Reclast® (zoledronic acid) Injection

Presentation to the Joint Meeting of the Reproductive Drugs and Drug Safety and Risk Management Advisory Committees

Christina Bucci-Rechtweg M.D.
Global Program Medical Director
Novartis Pharmaceuticals Corporation

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Reclast (zoledronic acid) Injection

U.S. Prescribing Information

- Reclast is administered as a 5 mg i.v. injection of zoledronic acid*

INDICATIONS AND USAGE

1.1 Treatment of Osteoporosis in Postmenopausal Women

Reclast is indicated for treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, diagnosed by bone mineral density (BMD) or prevalent vertebral fracture, Reclast reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures). In patients at high risk of fracture, defined as a recent low-trauma hip fracture, Reclast reduces the incidence of new clinical fractures [*see Clinical Studies (14.1)*].

1.2 Prevention of Osteoporosis in Postmenopausal Women

Reclast is indicated for prevention of osteoporosis in postmenopausal women [*see Clinical Studies (14.2)*].

* Zoledronic acid is also approved as Zometa® for use in patients with advanced cancer in bone, with different comorbidities utilizing a different dose and regimen

Reclast (zoledronic acid) Injection

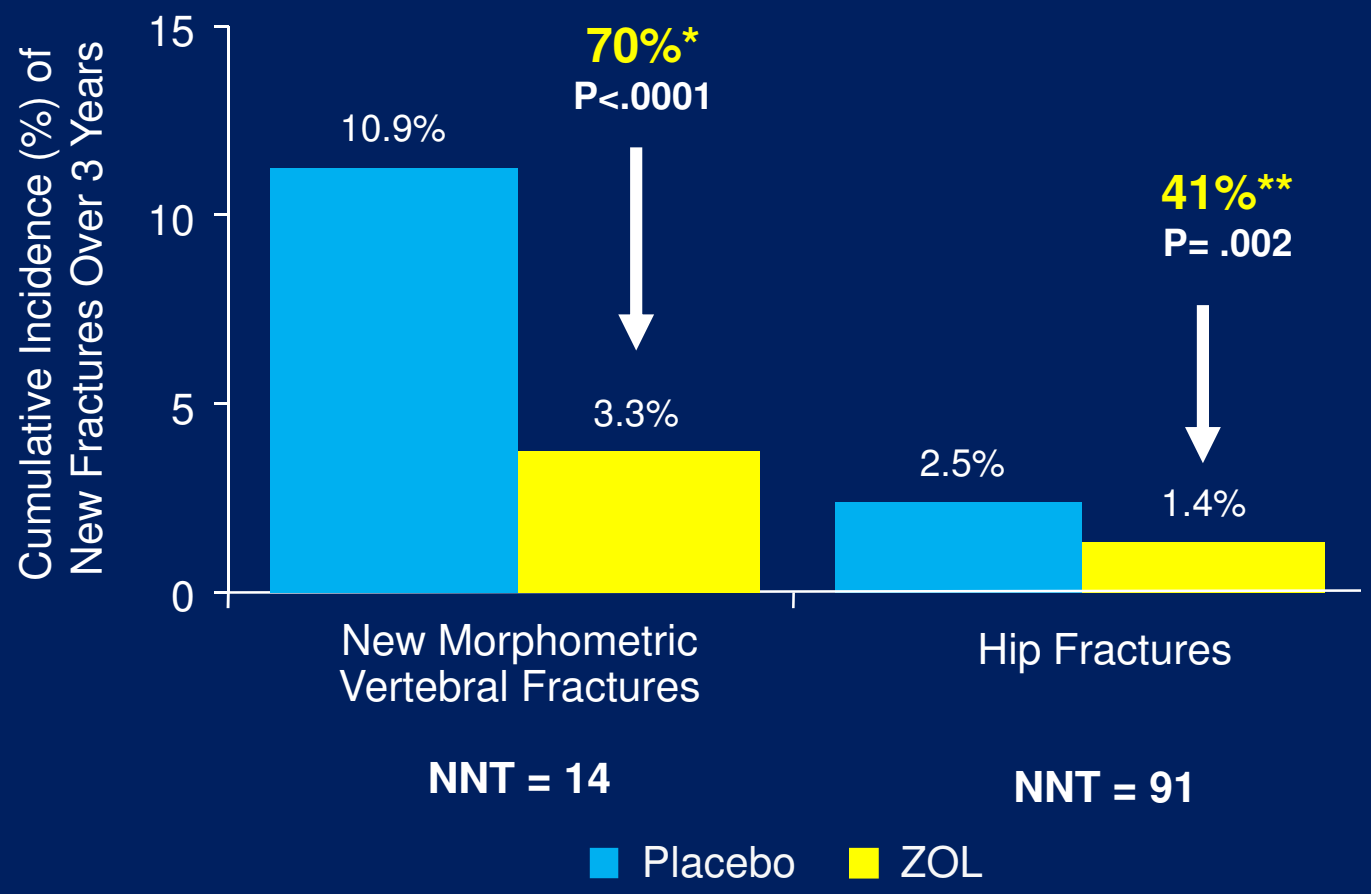
Clinical Development Overview

Study	Population	Duration	N	Regimen	Comparator
Pivotal Fracture Trial (PFT)	PMO	3 yrs	7736	Annual	Placebo
PFT Extension	PMO	3 yrs	2456	Annual	Placebo
Recurrent Fracture Trial (RFT)	Incident hip fracture	End-point driven (mean = 1.9 yrs)	2127	Annual	Placebo
Prevention of Bone Loss	Osteopenia	2 yrs	581	Single & annual	Placebo
Glucocorticoid-induced Osteoporosis	Prevention & Treatment	1 yr	833	Single	Risedronate (RIS)
Male osteoporosis	Men	2 yrs	302	Annual	Alendronate (ALN)
Male osteoporosis	Men	2 yrs	1199	Annual	Placebo

Total Reclast exposure in clinical trials (>20,000 patient-years)

Pivotal Fracture Trial (PFT)

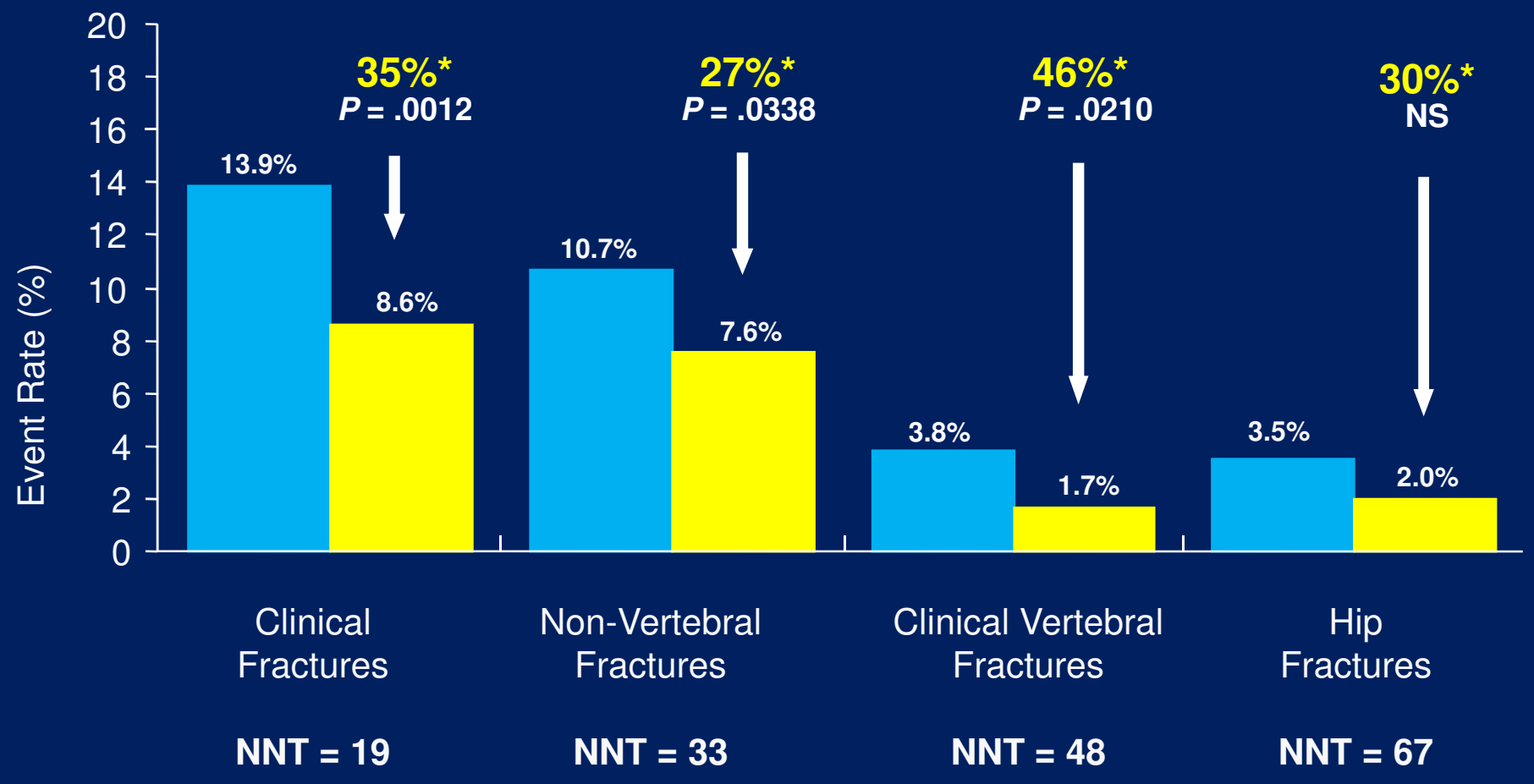
Efficacy Endpoints



*Relative risk reduction vs. Placebo
**Hazard ratio
Black DM, et al. *N Engl J Med*. 2007;356:1809-1822.

Recurrent Fracture Trial (RFT)

Subsequent Fracture Risk in Patients with Incident Hip Fracture



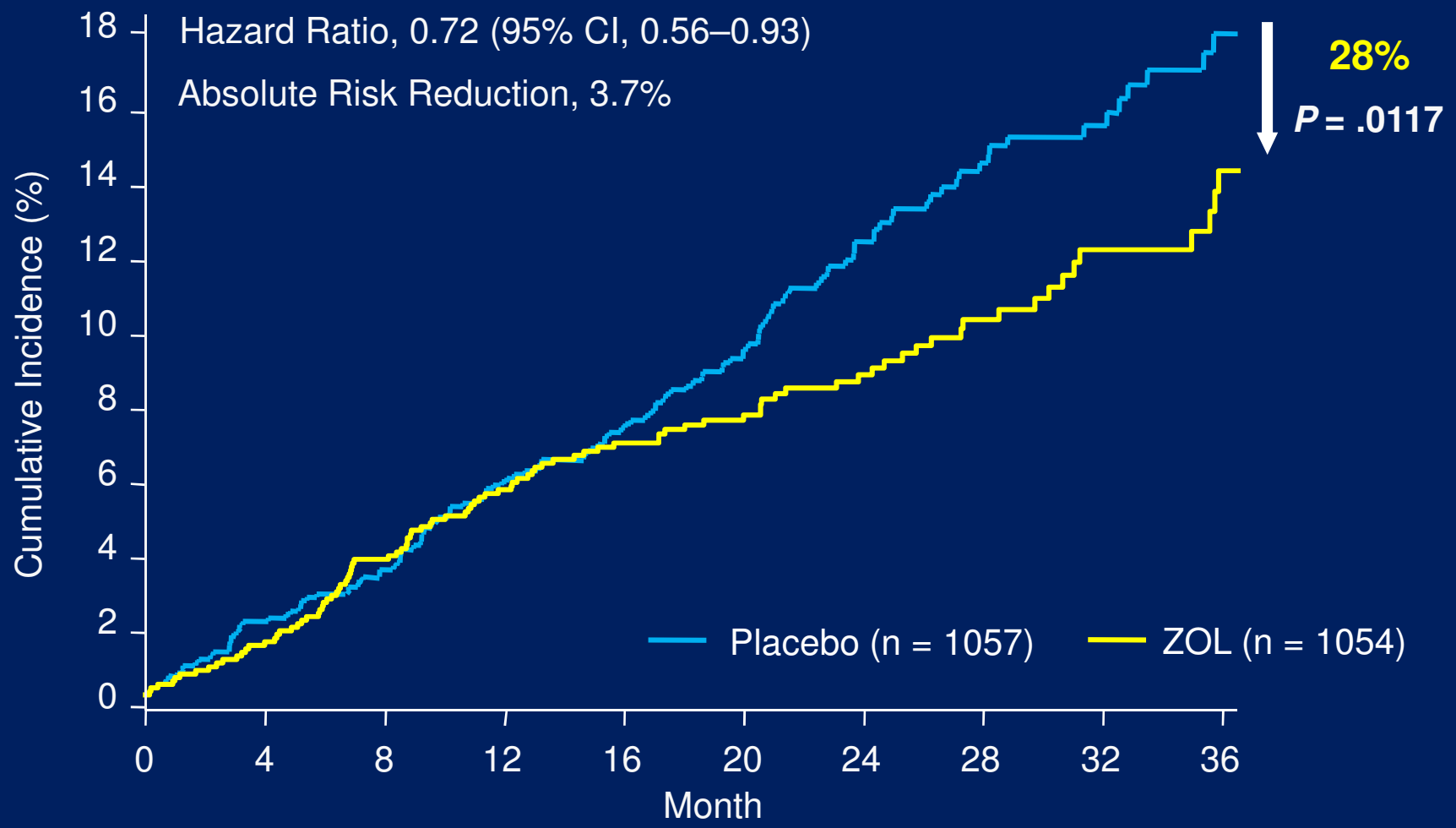
* Cumulative event rates based on Kaplan-Meier estimates at Month 24

Placebo ZOL

Lyles KW, et al. *N Engl J Med.* 2007;357:1799-809

Recurrent Fracture Trial (RFT)

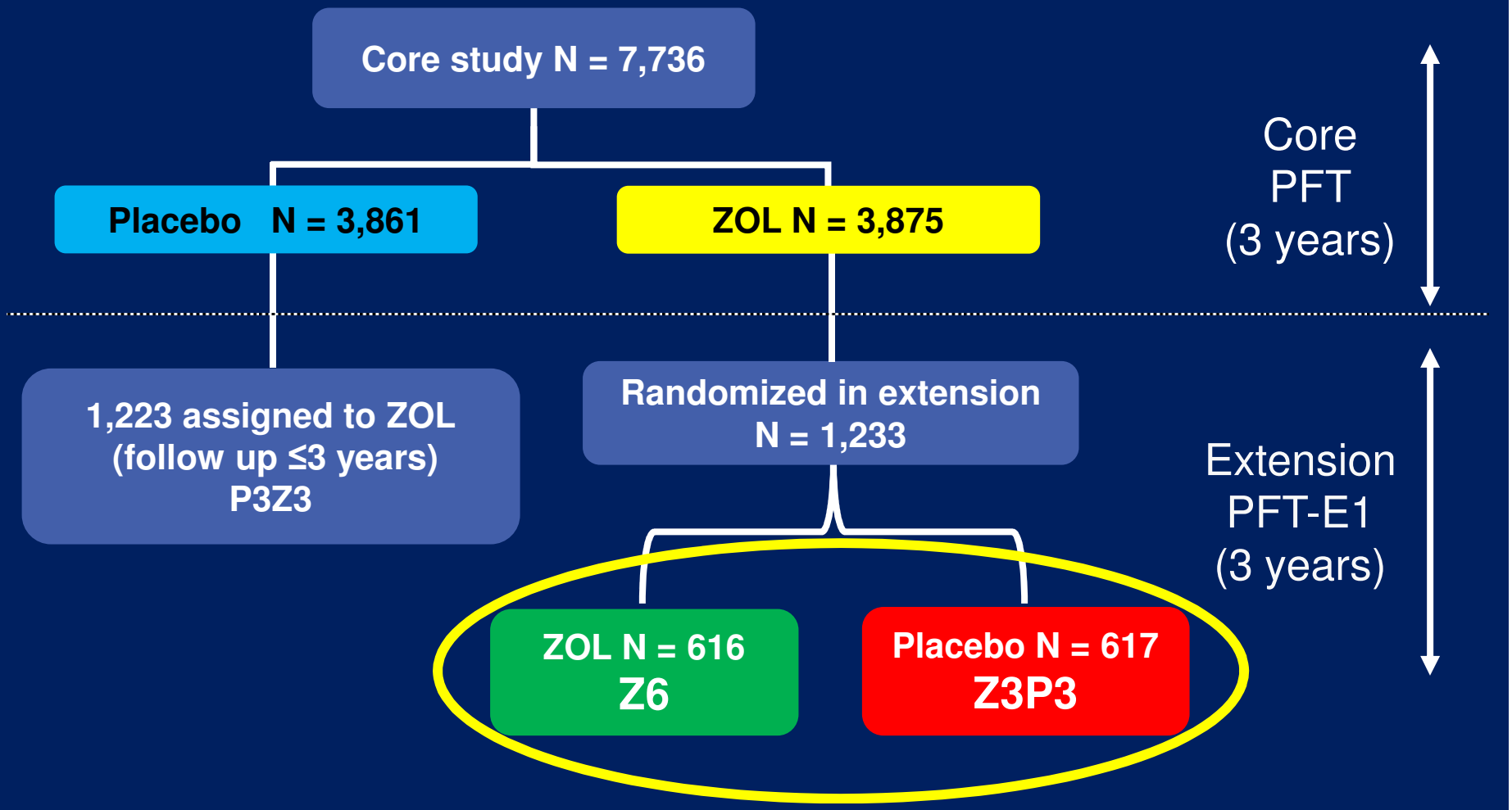
All-Cause Mortality



Lyles KW, et al. *N Engl J Med.* 2007;357:1799-809

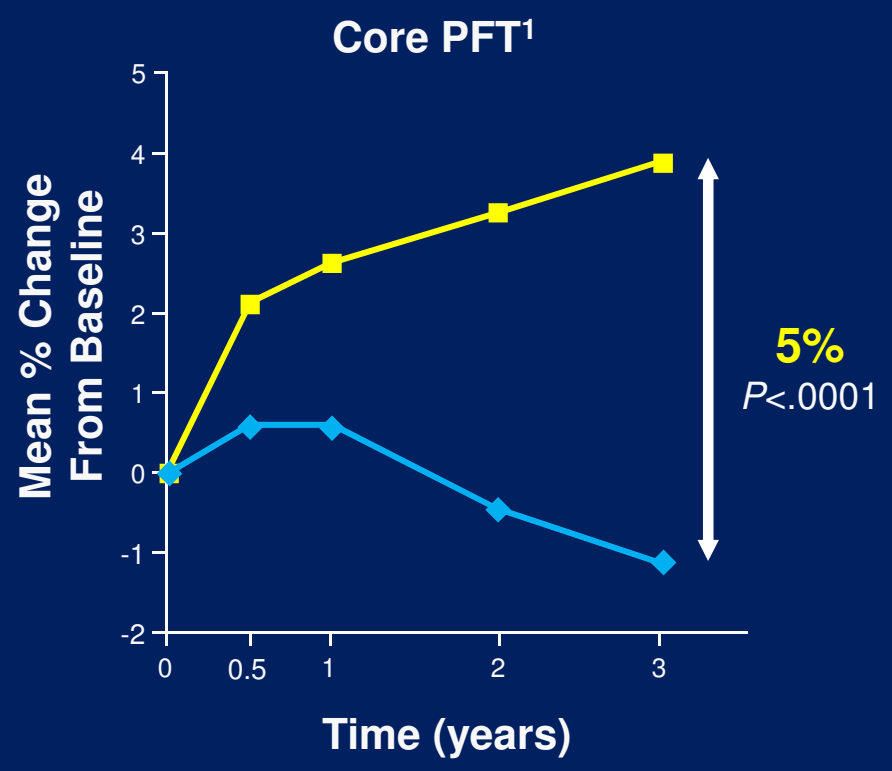
Pivotal Fracture Trial (PFT) and Extension (PFT-E1)

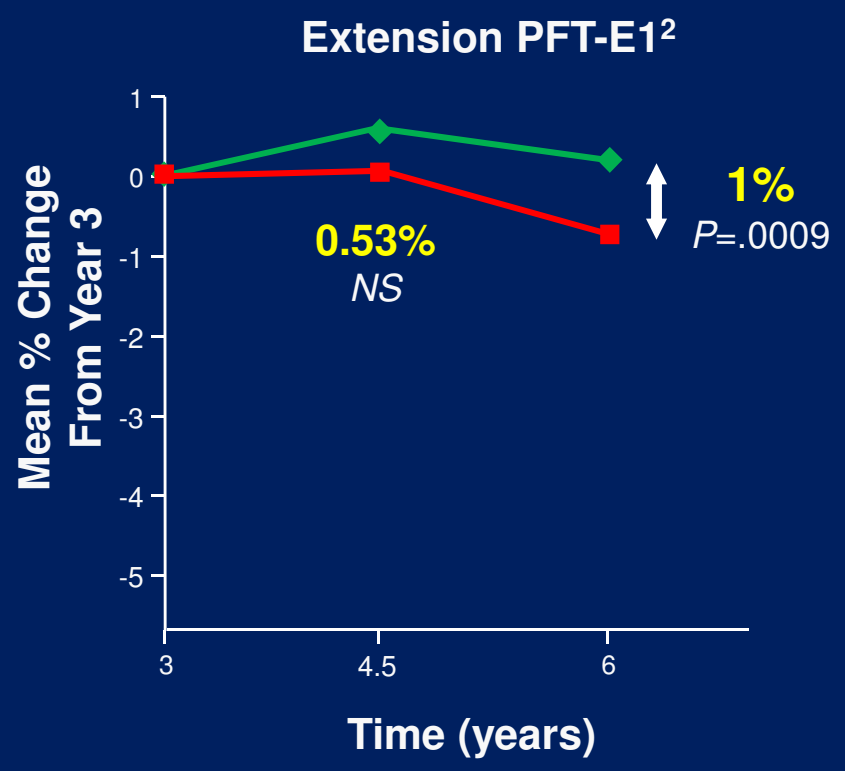
Patient Disposition



Pivotal Fracture Trial (PFT) and Extension (PFT-E1)

Femoral Neck BMD





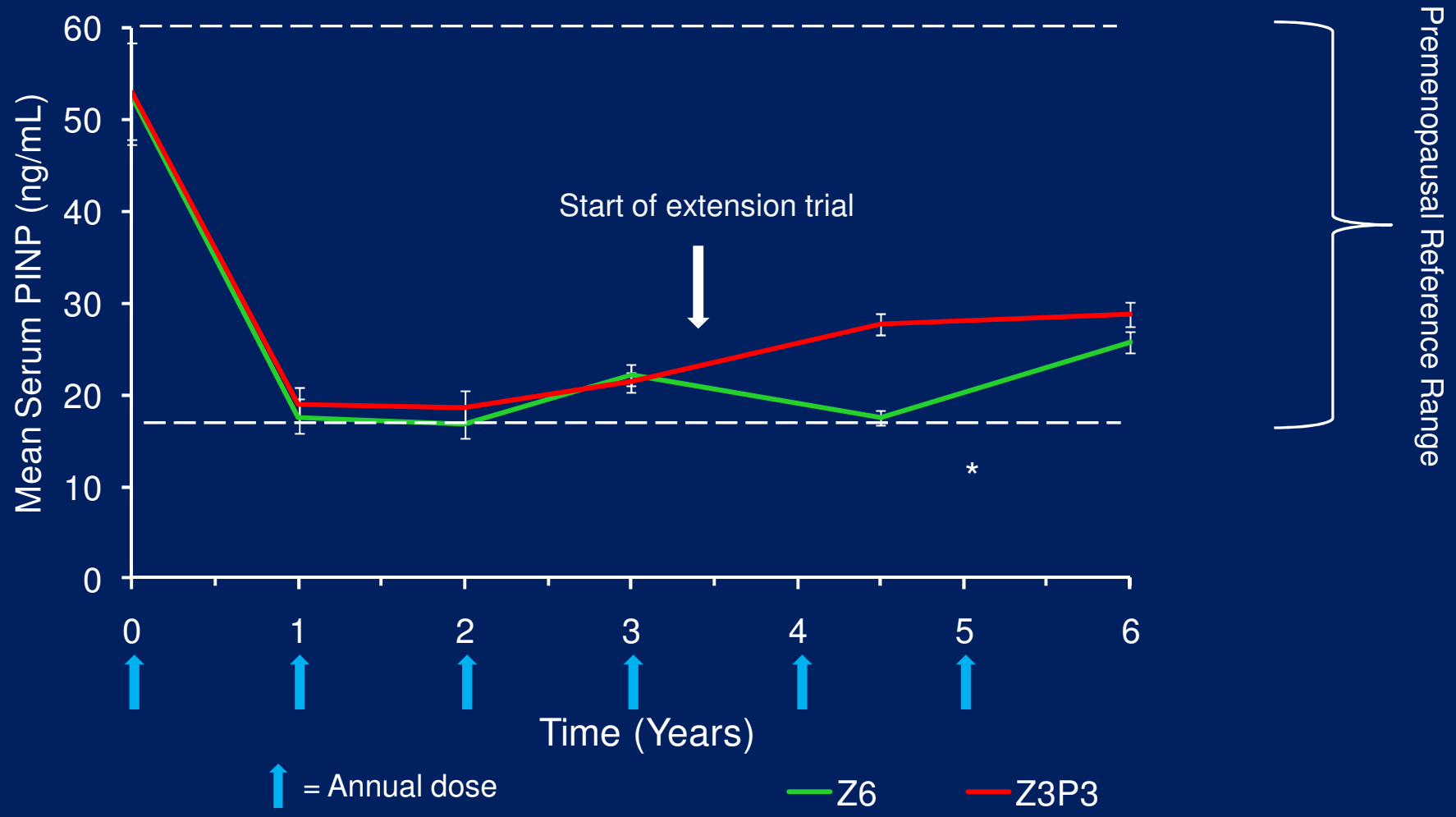
PBO (n=3083) ZOL (n=3067)

Z3P3 (n=470) Z6 (n=451)

[1] Black DM, et al. *N Engl J Med.* 2007;356(18):1809-1822.; [2] Black et al. ASBMR 2010.

Pivotal Fracture Trial Extension (PFT-E1)

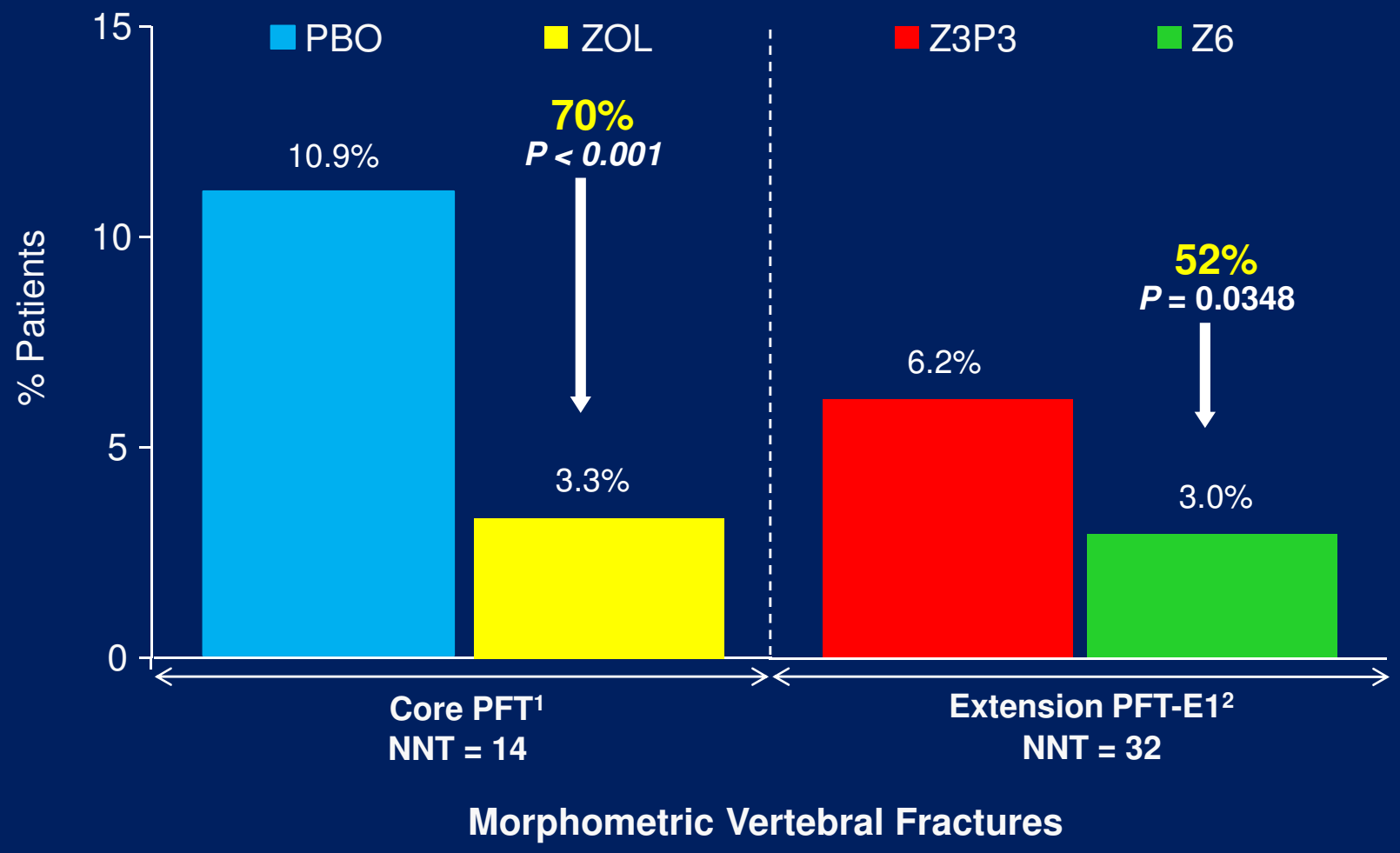
Bone Turnover Markers Over Time



*P <.0001, between treatment comparison of the relative change in PINP to Year 3, Z6 vs Z3P3
Black et al. ASBMR 2010.

Pivotal Fracture Trial (PFT) and Extension (PFT-E1)

New Morphometric Vertebral Fractures



[1] Black DM, et al. *N Engl J Med.* 2007;356:1809–1822.; [2] Black et al. ASBMR 2010.

Pivotal Fracture Trial Extension (PFT-E1)

Post Hoc Analysis of >3 Years Reclast Treatment

- Objectives:
  - Identify predictors of high and low risk for vertebral fracture
  - Determine whether the observed treatment effect of continued therapy on vertebral fracture is consistent across predictors for risk

- Methods:
  - Logistic regression in the discontinuation group (Z3P3)
    - Variables:
      - PFT-E1 baseline: Age, hip BMD, PINP, prevalent vertebral fracture
      - During Core PFT: Incident vertebral/non-vertebral fracture, weight loss, % change hip BMD
  - Analysis of treatment effects (comparing Z6 and Z3P3) in subgroups defined by significant predictors of risk for vertebral fracture
  - Parallel analyses for non-vertebral fractures (Cox models)

Courtesy Dr. F. Cosman

Pivotal Fracture Trial Extension (PFT-E1)

Post Hoc Analysis of >3 Years Reclast Treatment

Predictors of risk for vertebral fracture (Z3P3)

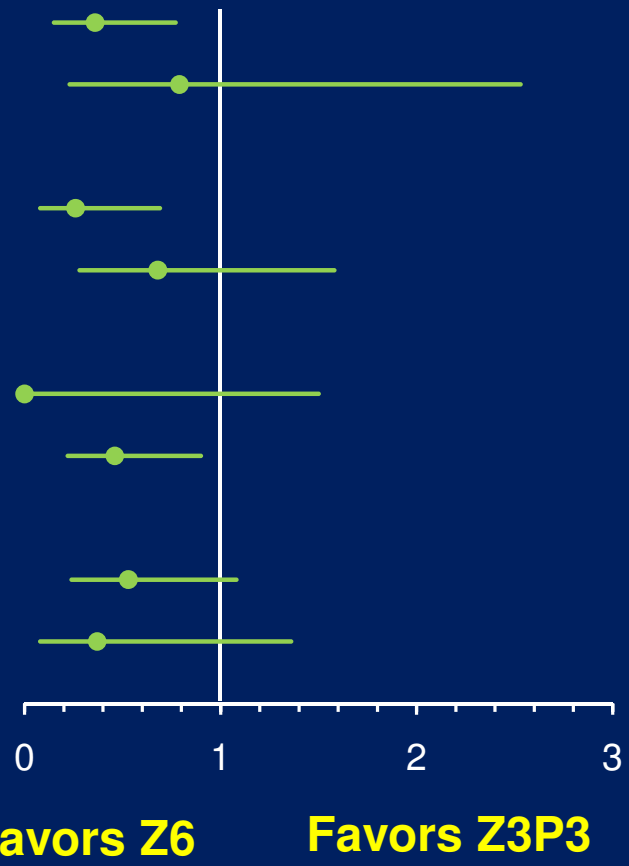
Variable	OR (95% CI)	p-value
Low FN BMD T-score (≤-2.5) at Extension baseline	3.3 (1.4, 8.0)	0.008
Low Total Hip BMD T-score (≤-2.5) at Extension baseline	4.01 (1.8, 8.9)	0.0007
Incident vertebral fracture on ZOL during Core	4.74 (1.3, 16.7)	0.0156
Prevalent vertebral fracture at Extension baseline	1.84 (0.7, 4.4)	NS

Pivotal Fracture Trial Extension (PFT-E1)

Post Hoc Subgroup Analysis of >3 Years Reclast Treatment

Treatment effects in sub-groups by predictors of risk (Z6 vs Z3P3)

Variable	Subgroup	OR (95% CI), Z6 vs Z3P3	Z6 vs Z3P3	NNT
FN BMD T-score at Extension Baseline	≤-2.5		9/257 vs 23/250	18
	>-2.5		5/210 vs 7/235	167
Total Hip BMD T-score at Extension Baseline	≤-2.5		5/120 vs 16/112	10
	>-2.5		9/347 vs 14/373	87
Incident vertebral fracture on ZOL during Core	Yes		0/11 vs 4/16	4
	No		12/454 vs 26/467	34
Prevalent vertebral fracture at Extension baseline	Yes		11/268 vs 23/307	30
	No		3/201 vs 7/179	42



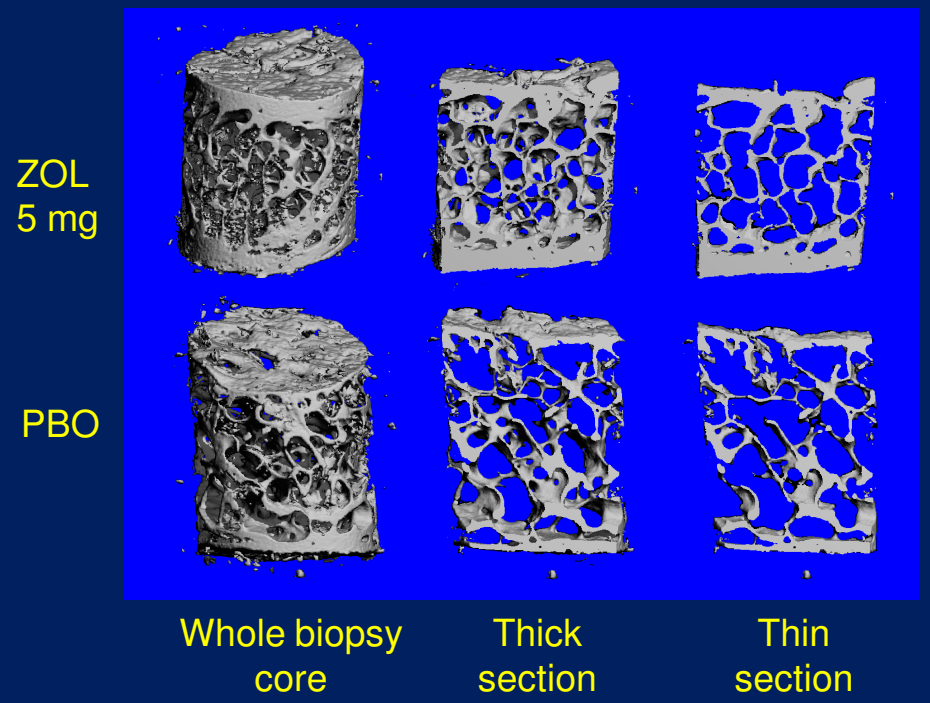
Reclast Safety

Skeletal Events of Special Interest

Pivotal Fracture Trial (PFT) and Extension (PFT-E1)

Bone Biopsies

- Qualitative, quantitative and micro CT assessments
- Annual dosing for 3 years resulted in a preservation of bone structure and material properties without evidence of adynamic bone[1]
- 5 specimens in PFT-E1 with trabecular double-label



[1] Recker RR, et al. *J Bone Miner Res*. 2008;23:6-16.

Reclast Clinical Evaluation

Maxillofacial Safety

- Program-wide prospective event adjudication for events of special interest
- Maxillofacial (ONJ)
  - External, blinded, expert committee utilizing 60 *pre-defined* MedDRA search terms for adverse and serious adverse events of special interest
  - ONJ definition* : Exposed bone with delayed healing despite 6 weeks of appropriate medical care

*Predates current ASBMR definition

Reclast Clinical Trials

Osteonecrosis of the Jaw (ONJ)

Program-Wide Adjudication of Reclast Clinical Trials

Study	Study Drug	Age/ Sex	Lower Level Term	Confounding factors	Treatment	Resolution
PFT	Placebo	67/F	Osteitis	Corticosteroids	Debridements Antibiotic	Resolved
PFT	ZOL	70/F	Dentoalveolar abscess, periodontal infection	Insulin dependent diabetes Never had regular dental care	Antibiotics	Resolved
PFT-E1	ZOL (Z6)	77/F	Osteonecrosis of the jaw	Smoker, poor dental hygiene, loss of a tooth	Debridements Antibiotics	Resolved
PFT-E1	ZOL (P3Z3)	78/F	Tooth infection	Alcohol use, dental caries, periodontal disease	Debridements Antibiotics	Resolved

Post-marketing Surveillance

Osteonecrosis of the Jaw (ONJ)

- >2.3 million patient-years of exposure*
- Safety database queried utilizing *pre-defined* MedDRA terms
- Reporting rate of 4.5 / 100,000 patient-years†
  - 58% of cases were reported with one or more risk factor
  - Identified risk factors, including preceding dental procedures, concomitant use of steroids, poor oral hygiene or prior use of other bisphosphonates
  - 21% of cases reported with exposed jaw bone
- Rate is consistent with the risk associated with oral bisphosphonate therapy[1] (1-10 / 100,000 patient-years)

* Cutoff date: 30 June 2011 † Challenge with post-marketing spontaneous reports: lack of diagnostic evidence (i.e. exposed necrotic jaw bone and event duration)

[1] Khosla et al. *J Bone Miner Res.* 2007;22(10):1479-91.a

Reclast (zoledronic acid) injection

Atypical Subtrochanteric Femoral Fracture

- Clinical Trials
  - No atypical fractures reported
  - Clinical trials database queried (MedDRA terms hip, femur, femoral neck)
    - 5 unconfirmed events in area of interest (3 Reclast vs. 2 Placebo)
- Post-marketing surveillance*
  - Safety database queried (MedDRA terms hip, femur, femoral neck)
  - Reports of subtrochanteric, diaphyseal and "atypical" femur fracture not confirmed to include the "Major features" [1]
    - Nature of preceding trauma or radiographs not available
  - Estimated reporting rate of 0.6 / 100,000 patient-years

* Cutoff date: 30 June 2011 (> 2.3 million patient-years exposure)

[1] Shane et al. *JBMR*. 2010. 25(11): 2267-2294

Benefit / Risk

- The benefit/risk of Reclast 5 mg i.v. during long-term treatment (> 3 years) is consistent with the profile established in registration trials

- Clinical trial evidence of clinically meaningful reduction in fracture risk
  - NNT for vertebral fracture
    - Over 3 years[1] = 14, in the 3 year extension study = 32
  - NNT for hip fracture
    - Over 3 years[1] = 91
  - 28% reduction in all cause mortality[2]
- Skeletal events of special interest very rarely reported in clinical trials
- Post-marketing experience reinforces rarity of events in clinical practice

[1] Adapted from Black, et al. *N Engl J Med.* 2007;356:1809-1822; [2] Lyles KW, et al. *N Engl J Med.* 2007;357:1799-809.

Novartis Recommendation

- Novartis is committed to ensuring patient safety
  - Ongoing 5-year epidemiology study to assess the incidence of rare safety events
  - Ensuring the USPI reflects the most up-to-date information related to identified and potential risks with long-term Reclast therapy
- Six year data support a positive Benefit/Risk for long-term Reclast therapy
  - *Post hoc* analysis provides insights on which patients:
    - May benefit most from continued treatment beyond 3 years
    - May be considered for treatment discontinuation for up to 3 years

➢ Decision to continue or interrupt Reclast therapy beyond 3 years should be made on an individual patient basis