

The Future of Osteoporosis Care in Research and Practice

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Treatment Summary

- We have the tools to identify patients at risk; in FRAX[®], bone mineral density (BMD), age and previous fractures in particular are strong, independent predictors of fracture risk
- Treatments significantly decrease fracture risk:
 - “Antiresorptive” therapy produces a modest BMD increase, yet decreases fracture risk—especially in the spine—much faster and to a larger extent than predicted by the relatively small change in BMD. This implies an important improvement in bone “quality”
 - Anabolic therapy with teriparatide increases BMD more than antiresorptive treatment, but it is not yet obvious that fracture protection is greater

Treatment Summary, continued

Even though current treatment agents significantly reduce fracture risk, major challenges remain

- Bone loss *per se* produces no symptoms—and treatment success is defined as the absence of fracture; that absence may not be very impressive from a patient perspective
- No treatment agent meets the ideal profile—inexpensive, easy to take, uniformly effective, entirely free of risk
- Perceived risk of therapy may outweigh perceived benefit
- Patient motivation to “comply” and “persist” with therapy may vary
- It is still not obvious which patient “should” be treated with which agent at what point in time

Objective of Intervention

The most important clinical objective is the prevention of fractures—both vertebral and non-vertebral fractures

Changes in surrogate markers--bone mineral density (BMD) and biochemical markers of bone turnover--are “necessary” but are not “sufficient”

Non-Pharmacological Options

- Taken as a whole, non-pharmacological options seem to be relatively inexpensive, and modestly effective
- Exercise in particular has other health benefits, although the same is likely to be true for diet optimization
- Optimization of the diet, exercise and fall prevention should be viewed as important adjuncts to the treatment of osteoporotic patients

FDA-Approved Therapeutic Options in the USA

Prevention

Stops bone loss

Estrogen

Alendronate
Risedronate
Ibandronate
Zoledronic acid
Raloxifene

Treatment

Reduces vertebral fractures

Calcitonin

PTH (teriparatide)
Denosumab

Normal Coupling of Bone Remodeling

Resorption = Formation

- Most treatment agents (bisphosphonates, SERMs, calcitonin, estrogen) act primarily on the left side of the equation—to decrease bone resorption
- A decrease in resorption is followed by a decrease in formation—and BMD improvement tends to “plateau” after several years
- Only teriparatide acts on the right side of the equation—to stimulate formation

Antiresorptive Treatment: Summary

- **Antiresorptive treatment decreases fracture risk more rapidly and to a larger extent than one would predict from the relatively small changes in BMD**

Fracture protection can be observed in the absence of a significant change in BMD

- **Fracture protection persists even when the BMD reaches a plateau**

BMD stability does not mean “non-response”

- **Fracture reduction is most conspicuous in older patients with prevalent vertebral fractures**

Anti-resorptive Agents: Clinical Trial Results

Trials of Different Agents Cannot Be Compared Directly

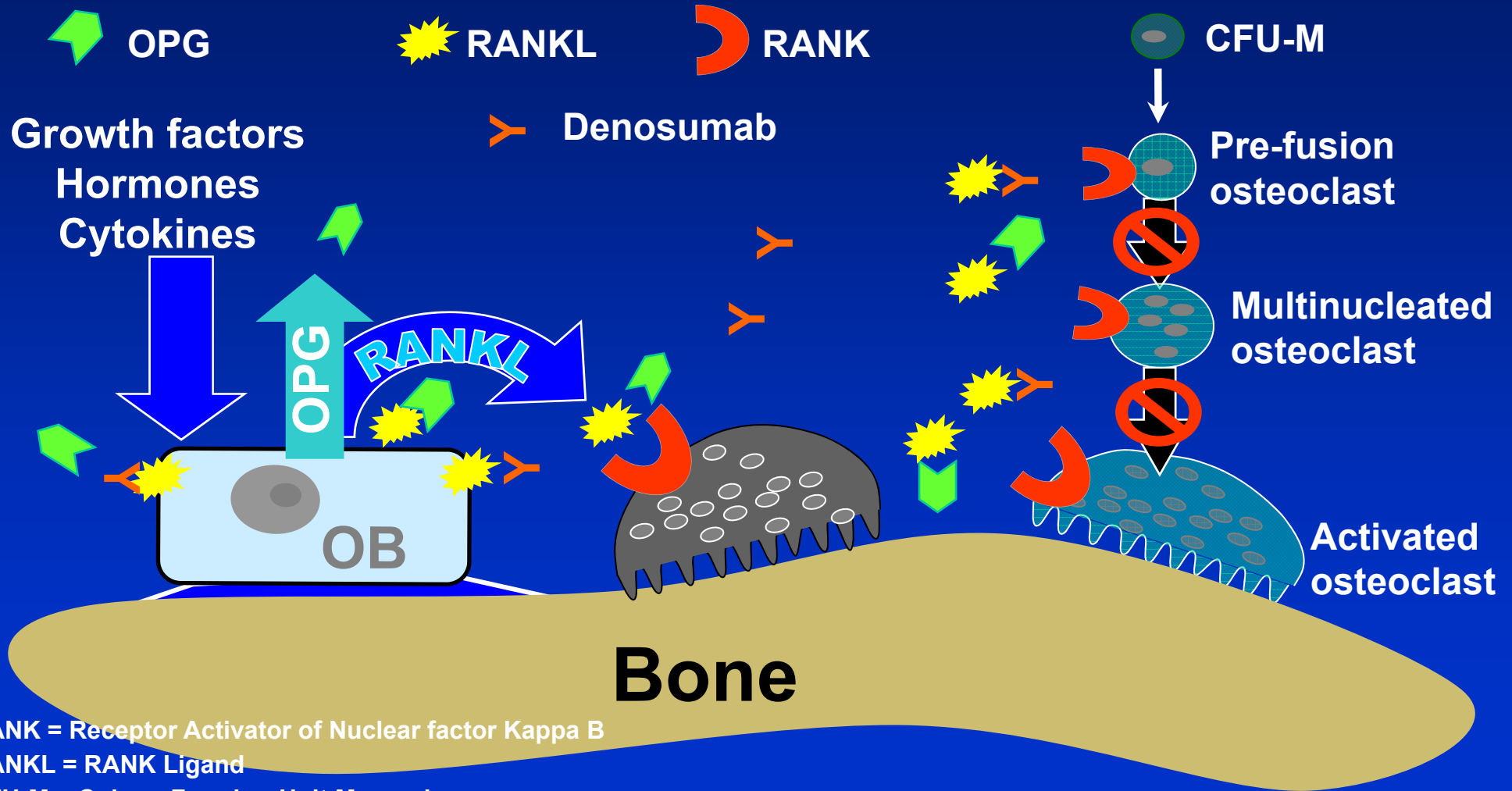
Effect on fracture risk

<u>Agent</u>	<u>Spine</u>	<u>Non-spine</u>	<u>Hip</u>
Estrogen	+	+	+
Raloxifene	+	-	-
Calcitonin	+	-	-
Denosumab	+	+	+
Alendronate	+	+	+
Risedronate	+	+	+
Ibandronate	+	§	-
Zoledronic acid	+	+	+

+ documented in randomized, controlled trial; - effect not documented

§ effect documented only in a post hoc analysis of a high-risk sub-group (femoral neck T score < -3)

RANKL Antibody/RANKL: Activation Of Osteoclasts

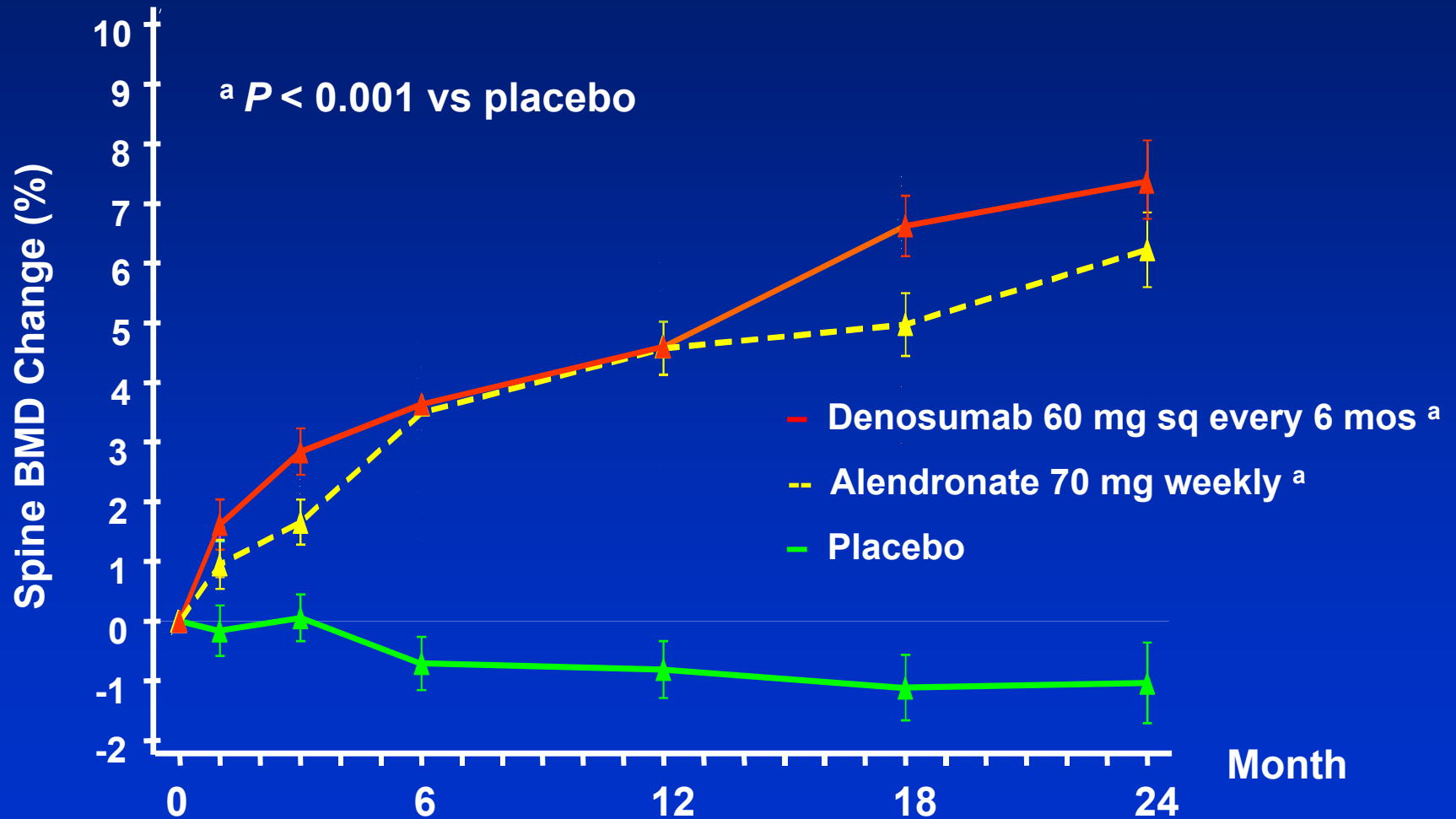


RANK = Receptor Activator of Nuclear factor Kappa B
RANKL = RANK Ligand
CFU-M = Colony-Forming-Unit Macrophage
OPG = Osteoprotegerin

Adapted from Boyle, et al. *Nature* 2003;423:337

Denosumab vs Alendronate

% Change Spine BMD



Adapted in part from McClung MR, et al. *N Engl J Med.* 2006;354:821-31

Denosumab Fracture Trial: FREEDOM

Fracture **RE**duction **E**valuation of **D**enosumab in **O**steoporosis every 6 **M**onths

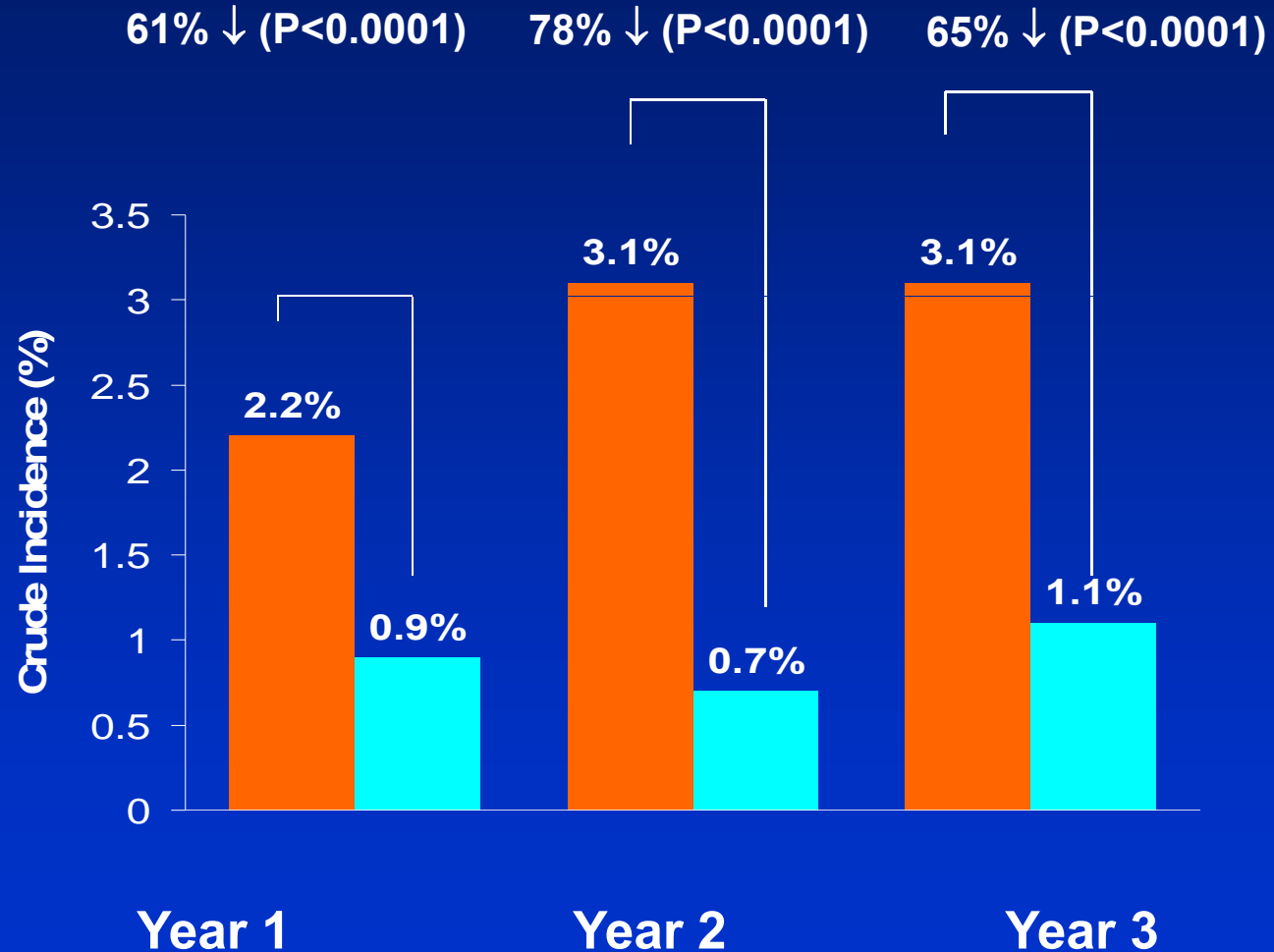
- Phase 3 RCT in postmenopausal women age 60–90 with lumbar spine or total hip T-score <-2.0 and ≥-4.0
- Randomized to denosumab 60 mg Q6M vs PBO
- Endpoints
 - Primary: new vertebral fractures at 36 months
 - Secondary: time to first hip and nonvertebral fractures

Cummings SR, et al. Presented at 30th Annual Meeting of the ASBMR, Montreal 2008. Abstract 1286.

Cummings SR, et al. *N Engl J Med.* 2009;368:756-765

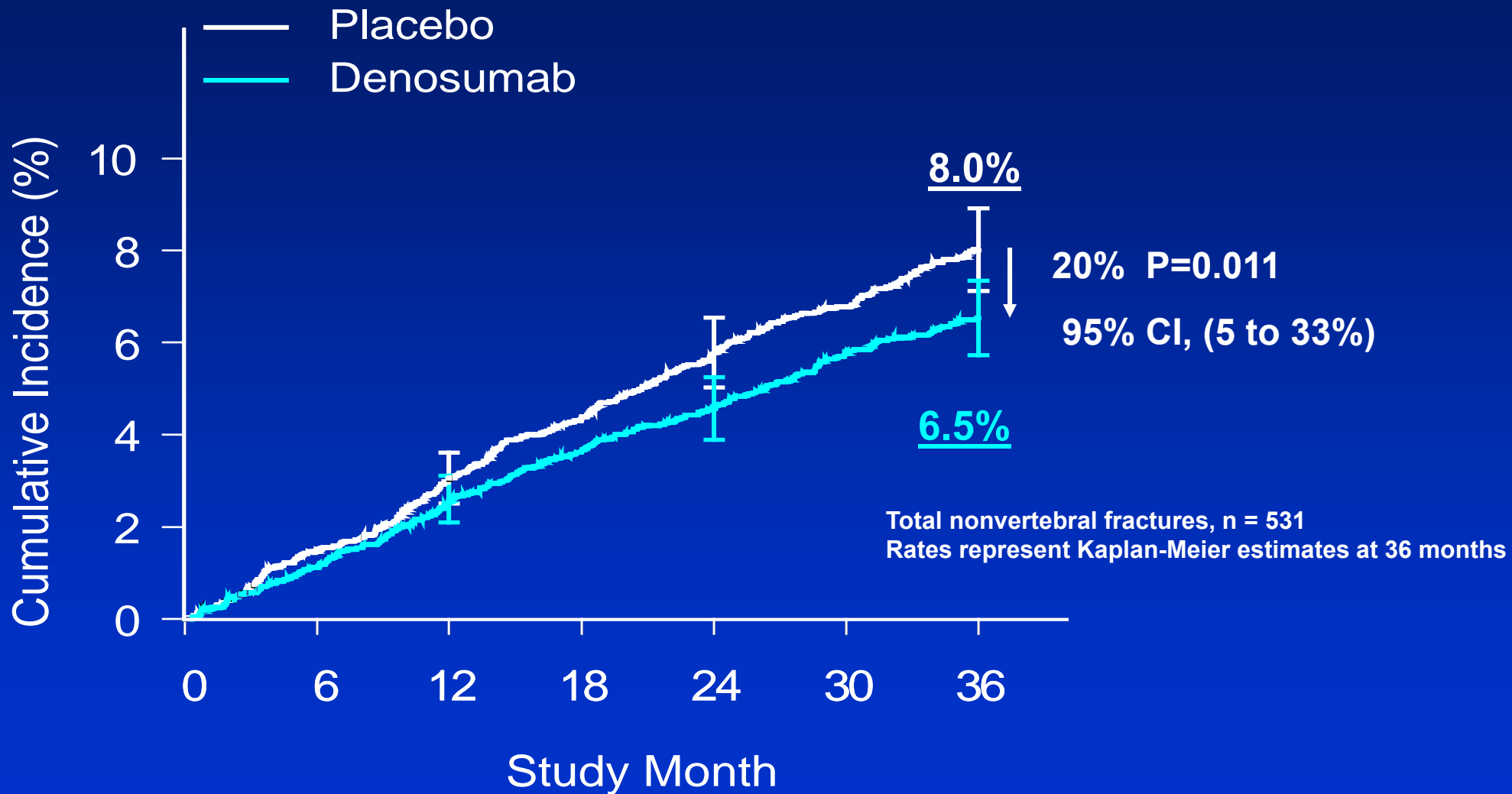
FREEDOM: Vertebral Fracture Risk Reduction

■ Placebo
■ Denosumab



Cummings SR, et al. Presented at 30th Annual Meeting of the ASBMR, Montreal 2008. Abstract 1286.
Cummings SR, et al. *N Engl J Med.* 2009;368:756-765

FREEDOM: Nonvertebral Fractures



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Cummings SR, et al. *N Engl J Med.* 2009;368:756-765

FREEDOM: Selected Safety Data

Event	Placebo	Prolia
Cancer	3.2%	3.7%
Infection	3.4%	4.1%
Cellulitis *	<0.1%	0.3%
Concussion *	0.3%	<0.1%

*** > 0.1% and $p < 0.01$**

Novel Therapies

- **SERMs: lasofoxifene, bazedoxifene**
- **Strontium**
 - **strontium ranelate**
 - **strontium malonate**
- **Anti-sclerostin antibody**
- **Cathepsin K inhibitor – odanacatib**
- **Cyclic analog of PTH (1-31)**
- **Calcium receptor antagonist – “calcilytic”**

The Concept of a SERM

Selective Estrogen Receptor Modulator

- **Binds to the estrogen receptors**
- **Produces an estrogen agonist effect in some tissues**
- **Produces an estrogen antagonist effect in others**

SERMs

Selective Estrogen Receptor Modulators (EAAs: Estrogen Agonist/Antagonists)

- tamoxifen
- raloxifene
- lasofoxifene
- bazedoxifene

Bazedoxifene: “BZA”: Investigational SERM

Pivotal fracture trial compared placebo, BZA 20 mg daily, BZA 40 mg daily and raloxifene 60 mg daily over 3 years

- Spinal BMD increase at 24 months – roughly 1.5% relative to placebo
- New vertebral fracture risk reduction: 42%, 37% and 42% with BZA 20, BZA 40 and raloxifene, respectively
- Non-vertebral fracture risk reduction of 40% with BZA in a subgroup (FN T-score ≤ -3.0 or ≥ 1 moderate/multiple vertebral fractures), but not in the entire study group
- Increase in hot flashes and venous thromboembolic events, relative to placebo

Lasofoxifene: Investigational SERM

Postmenopausal Evaluation and Risk reduction with Lasofoxifene The PEARL Trial

Major outcomes at the end of 5 years:

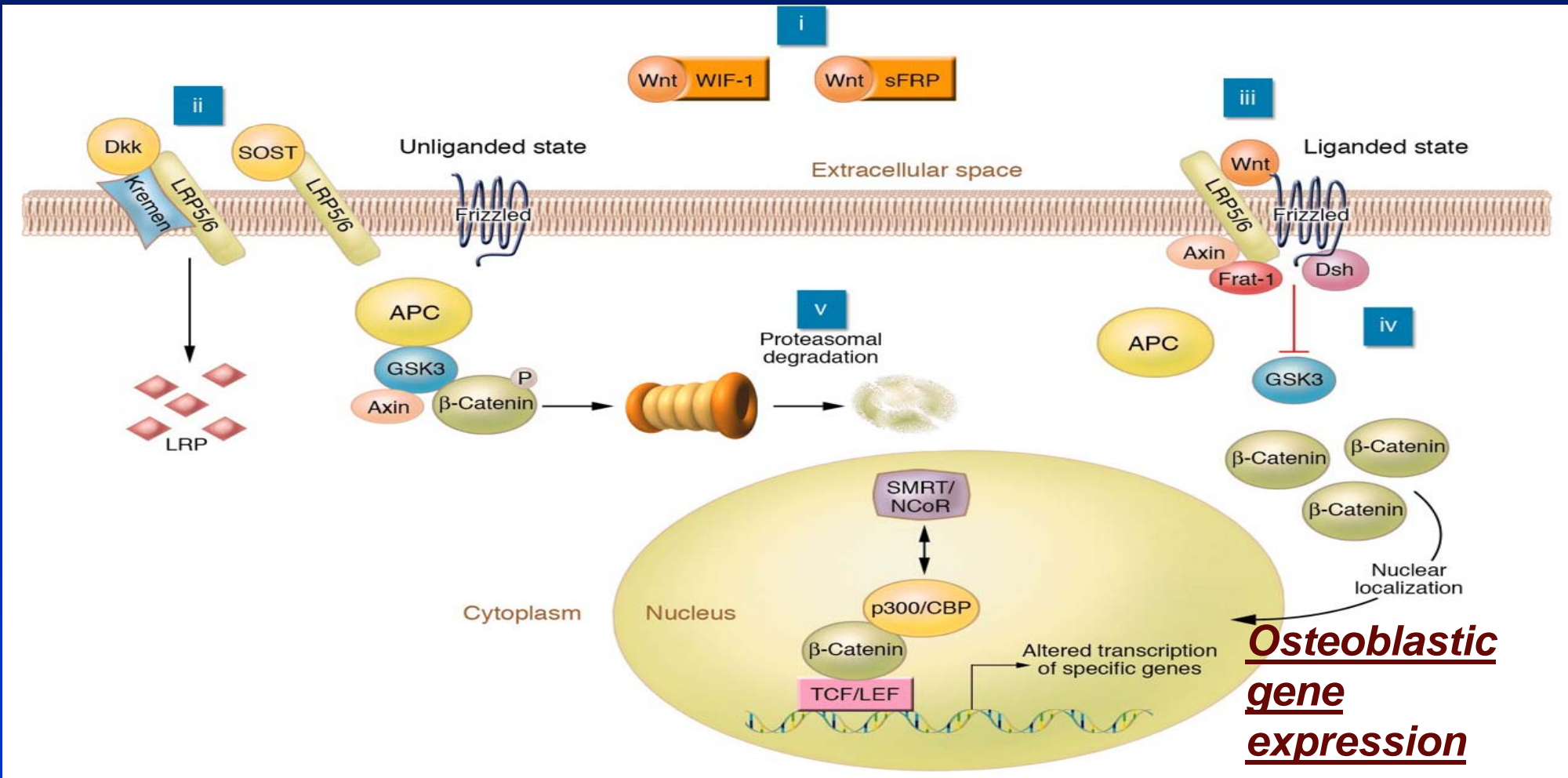
- 42% and 31% reductions in vertebral fracture with lasofoxifene 0.5 mg and 0.25 mg, respectively**
- 24% reduction in non-vertebral fracture with lasofoxifene 0.5 mg; no significant effect on hip fracture alone**
- 85% reduction in invasive breast cancer with lasofoxifene 0.5 mg**
- Reductions in coronary artery disease and stroke**
- Increases in venous thromboembolic disease**
- Increases in leg cramps, hot flushes, uterine polyps, endometrial hypertrophy, vaginal candidiasis and arthralgias with lasofoxifene**
- 38% increase in all cause mortality with lasofoxifene 0.25 mg, no significant increase with lasofoxifene 0.5 mg**

Cummings SR, et al. *N Engl J Med* 2010;362:686-696

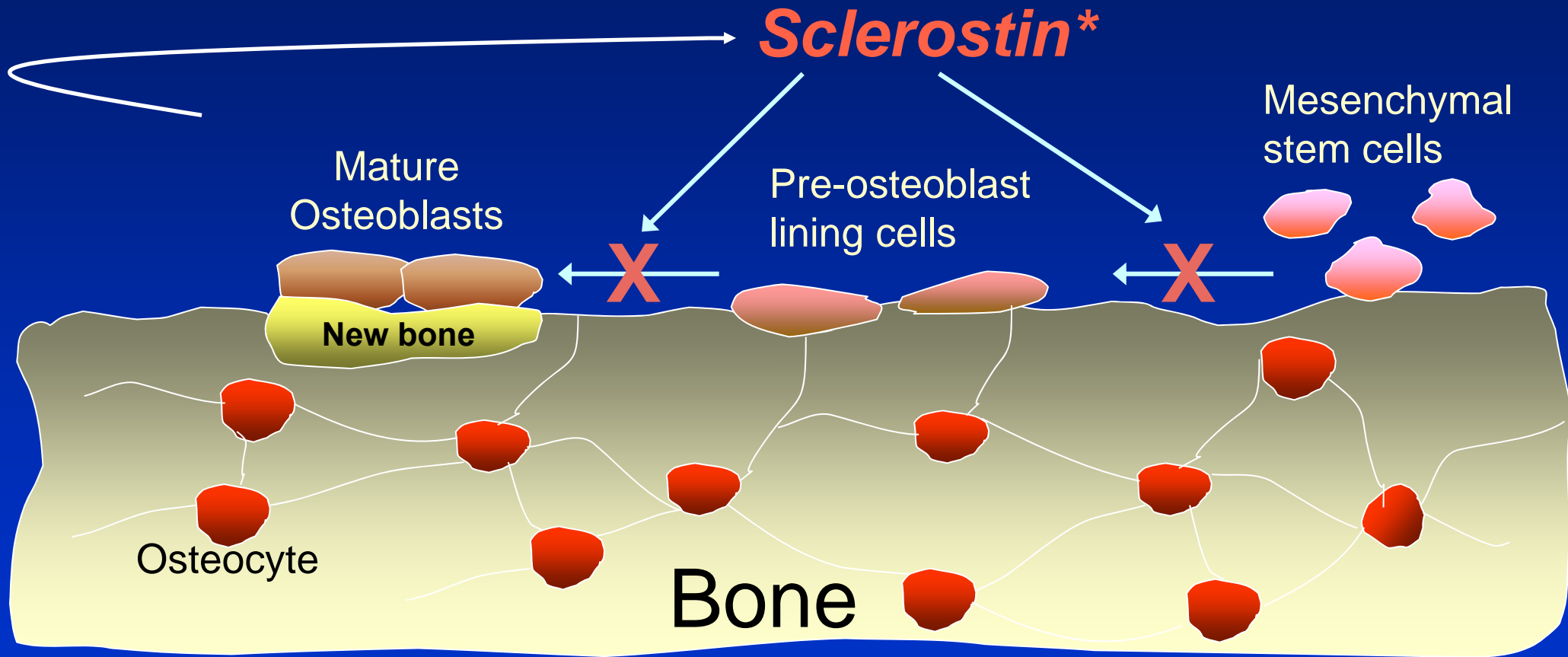
Strontium

- Available in Europe as powdered strontium ranelate
 - Efficacy established in “classic” 3-yr fracture studies
 - Decreases vertebral fracture by 41%
 - Decreases hip fracture by 36%
 - Said to be both anabolic and anti-resorptive—but the histologic data have not been strongly supportive
 - Part of the BMD increase is attributable to the incorporation of strontium—a heavy metal—in bone
- Highlights
 - Why doesn't strontium ranelate enter the US market?
 - New salt being studied (strontium malonate) - Phase 2b

Wnt, LRP5, Sclerostin Pathway



Sclerostin Secreted by Osteocytes Negatively Regulates Bone Formation



Ott SM. *JCEM* 2005;90: 6741-6743

Semenov MV, et al. *JBC* 2006;281: 38276

Slide courtesy of Dr. Dolores Shoback

Semenov M, et al. *JBC* 2005;280: 26770

Li X, et al. *JBC* 2005; 280:19883

A New Anabolic Approach: Inhibit A Regulator Of Bone Formation

- **Sclerostin**
 - From osteocytes¹
 - Inhibits the anabolic Wnt signaling pathway²
 - Deficiency results in a sclerosing bone disease (sclerostosis)³
 - Antibody to sclerostin restores bone mass and bone architecture in rats and monkeys^{2,5}
 - Clinical trials just beginning

¹ van Bezooijen, et al. *J Bone Miner Res.* 2005;20 (Suppl 1):S9

² Warmington K, et al. *J Bone Miner Res.* 2005;20(Suppl 1):S22

³ Gardner JC, et al. *J Clin Endocrinol Metab.* 2005

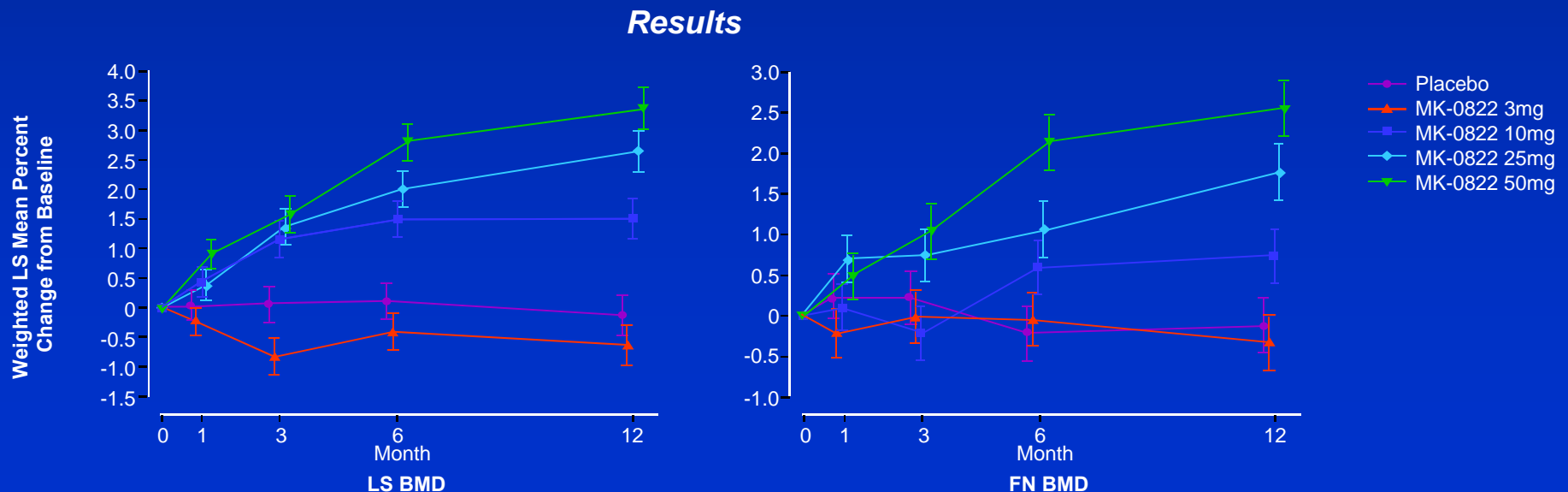
⁵ Ominsky M, et al. *J Bone Miner Res.* 2006;21(Suppl 1):S44

Anti-Sclerostin Antibody

- **Anti-sclerostin antibody – first human study**
 - 48 healthy postmenopausal women
 - Doses: 0.1 to 10mg/kg: single subcutaneous dose
 - Followed for 85 days
- **Results**
 - Dose-related increases in P1NP (similar results for BSAP and OC, two other markers of bone formation)
 - sCTX decreased >50% for the 5 and 10mg/kg doses
 - Increases in BMD at 3 months with the 5 and 10mg/kg doses
 - Spine: 3-5%
 - Total hip: 1.5-3%

Cathepsin K Inhibitor – Odanacatib (MK-0822)

- Postmenopausal women with low BMD: 1-year results
- N=399; received 3, 10, 25, or 50 mg once weekly vs placebo
- Endpoints: changes in BMD and biochemical markers
- Idiosyncratic results from 3 mg dose
 - No increase in BMD or markers higher than in placebo arm
 - Reason for these findings is unknown



Ostabolin-C – Cyclic Analog of PTH (1-31)

- **Phase II trial results – 1-year increases in BMD**
- **N=261; postmenopausal women with BMD T-score \leq -2**
- **Doses: 7.5, 15, 30 or 45 mcg/day subcutaneously**
- **Results**
 - **Spinal BMD (45 mcg dose) – 11% increase**
 - **Total Hip BMD (45 mcg dose) – 2.4% increase**
 - **P1NP: >120% increase; osteocalcin: >100% increase**
 - **Adverse events**
 - **Mild nausea – transient**
 - **Hypercalcemia - infrequent**
- **Pulmonary inhalation – Phase I**

Calcium Receptor (CaR) Antagonist: “Calcilytic”

- **Antagonism of the CaR in the parathyroid gland stimulates endogenous PTH secretion**
- **Short-term pharmacokinetic studies are modestly encouraging**

Treatment: Summary

Safe and effective therapies are available

Antiresorptive agents

- Prevent bone loss and preserve architecture
- Improve quality of bone
- Reduce the risk of vertebral fractures (all agents)
- Alendronate, risedronate, zoledronic acid and denosumab proven to reduce the risk of nonvertebral and hip fractures

Anabolic agent: rhPTH [1-34] (teriparatide)

- Increases bone density and size
- Improves quality of bone
- Reduces the risk of vertebral and nonvertebral fractures; no hip fracture data

Patient factors determine the most appropriate drug to use

Drugs to Treat Osteoporosis

Agent	Cost per year ¹	<u>Effect on Fracture Risk</u>		
		Vertebral	Nonvert	Hip
Raloxifene	\$976*	✓	--	--
Calcitonin	\$1,517*	✓	--	--
Brand alendronate	\$1,103	✓	✓	✓
Generic alendronate	\$108			
Risedronate	\$1,110	✓	✓	✓
Ibandronate (oral)	\$1,024	✓	--	--
Ibandronate (IV)	\$1,938			
Zoledronic acid	\$1,249	✓	✓	✓
Teriparatide	\$9,786	✓	✓	--

✓: antifracture efficacy proven in clinical trial --: antifracture efficacy not proven in clinical trial

¹ AWP (Average Wholesale Price) varies by region and distributor

* Medi-Span Drug Data. Price Rx® Prescription drug database (Accessed 30 October 2009)

Red Book: Pharmacy's Fundamental Reference. Thomson Medical Economics: Montvale, NJ. 2007.