Excellence in Clinical Research Seminars

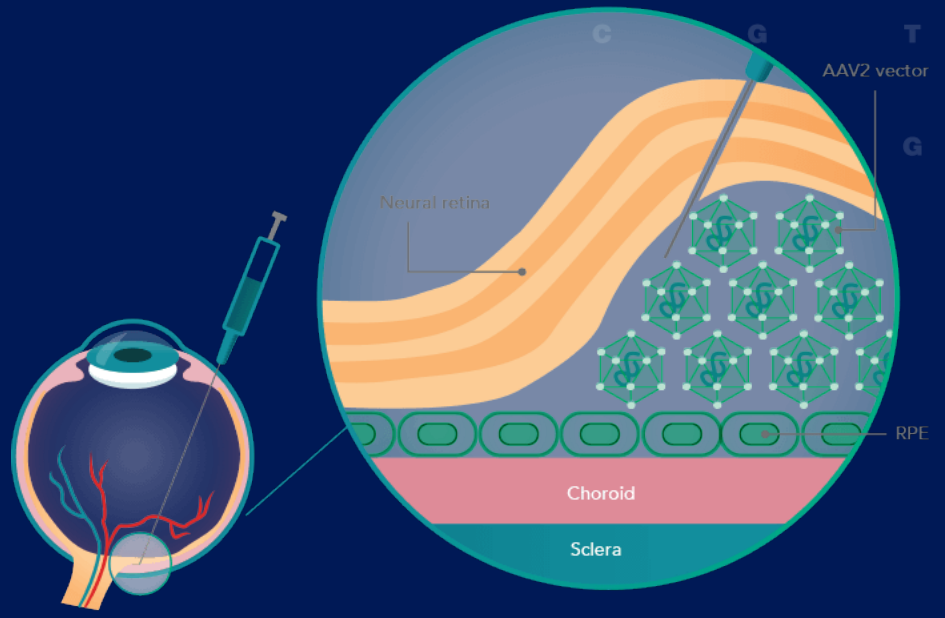
October 27th, 2021

National Human Genome Research Institute

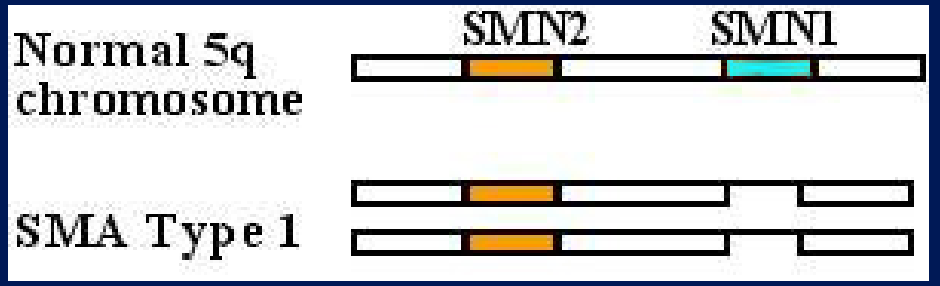
The Forefront of Genomics®

Motivation and Goal

- Genetics is both a diagnostic and therapeutic specialty
- We aim to discuss interventional clinical research
- We welcome active participation and suggestions



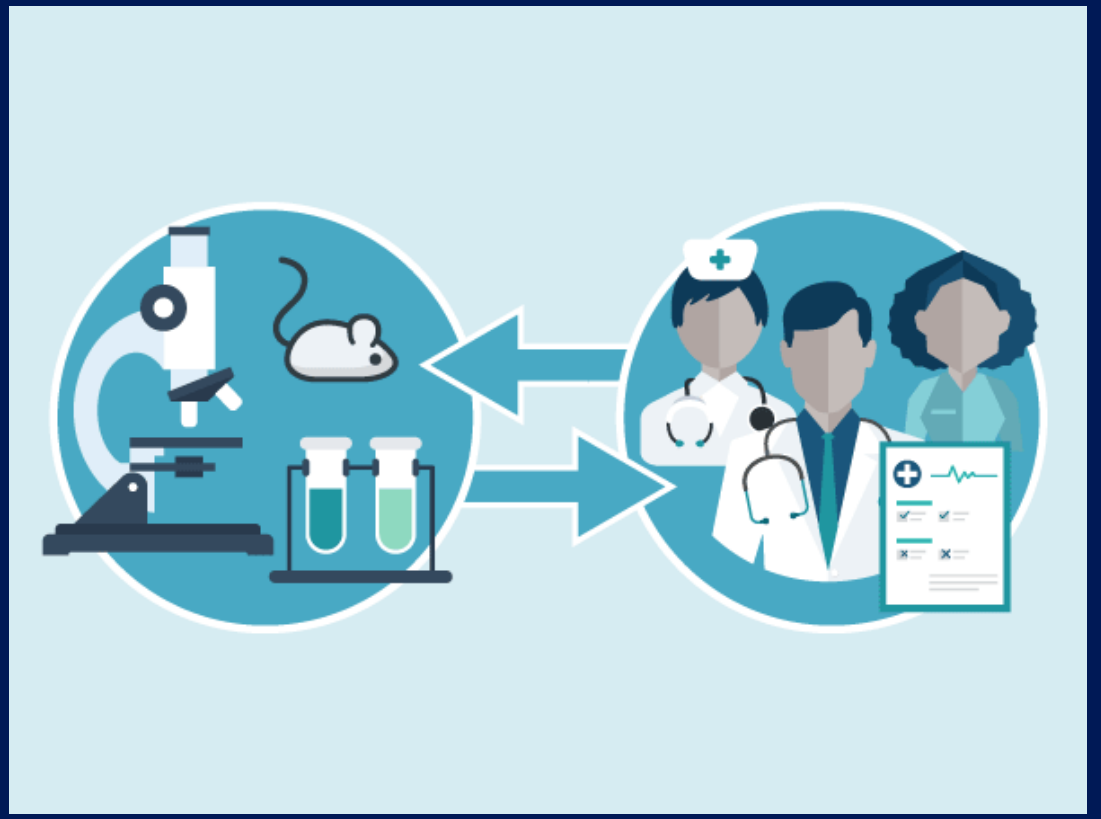
Voretigene FDA approved in 2017



Onasemnogene FDA approved in 2019

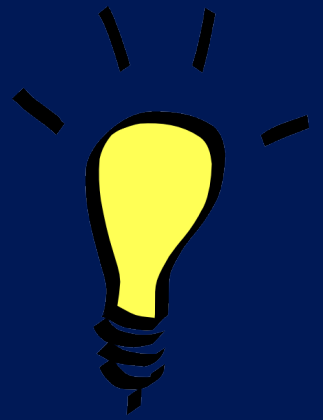
Topics

- Study design
- Preclinical research
- Regulatory Affairs
- Data Management
- Funding/Budgets
- Working with Industry
- Ethics



Building a Study

- Research Question
- Building a Team
- Trial Design
- Eligibility Criteria
- Outcomes and Endpoints
- So many other considerations
  - regulatory, operation, reporting and publication



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2021-22 NHGRI Seminars

Excellence in Clinical Research

October 27, 2021
2:30PM EDT

Clinical Trials in Rare Disorders: Teriparatide in Adults with Osteogenesis Imperfecta

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JCI The Journal of Clinical Investigation

Evaluation of teriparatide treatment in adults with osteogenesis imperfecta

Eric S. Orwoll, … , Sandesh C.S. Nagamani, Brendan Lee

J Clin Invest. 2014;124(2):491-498. https://doi.org/10.1172/JCI71101.

Clinical Medicine

Background. Adults with osteogenesis imperfecta (OI) have a high risk of fracture. Currently, few treatment options are available, and bone anabolic therapies have not been tested in clinical trials for OI treatment.

Methods. 79 adults with OI were randomized to receive 20 μg recombinant human parathyroid hormone (teriparatide) or placebo for 18 months in a double-blind, placebo-controlled trial. The primary endpoint was the percent change in areal bone mineral density (aBMD) of the lumbar spine (LS), as determined by dual-energy X-ray absorptiometry. Secondary endpoints included percent change in bone remodeling markers and vertebral volumetric BMD (vBMD) by quantitative computed tomography, estimated vertebral strength by finite element analysis, and self-reported fractures.

Results. Compared with the placebo group, the teriparatide group showed increased LS aBMD (6.1% ± 1.0% vs. 2.8% ± 1.0% change from baseline; $P < 0.05$) and total hip aBMD (2.6% ± 1.0% vs. –2.4% ± 1.0% change; $P < 0.001$). Vertebral vBMD and strength improved with teriparatide therapy (18% ± 6% and 15% ± 3% change, respectively), but declined with placebo (–5.0% ± 6% and –2.0% ± 3% change; $P < 0.05$ for both comparisons). Serum procollagen […]

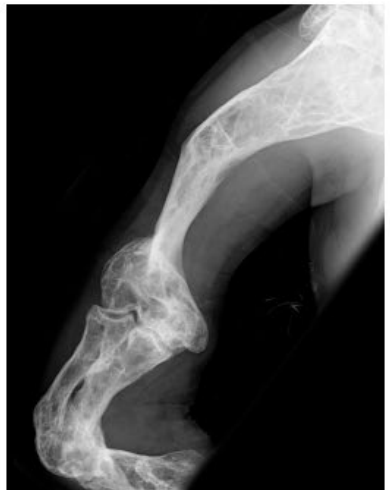
Why We Feature This Clinical Trial

- It is the largest placebo-controlled, randomized trial in adults with OI
- It was the first trial in OI involving an anabolic agent
- Sufficiently powered to detect difference in primary outcomes
- But is it enough to progress from IND to NDA?

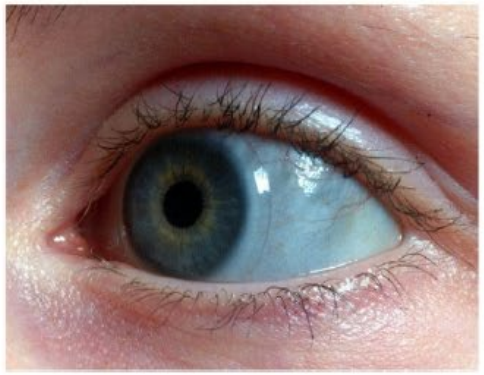
Osteogenesis Imperfecta (OI)

- Heritable connective tissue disorder
- Incidence: 1:15,000 live births
- Variable presentation

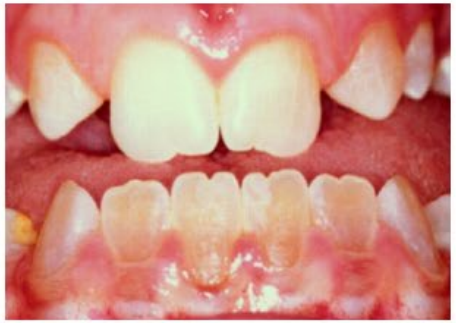
Fractures



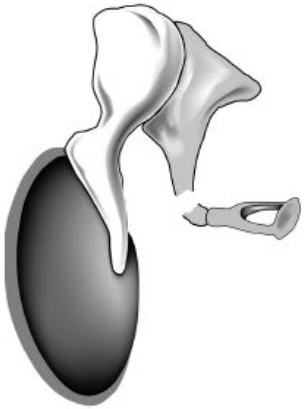
Blue Sclera



Dentinogenesis Imperfecta

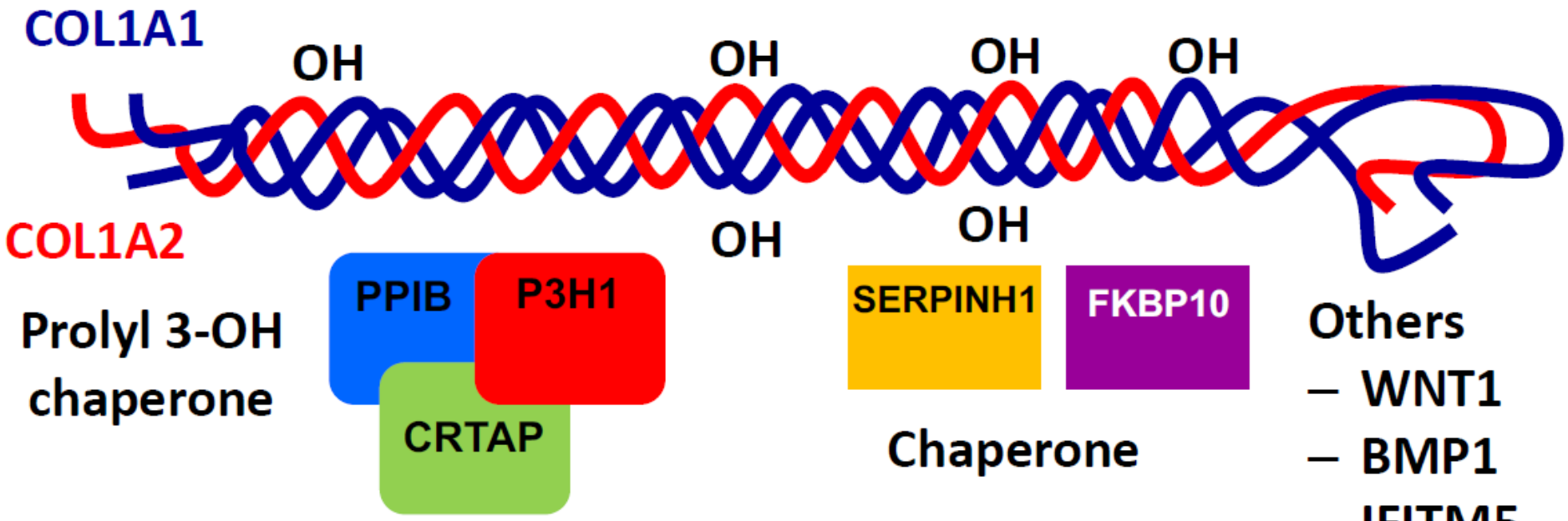


Hearing loss



Illustrations: courtesy of Dr Nagamani et al

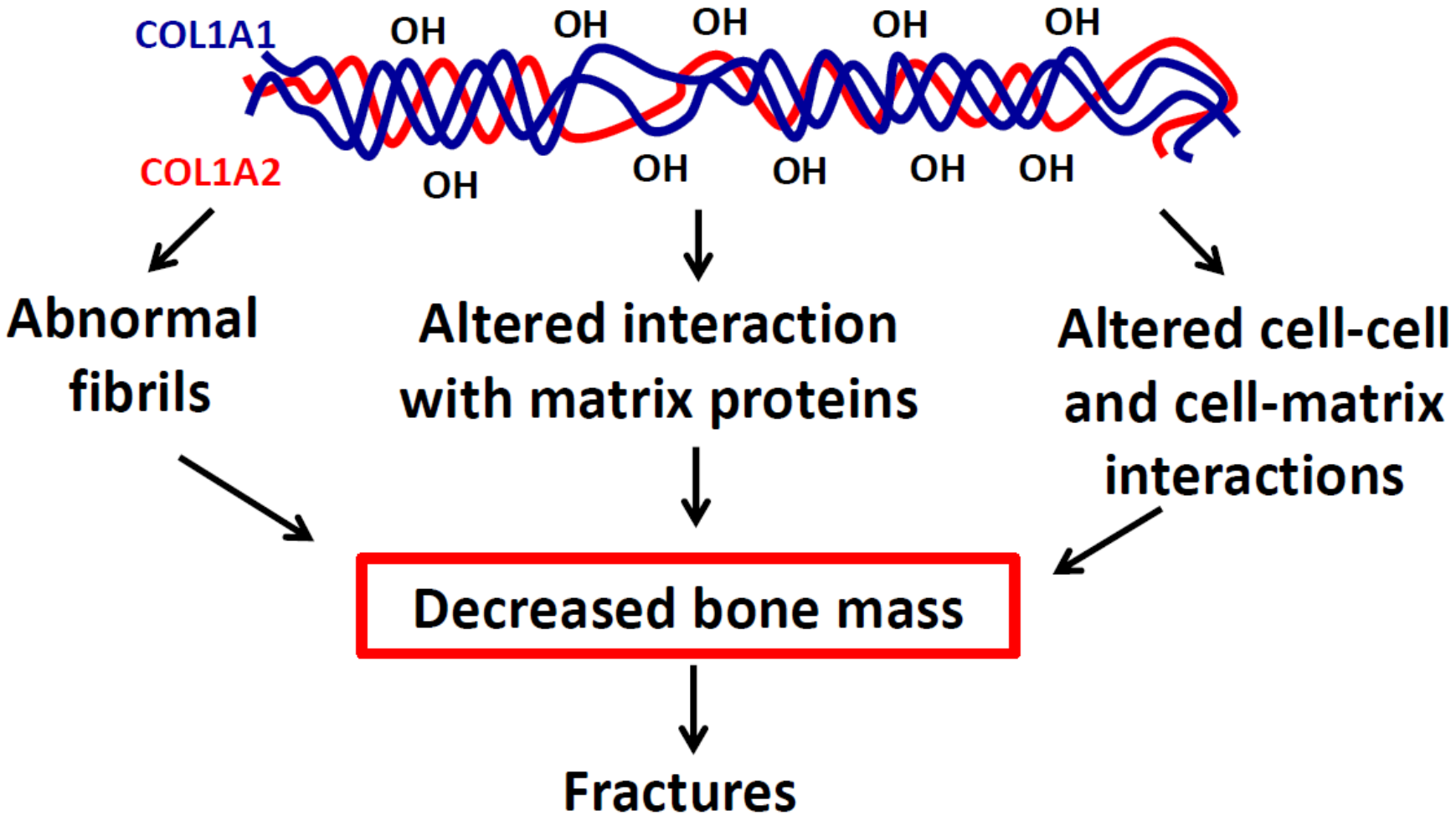
Genetic Heterogeneity of OI



Others
- WNT1
- BMP1
- IFITM5
- PEDF
- SP7
- TMEM38B

Illustrations: courtesy of Dr Nagamani et al

Molecular Mechanisms Leading to Fractures

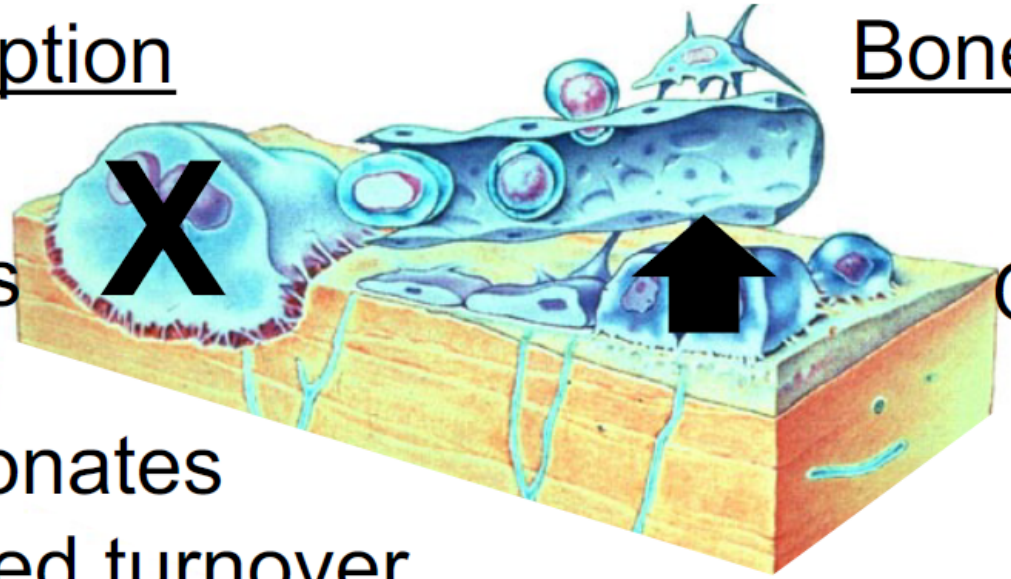


Illustrations: courtesy of Dr Nagamani et al

Study Rationale: Bone Resorption vs Bone Formation

Bone resorption

Bone formation



Osteoclasts

Osteoblasts

Bisphosphonates

- ✓ Decreased turnover
- ✓ Increased BMD
- ✓ Decrease in pain
- ✓ Increased quality of life

?

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Illustrations: courtesy of Dr Nagamani et al

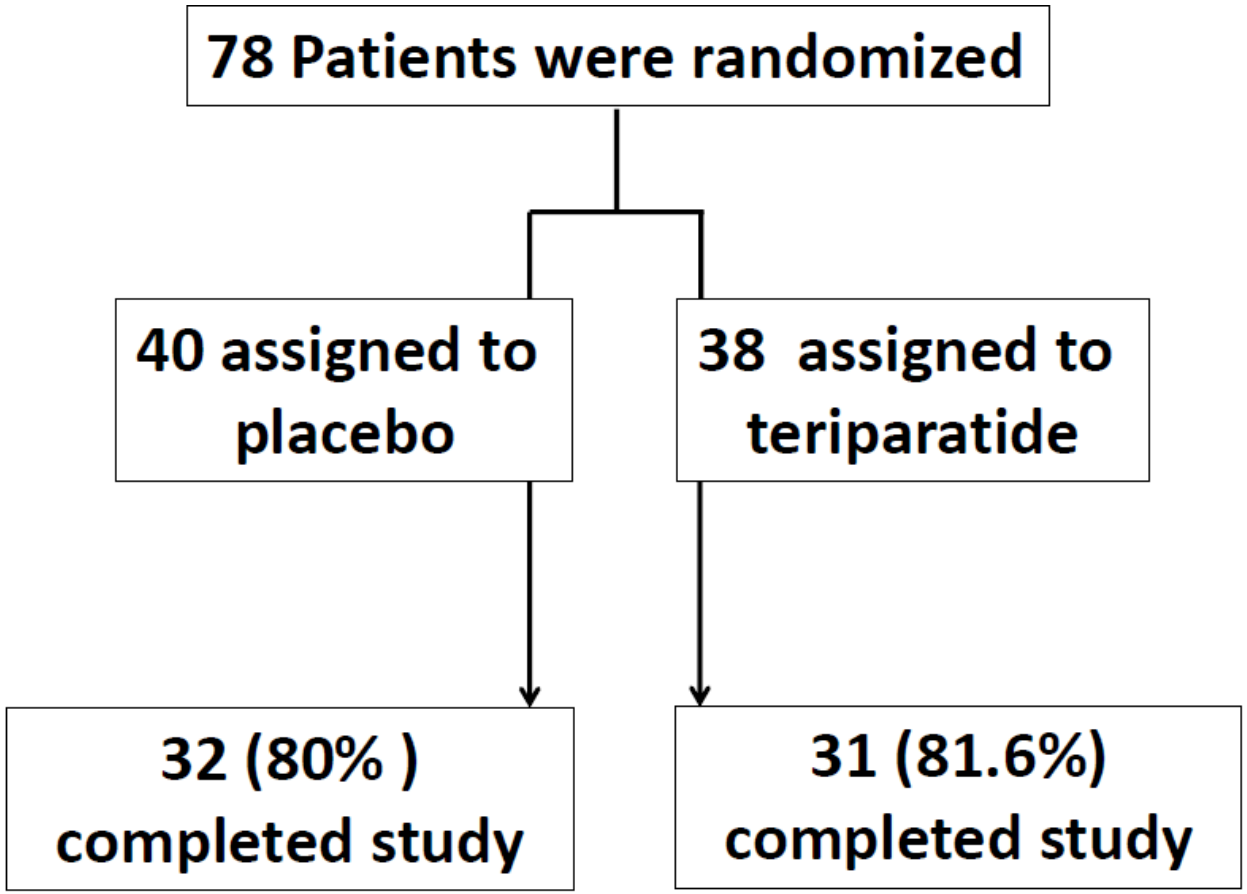
Study Rationale: Teriparatide as Anabolic Agent to Stimulate Bone Formation

- 1-34 amino acids of the N-terminus of parathyroid hormone
- Regulatory status:
  - Approved for treatment of osteoporosis women after menopause
  - Robust increase in lumbar spine BMD
  - Modest increase in the hip BMD
  - Decrease in fractures
- Can it increase BMD in subjects with OI by stimulating bone formation?

Critical Decisions

- A regulatory pathway
- Study design
- Sample power calculations
- Cohort
  - Inclusion and exclusion criteria
- Outcomes
  - Primary
  - Secondary
  - Exploratory

Study Design: Randomized, Double-Blind, Placebo-controlled, Parallel-Group, Non-Crossover



Illustrations: courtesy of Dr Nagamani et al

Power Calculation

- 5% difference between treatment and placebo groups
- Assumptions
  - 80% power
  - 2-tailed $\alpha = 0.05$
  - 15% subject dropout rate
- 90 participants

Study Cohort

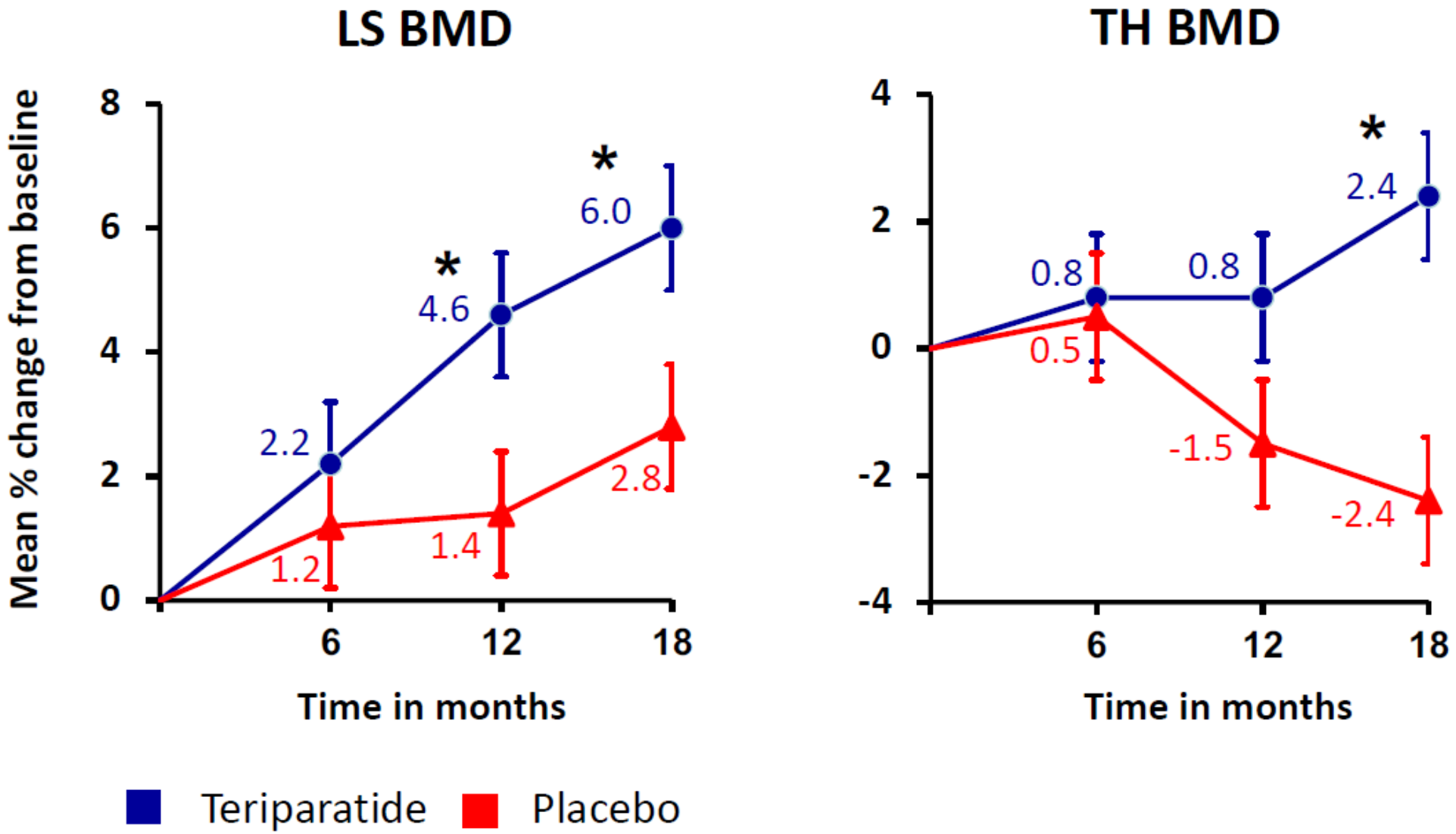
- Inclusion criteria
  - Adults with a clinical diagnosis of OI and fused epiphyses
- Exclusion criteria
  - Bisphosphonate therapy with 12 months of enrollment
  - Abnormal ALP, AST, ALT, elevated serum creatinine, hypo- and hypercalcemia

Trial Endpoints

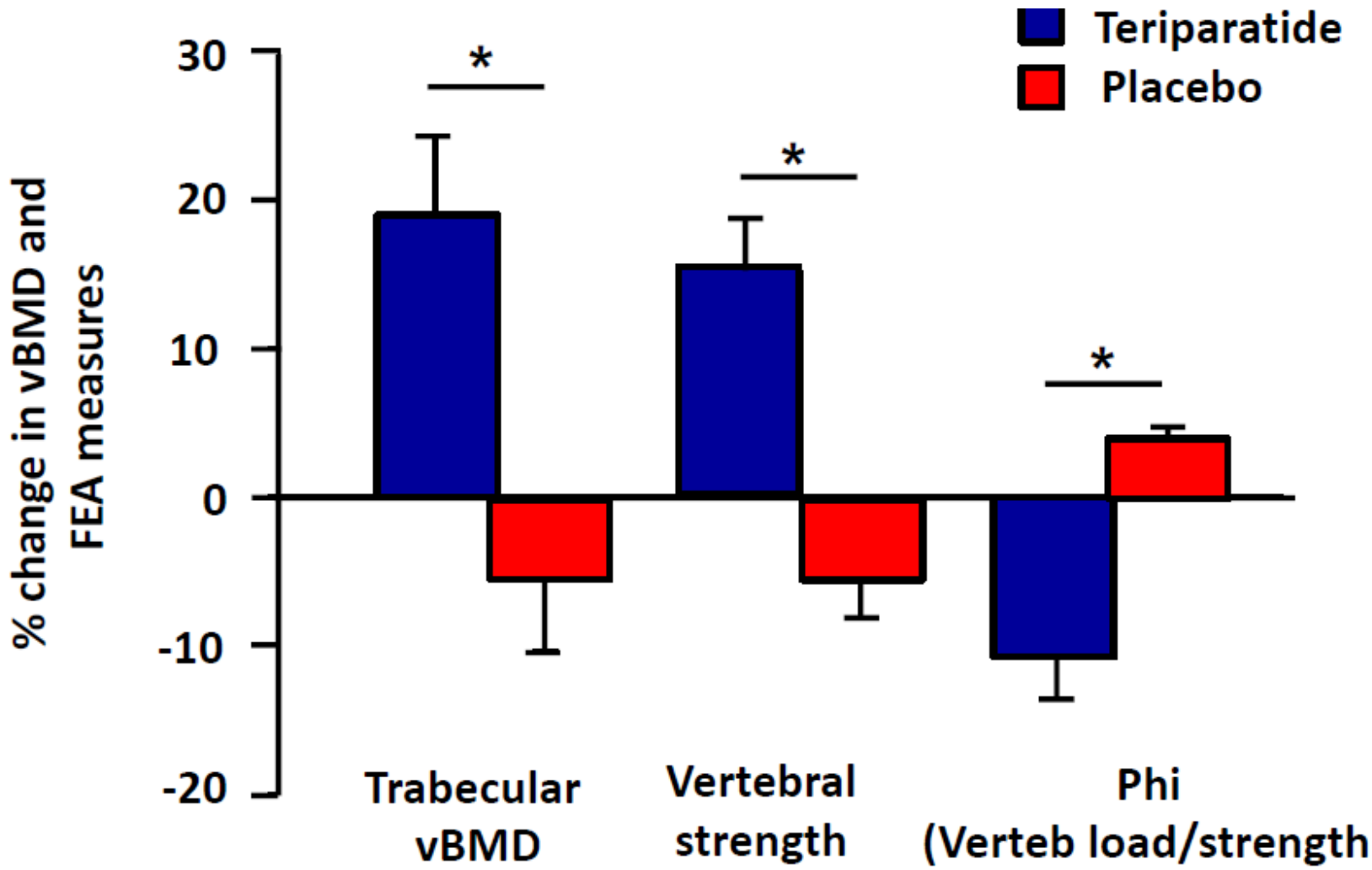
- Primary endpoint
  - Change in the areal BMD at the spine and hip measured by DEXA
- Secondary endpoint
  - Volumetric change in BMD at vertebrae measured by high resolution qCT
  - Estimated vertebral strength by finite element analysis
  - Self-reported fractures

Results

Teriparatide Increases BMD

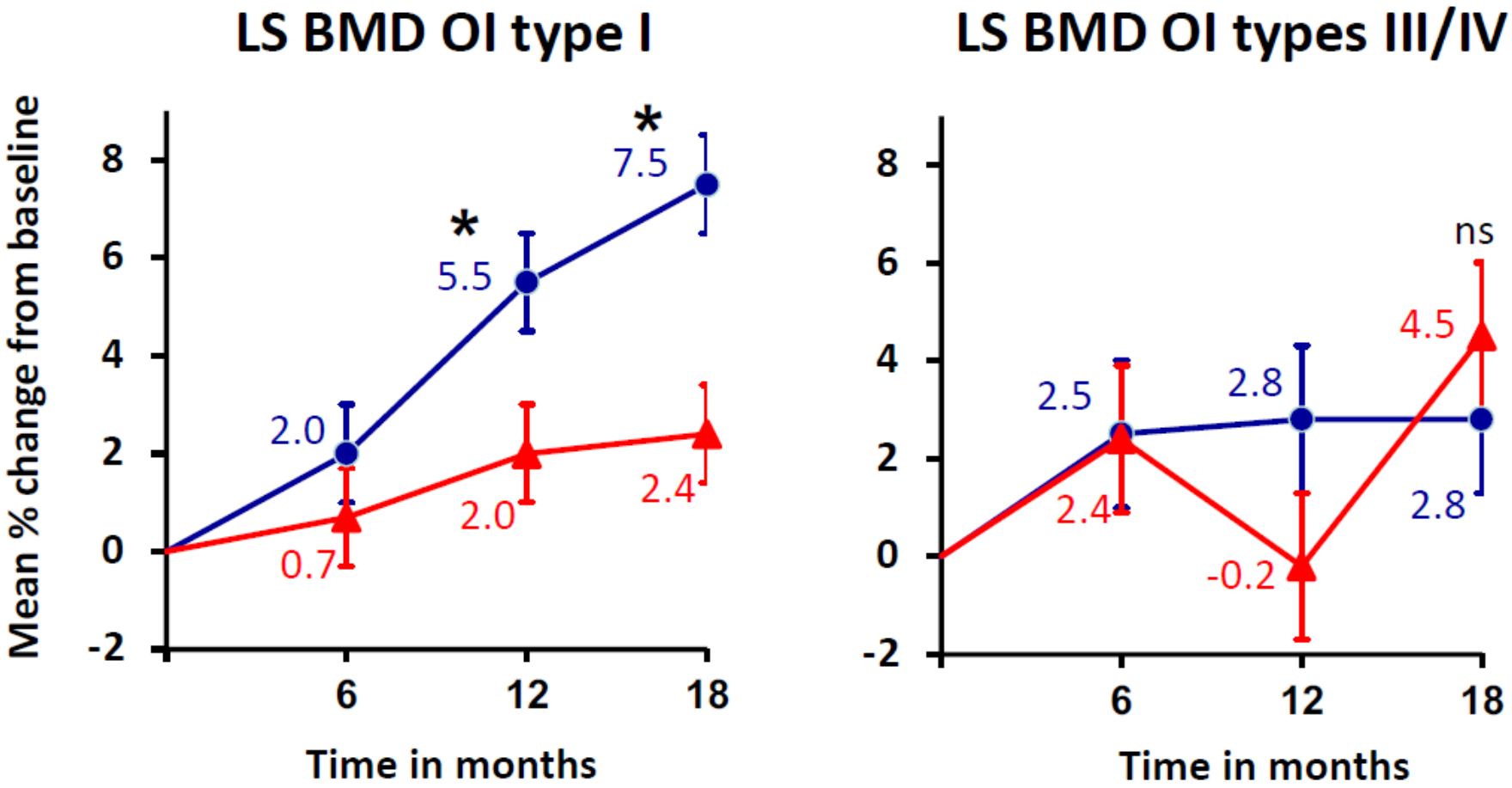


Teriparatide Increases Bone Strength



Illustrations: courtesy of Dr Nagamani et al

Outcomes May Vary Depending on the OI Type



Illustrations: courtesy of Dr Nagamani et al

Safety

- Teriparatide's safety profile
  - No differences were observed between the intervention and placebo groups
  - Serious adverse events?
  - Safety outcomes
- Follow up studies on the risk of osteosarcoma?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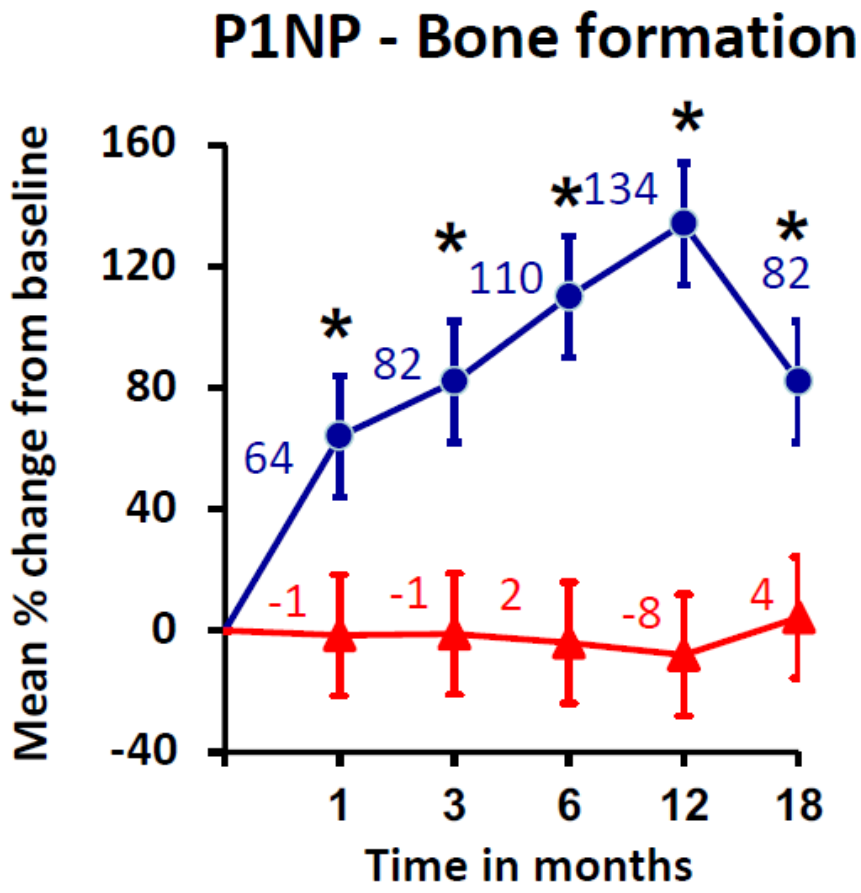
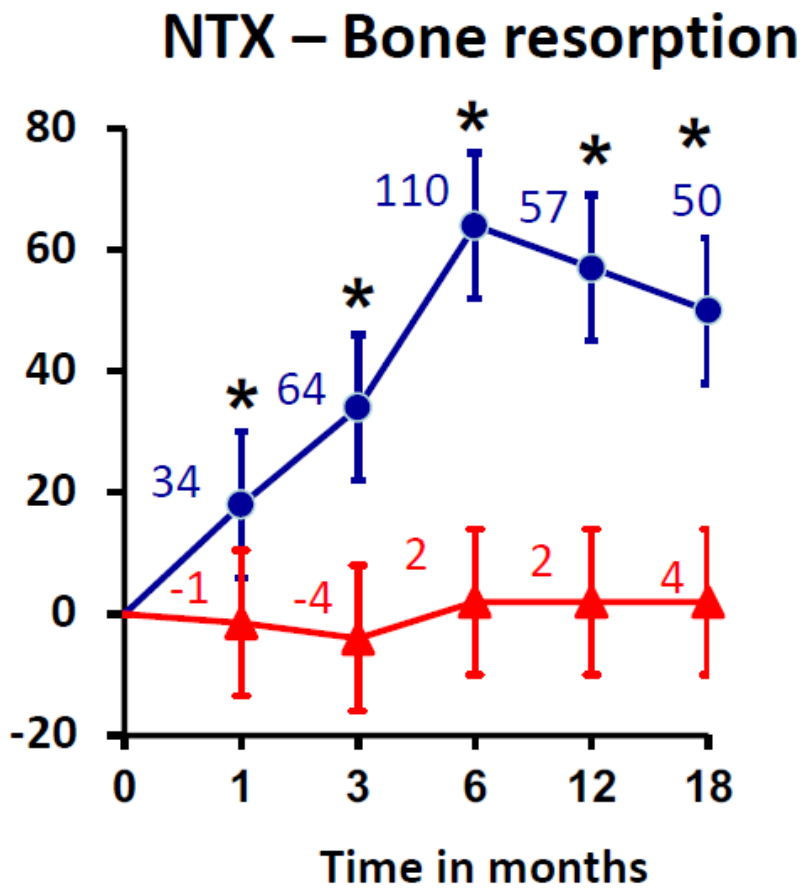
Teriparatide Increases Bone Remodeling





Teriparatide Placebo

Illustrations: courtesy of Dr Nagamani et al