BONIVA®
(ibandronate sodium)

Joseph Kohles, PhD
International Medical Leader

September 9, 2011

FDA Questions to Sponsors

1. Provide an opinion and discussion of whether efficacy and safety data of BONIVA support **long-term use**

2. Provide an opinion and discussion of whether either restricting the duration of use or implementing a **drug holiday** may be beneficial for patients requiring long-term treatment

BONIVA Presentation Roadmap

Pivotal Data

- Fracture trials
- Bridging BMD trials

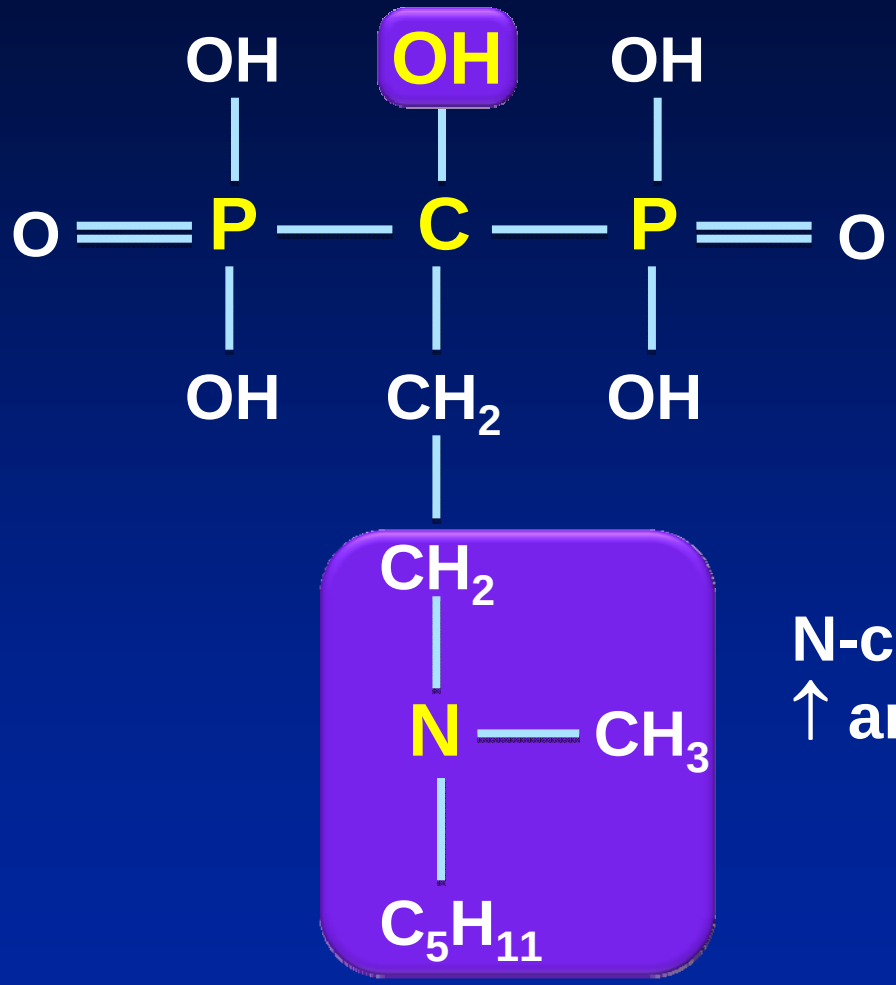
Long-term Data

- Extension trials
- Bone biopsy

Safety

- Overall safety
- Topics of special interest
  - Atypical fractures
  - ONJ
  - Esophageal cancer

BONIVA Characterization



OH group at R1 ↑ affinity for bone mineral

N-containing group within R^1 ↑ antiresorptive potency[2,3]

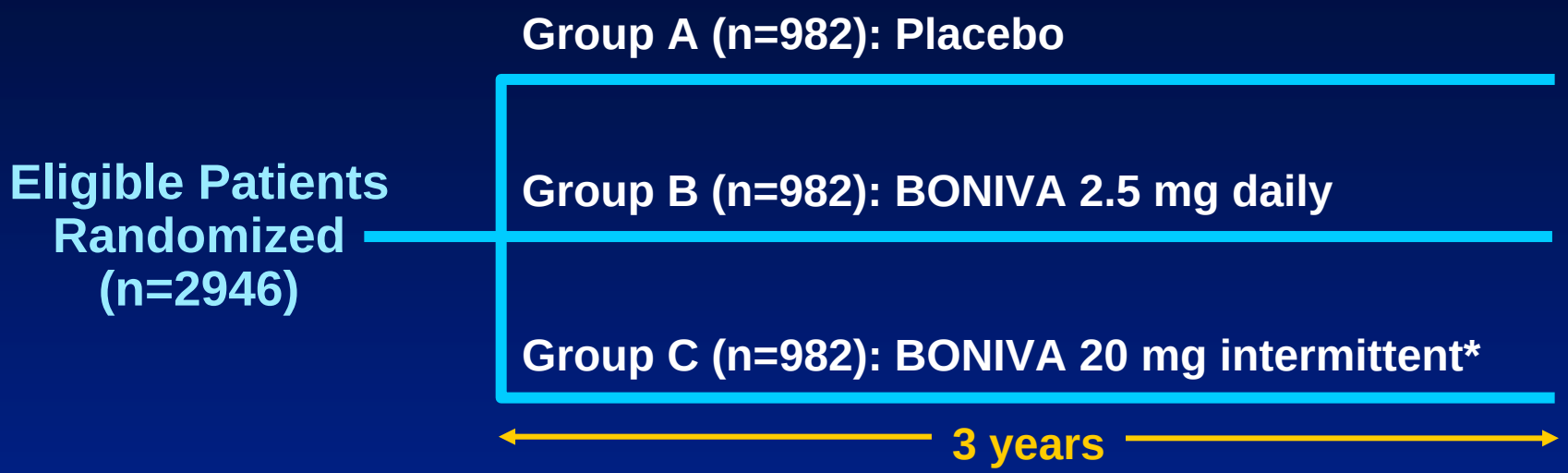
1. Van Beek E, et al. *J Bone Miner Res* 1994;9:1875–82
2. Shinoda H, et al. *Calcif Tissue Int* 1983;35:87–99
3. Geddes AD, et al. *Bone Miner Res* 1994;8:265–306

BONIVA Development Program

Total Patients Treated	**>11,000**
Total Trials	**38**
# of trials with oral formulation	27
# of trials with IV formulation	11
Total Doses Tested* (Daily to Quarterly)	**18**
Oral Formulation	10 (0.25-150 mg)
IV Formulation	8 (0.125-6 mg)

* BONIVA approved and marketed doses: 150 mg po monthly, 3 mg IV quarterly

BONE Pivotal Fracture Trial Design

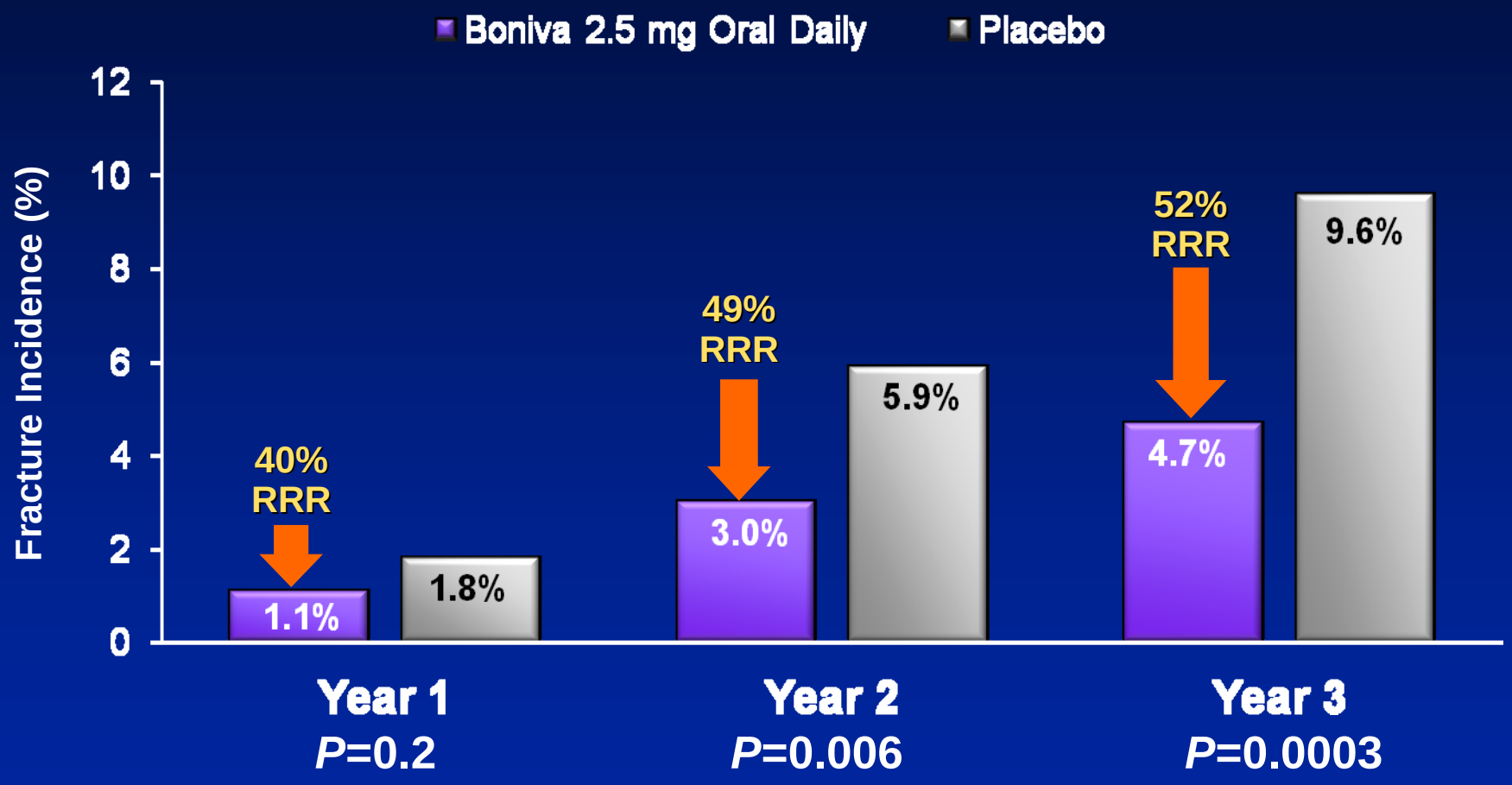


- Randomized, double-blind, placebo-controlled, multi-center trial
- Population: age 55-80, BMD LS T-score < -2.0
- Primary endpoint: new morphometric vertebral fractures at 3 years

*20 mg QoD x 12 doses

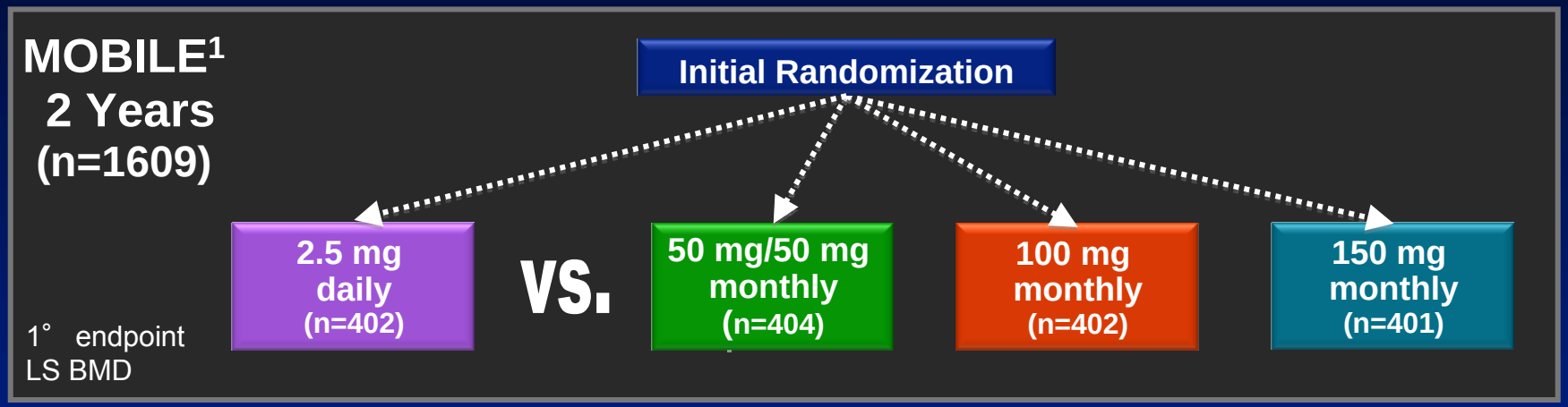
Chesnut CH, et al. *J Bone Miner Res.* 2004;19:1241-1249.

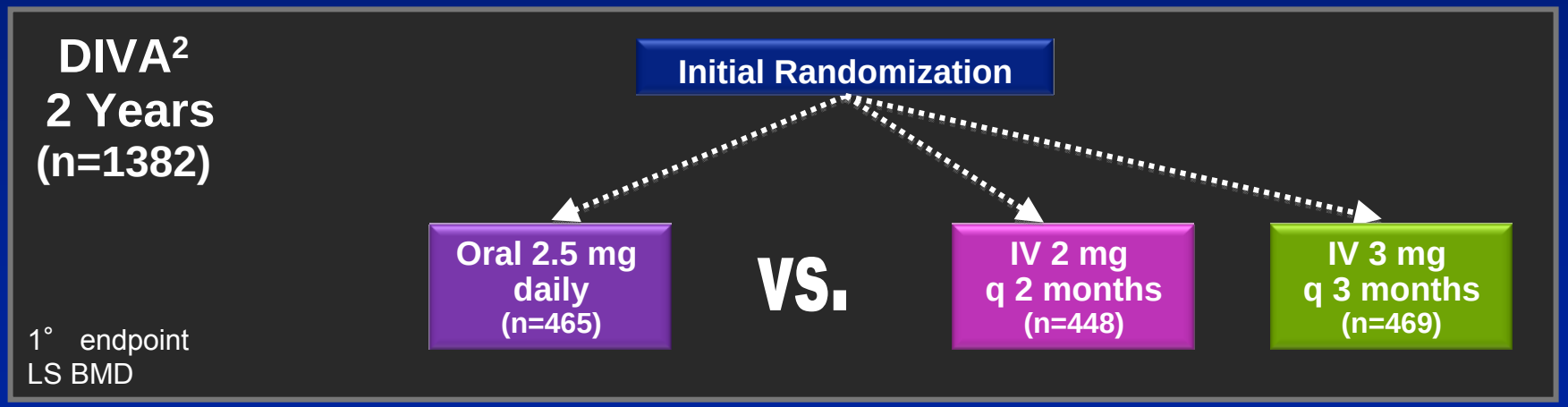
BONE Study:
BONIVA Reduced New Vertebral Fractures



Chesnut CH, et al. *J Bone Miner Res*. 2004;19:1241-1249.

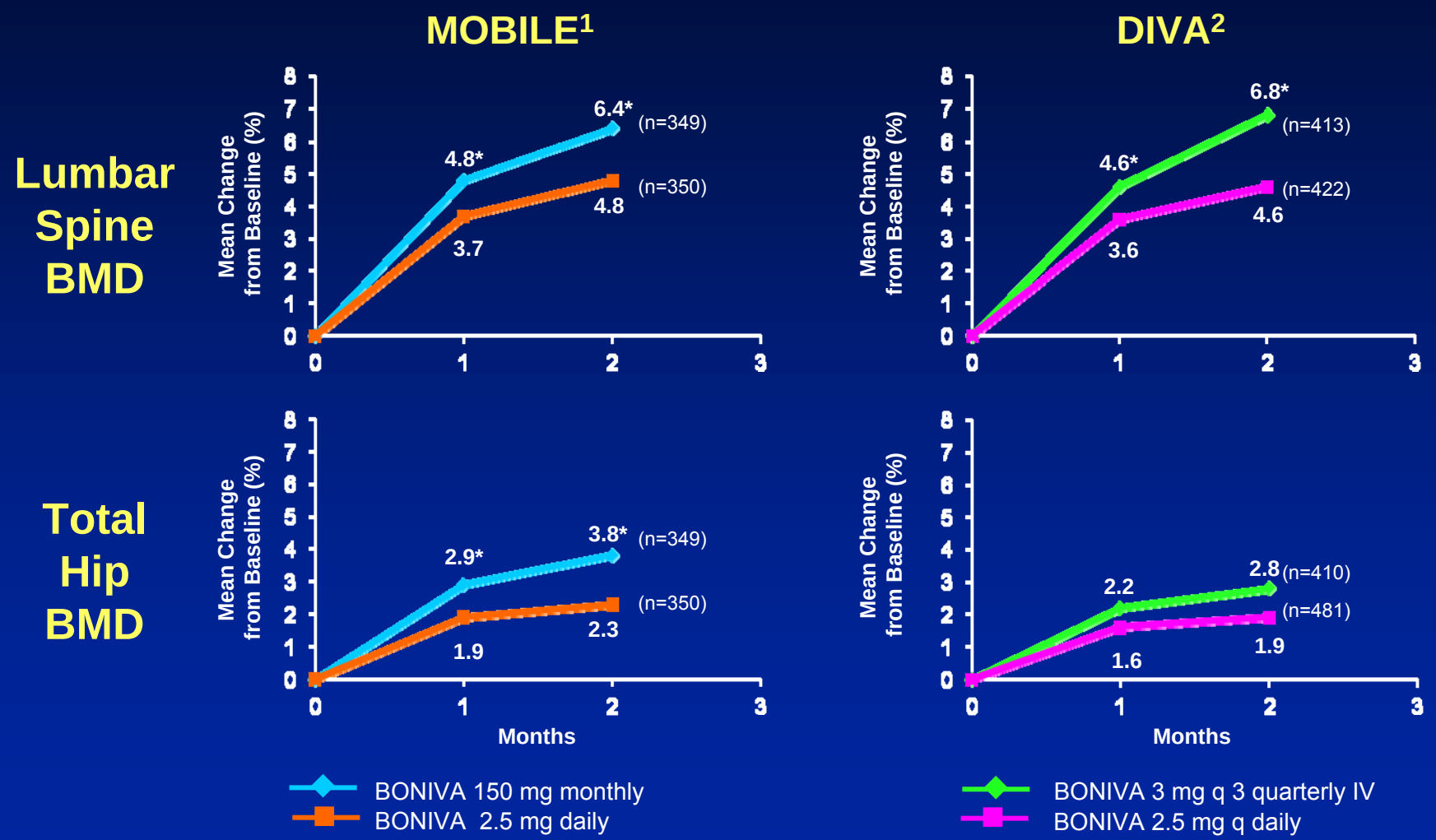
MOBILE and DIVA BMD Bridging Studies





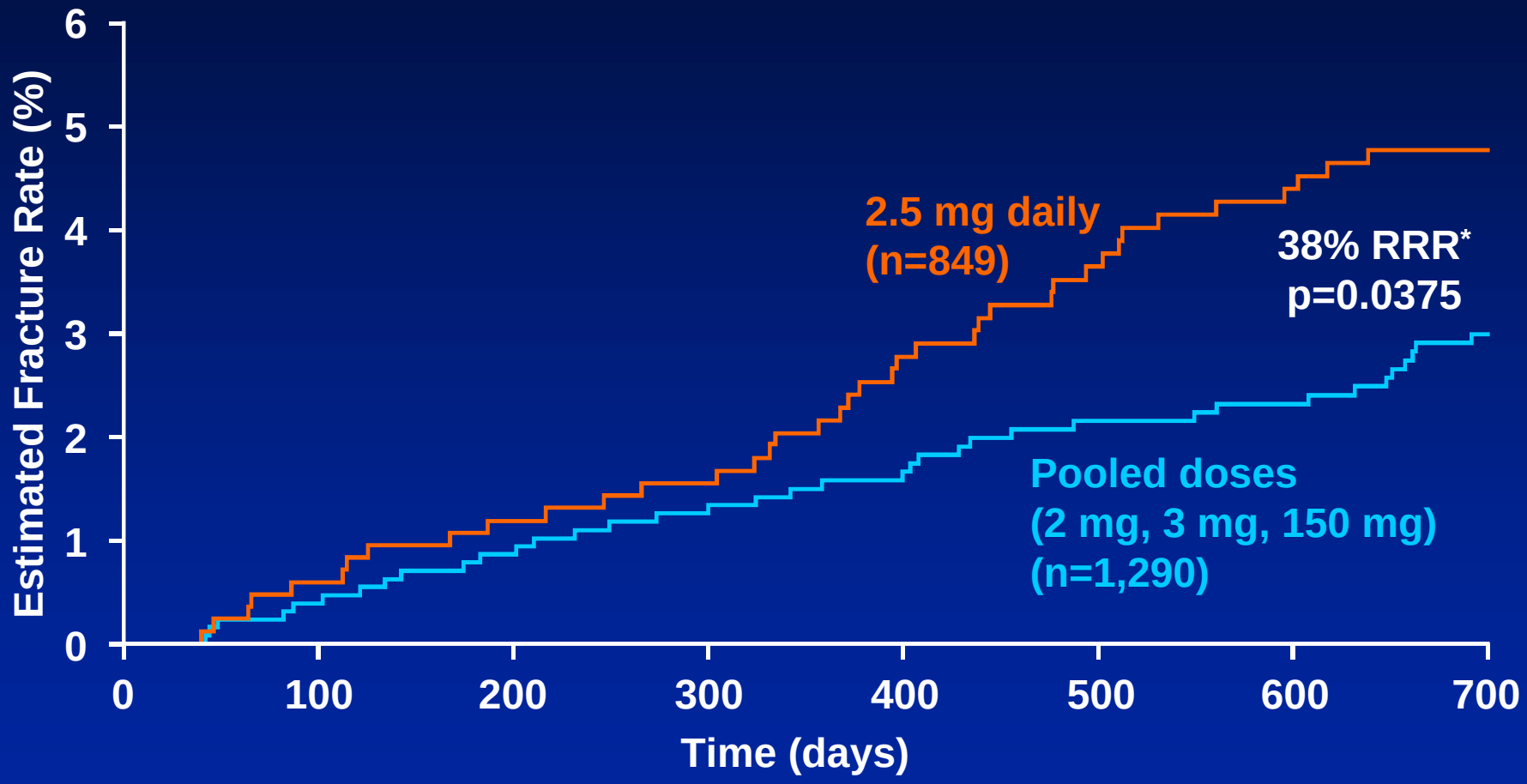
1. Reginster JY et al. *Ann Rheum Dis.* 2006;65:654-661.
2. Eisman JA et al. *J Rheumatol*. 2008;35:488-497.

BONIVA Increased BMD in Lumbar Spine and Total Hip



1. Reginster JE et al. *Ann Rheum Dis* 2006; 65: 654-661
2. Eisman JA et al. *J Rheumatol* 2008;35;488-497

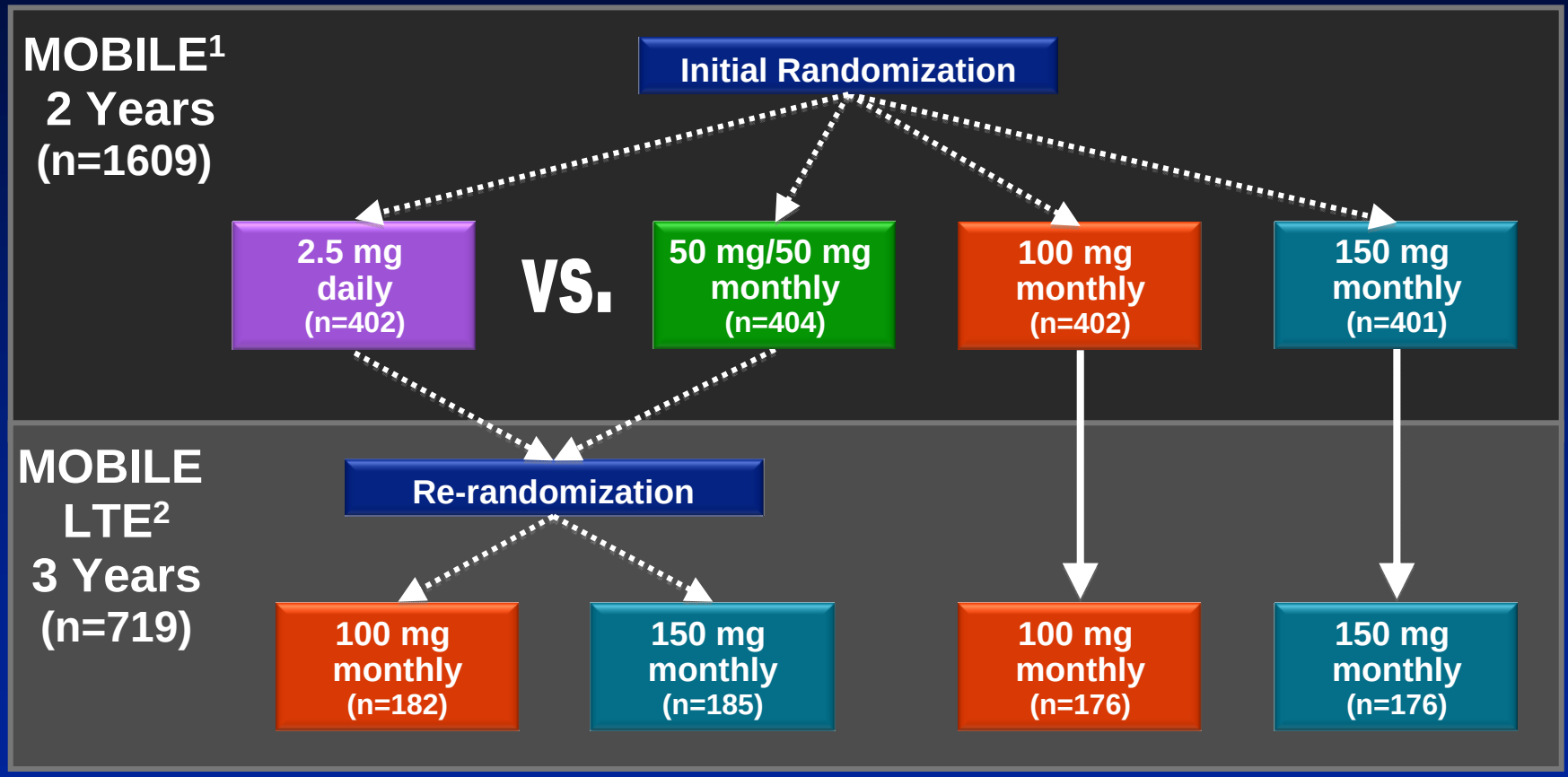
Time to All Clinical Fractures



* Adapted from Cox regression analyses for difference in RR of fracture with pooled doses versus daily dose

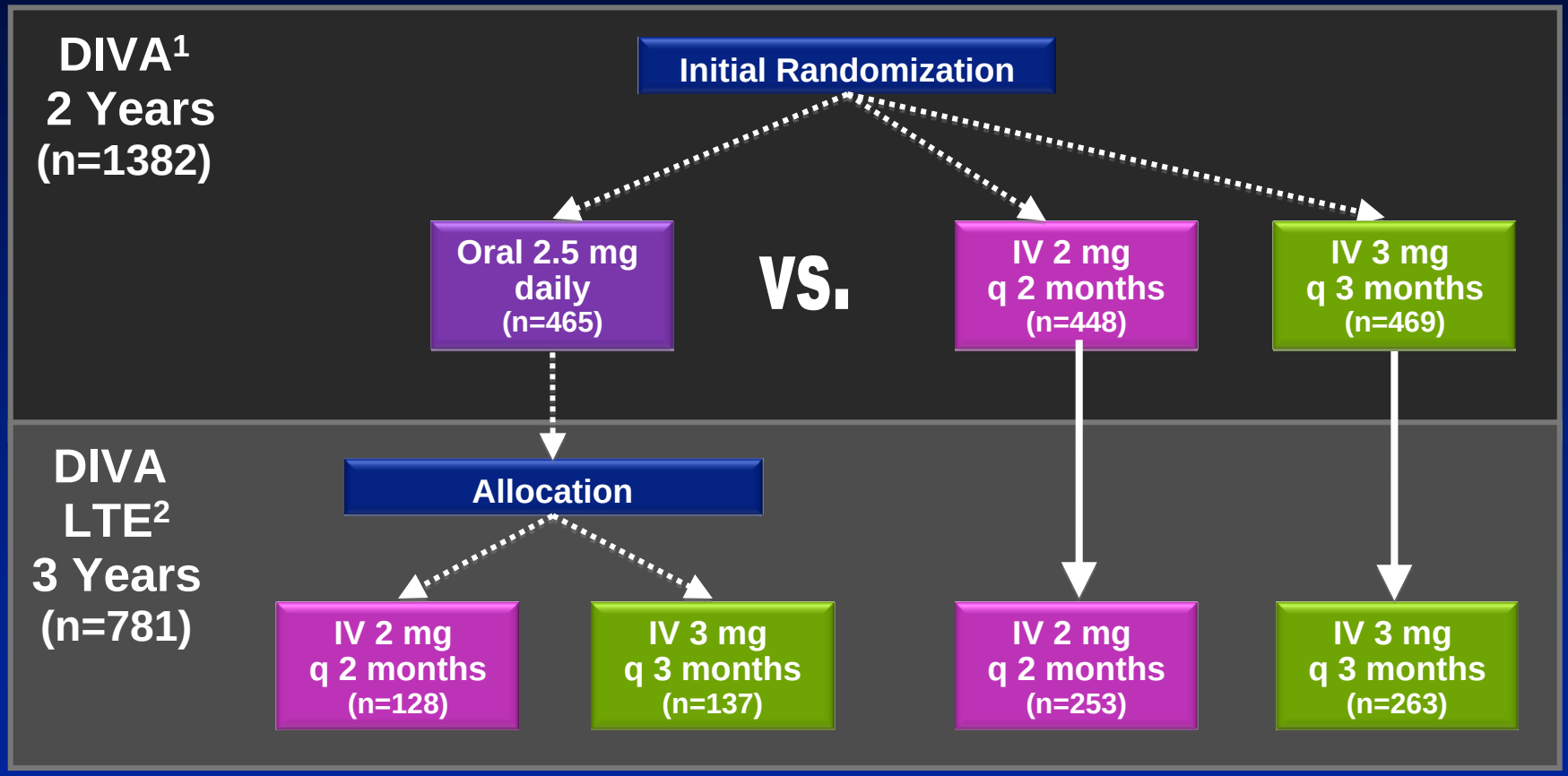
Cranney A, et al. *Osteoporos Int* 2009;20:291–7

MOBILE Long Term Extension (LTE) Study: Monthly Oral Treatment for Up to 5 Years



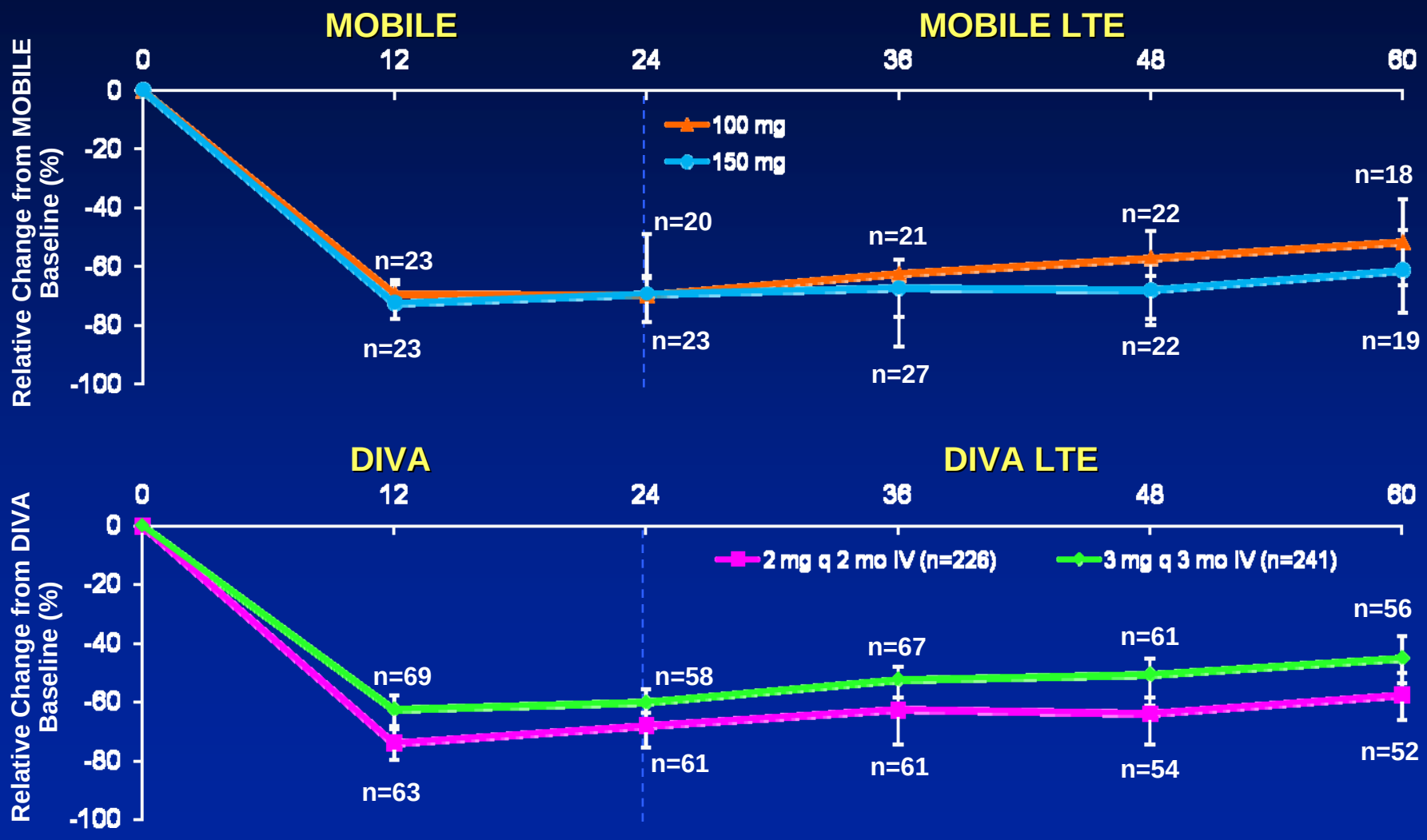
1. Reginster JY et al. *Ann Rheum Dis.* 2006;65:654-661.
2. Osteoporosis International 2011, in press

DIVA LTE Study: Quarterly IV Treatment for Up to 5 Years



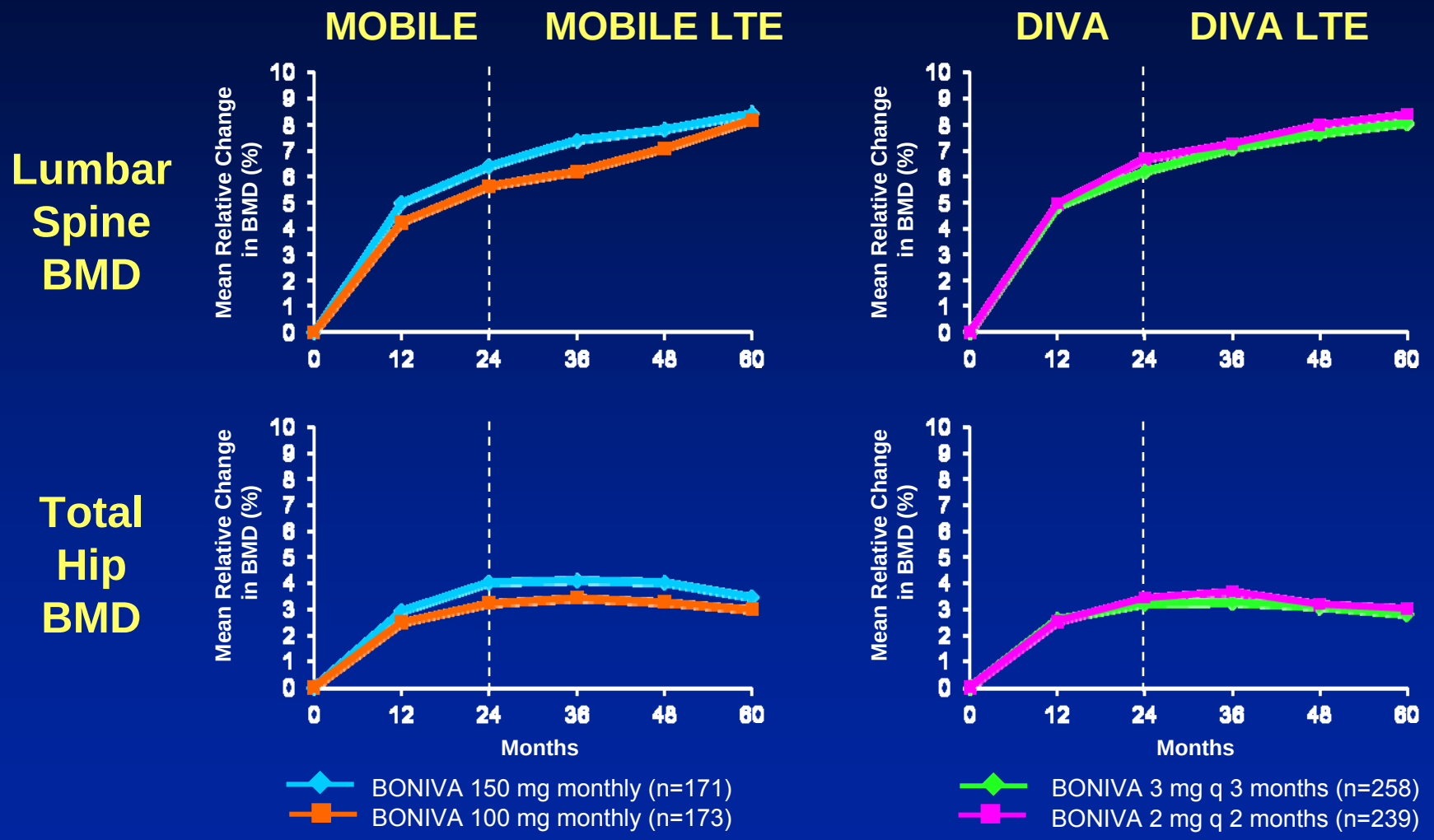
1. Eisman JA et al. *J Rheumatol.* 2008;35:488-497.
2. Osteoporosis International 2011, in press

BONIVA Normalizes Bone Turnover: Serum P1NP Maintained for Up to 5 Years



Garnero P. et al, *Clin Chem* 54(188-196)

BONIVA Maintains Increased BMD in Lumbar Spine and Total Hip for up to 5 Years



Osteoporosis International 2011, in press

DIVA and MOBILE LTE: Incidence of Fractures by Year

Pooled Doses: 150 mg, 2 mg IV, 3 mg IV

	All Clinical n/N (%)	**All Nonvertebral Fractures** n/N (%)
Year 0-1	20/692 (2.89%)	15/692 (2.17%)
Year 1-2	21/692 (3.03%)	13/692 (1.88%)
Year 2-3	20/692 (2.89%)	13/692 (1.88%)
Year 3-4	26/667 (3.90%)	19/667 (2.85%)
Year 4-5	21/644 (3.26%)	14/644 (2.17%)

Bone Quality:
Normal Bone Structure Maintained

Study	Evaluable Biopsy Cores
BONE[1]	Year 2 (n=45) Year 3 (n=55)
DIVA[2] **& LTE**[3]	Year 2 (n=109) Year 5 (n=46) Year 2 & 5 (n=29)

Qualitative Assessment:

- Newly formed bone retained lamellar structure
- No signs of woven bone, marrow fibrosis, or indicators of osteomalacia

Quantitative Assessment:

- No impairment in mineralization of bone matrix
- Bone remodeling at pre-menopausal levels[4]

1. Recker R. et al. 2004, Osteoporos Int 15:231-237.
2. Recker R. et al. Bone 2010: 46: 660–665
3. Osteoporosis International 2011, in press
4. Recker R, et al. J Bone Miner Res 2004;19:1628–33

BONIVA Demonstrates Sustained Long-Term Efficacy Up to 5 Years

- Oral monthly and IV quarterly are superior to oral daily
- BMD continued to increase at lumbar spine
- BMD increases at all hip sites were maintained above baseline
- BTM reductions sustained within premenopausal range
- Low clinical fracture rates maintained over time
- Biopsy results confirmed normal bone quality

BONIVA Presentation Roadmap

Pivotal Data

- Fracture trials
- Bridging BMD trials

Long-term Data

- Extension trials
- Bone biopsy

Safety

- Overall safety
- Topics of special interest
  - Atypical fractures
  - ONJ
  - Esophageal cancer

Safety of BONIVA Is Well Characterized in Clinical Trials

BONE	Safety profile of 2.5 mg daily well tolerated overall
MOBILE/DIVA	Safety profile of 150 mg oral monthly and 3 mg IV quarterly similar to 2.5 mg daily
MOBILE LTE/ DIVA LTE	No change in safety profile up to 5 years

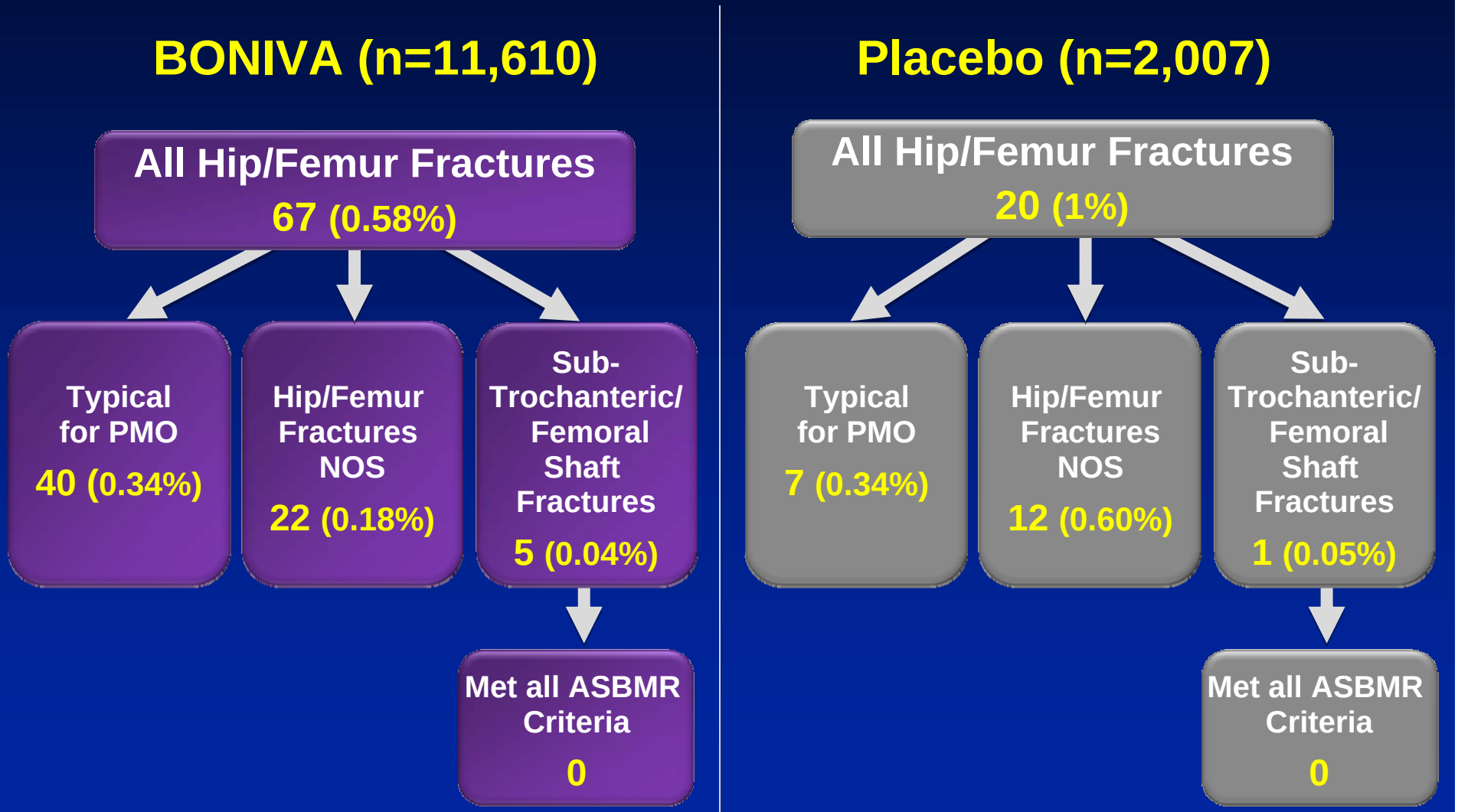
Topics of Special Interest: Atypical Fractures and ONJ

- Data Sources
  - Clinical development program
  - Post-marketing spontaneous reports
  - Scientific literature
- Thorough review and adjudication of all cases
  - Performed independently by a team of internal physicians
  - Based on ASBMR criteria*

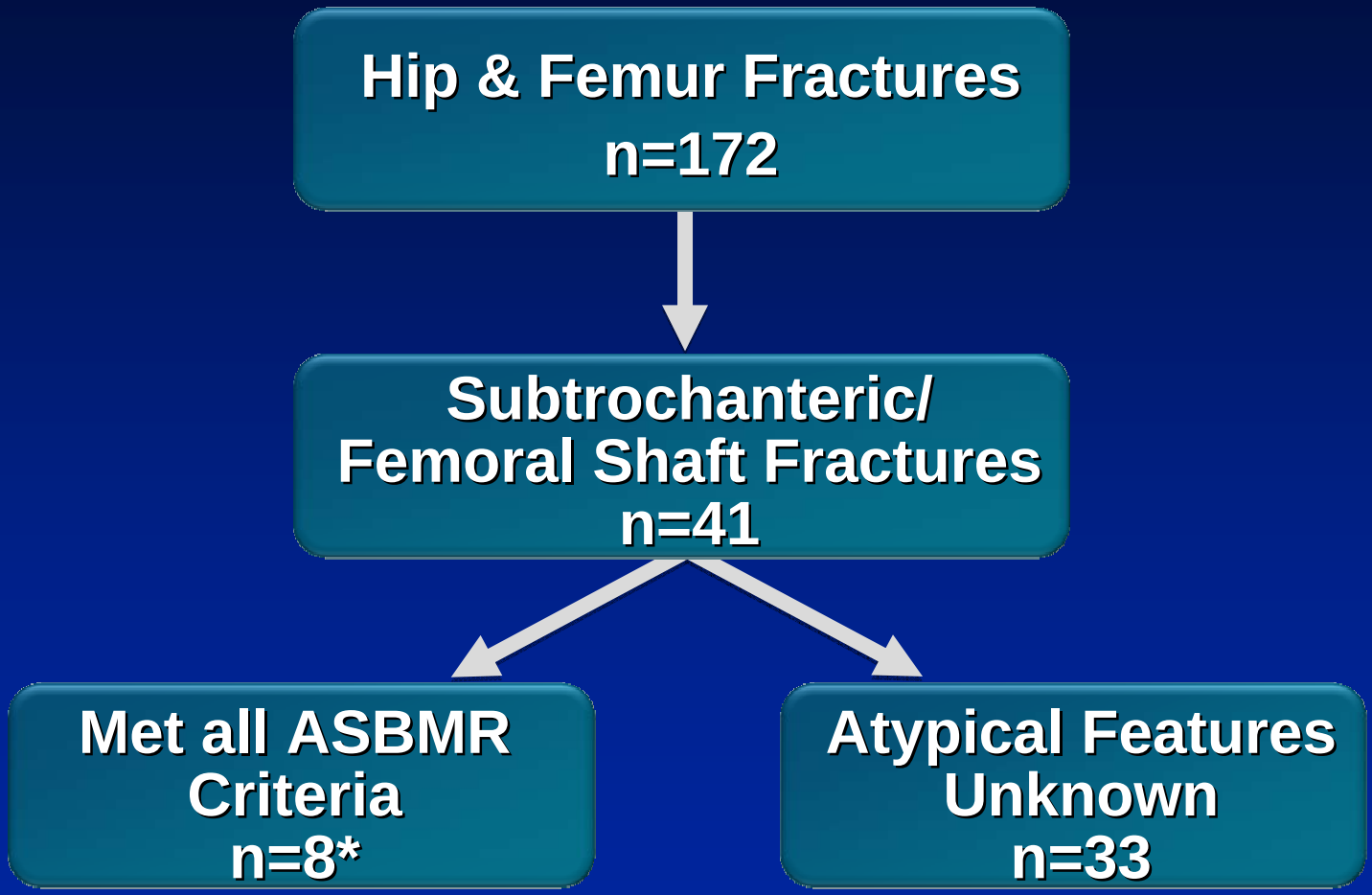
*Khosla S, et al. Bisphosphonate-associated osteonecrosis of the jaw: Report of a task force of the American Society for Bone and Mineral Research (ASBMR). *J Bone Miner Res* 2007; 22(10):1479-91.

Shane E, et al. Atypical subtrochanteric and diaphyseal femoral fractures. *J Bone Miner Res* 2010;25:2267-2294.

Clinical Development Program Review of Hip and Femur Fractures



Spontaneous Reporting/Literature Review



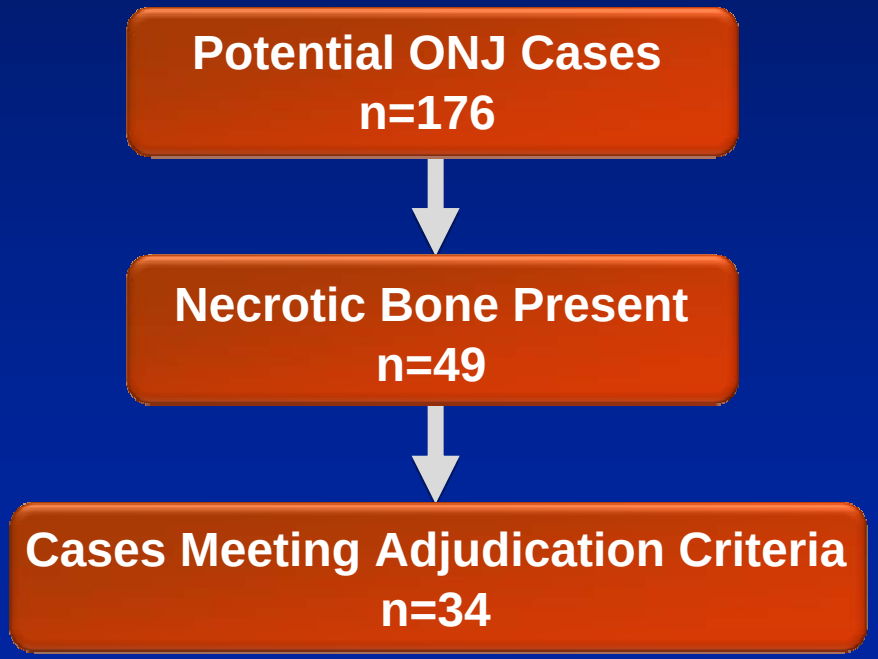
* Duration of total bisphosphonate use 1-16 years

Detailed Review of ONJ

Clinical Development Program

No reports meeting ASBMR criteria with BONIVA treatment for up to 5 years

Spontaneous Reporting/ Literature



Atypical Fracture & ONJ Data Summary

- Reports are very rare
  - Crude reporting rate for subtrochanteric/ femoral shaft with atypical features (n=8)
    - 0.3 per 1,000,000 patients
  - Crude reporting rate for ONJ (n=34)
    - 2.1 per 1,000,000 patients

Esophageal Cancer

- Clinical development program
  - 2 cases reported, incidence rate 7.4 per 100,000 patient years

Background incidence 11.2 per 100,000 patient years*

- Spontaneous reports
  - 6 reports
  - Crude reporting rate 0.5 per 1,000,000 patients exposed

* Ries LAG et al, eds. SEER Cancer Statistics Review, 1973-1998, National Cancer Institute, 2001; **F > 65 yo**

Risk Management

- Risk assessment
  - Full case adjudication
- Risk communication
  - Package insert updated with information on ONJ and atypical fractures
  - Medication guide dispensed with prescription
  - Updated promotional material
- Enhancement of data quality
  - Guided questionnaires for ONJ and atypical fractures

FDA Question #1 to Sponsors

Provide an opinion and discussion of whether efficacy and safety data of BONIVA support long-term use

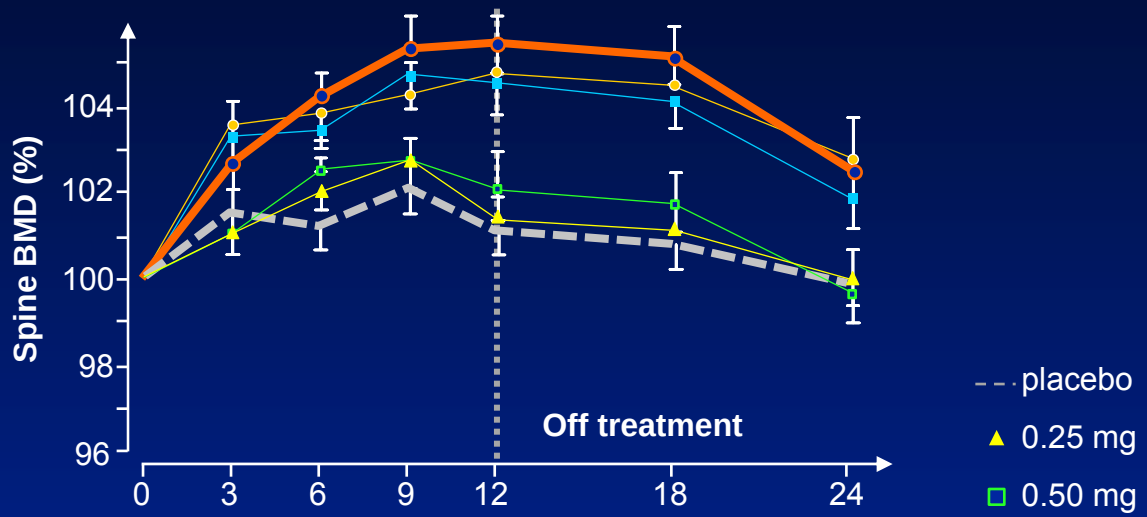
- BONIVA treatment for up to five years is safe and effective
- Benefit/risk profile remains favorable

FDA Question #2 to Sponsors

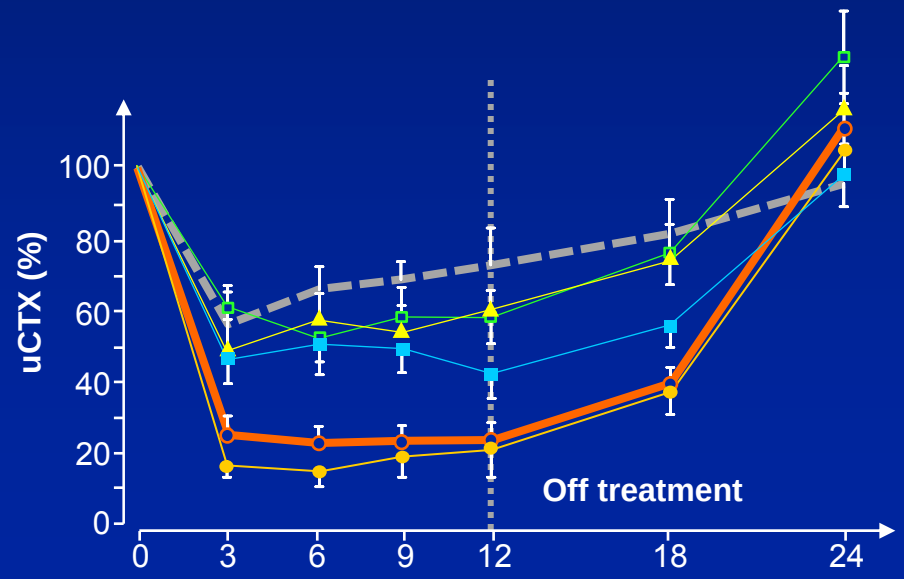
Provide an opinion and discussion of whether either restricting the duration of use or implementing a drug holiday may be beneficial for patients requiring long-term treatment

BONIVA Offset Data

After cessation of therapy, BMD declines over time



After cessation of therapy, bone resorption markers increase to baseline levels



Ravn et al. *BONE* 1998, 22:559–564

Risk Factors for Osteoporotic Fracture

- Age
- Gender
- Ethnicity
- Prior osteoporotic fracture
- BMD
- Low BMI
- Medications, e.g., glucocorticoids
- Low calcium/ Vitamin D intake
- Rheumatic and autoimmune diseases
- Secondary osteoporosis
- Family history of hip fracture
- Current smoking
- Alcohol intake
- Inadequate physical activity/immobilization

Question #2: Drug Holiday

Sponsor's Opinion

- Need for continued therapy should be re-evaluated periodically
- A drug holiday may be appropriate for some patients
- Any interruption of treatment should be based on individual benefit/risk assessment
  - Individual patient risk factors
  - Patient's response to treatment
- Treating physician is the best position to make this determination

BONIVA
(ibandronate sodium)

Joseph Kohles, PhD

September 9, 2011