that the limited size of the project in terms of countries involved and patients recruited also played to its disadvantage. However, contacts, interactions, and meetings he had with the other ECT Project Leader, Professor Stephan Bielack (DE) from EURAMOS, were considered very interesting and constructive.

Researchers faced many difficulties and practical problems on a national basis in order to be able to start their respective trials. Researchers participated in several EUROCORES Management Committee meetings and in an EMRC Plenary Meeting in 2006, where they had the opportunity to share their experiences and to communicate the challenges encountered to the ESF staff and to the managers from the national research institutions involved.

The Project Leader reported that PROFIDYS deeply suffered from the insufficient involvement of three national Principal Investigators who initially agreed to participate. This was deemed a consequence of the lack of institutional support for coordinating the applications for regulatory procedures, and became a source of delays. Notwithstanding, the benefits of being part of the EUROCORES Programme were many in terms of collaborative initiatives and networking opportunities, as described elsewhere: the establishment of two French Reference Centres with an increasing network of associated units, the development of recommendations for the clinical management of patients with fibrous dysplasia, the constructive interactions with the patients' association, including contact of the ASSYMCAL with non-French patients leading to the organisation of patients' meetings in France in 2008 and 2011 (the latter with two meetings, in Lyon and Paris, funded by the ESF) and the design of new scientific projects.

7.

Networking, training and dissemination



7.1 EURAMOS

Networking Activities

- Second International Meeting on Future Clinical Trials for the Adjuvant Treatment of Osteosarcoma: Creating a Strategic Consensus. 27-28 February 2012, London, UK. Chaired by Jeremy Whelan. Team members participating: 30 attendees.
- First International Meeting on Future Clinical Trials for the Adjuvant Treatment of Osteosarcoma: Prioritising the Questions. 15-16 March 2010, London, UK. Chaired by Jeremy Whelan. Team members participating: 46 attendees.
- European Forum for Good Clinical Practice (EFGCP) Multidisciplinary Workshop: A Single Clinical Trial Application (CTA) in Multinational Clinical Trials - Dream or Option? 9 July 2009, Brussels, BE. Interaction with competent authorities in a pan-European investigator-driven trial: the EURAMOS-1 experience. Invited presentation by Matthew Sydes. Team members participating: 1.
- ESF Forward Look (FL) 'Investigator-Driven Clinical Trials'. In his function as Project Leader of the ECT-EURAMOS, Stefan Bielack participated in the scientific organising committee of an ESF Forward Look activity on clinical trials and co-chaired one of the five strategic themes, namely 'Management of Investigator-Driven Clinical Trials'. A strategic workshop on this theme was held in London on 29 May 2008 and its results were further discussed and refined at the Consensus Conference Investigator-Driven Clinical Trials held in Strasbourg, FR on 29-30 September 2008 which resulted in key recom-

mendations on future strategies to strengthen investigator-driven clinical trials and patient-oriented research in Europe.

- ESF FL 07-001 'Investigator-Driven Clinical Trials' Strategic Workshop: Management of Investigator-Driven Clinical Trials'. 29 May 2008, London, UK. Co-chair: Stefan Bielack.
- Pan-European Sarcoma Trials: Moving forward in a climate of increasing economic and regulatory pressure. 30 November – 2 December 2006, Stuttgart, DE. Conference chair: Stefan Bielack. 13 EURAMOS team members were presenters or session chairs, plus over 100 attendees.
- EURAMOS networking meetings. 29-30 January 2004; Frankfurt, DE. 15 September 2004, Oslo, NO. 14 June 2005, Stuttgart, DE.

Training Activities

- Third Training Course on Pan-European Clinical Trials under current EU regulations. 24-25 January 2008, London, UK. Attended by 140 data managers, study nurses and junior clinical investigators.
- Second Training Course on Pan-European Clinical Trials under current EU regulations. 5-6 October 2006, Oslo, NO.
- Managing an international clinical trial: Roles, Responsibilities and mechanisms of the EURAMOS-1 trial organisations and committees. 4-5 May 2006, London, UK. Organised by the MRC CTU. Training Sessions, Workshop and Meetings. Team members participating: 42.
- First Training Course on Pan-European Clinical Trials under current EU regulations. 2-3 December 2005, Stuttgart, DE. Attended by 150 data managers, study nurses and junior clinical investigators.

Dissemination Activities

- Pediatric Clinical Trials Session on Osteosarcoma, 1 November 2005, Paris, FR. Conference session at ECCO 13. Organised by EURAMOS. Team members participating ca. 10
- Oral and poster presentations about findings from the activation and recruitment period of EURAMOS-1 at multiple international conferences (see list below).

Not counting the training courses on European Clinical Trials, which had their own important merits but are discussed below, the most important networking activity for this CRP was the following meeting: Pan-European Sarcoma Trials: Moving forward in a climate of increasing economic and regulatory pressure, 30 November – 2 December 2006, Stuttgart, DE. A detailed meeting report was published in *Sarcoma*. The meeting brought together researchers from the osteosarcoma community with other European sarcoma experts (soft tissue and Ewing's), representatives from learned medical societies, and key stakeholders from competent authorities and funding bodies in order to discuss the challenges and solutions for Pan-European Sarcoma Trials. The meeting resulted in multiple opportunities to collaborate with partners from within and outside the EURAMOS group, and also resulted in media coverage in high impact journals, most notably two articles in *Lancet Oncology*. A further article in *Nature Medicine* followed the issues raised during the Pan-European Sarcoma Trials meeting in Stuttgart by highlighting the plight faced by European pediatric soft-tissue researchers with their new trial. Topics discussed during the meeting were taken up by the European Society of Pediatric Oncology (SIOP-Europe).

Participating researchers found that the most useful training activity was certainly the course series "Pan-European Clinical Trials under current EU regulations: A training course for data managers, study nurses and junior clinical investigators". Three such training courses were organised by the EURAMOS group in conjunction with partners (Stuttgart 2005, Oslo 2006, London, 2008). An audience that in many cases had only limited exposure to GCP and relevant European regulations was trained on how to perform multinational, GCP-conform trials. Feedback both from participants and other European trials confirms that these training exercises were of benefit not only for the day-to-day running of the EURAMOS trial, but also made things a lot easier for other pediatric oncology IDCTs.

Researchers also found that the most valuable dissemination activities were regular presentations of the progress of the EURAMOS trial at various national and international meetings and conferences. The Annual Conferences of the European Musculo-Skeletal Oncology Society (EMSOS), which cater to orthopaedic surgeons, medical and pediatric oncologists, radiologists, pathologists, basic researchers, nurses, and others, may be mentioned as an example of particularly useful platforms for dissemination through oral presentations and person-to-person discussions. As mentioned above, multiple medical specialties and support services from multiple countries and sites were involved in the trial. Being able to regularly report on the advances made regarding organisational, regulatory, and recruitment allowed for a high compliance with the trial over the course of several years. Notably, recruitment into the trial did not slack off after the few first years, as is otherwise often observed, documenting the continued interest of the bone sarcoma community in this study. An even wider (scientific) public could be informed about avenues through which multinational multicentre trials might be performed in an era of increased regulatory demands.

Publications

As previously mentioned, this is an ongoing clinical trial, the results of which are not yet known. Although the trial has completed recruitment, patients are currently in follow-up. Primary results are expected around 2013-2014 for the Good Responders randomisation and around 2015-2017 for the Poor Responders randomisation. Dissemination through peer-reviewed publications will be performed once those results are available.

Jeremy Whelan, Jane Hook, Stefan S. Bielack, Neyssa Marina, Sigbjørn Smeland, Gordana Jovic, Mark D. Krailo, Thomas Kühne, Mikael Eriksson, Trude Butterfass-Bahloul, Lisa A. Teot, Leo Kager, Hans Gelderblom, Kirsten Sundby Hall, Pancras C. W. Hogendoorn, Matthew Robert Sydes, Mark L. Bernstein, EURAMOS; EURAMOS-1 study: Recruitment, characteristics, and initial treatment of more than 2,000 patients with high-grade osteosarcoma. *J Clin Oncol* 30, 2012 (suppl; abstr 10081).

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- S. Smeland, O. Steen Nielsen, K. Sundby Hall, M. Eriksson, M. Tarkkannen, T. Böhling, L. Hjorth. EURAMOS-1, A randomized European/American Osteosarcoma Study. The 35th Meeting of the Scandinavian Sarcoma Group, Malmö, May 4-6, 2011 http://www.ssg-org.net/wp-content/uploads/2011/05/Abstracts_Malmo_2011.pdf.
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- Stefan Bielack, Mathew Sydes, Trude Butterfass-Bahloul, Gabriele Calaminus, Dorothe Carrle, Neyssa Marina, Rachel Morgan, Adelheid Oellers, Sigbjørn Smeland, Monique Tomiczek, Jeremy Whelan, Mark Bernstein: Overcoming hurdles to patient oriented clinical research: successful multinational cooperation in the European and American Osteosarcoma Study (EURAMOS1). Abstract O.127 In: SIOP 2008, Berlin, Germany, 3-6 October 2008.
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News & Views-type articles

Cannell, E. Clinical Trials Directive slows registration of pediatric studies. *Lancet Oncology* 2007; 8: 10

Cannell, E. Art exhibition brings patients' stories to life. *Lancet Oncology* 2007; 8: 109-110

Keim, B. Tied up in red tape, European trials shut down. *Nature Medicine* 2007; 13: 110.

Others

Heidi Oellers. Monitoring 'Investigator initiated trials'. Oder: So viel wie nötig. So wenig wie möglich. Mitteilungen der Deutschen Gesellschaft für Gute Forschungspraxis e.V., issue 58, März 2011, pages 9 – 10. (Review).

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Carrle D, Dantonello T, Bielack S. Meeting report: Pan-European Sarcoma Trials: Moving forward in a Climate of Increasing Economic and Regulatory Pressure. *Sarcoma* vol. 2007, article ID 76405 (Meeting Report).

Books

Jaffe N, Bruland O, Bielack S (eds.): Pediatric & Adolescent Osteosarcoma: Progress from the past, Prospects for the Future. Springer Verlag (2009) ISBN: 978-1-4419-0283-2.

Marina N, Bielack S, Whelan J, Smeland S, Krailo M, Sydes M, Bernstein M. International collaboration is feasible in trials for rare conditions: the EURAMOS experience. In: Jaffe N, Bruland O, Bielack S (eds.). Pediatric & Adolescent Osteosarcoma: Progress from the past, Prospects for the Future. Springer Verlag (2009).

Presentations in scientific meetings

Oral presentations

- European Society for Musculoskeletal Oncology EMSOS 2012, Bologna, Italy. Institutional variables in the European and American Osteosarcoma Study EURAMOS-1: Pediatric and adolescent vs. young adult osteosarcoma patients.
- Deutscher Krebskongress, 2012, Berlin, Germany. Standortbestimmung Weichteil- und Knochensarkome (invited).
- European Society for Musculoskeletal Oncology EMSOS 2011, Gent, Belgium. Osteosarcoma treatment in Europe and elsewhere is far from being centralized: Lessons from EURAMOS-1 (NCT00134030).
- The 35th Meeting of the Scandinavian Sarcoma Group 2011, Malmö, Sweden. EURAMOS-1, A randomized European/American Osteosarcoma Study.
- Japanese Society of Clinical Oncology JSCO University 2011, Nagoya, Japan: Year in review in Europe - Bone sarcomas from a pediatric perspective (invited).
- European Society for Musculoskeletal Oncology EMSOS 2010, Birmingham, UK. Age-specific recruitment variations in a large intergroup osteosarcoma study, EURAMOS-1 (NCT00134030).
- XVIth National Pediatric Oncology Congress of The Turkish Pediatric Oncology Group, 2010, Samsun, Turkey. Treatment of osteosarcoma (invited).
- 12th International Pediatric Hematology Oncology Update Meeting, 2010, Edinburgh, UK. Osteosarcoma – what is new in local and systemic therapy? (invited).
- 35th Congress of the European Society for Medical Oncology ESMO, 2010, Milan, Italy – Osteosarcoma (invited).
- Connective Tissue Oncology Society Meeting 2009, Miami, FL, USA. EURAMOS-1 – A successful transatlantic co-operation in osteosarcoma.
- European Society for Musculoskeletal Oncology EMSOS 2009, Stuttgart, Germany. The European and American osteosarcoma study group protocol, EURAMOS-1: successful transatlantic cooperation in osteosarcoma.
- Osteologie 2009 Frankfurt, Germany Osteosarkomtherapie bei Kindern und Erwachsenen (invited).
- Halbjahrestagung der Arbeitsgemeinschaft Knochentumoren, 2009, Stuttgart, Germany. Internationale multizentrische Knochensarkomstudien bei Kindern, Jugendlichen und Erwachsenen (invited).
- International Society of Pediatric Oncology SIOP 2008, Berlin, Germany. Overcoming hurdles to patient oriented clinical research: successful multinational cooperation in the European and American Osteosarcoma Study (EURAMOS1).
- International Society of Pediatric Oncology SIOP 2008, Berlin, Germany. Meet-the-Expert Session Osteosarcoma (invited).
- German Society for Pediatric Oncology and Hematology GPOH 2008, Vienna, Austria. EURAMOS1/COSS – Progress report.
- Childrens' Oncology Group COG Fall Meeting 2008, Denver, CO, USA. Workshop: EURAMOS-1 Investigators meeting.
- European Society for Musculoskeletal Oncology EMSOS 2008, Warsaw, Poland. 2008 Update on the European and American Osteosarcoma Study EURAMOS-1 (A trial conducted as part of ECT-EUROCORES).
- 33rd Congress of the European Society for Medical Oncology ESMO, 2008; Stockholm, Sweden; STATE OF THE ART APPROACH IN SELECTED CURABLE TUMORS: Bone Sarcomas (invited).
- KKSN-SYMPOSIUM Clinical trials in Europe 2007, Cologne, Germany (invited).
- EURAMOS Trial of the European and American Osteosarcoma Study Group.
- Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Onkologie 2007; Basel, Switzerland. Osteo- und Ewing Sarkom (invited).
- Nordic Society for Pediatric Hematology and Oncology NOPHO 2007, Reykjavik, Iceland The Mary Béve Symposium on Osteosarcoma (invited).
- European Society for Musculoskeletal Oncology EMSOS 2007, Porto, Portugal. Successful multinational implementation of the European and American Osteosarcoma Study EURAMOS-1 within the European Science Foundation's ECT-EUROCORES scheme.
- American Society of Pediatric Hematology-Oncology ASPHO 2007, Toronto, Canada. EURAMOS1 (presented in an osteosarcoma symposium).
- 38th Annual Conference of the International Society of Pediatric Oncology (SIOP) 2006,

- Geneva, Switzerland. Curing osteosarcoma – Progress or stagnation? (keynote lecture).
 European Society for Musculoskeletal Oncology EMSOS 2006, Moscow, Russia. Successful multinational implementation of the European and American Osteosarcoma Study EURAMOS-1 within the European Science Foundation's ECT-EUROCORES scheme.
 Connective Tissue Oncology Society CTOS 2006, Venice, Italy. EURAMOS update.
 Gemeinsame Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Onkologie 2006; Basel, Switzerland. Meet the Expert: Osteosarkome (invited).
 27. Deutscher Krebskongress, APO/GPOH-Symposium „Knochtumoren“, 2006, Berlin, Germany. Systemische Therapie des Osteosarkoms (invited).
 European Clinical Cancer Conference ECCO 2005, Paris, France (invited to organize osteosarcoma symposium). A multinational, transatlantic study in “classical” osteosarcoma patients – European and American Osteosarcoma Study EURAMOS 1. How can we perform multinational trials without breaking the law? How can coordinating data centres function in pan-European trials? Obligations & Infrastructure, as exemplified by EURAMOS 1. Who pays? Funders perspective, by the European Science Foundation.
 German Society for Pediatric Oncology and Hematology, GPOH, Berlin, Germany 2005. Durchführung von Therapiestudien unter 12. AMG-Novelle und GCP am Beispiel der EURAMOS 1 Studie der COSS-Gruppe.
 Arbeitsgemeinschaft Knochtumoren 2005, Homburg/S., Germany (invited). EURAMOS: Die neue europäisch-amerikanische Osteosarkomstudie.
 European Society for Musculoskeletal Oncology EMSOS 2005, Trieste, Italy. The European Science Foundation's Pan-European Clinical Trials (ECT) EUROCORES: EURAMOS 1: Scientific, regulatory and funding issues of a Pan-European / American osteosarcoma study.
 Sarcoma Meeting Stuttgart SMS 2005, Stuttgart, Germany. EURAMOS 1: A model for the future of clinical research in osteosarcoma.
 European Society for Musculoskeletal Oncology EMSOS 2004, Oslo, Norway (keynote talk). EMSOS-Lecture: Clinical trials - State of the art in Europe.

Posters

- American Society of Clinical Oncology ASCO 2012, Chicago, USA. EURAMOS-1 study: Recruitment, characteristics, and initial treatment of more than 2,000 patients (pts) with high-grade osteosarcoma.
 British Sarcoma Group BSG 2012, Oxford, UK. EURAMOS-1 (NCT00134030), a collaborative international randomised phase III trial in osteosarcoma: the UK experience.
 International Society of Pediatric Oncology SIOP 2011, Auckland, New Zealand. Lack of centralization and under-recruiting of young adults: lessons from Euramos-1/AOST0331 (NCT00134030).
 International Society of Pediatric Oncology SIOP 2011, Auckland, New Zealand. Quality of life (QOL) in osteosarcoma: preliminary results of the initial treatment period of EURAMOS-1 (NCT00134030).
 American Society of Clinical Oncology ASCO 2010, Chicago, IL, USA. Quality of life (QoL) in osteosarcoma: First results of the presurgery treatment period of EURAMOS-1 (NCT00134030).
 British Sarcoma Group BSG 2008, Sheffield, UK. Successful trans-Atlantic collaboration in a randomised controlled trial in osteosarcoma: EURAMOS-1 – a potential model for collaboration in rare diseases.
 National Cancer Research Institute Conference 2007, Birmingham, UK. Successful trans-Atlantic collaboration in a randomised controlled trial in osteosarcoma: EURAMOS 1 – a potential model for collaboration in rare diseases.
 European Clinical Cancer Conference ECCO 14, 2007, Barcelona, Spain. Successful trans-Atlantic collaboration in a randomised controlled trial in osteosarcoma: EURAMOS 1.
 International Society of Pediatric Oncology SIOP 2006, Geneva, Switzerland. EURAMOS1 An international randomised study in a rare cancer: Last of a soon to be extinct species or hope for the future?

Abstracts

- American Society of Clinical Oncology Annual Meeting, ASCO 2007. Abstract: International collaboration is feasible in trials for rare conditions: the EURAMOS experience.

Public outreach

Press releases

Press release regarding conference ‘Pan-European Sarcoma Trials: Moving forward in a climate of increasing economic and regulatory pressure’, 30 November – 2 December 2006, Stuttgart, Germany.

Several newspaper articles in German papers regarding conference ‘Pan-European Sarcoma Trials: Moving forward in a climate of increasing economic and regulatory pressure’, 30 November – 2 December 2006, Stuttgart, Germany.

Presentations to patient/parent groups

International Conference – Teenage Cancer Trust 2008, London, UK. EURAMOS-1 Trial Update.

DLFH-Mitgliederversammlung (German Pediatric Cancer Parent Group) 2011, Stuttgart, Germany. Knochentumoren bei Kindern und Jugendlichen.

Other activities / outputs

Websites

www.euramos.org
http://www.olgahospital-stuttgart.de/index.php?option=com_remository&Itemid=27
<http://www.ssg-org.net/treatment-protocols-and-recommendations/ongoing>

Training Courses

‘Pan-European Clinical Trials under current EU Regulations: A training course for data managers, study nurses and junior clinical investigators initiated by the EURAMOS group’. Stuttgart 2005, Oslo 2006, London, 2008.

Organisation of a national meeting for survivors of bone and soft tissue sarcomas (patients and relatives), 2009, Stuttgart, Germany, together with Deutsche Kinderkrebsstiftung.

7.2 PROFIDYS

Networking

The most important networking activity was the elaboration of recommendations for the management of patients with fibrous dysplasia and with McCune-Albright syndrome. A working group was convened under the auspices of the French Society of Rheumatology and with the initiative of the Reference Centres involved in the management of patients with this disease. The project manager conducted a systematic review of the relevant literature for the past 10 years. The literature retrieval was performed through automated and other databases with a validated search strategy using 17 keywords or keyword groups. Four meetings of the working group, including representatives of all medical specialties involved in the management of fibrous dysplasia and McCune-Albright syndrome, were held during which evidence from available literature was discussed and a state of the art document was drawn with suggested recommendations and guidelines for the management of these patients. The final document has been submitted to the French “Haute Autorité de Santé” for approval and official endorsement (currently in progress).

These recommendations, together with the major networking effort of the Reference Centre on Fibrous Dysplasia, are expected to lead to major improvements in the management of the disease and to stimulate future clinical research on various aspects of the disease. Discussions within the PROFIDYS Steering Committee have led to a proposed extension of the recommendations to other European countries. This will be further discussed after the formal endorsement of recommendations in France.

Training Activities

Professor Devogelaer accompanied by his study nurse attended a Training Course on “Pan-European Clinical Trials under current EU Regulations”, held on 2-3 December 2005 in Stuttgart, DE.

Researchers participated in a French-only teaching session during the National Congress of Rheumatology in November 2010, gathering about 50 rheumatologists. Researchers considered this was a good, informative and interactive session with 3 speakers covering the different aspects of fibrous dysplasia: pathophysiology (Philippe Orcel), diagnostic aspects (Roland Chapurlat, Caroline Rey-Jouvin, Philippe Orcel) and therapeutic aspects (Roland Chapurlat).

Dissemination

It was originally projected to run several meetings during the trial, with the participation of patients, research nurses and investigators, from all participating countries. The Project Leader reported that this never came into fruition, largely due to the serious delays in starting the trial and the subsequent withdrawal of three countries, representing six potential investigating centres.

Patients' informative meetings were organised on three occasions. The first meeting, held in April 2008 in Paris, was organised by the ASSYMCAL, where the PROFIDYS trial was presented. Many patients had not previously heard about the trial. The discussion raised much interest among patients and some expressed the wish to participate in the study and were subsequently recruited. Several patients from other European countries attended this meeting. Two additional patients' informative meetings were organised in 2011, under the auspices of the ESF and with the strong support of the ASSYMCAL which was instrumental for the success of both meetings. Belgian investigators, nurses, and patients attended the meeting in Paris. These meetings were very important for delivering clear messages on the disease, sharing experiences and for targeting issues for future research.

Publications

Articles

- Chapurlat RD, Gensburger D, Jimenez-Andrade JM, Ghilardi JR, Kelly M, Mantyh P. Pathophysiology and medical treatment of pain in fibrous dysplasia of bone. *Orphanet J Rare Dis*. 2012 May 24; 7 Suppl 1: S3.
- Chapurlat RD, Orcel P. Fibrous dysplasia of bone and McCune-Albright syndrome. *Best Pract Res Clin Rheumatol*. 2008 Mar; 22(1): 55-69. Review.
- Orcel P, Chapurlat R. [Fibrous dysplasia of bone]. *Rev Prat*. 2007 Oct 31; 57(16): 1749-55. [Article in French].
- Chanson P, Salenave S, Orcel P. McCune-Albright syndrome in adulthood. *Pediatr Endocrinol Rev*. 2007 Aug; 4 Suppl 4: 453-62. Review.
- Chapurlat RD. Medical therapy in adults with fibrous dysplasia of bone. *J Bone Miner Res*. 2006 Dec; 21 Suppl 2: P114-9. Review.
- Chapurlat R. Current pharmacological treatment for fibrous dysplasia and perspectives for the future. *Joint Bone Spine*. 2005 May; 72(3): 196-8.
- Devogelaer JP. Treatment of bone diseases with bisphosphonates, excluding osteoporosis. *Curr Opin Rheumatol* 2000; 12: 331-335.

News & Views-type articles

- Orcel P, Rey-Jouvin C, Chapurlat R. Dysplasie fibreuse et syndrome de McCune-Albright: recommandations de prise en charge. *Lettre du Rhumatologue* 2012.
- Orcel P. Dysplasie fibreuse des os et syndrome de McCune-Albright: établissement de recommandations de prise en charge. *Réflexions Rhumatologiques* 2011.
- Rey-Jouvin C, Bousson, Orcel P. Dysplasie fibreuse des os et syndrome de McCune Albright: établissement de recommandations de prise en charge. In Kahn MF *et al.* (eds), *L'Actualité rhumatologique* 2011. Elsevier, Paris.
- Orcel P. Dysplasie fibreuse des os: une nouvelle approche thérapeutique? *Rhumatos*, Avril 2010; vol. 7: numéro 57.
- Orcel P, Chapurlat R. Dysplasie fibreuse des os: perspectives thérapeutiques. *Médecine Clinique endocrinologie & diabète*, n° 30, Septembre-Octobre 2007.
- Orcel P, Chapurlat R. Dysplasie fibreuse des os: acquisitions récentes. *Opinions actuelles en rhumatologie*. Edimark, 2003.

Books

- Orphan Skeletal Diseases – *Baillière's Best Practice & Research Clinical Rheumatology*, Elsevier, London, 2008.
- Orcel P, Bousson V, Laredo JD. Dysplasie fibreuse. In Laredo, JD, Wybier M, Bousson V (eds). *Radiologie Ostéoarticulaire*. Sauramps, Paris, 2012. (*in preparation*)

Presentations in scientific meetings

Oral presentations

- Scientific communication: Malines C, Chapurlat R, Bousson V, Le Merrer M, Baujat G, Orcel P, pour le groupe de travail du PNDS. Dysplasie fibreuse des os et syndrome de McCune-Albright: établissement de recommandations de prise en charge sous l'égide de la SFR. 23^e Congrès Français de Rhumatologie, Paris - La Défense, 28 novembre – 1^{er} décembre 2010. Communication R01. *Rev Rhum* 2010; 77S: A129.
- Invited lecture: Roland Chapurlat: Treatment of fibrous dysplasia of bone, British Endocrine Society, Harrogate, UK, April 7-11, 2008.
- Invited lecture: Roland Chapurlat: Treatment of fibrous dysplasia of bone in adults, Paget's Foundation Meeting, Fort Lauderdale, Florida, USA, January, 12-14, 2006.

Invited Lecture: Philippe Orcel: Fibrous dysplasia Mediterranean Society for Osteoporosis and other Skeletal Disorders, IIIrd International Congress, Naples, Italy, October 1-3, 2005.

Posters

Orcel P, Malines C, Bousson V, Le Merrer M, Baujat G, Chapurlat R, for the working group. French guidelines for the management of fibrous dysplasia and McCune-Albright syndrome. Third joint meeting of the European Calcified Tissue Society and the International Bone and Mineral Society, Athens, Greece, 7-11 May 2011.

Orcel P, Rolland D, Sorel M, Vigneron AM. Premiers patients traités par risédronate pour une dysplasie fibreuse: action antalgique rapide. 18^e Congrès français de Rhumatologie, Paris-La Défense, France, 4-7 Décembre 2005, affiche Me51. *Rev Rhum* 2005; 72: 1118.

Others

PROFIDYS newsletter featuring the progress of the trial, disseminated to all investigators, and posted on the website.

Websites

<http://www.dysplasie-fibreuse-des-os.info>
(French)

<http://www.dysplasie-fibreuse-des-os.info/english>
(English)

Under construction:

<http://www.dysplasie-fibreuse-des-os.info/german> (German)

<http://www.dysplasie-fibreuse-des-os.info/dutch>
(Dutch)

Lectures

Orcel P. La dysplasie fibreuse en 2009: actualités sur la pathogénie et la thérapeutique. Journées de l'Hôtel Dieu de France. Beyrouth, Liban, 4 April 2009.

Orcel P. La dysplasie fibreuse en 2009. Congrès de la Ligue Tunisienne Anti-Rhumatismale. Tunis, Tunisie, 2 May 2009.

Orcel P. Series of 4 lectures on Fibrous dysplasia in Québec, Canada (Québec City, Trois-Rivières, Sherbrooke and Montréal), October 2010.

Orcel P. Lectures in local Continuing Medical Educational (CME) meetings or Rheumatology departments meetings in 2009, 2010, 2011.

Teaching session

French congress of Rheumatology 2010. Full 1-hour session on fibrous dysplasia with talks by P. Orcel and R. Chapurlat. Paris, 28 November 2010.

Patients' meetings

Meeting organised by ASSYMCAL, Paris, 19 April 2008. Presentation of the PROFIDYS trial.

Patients' meeting organized by the National Fibrous Dysplasia Reference centre, Lyon, 16 April 2011 (networking activity of the PROFIDYS project with financial support by ESF).

Patients' meeting organised by the National Constitutive bone diseases Reference centre, Paris, 2 July 2011 (networking activity of the PROFIDYS project with financial support by ESF).

8. Overall self-assessment and follow-up



8.1 EURAMOS

The European and American Osteosarcoma Study (EURAMOS) completed recruitment into the largest osteosarcoma study ever performed, a study of 2,260 patients, within just over six years from registration of the first patient. This was achieved despite having to deal with the consequences of the varying stages of implementation of the European Clinical trials Directive 2001/20/EC into national law encountered during the early stages of the trial. On the downside, the measurement of angiogenic factors in serum which was envisioned as part of a companion study did not materialise.

As a whole, the planned processes for trial management as well as the efficacy and safety monitoring procedures worked very well and the processes and infrastructures announced in section 3 and section 4 of the full proposal submitted to ESF were implemented very successfully. This was experienced as a positive and encouraging example by other researchers from pediatric oncology and elsewhere who were also trying to build systems which would allow them to perform multicentre trials in the era of the EU Directive.

Initially, it had been estimated that EURAMOS would recruit 400 patients per year, of whom 360 would be randomised, amounting to only four years of recruitment. Two main factors contributed to the necessary lengthening of the time the trial had to remain open. First, it was not possible to open the trial at the same time in all participating countries. This was due to varying regulatory challenges posed by national competent authorities, as well as to funding issues in those countries whose ESF Member Organisations had opted out of the EUROCORES. As a consequence, the first

country (Germany, funded by DFG) started registration in April 2005, while the last of the European applicants of the full proposal, those from Austria (not funded by their Member Organisation) were only able to start registration in February 2008. Nevertheless, the observed average recruitment rate of over 360 per year is quite close to the projection ($n=400$), as is the number of 146 European sites contributing patients ($n=185$ projected in the full proposal).

Researchers did, however, encounter a much higher rate of non-randomisation than the anticipated 10%, namely 41%. The main cause for this is that randomisation was performed only after surgery, after 3 months of intensive treatment, a time when many patients could no longer tolerate the thought of treatment intensification and prolongation. Similar rates of randomisation refusal have recently been reported from other sarcoma trials with delayed randomisation. Efforts to increase the randomisation rate were implemented during three investigator training courses and resulted in some, albeit limited success. The final randomisation rate for the three European groups, which participated in the training activities, was 66%; it was 52% for the North American partners.

The EURAMOS group succeeded in building a multinational infrastructure which allowed the completion of an osteosarcoma study of unprecedented size and infrastructural complexity. If estimations are correct, primary and secondary aims of the study will be reached. Results from the good responder randomisation are expected in 2013-2014, those from the poor responder randomisation in 2015-2017, depending on the number of observed events. In addition, the joint trial has brought investigators from all over Europe and North America

and even Australasia much closer together, forming a solid base for further cooperative activities.

Regarding follow-up, the four multinational groups participating in EURAMOS have given their solid commitment to continue their cooperation in future osteosarcoma trials, as all have experienced the collaboration as a success. Other groups have expressed their interest to join the consortium. Two intergroup meetings discussing trial concepts and strategies were held in London, thanks to support by the ESF. Consensus was achieved regarding the agent to be studied in the next intergroup trial, namely the macrophage activator mifamurtide (L-MTP-PE). Further development of the trial concept was impeded by the different licensing status of the drug in Europe and North America, and by unwillingness of the license holder to support the drug for the trial. Efforts to activate such a trial are yet ongoing.

An important European initiative which emerged as a result of the collaboration was the strong representation of bone sarcoma research in the FP7 European Network for Cancer Research in Children and Adolescents (ENCCA, <http://www.encca.eu/index.php?id=18#>). Work package WP7 (Integrating clinical trials and tumour biology in bone sarcoma) is chaired by the ECT-EURAMOS project leader, and other ECT-EURAMOS partners are also represented. This WP aims to link major bone sarcoma groups of specialists and networks such as EURAMOS, EURO-E.W.I.N.G and EuroBoNet. To do this a multinational platform specialised in bone sarcoma trials (Phase II-IV) with a focus on integrated biology tumour research is being established, extending beyond osteosarcoma to include all bone sarcomas of young individuals. The WP consists of five tasks, each one addressing different aspects relevant to bone sarcoma research and treatment.

Multinational collaboration in the EURAMOS study is not only experienced as a success by the four groups which undertook the study, but also by most if not all other osteosarcoma groups worldwide. As a result, the osteosarcoma groups from France (Société Française de lutte contre les Cancers et leucémies de l'Enfant et de l'adolescent, SFCE, and Groupe Sarcome Français et du Groupe d'Etude de Tumeurs Osseuses, GSF-GETO), Spain (Grupo Español de Investigación en Sarcomas, GEIS), Italy (Italian Sarcoma Group, ISG), Australia and New Zealand (Australasian Sarcoma Group ASSG), and the North American medical oncology Sarcoma Alliance through Research and Collaboration (SARC) are now participating in the EURAMOS

Strategy Group, and the Japanese Clinical Oncology Group (JCOG) has also participated in selected activities. It is envisioned that further clinical osteosarcoma trials should be built upon an even stronger basis than the first EURAMOS trial. In addition to phase III trials such as the first EURAMOS study, the collaborating groups are now discussing phase II concepts. As the most recent example of such activities, an intergroup meeting was held on the occasion of the Annual Meeting of the American Society of Clinical Oncology, ASCO, on 3 June 2012 in Chicago, USA. It defined entry criteria and endpoints for such studies, among other topics. A consensus statement is currently being drafted. It is expected to result in a joint publication upon which future trials can be built.

8.2 PROFIDYS

The PROFIDYS project was designed to evaluate the efficacy of a bone-targeted drug on skeletal symptoms in patients with fibrous dysplasia. This is the first randomised controlled trial designed to include a sufficient number of patients to enable the demonstration of the efficacy of a nitrogen-containing bisphosphonate (risedronate) in reducing skeletal symptoms in this disorder.

The PROFIDYS Project Leader reported that it was as yet premature to assess the output due to the delays encountered so far. Despite the approval of the project by the French Ethics Committee on 4 May 2005 and the approval by the French regulatory agency (AFSSAPS) on 24 August 2006, the trial was only launched in July 2007. Further delays occurred because of requested protocol amendments by different participants, the pending approval of which resulted in suspension of patient inclusion during the summer and autumn of 2008 and during the summer of 2009. In 2010 and 2011, researchers were confronted with the withdrawal of the three UK investigating centres and of the three German investigating centres. At the time of reporting, the PROFIDYS trial was being carried out in five centres: three in France, one in Belgium, and one in The Netherlands.

Regarding recruitment, there were 69 patients in the trial at the time of reporting. This represents 62% of the target number. Patient distribution is balanced between centres, at least among the four centres which started the trial in 2007 (Paris Lariboisière, Lyon, Paris Cochin, and Brussels). The Project Leader reported that the recruitment curve is essentially adequate, in spite of recruitment hav-

ing been suspended for 12 months (out of the 50 months of total duration of the trial to the date of reporting). Investigators were particularly motivated to continue recruitment efforts, especially with the help of patients' organisations, networks of reference centres and competence centres on rare bone diseases.

The PROFIDYS project has encouraged the response to the call for establishment of reference centres in the context of the French government 'Rare Diseases Plan' in 2004. As a result of this, two new reference centres were established in Paris and Lyon, working closely with another reference centre, as described above. Meetings have been organised by the network of competence centres coordinated by the Lyon reference centre, which allows the exchange of views on management issues pertaining to this disease. This network, which is also closely connected to the French patients association ASSYMCAL, has as its main aim the improvement of the clinical management of patients with fibrous dysplasia.

The second major achievement of the project was the development of recommendations and guidelines for the management of fibrous dysplasia and McCune-Albright syndrome. This was achieved by means of a thorough and systematic review of the relevant literature leading to the compilation of a state of the art document, which was very recently approved and officially endorsed by the French 'Haute Autorité de Santé'. These recommendations, together with the major networking effort of the Reference Centre on Fibrous Dysplasia, are expected to lead to major improvements in the management of the disease and to stimulate further clinical research on this rare bone disease.

Patients' meetings have been recently organised with the support of the ESF and within the frame of networking activities validated by the ESF from the PROFIDYS project work plan. The Project Leader reported that these meetings were very interactive and represent a wonderful opportunity for patients to share their experiences with other patients and with specialist physicians involved in the day-to-day management of their bone disease, and for researchers to present research progress and discuss new projects and future protocols, in order to secure patients' adherence to current protocols and participation in new clinical research trials. At the time of reporting, the goal of researchers was to organise further similar meetings and to encourage international participation of patients.

The collaboration between French centres was deemed optimal and led to two research grant appli-

cations to the French national hospital research program (PHRC), as reported above.

Discussions within the PROFIDYS Steering Committee resulted in a proposal for the recommendations for the management of fibrous dysplasia to be extended to other European countries participating in the PROFIDYS project. This will be further discussed after the formal endorsement of these recommendations in France.

The Project Leader emphasised that it would be important to apply further efforts to improve and extend the network of 'fibrous dysplasia specialists' and to develop the contact between physicians and patients through various means: newsletters, regular patients' meetings, training and teaching sessions, information and education using internet tools (websites, e-learning, blogs, etc.). This would improve the global care of the disease. The ideal objective would be to globally connect patients and physicians on a European basis. Language obstacles should be anticipated and managed appropriately.

The Project Leader stated that it is also necessary to extend collaboration and networks in countries outside Europe. Researchers' contacts with colleagues from abroad and discussions during national meetings are incentives for developing new research projects in several areas of the disease: progress in imaging technologies should pave the way for original research projects in the field of fibrous dysplasia addressing potential improvements in diagnostic and prognostic value of novel techniques, and prediction and assessment of response to different bone-targeted treatments; molecular studies could help improve diagnostic procedures while precluding the use of invasive tissue sampling; new therapeutic targets could be identified such as interleukin-6 (IL-6) and alternative drugs could be tested (a trial testing tocilizumab, a monoclonal antibody against the interleukin-6 receptor, IL-6R, will actually be initiated by late 2012). RANK-ligand denosumab, a monoclonal antibody against the RANK-L, is currently used in other bone diseases and could be promising in fibrous dysplasia. These fascinating avenues need to be explored through a collaborative international effort in order to gather the number of patients needed for an appropriate answer to these research questions.

Despite all reported difficulties, the Project Leader found that the PROFIDYS project had generated a real interest in the scientific community and is therefore likely to lead to a mobilisation necessary to enable such progress.

9.

Feedback on the ECT Programme and the EUROCORES Scheme



9.1 EURAMOS

Looking back at the many challenges faced during the conception, activation and running of the study, researchers agreed that the EURAMOS study could not have been performed without being a part of the ECT EUROCORES Programme. Also, the additional visibility gained by the EURAMOS project, and the multiple opportunities the ECT-EUROCORES Programme gave for networking, dissemination and teaching were an incredibly important and valuable add-on to running the trial *per se*.

It became somewhat obvious, however, that the EUROCORES Scheme in the form researchers encountered it was only partially suited for multinational clinical trials in which many partners with similar expertise and contributions join together to achieve the necessary sample size, rather than having partners with different areas of expertise join together in order to achieve synergy. Another drawback encountered was the heterogeneity of responses from the ESF MOs to the funding recommendations. It became quite clear that some MOs had not been interested in the ECT EUROCORES from the very beginning and would not consider funding their country's Individual Projects regardless of the perceived merit of the chosen proposals, but only voiced their reservations after the review had been completed. This made things more complicated than if it had been clear from the beginning which partners could and which could not expect funding in case of a positive review.

The EURAMOS Project Leader and his team are very grateful to those MOs which did fund the trial that they allowed their support to be used to fund the central infrastructure of the trial, the

Coordinating Data Centre, the Safety Desk, and the QoL Data Centre, even if they were not located within their own country. This was essential in allowing the EUROCORES Scheme to work for a Pan-European clinical trial. Finally, the EURAMOS investigators thank the ESF and the funding ESF MOs for their immense support.

9.2 PROFIDYS

Tremendous hopes were initially raised by the possibilities and opportunities that would arise by joining the EUROCORES Programme. Being faced with a rare disease, researchers perceived that it would be extremely difficult to consider setting up a therapeutic protocol for patients with fibrous dysplasia, with patients' recruitment limited only to the French population. As mentioned earlier in this report, sharing the initial stages of building the project with the other EUROCORES CRP project selected at the same time, EURAMOS, proved to be of great help.

However, PROFIDYS researchers did not anticipate the difficulties associated with the lack of communication between institutions, including the ESF, Inserm and the Direction of Clinical Research of their Hospital institution (AP-HP). The Project Leader expected a better communication from the side of ESF too.

Researchers regretted not having had better contact with the European Clinical Research Infrastructures Network (ECRIN, www.ecrin.org), which they understood was to provide assistance to investigators for coordinating the implementation of regulatory procedures required to start the project. Since different countries are subjected to

different rules, the Project Leader estimated that harmonisation was extremely difficult, despite several meetings with the ESF Management Committee. Consequently, problems in some European participating countries delayed regulatory procedures in Belgium and The Netherlands. The withdrawal of investigators from the UK and Germany had a greater negative impact, since it eliminated six investigating centres. The many stumbling blocks resulted in the UK investigators not being sufficiently motivated to pursue application for the required local procedures. The German investigators did apply to the relevant local regulatory authorities but the issues raised by these authorities and by the German Ethics Committee jeopardised the whole project and finally precluded the participation of Germany in the trial. The PROFIDYS team also faced difficulties in setting up the coordinating sponsor, with a consequent delay in launching the project (effective only in 2007).

Researchers also reported having understood they could count on additional funding from the ESF, which was not the case. The need for the participants to apply for national funding grants meant further delays generated by several re-evaluations of the protocol by diverse funding institutions, raising various issues and requiring minor protocol amendments and an overall destabilising effect on some principal investigators and project coordinators in the rather lengthy period between the initiation of the project and the final approval of the protocol and start of the study.

The Project Leader reported that an improvement of the support to investigators by the institutional environment is clearly needed, especially in the case of the global coordination of such a multicentre, multinational European project, involving a number of different national regulatory authorities.

The ESF would hereby like to:

1. Acknowledge the difficulties described by Professor Philippe Orcel. PROFIDYS illustrates the current difficulties in setting up pan-European Investigator-Driven Clinical Trials (IDCTs), the focus of the ESF-EMRC attention for many years. The EMRC has been strongly advocating the revision of the EU Clinical Trials Directive (EUCTD, 2001/20/EC) since the publication of its Forward Look final report IDCT in March 2009 (<http://www.esf.org/activities/forward-looks/medical-sciences-emrc/completed-forward-looks-in-medical-sciences/fl-07-001-investigator-driven-clinical-trials.html>) and the publication of the position paper

‘Proposal for a Revision of the “Clinical Trials Directive” (2001/20/EC) and other recommendations to facilitate clinical trials’ in December 2011 (<http://www.esf.org/research-areas/medical-sciences/publications.html>). These documents identified the important issues that currently hamper clinical trials and worked out proposals on how to facilitate these at the trans-national level.

2. Clarify its role. The ESF’s role is to manage the calls for proposals, the selection of CRPs such as PROFIDYS and the coordination of networking and dissemination activities, but not to relieve the administrative burden related to the (pre-) launch of clinical trials in individual European countries.
3. Clarify the national funding and support issues that arose. Clinical research funding is managed at the national level, as there is no ‘common pot’ funding managed by the ESF. Therefore, researchers still have to apply for funding to their national organisations. This is a common misunderstanding shared by many researchers involved in EUROCORES Programmes (not only PROFIDYS). Also, the ESF does not have the power to support to researchers wishing to launch a clinical trial.
4. Express its opinion about the alleged ‘lack of communication’ from the part of the ESF. Several of the last communications from the ESF side pertained to the final report, which was submitted by Professor Orcel to the ESF a year after the official deadline and could thus not be assessed on time by the ECT Review Panel. At the time of writing this report, other final reports of activities that took place in 2011 have still not been submitted to ESF, and the Management Committee has already been made aware of this situation. On the positive side, and as acknowledged by Professor Orcel, “several meetings with the ESF Management Committee” took place, which is unusual for a EUROCORES Programme and shows the ESF involvement and commitment in the (pre-)launch phase. Also, there have been frequent communications with the PROFIDYS team and its Project Leader through various channels throughout an extended period of time, especially before and during the launch of the clinical trial up to 2007-2008. Dr Carole Moquin-Pathey who coordinated ECT until 2009 even succeeded in getting additional support and funding from the AP-HP. Therefore, the ESF does not fully agree with Professor Orcel’s statement.

Finally, EMRC would like to add that it welcomes the revision of the European Directive on Clinical Trials and the efforts to convert it into a Regulation, which hopefully will improve harmonisation in the area of clinical trials regulation in Europe. The details of the implementation process are still to be assessed. EMRC has worked for years to improve the situation for investigator- driven clinical trials and is grateful to have been involved in Directorate General SANCO's consultation process with other academic and industrial stakeholders. EMRC is pleased to see that many areas of concern appear to have been addressed and hope that this regulation will lead to a better situation in the area of IDCTs. The ESF hopes that pan-European clinical trials such as PROFIDYS will be facilitated in the future.

10.

Final evaluation and recommendations: consensus statement



The assessment performed by the Review Panel was based only on the EURAMOS final report. The PROFIDYS report was submitted way after the deadline established. Out of the nine members of the Review Panel, five members contributed to this assessment: Patrick Bossuyt (NL), Tamas Doczi (HU), Outi Hovatta (SE), Luc Van Bortel (BE) and Magi Farre (ES).

In this final evaluation by the Review Panel, EURAMOS was quantitatively and qualitatively assessed on the basis of the following criteria:

1. Progress of the CRP: achievement of goals, integration of teams' outputs
2. Programme integration of both CRPs (EURAMOS and PROFIDYS) into the EUROCORES Programme objectives
3. Networking, training and dissemination activities

10.1 Progress of EURAMOS: achievement of its goals, integration of teams' outputs

EURAMOS is an ongoing clinical trial that features an unprecedented multinational research collaboration aimed at improving the treatment strategy of a rare malignant disease affecting children and young adults by means of an old drug. EURAMOS is the largest clinical trial in osteosarcoma ever carried out, and its delivery constitutes a unique feat. The recruitment rate (2,260 patients in six years) and follow-up have been globally outstanding, all the more when considering that this clinical trial deals with a rare disease. However, countries like Finland could have recruited larger amounts of patients. The collaboration between teams was very successful, and the global output is excellent so far as demonstrated by indicators such as scientific publications and dissemination activities. EURAMOS participants have also pioneered new forms of implementation of the European Clinical Trials Directive, which actually delayed recruitment of patients. EURAMOS ran out of time due to problems with EU Directive implementation and to lower than expected randomisation rates, and thus the extension granted was well justified. Other indicators of the added value and spill-over benefits of EURAMOS are the establishment of a vast professional network, the organisation of training activities, and the increase in visibility for European legislative and regulatory bodies. Whenever this clinical trial achieves completion by 2013, the final results will surely be very useful for medical and pediatric oncology worldwide, with foreseeable positive impact in clinical oncology, patient care, organising procedures, etc.

10.2 ECT Programme integration

Even if EURAMOS has delivered outstanding results so far, at the time of evaluation by the Review Panel, there were no data from PROFIDYS to compare it to. Therefore, it was not feasible for this panel to judge the whole ECT EUROCORES Programme based on the final report of only one CRP. Research in rare diseases is somewhat complex to integrate, and this would have been an excellent opportunity to test new ways to achieve this. The output of EURAMOS and the current situation in oncology worldwide suggests that there is an incredible potential and a substantial societal need for Pan-European Clinical Trials in several areas, and that valuable lessons can be extracted from this multinational collaborative effort.

10.3 Networking, training and dissemination

As stated in the previous section, the Review Panel deemed that at the time of the evaluation, it was not feasible to evaluate the entire ECT EUROCORES Programme based on the final report of only one CRP. At the individual level, EURAMOS has been very successful in organising well-planned networking and training activities that have benefitted all participants. Important research networks have been established, and follow-up research programmes have already been initiated. Dissemination activities, articles published in international journals, presentations, books and book chapters are all excellent outputs, especially taking into account that this clinical trial is still ongoing. EURAMOS is a fine example of an independent clinical trial and could serve as a model for similar multinational collaborative clinical trials in the future.

The availability of the ESF EUROCORES Scheme proved essential to carry out all these collaborative activities with high impact. Comparable results could not have been obtained without this programme. EURAMOS is likely to become a model for running clinical research in rare diseases. EURAMOS has had a very positive “snow ball effect”: many other countries in Europe (i.e. France, Italy or Spain) and outside (i.e. Japan, Australia, New Zealand and North America) are joining the EURAMOS team, making a global osteosarcoma programme possible. This may speed up recruitment, which most likely will translate into earlier results that may benefit patients worldwide.

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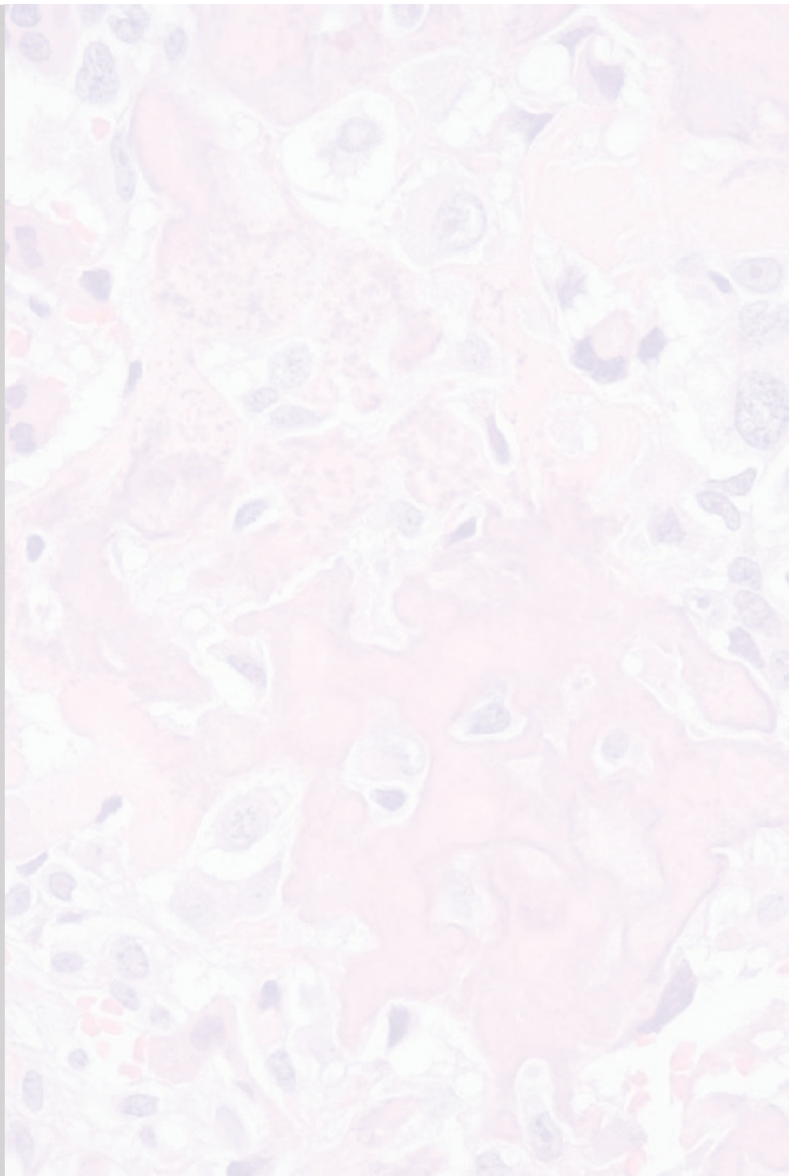
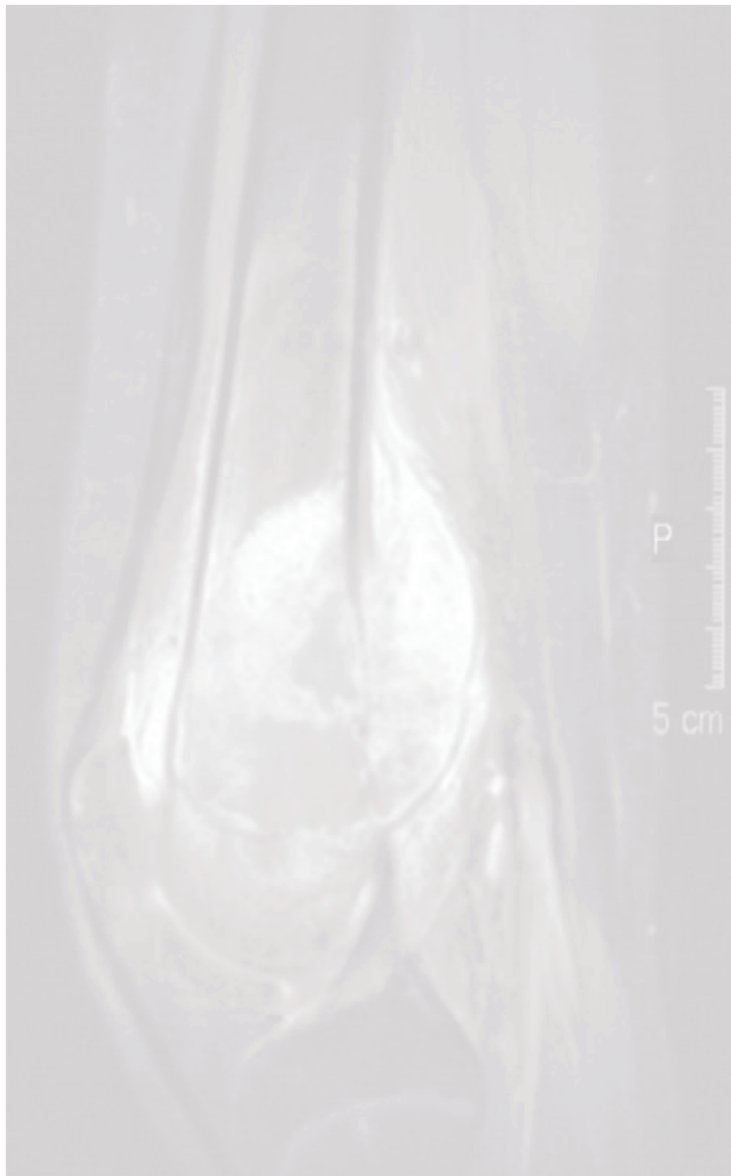
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September 2012 – Print run: 200