ERN Case Studies: BOND ERN

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RD-ACTION, EMA and DG SANTE Workshop:
How ERNs can provide added-value in the area of clinical research
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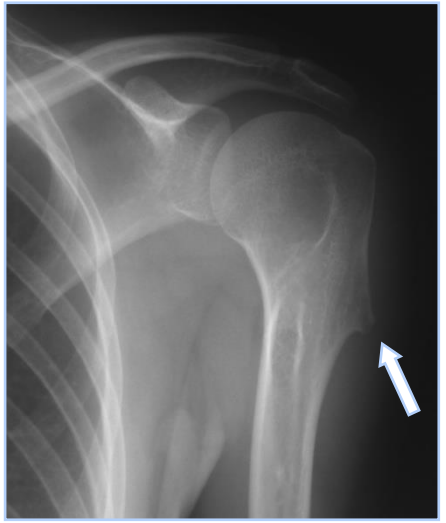
Venue: European Medicines Agency, London

MULTIPLE OSTECHONDROMAS

- Autosomal dominant skeletal disease (1/50,000)
- Multiple cartilage-capped benign bone tumours (OC)
- Lesions arise at external surface of bones formed by endochondral ossification
- 1- 5% → malignant transformation into peripheral chondrosarcoma
- OCs are rarely present at birth
- Increasing in number and size until skeletal maturity
  - Great variability in OC number and size, location and evolution, with varying degrees of orthopaedic deformity and functional impairments
  - Intra- and inter-familial phenotype variability



CLINICAL HETEROGENEITY

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2 genes linked to MO:

- **EXT1** (8q24.1-q24.13)

- **EXT2** (11p11-p12)

- Large spectrum of germline mutations scattered along EXT1/EXT2
- No specific genotype-phenotype correlations identified
- Percentage of MO affected patients without detectable EXT mutations

GENETIC HETEROGENEITY

Registry of Multiple Exostoses (REM)

Data collection started in 2003, and formalized as a Disease Registry in 2013 according to:

The Registry is an essential tool for translating research into improved care and therapeutic, pharmacological, clinical solutions. The Registry collects longitudinally patient's data and provides updated information to explain the MO disease and to support the stakeholders towards best practice.

Main aims of REM:

a) to promote more meaningful and accurate genotype-phenotype correlations,

b) to study MO epidemiology and natural history,

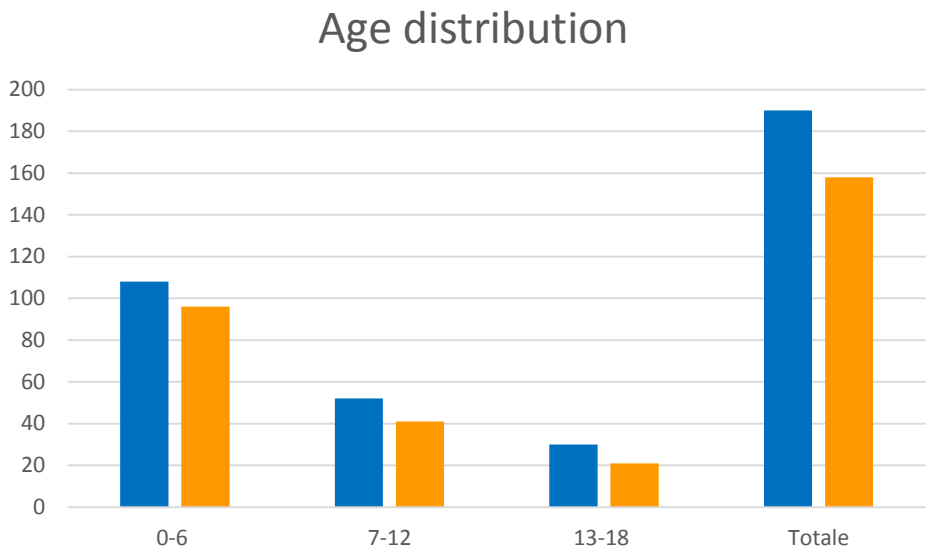
c) to provide data analyses for researches and studies,

REM Registry works in concert with Biobank of Genetic Sample (BIOGEN) for research pourposes

Registry of Multiple Exostoses (REM)

The Dataset

Data analyses involved determination of key clinical and radiologic variables available in the REM and analysed by a multi-disciplinary team. The dataset consisted of 190 MO paediatric patients evaluated by age (0-6 years, 7-12 years, 13-18 years) and overall. Among them,158 patients (83%) had at least one follow up visit.
IOR has obtained signed informed consent from all patients included in this Research Activities.



Blu 1 visit (190) Orange more than 1 visit (158)

Objectives

Aim of this study is to increase the epidemiologic knowledge and to investigate the natural history of MO disease in the paediatric population.
This will be helpful to comprehend disease evolution and pathological development of Ocs and to support choice of endpoints for interventional trials of potential therapeutics.

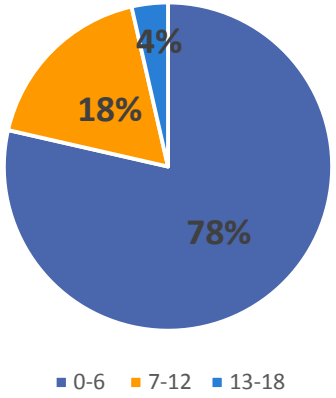
Preliminary Results

The mean age at MO diagnosis was 4.2 years (ranging from birth to 16 years). The mean age at the occurrence of first osteochondroma is 3.5 years.

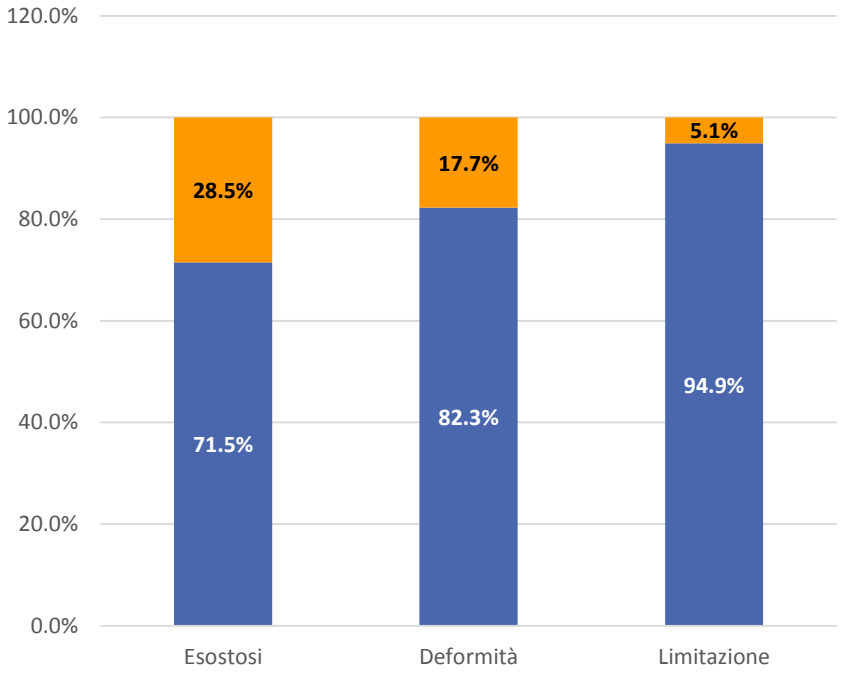
Deformities have been observed in 31.3% of patients in the 0-6 years group at baseline compared to ~50% of patients in the older age groups (the majority exhibits 1-2 deformities). Considering the entire follow-up period (55.8 months in overall population), the mean number and rate of new deformities tend to be greater in younger than in older patients.

Functional limitations were less frequently reported at baseline, occurring in about 16% of patients overall (less than one per patient), than OCs and limb deformities. The results are similar irrespective of patients' age. Despite the incidence of patients with a new functional limitation continues to increase in 0-6 years group, the incidence, the mean number and the rate of new functional limitations over the entire follow-up period were similar across the age groups.

Patients with at least 1 new deformity within 12 monthsi follow up



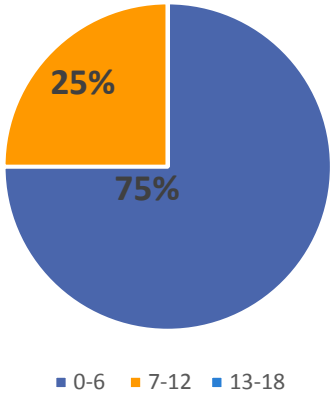
Distribution of clinical manifestations within 12 months follow up



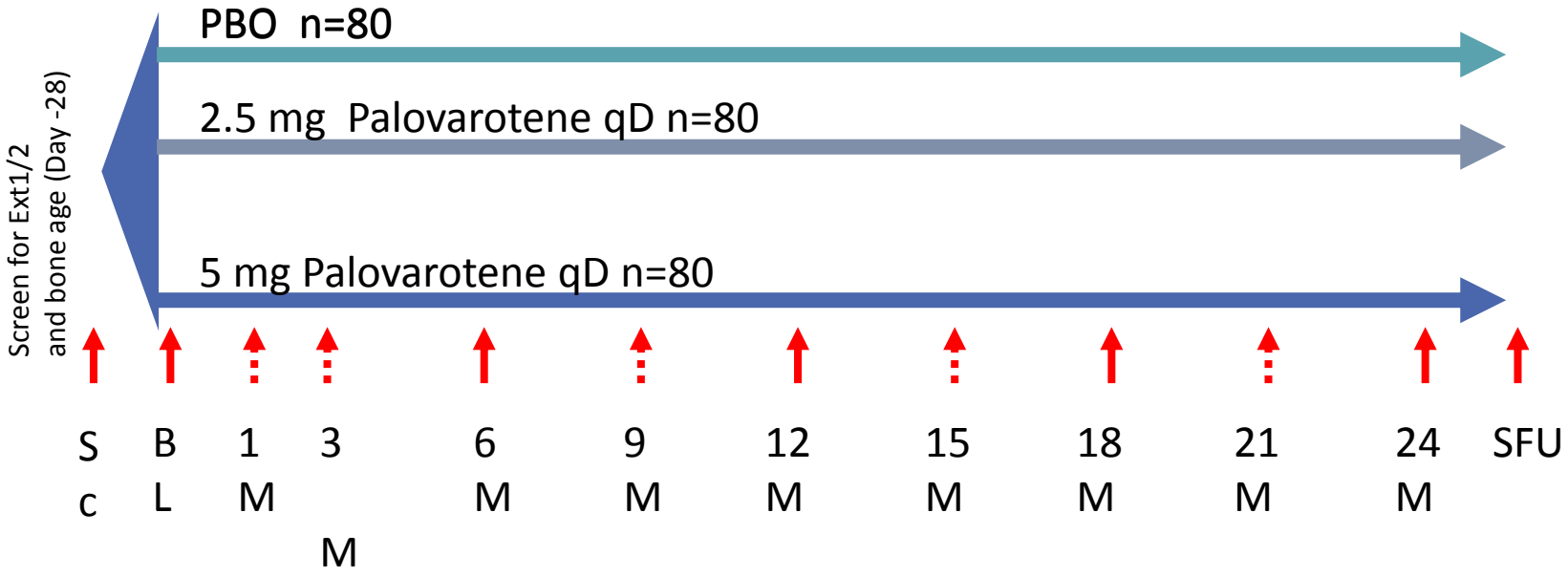
Blue: no events

Orange: at least 1 event

Patients with at least 1 new deformity within 12 months follow up



MO-Ped Trial: Study Design



M12 and M24 (EoT):
Whole body MRI
Radiographs for deformity

M6, M12, M18, M24 (EoT):
ROM
Patient reported outcomes
Linear and knee heights
DXA
Hand/wrist and knee X-rays Safety assessments

M3, M9, M15, M21 remote:
Safety assessments

M1 remote:
PK sampling

Site visit

Remote visit

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MO-PED Trial: Primary Objectives

- To evaluate the **efficacy** of two dosage regimens of palovarotene (compared with placebo) in **preventing new osteochondromas (OCs)** in subjects with multiple osteochondromas (MO) due to exostosin 1 (Ext1) or exostosin 2 (Ext2) mutations over a 2 year period.

MO-PED Trial: Secondary Objectives

- To compare the following effects of palovarotene with placebo:
  - The **volume of OCs** as assessed by magnetic resonance imaging (MRI).
  - The rate of **new or worsening skeletal deformities**.
  - The rate of **MO-related surgeries.**
- To evaluate the overall safety and **pharmacokinetics** of palovarotene at steady-state.

MO-PED Trial: Exploratory Objectives

- To compare the following effects of palovarotene with placebo:
  - The rate of **new or worsening functional limitations**.
  - **Pain and pain interference** due to OCs.
  - **Quality of life.**

Conclusions

- MGD and Clementia collaborated to obtain a comprehensive and contemporary understanding of the natural history of MO by exploring a wide range of patient information.

- The analyses evaluated clinical characteristics of MO patients including number and locations of clinically evident OCs, functional limitations, deformities, and surgical procedures at patients' time of entry into the registry and at the last follow-up. The higher incidence of new deformities at younger ages during follow-up is consistent with their underlying pathophysiology (growth of new OCs is coincident with patient growth).

- The incidence of patients with a new functional limitation continued to increase in the youngest age groups while the incidences in the older age group did not. The lower rate of functional limitation relative to the occurrence of new OCs and deformities may be attributable to surgical excision of a symptomatic OC and/or surgery performed to prevent or treat deformities.

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Thank you for your attention!