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Osteoporosis



Osteoporosis: Growing & Serious Medical and Economic Problem

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According to “International Osteoporosis Foundation” (<https://www.iofbonehealth.org/epidemiology>):

- Currently > 200 million people worldwide suffer from this disease.
 - Drivers:
 - ❖ (1) Population growth and the reduction in the use of Hormone Replacement Therapy (HRT) in postmenopausal women.
 - ❖ (2) New guidelines -> awareness of osteoporosis screening in older men.
- Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe.

Osteoporosis world-wide sales: USD\$10+ billions (2015)

- Ediol (VDRA) sales in Japan: Chugai's 7th biggest drug in 2015 with sales of ¥23bn.

Osteoporosis Current Treatment

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- Anti-resorptive (or anti-catabolic, SERMs, bisphosphonates, denosumab, etc.): No effect on bone formation, but reduce bone resorption
- Anabolic agents (PTH, VDRAs): Stimulate bone formation (and subsequently bone resorption) and increase BMD.

Note: BMD, bone mineral density; PTH, parathyroid hormone; SERMs, selective estrogen receptor modulators

VDRAs Current Clinical Applications

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- Mainly for secondary hyperparathyroidism (SHPT) associated with CKD
 - Primarily prescribed for Stage 5 CKD patients on dialysis
 - Low usage in Stage 3/4 CKD patients although existing data show that VDRAs provide survival benefits in CKD
- Also used to treat psoriasis and osteoporosis (ex-US; calcitriol, etc.)
- On-market VDRAs have serious hypercalcemic toxicity concerns limiting clinical use
 - Requirement for serum calcium monitoring and dose adjustment limits broader use

Problem & Solution

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Problem: Current osteoporosis therapies are limited by suboptimal efficacy, side effects

Solution:

- VS-105 (a novel VDRA) effectively improves bone parameters without side effects
- Potential indications: Osteoporosis, psoriasis, chronic kidney disease complications

Osteoporosis in Ovariectomized Rats

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- Female Sprague–Dawley rats at 8 months of age were given bilateral ovariectomy (OVX) at the beginning of the study.
- Two weeks after OVX, animals were administered vehicle (5% ethanol + 95% propylene glycol, 0.4 ml/kg), calcitriol, or VS-105 (3x/week, i.p.) for 90 days

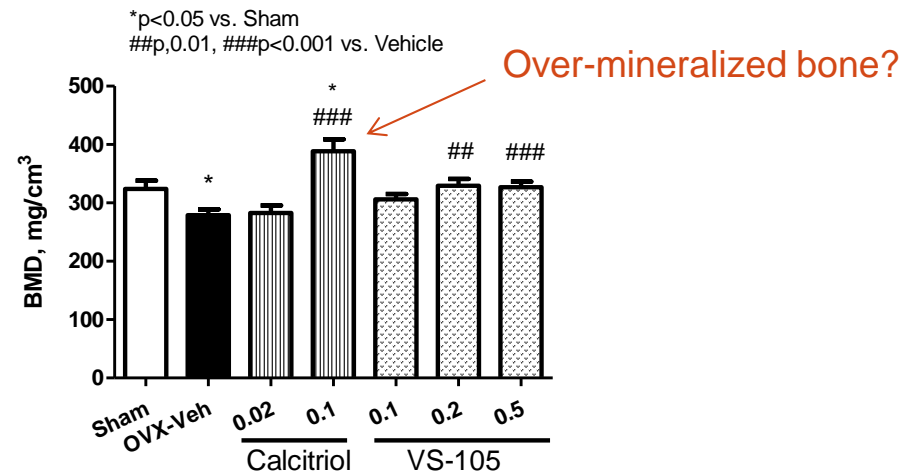
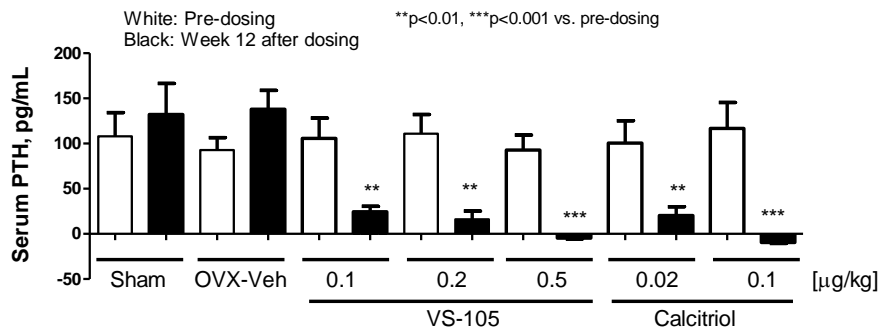
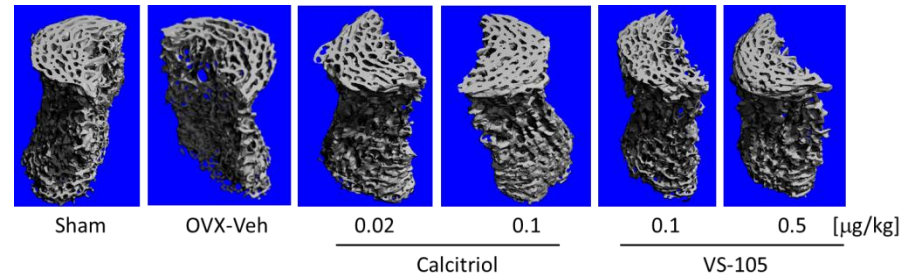
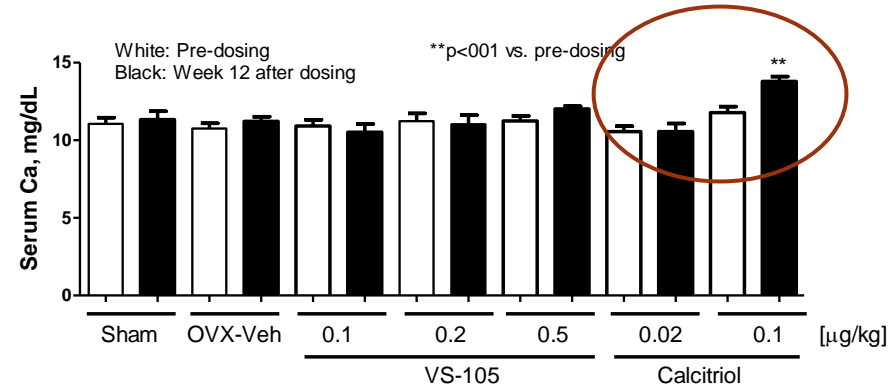
(Note: Other efficacy studies show that there is no difference in i.p. vs. oral dosing for VS-105)

- Parameters Measured
 - BMD of the lumbar vertebrae
 - Serum PTH and Ca

Serum Ca and PTH; Micro-CT Scan of L3

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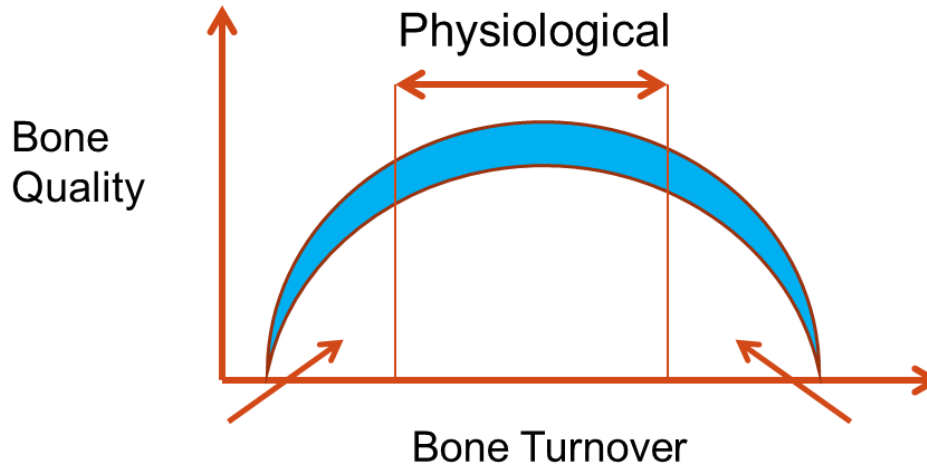
- Preclinical data in Female Sprague–Dawley rats with ovariectomy (OVX)



VS-105 vs. Current Therapies

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Too Little Turnover

- Aging bone
- Unrepaired micro-damage
- Over-mineralized bone

VS-105

Too Much Turnover

- Loss of bone mass and structure
- Stress risers
- Under-mineralized bone

Useful for treating osteoporosis because it restores the balance between bone resorption and bone formation to the normal level

Competitive Matrix

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Product	Indication	TI	Issues	2015 Sales
On-market VDRA _s	SHPT (Stage 3/4/5 CKD), psoriasis, osteoporosis	1-4	Hypercalcemic side effect: Required dose titration and serum Ca monitoring	\$1+ billion
Other on-market osteoporosis drugs	Anti-resorptive (SERMs, bisphosphonates, etc.) Anabolic agents (PTH, VDRA _s)	-	Anti-resorptive: Aging bone with unrepaired micro-damage PTH: Subcutaneous injection; decrease blood pressure; increases serum calcium; nausea, joint aches, pain, leg cramps.	\$10+ billion
VS-105	Osteoporosis, CKD complications, etc.	50	TBD	TBD

Note: CKD, chronic kidney disease; PTH, parathyroid hormone; SERMs, selective estrogen receptor modulators; SHPT, secondary hyperparathyroidism; TBD, to-be-determined; TI, therapeutic index; VDRA_s, vitamin D receptor agonists