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Report of the paediatric osteoporosis expert meeting

06 June 2014 – chaired by Viveca Odlind and Richard Veselý

Introduction

The Agency held a one-day workshop on 06 June 2014 on osteoporosis in children.

European experts in the field of paediatric osteoporosis discussed paediatric developments for the treatment of primary and secondary osteoporosis in children including osteogenesis imperfecta.

The main objectives of the meeting were:

- to identify elements for agreeing paediatric investigation plans in paediatric osteoporosis in line with good clinical practice and delivering conclusive outcomes;
- to identify possible approaches to enhance feasibility of paediatric osteoporosis trials.

The workshop was also attended by FDA representatives via teleconference.

The invited experts received pre-set questions and were asked to communicate their responses in advance of the meeting to facilitate the discussion.

The conclusions of the discussion reflect the views of the participants and do not represent the official policy or guidance of the Agency. The conclusions are without prejudice to the opinions of the EMA Paediatric Committee on individual applications for paediatric investigation plans or waivers.

The European Medicines Agency is working on the revision of the current scientific guideline on the evaluation of medicinal products for treatment of osteoporosis, where appropriate public consultation has been included.

Conclusions of the discussion:

1. Similarity of paediatric and adult osteoporosis and room for extrapolation

Although the mechanism of action of medicines is similar in adults and in children, there are many differences in the pathogenesis of bone disease, the effect of the treatment on the growing bone and relevant outcome measures. Also, the dosing and exposure/treatment effect ratio in children may be different. These factors do not allow full extrapolation and, therefore, clinical studies in children are

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normally necessary. However, the potential and extent of extrapolation need to be analysed individually for each new treatment for paediatric development, depending both on product characteristics and other factors. PK/PD and safety data are generally needed and cannot be extrapolated. Whether efficacy can be extrapolated will also depend on type of osteoporosis, as well as on underlying disease.

2. Feasibility of clinical trials in paediatric osteoporosis

In general trials in children are feasible, as there are enough paediatric patients available in specialised centres in Europe. However, there are relatively few patients diagnosed with osteogenesis imperfecta, OI, (possibly 1000-1500 in EU), which may pose feasibility challenges.

With regard to secondary osteoporosis, children with acute lymphoblastic leukaemia, Duchenne muscular dystrophy and chronic inflammatory conditions are those most in need for development of treatment options.

3. Use of placebo

Placebo-controlled parallel-group studies are the gold standard and are preferred whenever possible also for osteoporosis trials in children, with a cross-over design and short placebo exposure. Placebo and experimental treatment should be given on top of standard treatment, but combined anti-resorptive therapy should be avoided. In case of an acceptable safety profile of the new medicine, head-to-head comparison with standard treatment may be considered. The possibility to use placebo may differ between types of paediatric osteoporosis. Children with moderate to severe OI are generally treated with medicines (bisphosphonates) from an early age, which may affect the testing of additional medicines.

Use of alternative study designs for clinical trials in small populations should be considered wherever applicable.

4. Duration of studies

For an evaluation of the short-term outcome, the treatment should last at least one year, with a follow-up of at least another year. For an analysis of the long-term outcome it may be necessary to follow patients until the completion of bone growth. Because the marketing authorisation may be based on limited information on short-time efficacy and safety, it is necessary to collect further data from patients treated after marketing, such as in observational registry-type studies.

5. Age of children to be included into clinical studies

For secondary osteoporosis, children from 4 years need to be studied. For OI, studies should include all ages. Wherever necessary (taking into account clinical need and safety considerations), a staggered approach should be chosen, with earlier involvement of older children into clinical studies (before younger children).

6. Glucocorticoid induced osteoporosis as the concept

Glucocorticoids are used in treatment of many different diseases. The effect on bone is likely a combination of the underlying disease mechanism, the effects of the disease on physical activity, stage of growth and of the treatment with glucocorticoids (and possibly other medication). Therefore, it is

not totally appropriate to group these diseases together as “glucocorticoid-induced osteoporosis”. Nevertheless, it may be useful to combine patients with different underlying diseases together to increase feasibility of the study, adopting a research and development concept for “secondary osteoporosis”.

7. Outcome measures

The frequency of fractures should be used as the primary outcome measure in paediatric studies. Use of bone mineral density (BMD) measurements and laboratory markers as surrogates has limitations, and the predictive value for future fractures needs to be further studied. Development of a composite endpoint including number of fractures, bone mineral density and other parameters (quality of life including functioning, laboratory markers) might be useful to overcome methodological difficulties in measuring a clinically relevant benefit in clinical trials in children with osteoporosis.

List of participants

Role	Name
Chair/Vice-chair	Viveca Odlind, Läkemedelsverket MPA, Sweden / Richard Veselý, European Medicines Agency
Present:	Angeliki Siapkara, Medicines and Healthcare Products Regulatory Agency, United Kingdom
	Wolfgang Hogler, Birmingham Children's Hospital, United Kingdom
	Milan Bayer, Fakultní nemocnice Hradec Králové, Czech Republic
	Nick Bishop, University of Sheffield, United Kingdom
	Dirk Mentzer, Paul-Ehrlich-Institut, Germany
	Jan Mueller-Berghaus, Paul-Ehrlich-Institut, Germany
	Syed Faisal Ahmed, NHS Greater Glasgow & Clyde, United Kingdom
	Maria Luisa Bianchi, Istituto Auxologico Italiano IRCCS, Italy
Apologies:	Susanne Bechtold, Ludwig-Maximilians-Universität München, Germany