PATHWAYS IN Osteoporosis

Osteoporosis in Special Populations

IL/DNB/0037/14
November 2014

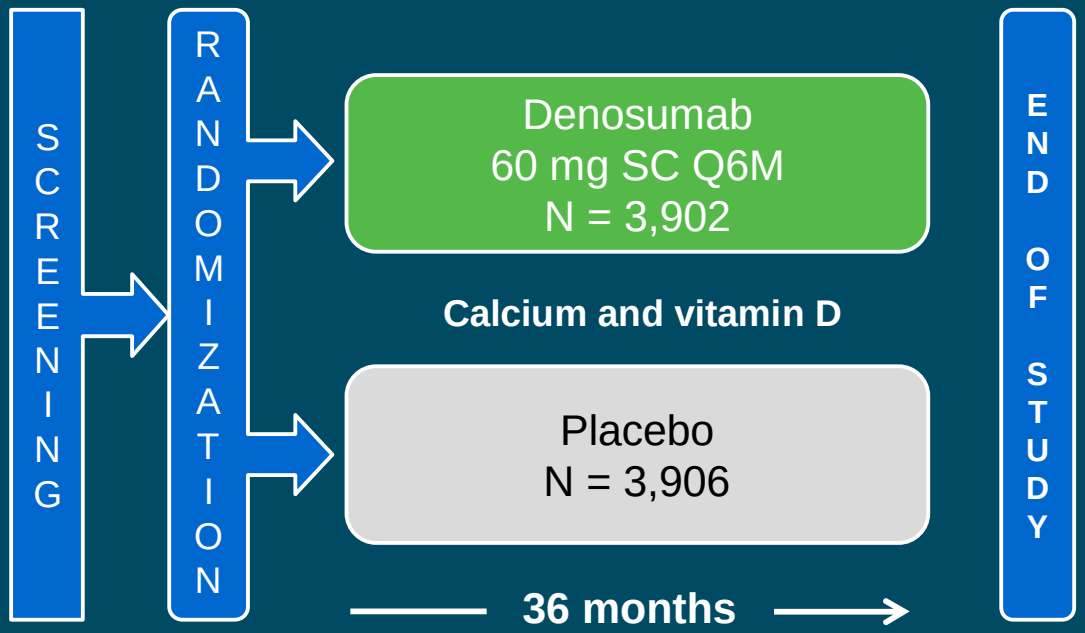
PATHWAYS IN Osteoporosis

Osteoporosis in Patients with Chronic Kidney Disease

Epidemiology

Study Design

FREEDOM Trial – Post-hoc analysis of kidney function



Aim

To determine the relationship between baseline kidney function (estimated GFR) and the effect of denosumab on fracture risk reduction and change in BMD

Study population

- 7,808 postmenopausal women
- 60–90 years old with T-score >−4.0 and < −2.5 at the lumbar spine or total hip

BMD = bone mineral density; GFR = glomerular filtration rate;
SC Q6M = subcutaneous once every 6 months

Jamal SA, *et al*. *J Bone Miner Res* 2011;26:1829–1835.

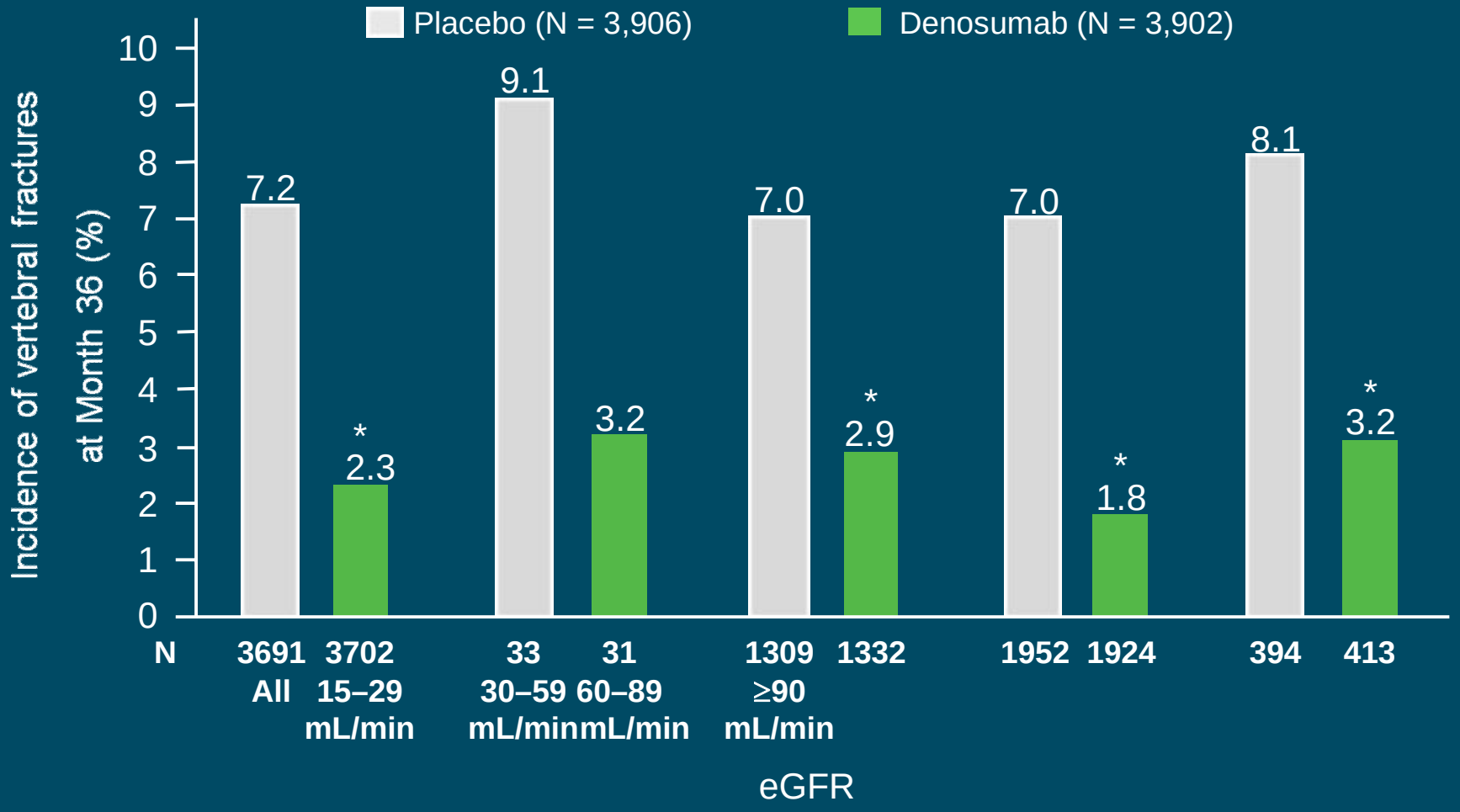
Denosumab in Osteoporosis with CKD: Effects on BMD are Independent of Kidney Function

Outcome	Stage 4 CKD eGFR 15−29 mL/min (N = 73)	Stage 3 CKD eGFR 30−59 mL/min (N = 2817)	Stage 2 CKD eGFR 60−89 mL/min (N = 4069)	Stage 1 CKD/normal eGFR ≥90 mL/min (N = 842)
Lumbar spine BMD, % change	5.0 (−0.8–10.8)	8.9 (8.4–9.3)*	9.0 (8.6–9.4)*	8.1 (7.2–8.9)*
Femoral neck BMD, % change	5.9 (3.3–8.5)*	5.1 (4.7–5.5)*	5.2 (4.9–5.5)*	5.6 (4.9–6.3)*
Total hip BMD, % change	5.9 (3.0–8.7)*	6.4 (6.1–6.7)*	6.4 (6.2–6.7)*	5.8 (5.2–6.3)*

*P <0.0002. N = number of randomized subjects. A difference in BMD % change >0 in favor of denosumab.
BMD = bone mineral density; CKD = chronic kidney disease;
eGFR = estimated glomerular filtration rate

Jamal SA, *et al*. *J Bone Miner Res* 2011;26:1829−1835.

Effect of Denosumab on Fracture Risk over 3 Years by Stage of Kidney Function



N = number of randomized subjects with an evaluation during the time period of interest. There were no subjects with creatinine clearance < 15 mL/min.
*P < 0.05

Jamal SA, *et al*. *J Bone Miner Res* 2011;26:1829–1835.

Denosumab in Osteoporosis with CKD: Adverse Event Rates are Independent of Kidney Function

	Stage 4 CKD		Stage 3 CKD		Stage 2 CKD		Stage 1 CKD	
	Placebo N = 37	Dmab N = 36	Placebo N = 1392	Dmab N = 1,410	Placebo N = 2034	Dmab N = 2,015	Placebo N=410	Dmab N = 423
Adverse events, n (%)	35 (94.6)	35 (97.2)	1307 (93.9)	1308 (92.8)	1875 (92.2)	1869 (92.8)	387 (94.4)	391 (92.4)
Serious adverse events, n (%)	13 (35.1)	15 (41.7)	351 (25.2)	392 (27.8)	509 (25.0)	502 (25.0)	99 (24.1)	95 (22.5)
Serious adverse events of infection, n (%)	1 (2.7)	4 (11.1)	49 (3.5)	60 (4.3)	66 (3.2)	79 (3.9)	17 (4.1)	16 (3.8)
Cardiovascular serious adverse events, n (%)	3 (8.1)	4 (11.1)	88 (6.3)	88 (6.3)	71 (3.5)	78 (3.9)	16 (3.9)	16 (3.8)

N = number of randomized subjects who received 1 dose or more of investigational product.
CKD = chronic kidney disease

Jamal SA, *et al*. *J Bone Miner Res* 2011;26:1829–1835.

Denosumab

- Denosumab indications
  - Treatment of osteoporosis in postmenopausal women at increased risk of fractures; denosumab significantly reduces the risk of vertebral, non vertebral and hip fractures
- Adequate intake of calcium and vitamin D is important in all patients
- Patients with severe renal impairment (creatinine clearance <30 mL/min) or receiving dialysis are at greater risk of developing hypocalcemia
- Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcemia

Prolia® (denosumab) SmPC, June 2013.

Conclusions

- CKD is a widespread disease with increasing global prevalence
- Patients with CKD (all stages) have higher fracture risk than aged-matched patients without CKD
- Denosumab is effective at reducing fracture risk and improving BMD in patients with osteoporosis and CKD
- Denosumab is not associated with an increase in adverse events among patients with osteoporosis and CKD

PATHWAYS IN Osteoporosis

Osteoporosis in Elderly Patients

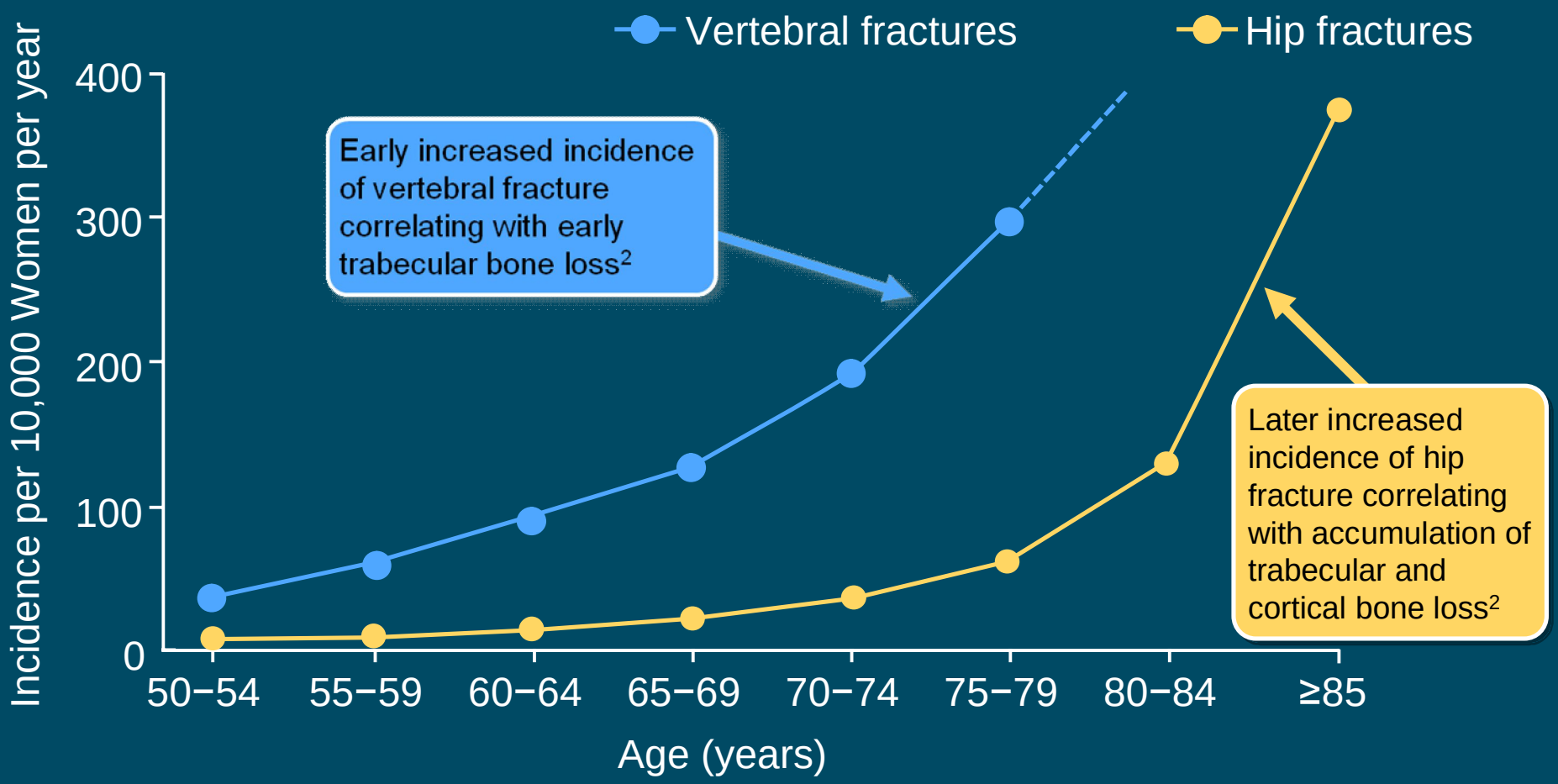
Treatment with Denosumab (FREEDOM)

Osteoporosis in Elderly Patients: Considerations

- General poor health and decreased mobility
- Low bone density, and a high fracture risk
- Decrease in dietary calcium intake and poorer vitamin D status
- Falls are often to the side, with direct impacts to the hip
- Falls are often unrelated to external obstacles – instead they are the result of postural instability, decreased muscular performance, malnutrition, comorbidities (e.g. poor vision, cognitive impairment) and medications

IOF. http://www.iofbonehealth.org/special-considerations-very-elderly. Accessed July 2013.

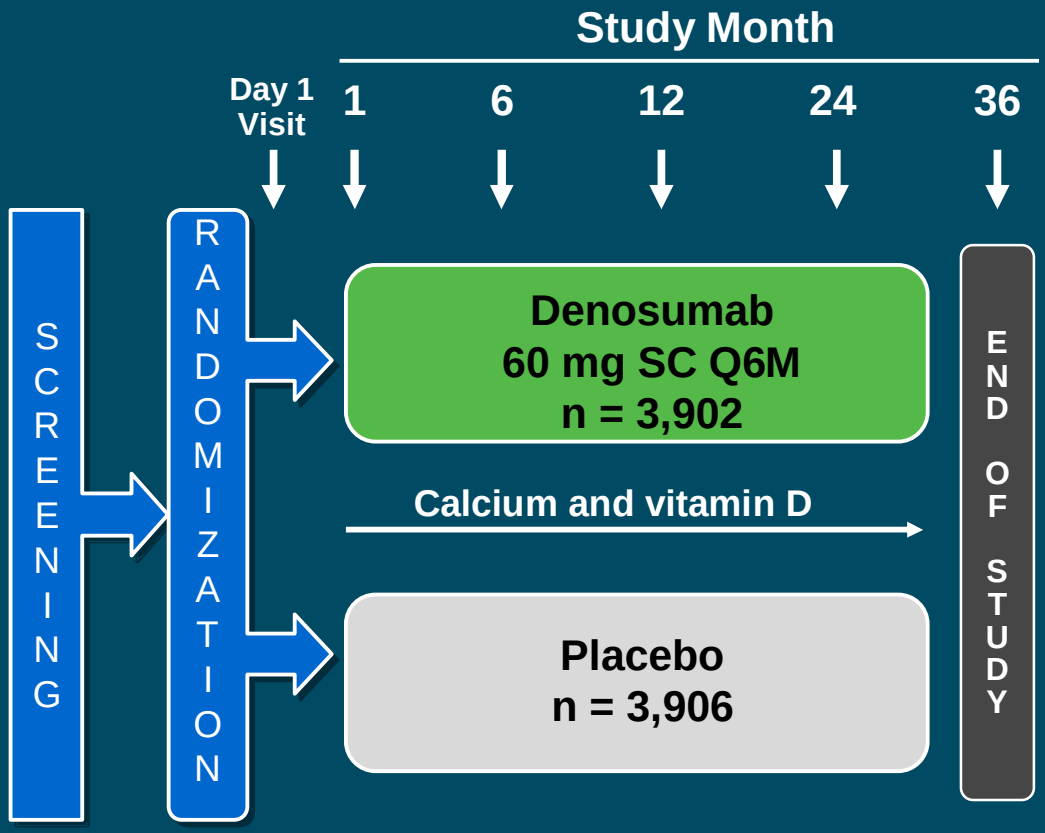
Vertebral and Hip Fracture Rates Exponentially Increase with Trabecular and Cortical Bone Loss[1]



1. Sambrook P, Cooper C. *Lancet* 2006;367:2010–2018.
2. Cooper C. Trends Endocrinol Metab 1992;3:224–229.

Study Design

FREEDOM Trial – Higher Risk Sub-analysis



Study population

- 7,808 postmenopausal women
- T-score < –2.5 at the lumbar spine or total hip and not < –4.0 at either site

Objective of this analysis

- Assess the effect of denosumab treatment on fracture risk in high-risk subsets of the Pivotal Phase III Trial population
  - New vertebral fractures
  - Hip fractures

- **International, placebo-controlled study**

SC = subcutaneously; Q6M = once every 6 months

Cummings SR, *et al. N Engl J Med* 2009;361:756–765.
Boonen S, *et al. J Clin Endocrin Metab*. 2011;96:1727–1736.

Definition of Higher Risk Subjects Used in Subgroup Analyses

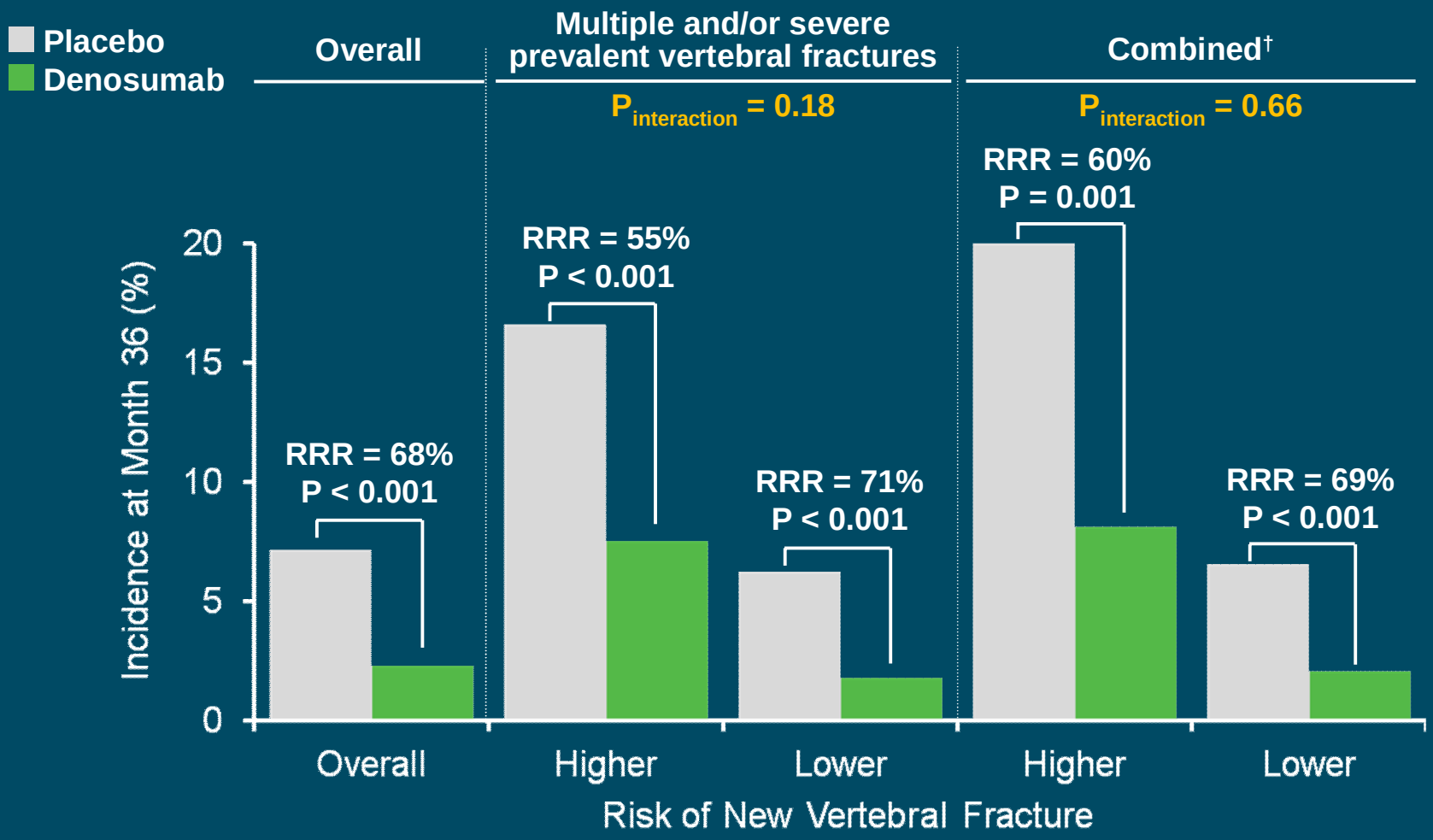
FREEDOM Trial – Higher Risk Sub-analysis

Outcome	Higher Risk Sub-analyses*
New Vertebral Fracture	*Any of the following:* • ≥ 2 preexisting vertebral fractures with any degree of deformity *or* ≥ 1 prevalent vertebral fracture with moderate or severe deformity, *or* both • Femoral neck BMD T-score ≤ −2.5 • Multiple and/or moderate or severe vertebral deformities with a femoral neck BMD T-score ≤ −2.5
Hip Fracture	*Any of the following:* • ≥ 75 years old • Femoral neck BMD T-score ≤ −2.5 • ≥ 75 years old and a femoral neck BMD T-score ≤ −2.5

* All analyses were done post hoc except for new vertebral fractures in women with a femoral neck BMD T-score ≤ −2.5.
BMD = bone mineral density

Boonen S, *et al. J Clin Endocrin Metab* 2011;96:1727–1736.

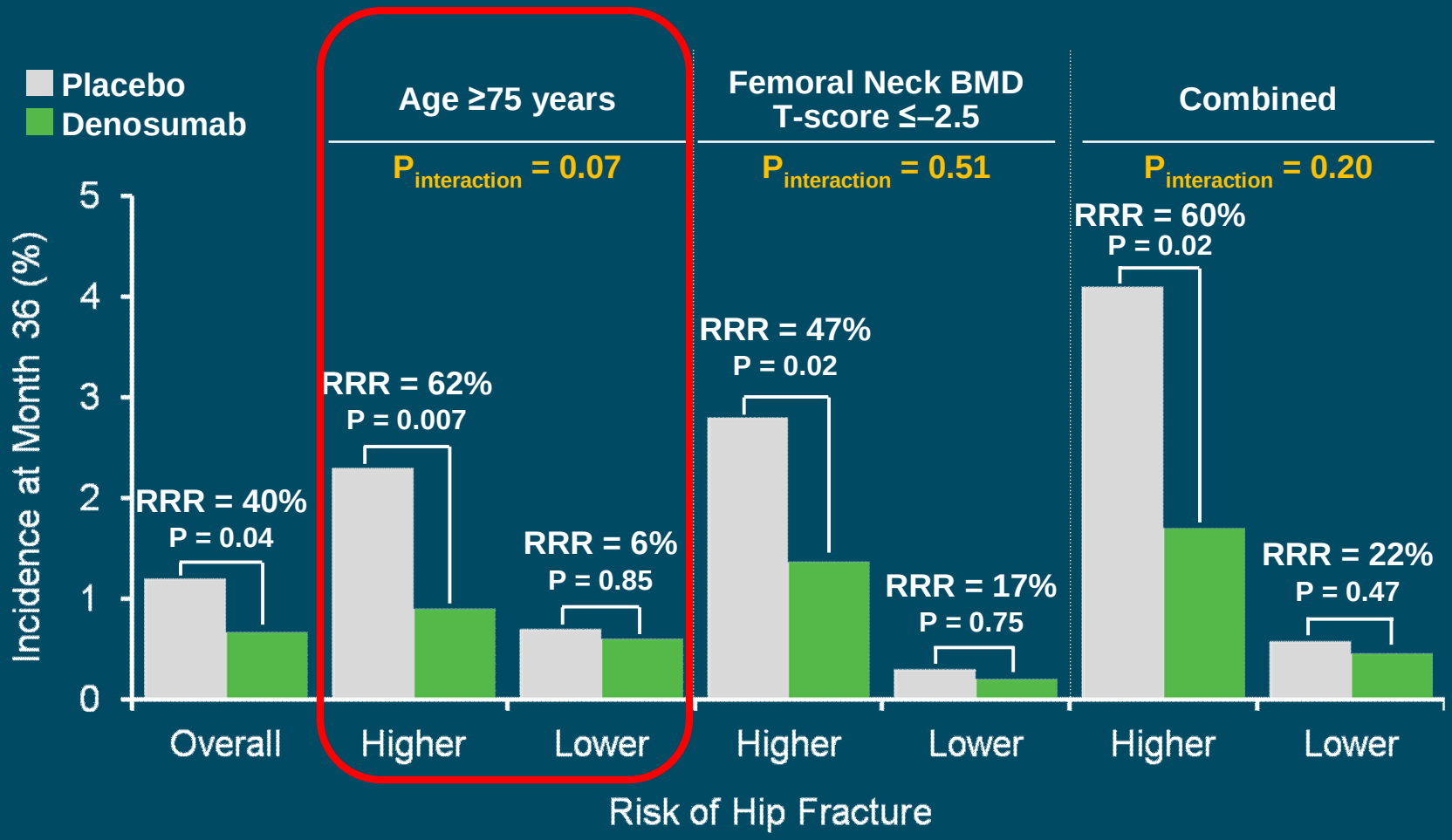
Denosumab Reduces New Vertebral Fractures in Higher Risk Populations



† Multiple and/or moderate or severe vertebral deformities with a femoral neck BMD T-score ≤−2.5.
RRR = relative risk reduction

Boonen S, *et al. J Clin Endocrin Metab* 2011;96:1727–1736.

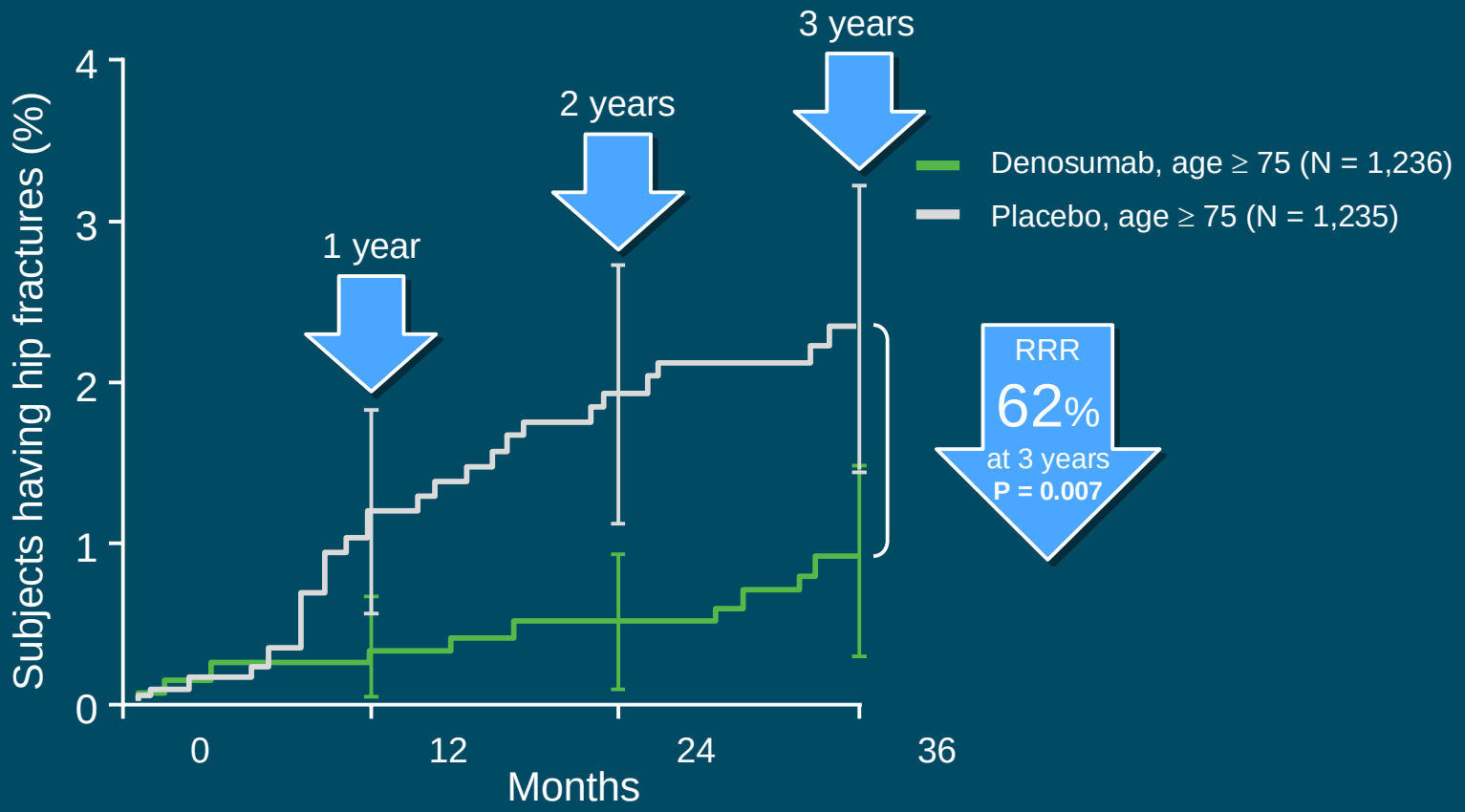
Denosumab Reduces New Hip Fractures in Higher Risk Populations



RRR = relative risk reduction

Boonen S, *et al. J Clin Endocrin Metab* 2011;96:1727–1736.

Denosumab Reduces Hip Fractures by 62%* in Patients Aged ≥75 Years (in a *Post Hoc* Analysis)[1]



- This early onset of action at the hip has not been documented with any other antiresorptive drug

Absolute risk reduction for denosumab vs placebo was 1.4% for hip fractures.
* Denosumab provided a hip fracture risk reduction of 6% (P = 0.85) in patients 60 to 74 years and 62% (P = 0.007) in patients 75 to 90 years. Age P interaction value = 0.07.
RRR = relative risk reduction

Boonen S, *et al. J Clin Endocrin Metab* 2011;96:1727–1736.

Adverse Events over 36 Months

FREEDOM Trial

	Placebo (N = 3,876)	Denosumab 60 mg Q6M (N = 3,886)
Adverse events, N (%)		
Infection	2,108 (54.4)	2,055 (52.9)
Malignancy	166 (4.3)	187 (4.8)
Injection-site reaction	26 (0.7)	33 (0.8)
Hypocalcemia	3 (0.1)	0 (0)
Delayed fracture healing	4 (0.1)	2 (0.05)
Femoral shaft fracture	3 (0.1)	0 (0)
Humerus non-union fracture	1 (0.03)	0 (0)
Osteonecrosis of the jaw	0 (0)	0 (0)
Adverse events occurring with ≥ 2% incidence and P ≤ 0.05, N (%)		
Eczema	65 (1.7)	118 (3.0)
Fall*	219 (5.7)	175 (4.5)
Flatulence	53 (1.4)	84 (2.2)

*Excludes falls occurring on the same day as a fracture

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

Serious Adverse Events over 36 Months

FREEDOM Trial

	Placebo (N = 3,876)	Denosumab 60 mg Q6M (N = 3,886)	P value
Serious adverse events, N (%)			
Malignancy	125 (3.2)	144 (3.7)	0.28
Infection	133 (3.4)	159 (4.1)	0.14
Cardiovascular events	178 (4.6)	186 (4.8)	0.74
Stroke	54 (1.4)	56 (1.4)	0.89
Coronary heart disease	39 (1.0)	47 (1.2)	0.41
Peripheral vascular disease	30 (0.8)	31 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Serious adverse events occurring with ≥ 0.1% incidence and P ≤ 0.01, N (%)			
Cellulitis (includes erysipelas)	1 (<0.1)	12 (0.3)	0.002
Concussion	11 (0.3)	1 (<0.1)	0.004

Adapted from: Cummings SR, *et al. N Engl J Med* 2009;361:756–765.

Summary

- Pharmacologic therapy to reduce fracture risk is effective and should be a very high priority in ambulatory, elderly patients at high risk of fracture
- In the FREEDOM higher-risk subanalysis, denosumab (60 mg SC every 6 months for 3 years)
  - significantly reduced the risk of new vertebral fractures in all patients
  - significantly reduced the risk of new hip fractures in higher risk patients (≥75 years old and/or femoral neck BMD T-score ≤ −2.5)
- Denosumab is a therapeutic option for women at high risk of fracture (i.e. ≥75 years, in whom hip fractures increase exponentially due to trabecular and cortical bone decay)
  - providing consistent anti-fracture efficacy
  - adverse events (AEs) and serious AEs were similar to the higher risk group in FREEDOM and events did not increase over time with denosumab treatment

Prolia - indication

- **Therapeutic indications**
- Treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures. In postmenopausal women Prolia significantly reduces the risk of vertebral, non vertebral and hip fractures.
- Treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. In men with prostate cancer receiving hormone ablation, Prolia significantly reduces the risk of vertebral fractures
- Prolia PI MOH approved

Prolia – active ingredients and administration

Generic name of the drug and active ingredient

Prolia 60 mg solution for injection in a pre-filled syringe.

Each pre-filled syringe contains 60 mg of denosumab in 1 ml of solution (60 mg/ml).

Dosage and method of administration

The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

Patients must be adequately supplemented with calcium and vitamin D

Administration should be performed by an individual who has been adequately trained in injection techniques.

Prolia

MANUFACTURER

- Amgen Europe B.V.
- Breda
- The Netherlands

LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd.

25 Basel St., Petach Tikva 4900202

Prolia is a registered trademark of Amgen Inc., and is being used under license by GlaxoSmithKline.

Prolia – important information

- לדיווח תופעות לוואי il.safety@gsk.com **או** בטלפון 03-9297100
- שרות מידע רפואי il.medinfo@gsk.com
- **למידע מלא יש לעיין בעלון לרופא כפי שאושר ע"י משרד הבריאות**

Prolia - Contraindications

- **Contraindications**
- Hypocalcaemia
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of PI
- Pregnancy: Prolia may cause fetal harm when administered to a pregnant woman. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth. Prolia is contraindicated in women who are pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

For full information please see MOH approved PI

Special warnings and precautions for use

- Calcium and Vitamin D supplementation
- Adequate intake of calcium and vitamin D is important in all patients.
- Precautions for use
- ***Hypocalcemia* -** It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of hypocalcaemia during treatment calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.
- In the post-marketing setting, severe symptomatic hypocalcaemia has been reported , with most cases occurring in the first weeks of initiating therapy, but it can occur later.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Skin Infections*** - Patients receiving Prolia may develop skin infections (predominantly cellulitis) leading to hospitalization. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.
- **Osteonecrosis of the jaw** has been reported rarely in clinical studies and in the post marketing setting in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis. Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (e.g. tooth extractions, dental implants, oral surgery), and co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, a diagnosis of cancer with bone lesions, concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck). It is important to evaluate patients for risk factors for ONJ before starting treatment. A dental examination with appropriate preventive dentistry is recommended prior to treatment with Prolia in patients with concomitant risk factors. All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment with Prolia. While on treatment, patients should avoid invasive dental procedures if possible.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Atypical Subtrochanteric and Diaphyseal Femoral Fractures -*** Atypical low-energy or low trauma *fractures of the* shaft have been reported in patients receiving Prolia. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with anti-resorptive agents. During Prolia treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Interruption of Prolia therapy should be considered, pending a risk/benefit assessment, on an individual basis.
- ***Suppression of Bone Turnover -*** In clinical trials in women with postmenopausal osteoporosis, treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with Prolia are unknown. The long-term consequences of the degree of suppression of bone remodeling observed with Prolia may contribute to adverse outcomes such as osteonecrosis of the jaw, atypical fractures, and delayed fracture healing. Monitor patients for these consequences.

For full information please see MOH approved PI

Special warnings and precautions for use

- ***Dry natural rubber*** - The needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions.
- ***Renal impairment*** - Patients with severe renal impairment (creatinine clearance < 30 ml/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients, see above.
- Warnings for Excipients
- Patients with rare hereditary problems of fructose intolerance should not use Prolia. This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg i.e. essentially ‘sodium-free’.

For full information please see MOH approved PI