BIOLOGICAL ACTIVITY:

Odanacatib is a potent, selective, and neutral inhibitor of cathepsin K (human/rabbit) with IC\textsubscript{50} of 0.2 nM/1 nM, and demonstrates high selectivity versus off–target cathepsin B, L, S.

IC\textsubscript{50} & Target: IC\textsubscript{50}: 0.2 nM (Human Cathepsin K), 1 nM (Rabbit Cathepsin K)

In Vitro: Odanacatib is a weak inhibitor of antigen presentation, measured in a mouse B cell line (IC\textsubscript{50}=1.5±0.4 μM), compared to the Cat S inhibitor LHVS (IC\textsubscript{50}=0.001 μM) in the same assay. Odanacatib also shows weak inhibition of the processing of the MHC II invariant chain protein Iip10 in mouse splenocytes compared to LHVS (minimum inhibitory concentration 1–10 μM versus 0.01 μM, respectively)\cite{1}. Odanacatib reduces resorption activity as measured by CTx release (IC\textsubscript{50}=9.4 nM) or resorption area (IC\textsubscript{50}=6.5 nM), but has no impact on OC activation. Odanacatib dose–dependently reduces CTx release with an IC\textsubscript{50}=9.4±1.0 nM. Odanacatib treated OC accumulates labeled degraded bone matrix proteins in CatK containing vesicles\cite{2}.

In Vivo: Odanacatib (30 mg/kg, orally, once daily) persistently suppresses bone resorption markers and serum bone formation markers versus vehicle–treated OVX monkeys. Odanacatib displays compartment–specific effects on trabecular versus cortical bone formation, with treatment resulting in marked increases in periosteal bone formation and cortical thickness in ovariectomized monkeys whereas trabecular bone formation is reduced\cite{3}. The bone volume/total volume (BV/TV) and bone mineral density (BMD) of the OVX + ODN–h group is significantly higher than that of the OVX + Veh group (p < 0.05). The expressions of Runx2, Collagen–I, BSP, Osterix, OPN and SPP1 are significantly lower in the OVX + ODN–h group than in the OVX + Veh group (p < 0.01). Compared with the OVX + Veh group, the expressions of Collagen–I, BSP, Osterix, OPN and ALP reduce in the OVX + ODN–l group, but are upregulated in the OVX + ODN–h group\cite{4}.

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: To assess cell survival, differentiated osteoclast (OC) at appr $7 \times 10^4$ cells/cm\textsuperscript{2} are re–seeded on bovine bone slices with or without 100 nM Odanacatib (ODN). Bone slices are fixed on days 2, 4, 6, and 12 with no media changes. Samples are stained for TRAP activity, and OC number.

Animal Administration: Odanacatib is added in 0.5% sodium carboxymethyl cellulose.\cite{4} Sixteen, 8–month–old, female Sprague–Dawley (SD) rats (weight, 385 ± 55 g) are given water and soft diet food ad libitum in a temperature–controlled environment with regular 12–h cycles of light and dark. The rats are randomised into 4 groups, with 4 rats in each group: sham group, OVX + Veh group, OVX + ODN–l group and OVX + ODN–h group. Following implant insertion, Odanacatib (ODN, 5 mg/mL) is administered to the OVX + ODN–l group and OVX + ODN–h group at concentrations of 1 mL/kg and 6 mL/kg, respectively, by gavaging once a day for 8 weeks. The OVX + Veh group is gavaged with 0.5% sodium carboxymethyl cellulose at a concentration of 6 mL/kg over the same duration. After the gavage administration, the rats of each group are sacrificed by injecting sodium pentobarbital intravenously. The implants are harvested and fixed in 10% buffered formalin together with the surrounding bone.
References:


