The Bone-Protective Effects of a Novel Selective Estrogen Receptor Modulator (pERD) in Ovariectomized Rats

Jukka Morko,1 Carsten Möller,2 ZhiQi Peng,1 Jukka Vääräniemi,3 Katja M Fagerlund,1 Tiina A Suutari,1 Jenni Bernoulli,1 Jukka P Rissanen,1 Andrea Wagenfeld,2 Arndt Schmitz,2 and Jussi M Halleen1
1 Pharmateutics Ltd, Turku, Finland; 2 Bayer Pharma AG, Berlin, Germany
E-mail correspondence to Jukka Morko (jukka.morko@pharmatest.com)

Introduction
Selective estrogen receptor modulators (SERMs) are a diverse class of compounds that bind estrogen receptors (ERs) and agonize or antagonize estrogen action in different tissue types.1,2 Due to a broad spectrum of physiological and pathological processes contributed by ERs, SERMs provide a potential therapeutic benefit for a variety of diseases including cancer, cardiovascular, metabolic and cognitive diseases, and postmenopausal osteoporosis. In a long-term treatment of postmenopausal osteoporosis, a traditional hormone replacement therapy is associated with an increased risk of breast and uterine cancer, cardiovascular diseases and dementia, and SERMs provide a therapeutic potential with less side effects.3,4 In preclinical studies, the bone specific actions of SERMs can be studied under estrogen deficiency in ovariectomized (OVX) animals and under physiological estrogen levels in healthy animals.

Aim of the Study
The aim of this study was to characterize the effects of a novel partial estrogen receptor agonist (pERD) on bone under estrogen deficiency in the rat OVX model. Reference treatments included 17β-estradiol (E2) as a complete agonist and raloxifene (RAL) as a SERM exhibiting activity against bone.

Materials and Methods
Study Design
Three-week-old Sprague-Dawley female rats were randomly divided into five groups (five females per group). The groups were 1) Sham operated control, 2) Sham operated control + vehicle, 3) OVX control rats + vehicle, 4) OVX control rats + E2 at 4.0 µg/kg/d and 5) OVX control rats + pERD (RAL) at 2.0 µg/kg/d. E2 was dissolved in absolute ethanol and administered intraperitoneally (i.p.); pERD was suspended in olive oil and administered orally. Three doses were given per week. Total study period was 10 weeks. Bone biochemical and morphometric parameters were measured at the end of the experiment. All serum samples were stored at -80 °C until analyzed.

Body and Uterine Weight
Bone Length and Ash Weight

Summary
pERD prevented the OVX-induced reduction in trabecular BMD, BMC and BV/TV in tibial metaphysis at 1.3 and 10 mg/kg/d p.o. (Fig. 3A, B). pERD prevented the OVX-induced stimulation in osteoclastogenesis (Oc.Si/B.S) in trabecular bone in tibial metaphysis at 1.3 and 10 mg/kg/d p.o. (Fig. 3C). pERD prevented the OVX-induced stimulation in trabecular bone mineralization and formation (MAR and BFR/BS) at 1.3 and 10 mg/kg/d p.o. (Fig. 3E, F).

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Conclusions
Treatment with the novel pERD for 8 weeks demonstrated a bone-protective agonist activity in trabecular bone at 1-10 mg/kg/d p.o. and in cortical bone at 3-10 mg/kg/d p.o. in young adult OVX rats.

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References