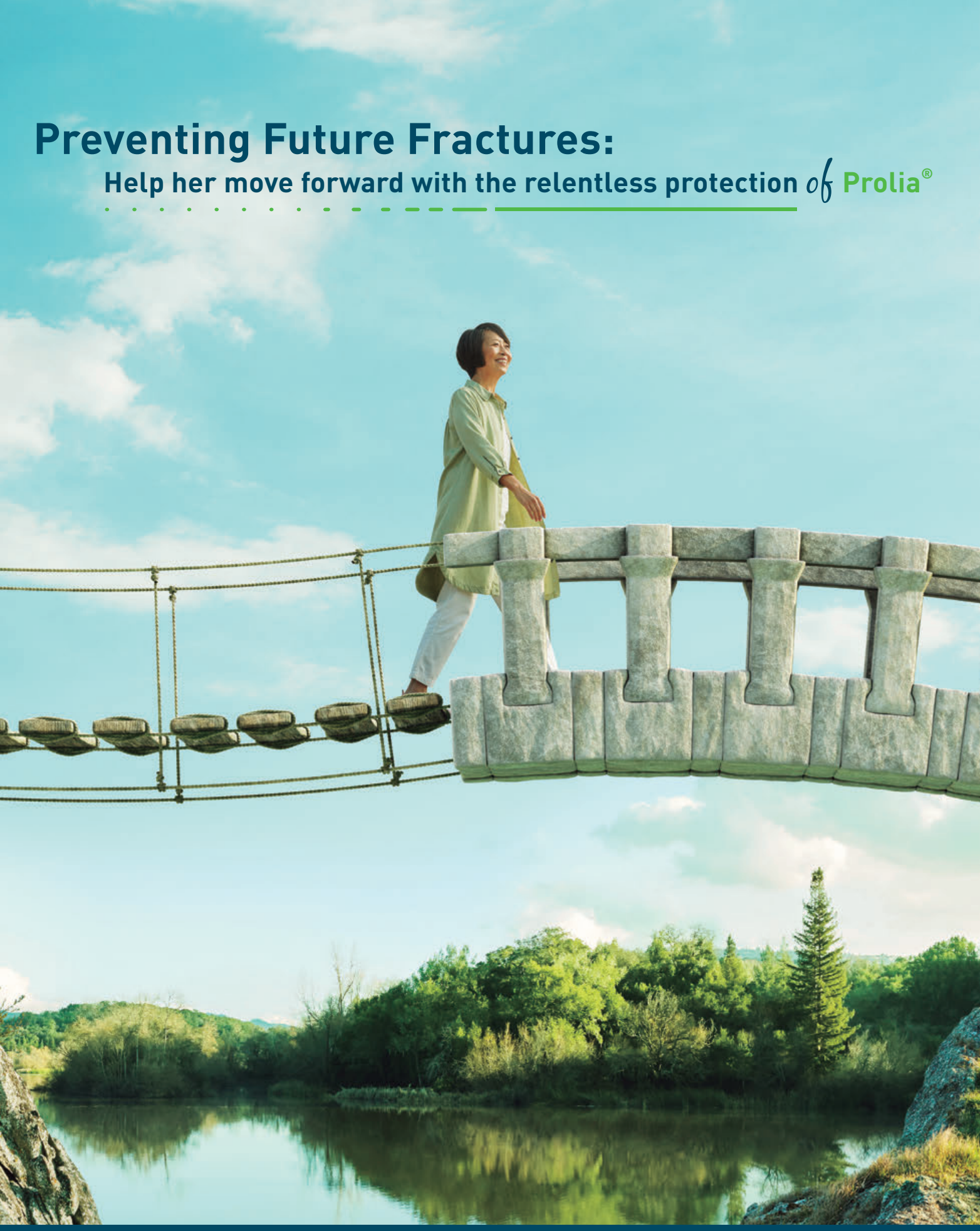
Preventing Future Fractures:

Help her move forward with the relentless protection of Prolia®



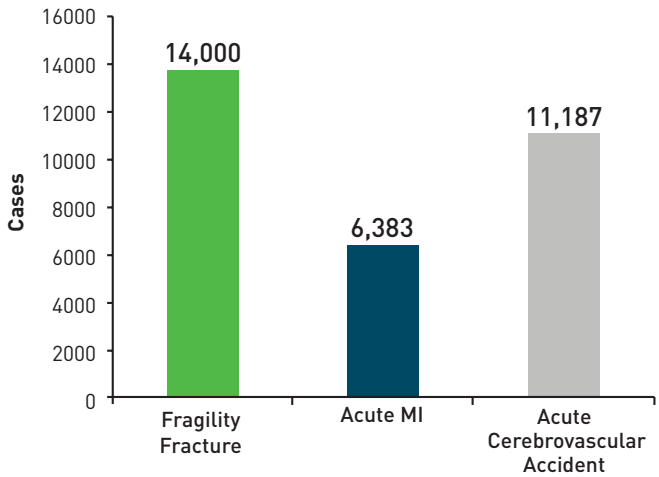
AMGEN®

博力加®
prolia®
denosumab

FRAGILITY FRACTURE IS A MAJOR HEALTHCARE BURDEN IN HONG KONG[1]

The incidence of fragility fracture is higher than that of acute myocardial infarction (MI) or acute cerebrovascular accident in Hong Kong[1]

Incidence of acute events in Hong Kong (2014)[1*]



Healthcare burden

A hip fracture costs **7 hospital bed days** & **23 rehabilitation bed days** on average[2]

17.3% patients die within a year of surgery[1]

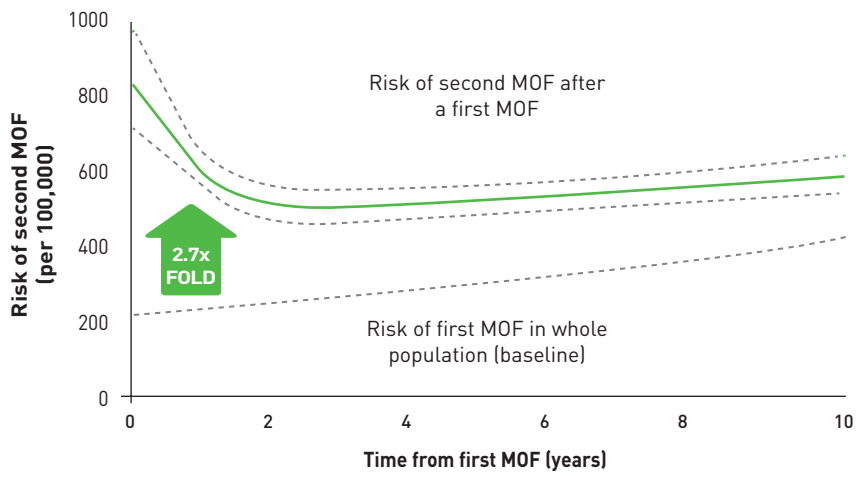
Direct medical cost **~HKD$69, 300** per case[3]

*Statistics from the Hospital Authority of Hong Kong.

Study Design:
Ref 1: Clinical data on fragility hip fracture patients admitted to six acute major hospitals in Hong Kong in 2012 were captured, including demographics, pre- and post-operative assessments, discharge details, complications, and 1-year follow-up information. Analysis was performed according to the local standards with reference to those from the British Orthopedic Association.
Ref 2: A study from Queen Mary Hospital (QMH) on a geriatric hip fracture clinical pathway in 2007. After implementing the pathway, length of stay in acute & convalescence hospital were measured. A total of 964 patients with hip fracture were analysed. All data were obtained from 2009.
Ref 3: Data obtained from an updated hip fracture projection of 9 Asian Federation of Osteoporosis Societies (AFOS) members in 2018. The direct medical cost per case in Hong Kong was reported as 8831.9 USD.

RISK OF FRACTURE IS INCREASED AFTER FIRST MAJOR OSTEOPOROTIC FRACTURE[4]

Incidence of second MOF of woman aged 75[4]



34% Patients re-fractured within 2 years[4]

40% Increased risk of getting a second fracture after 10 years[4]

15 YEARS The fracture risk remained above baseline after subsequent 15 years[4]

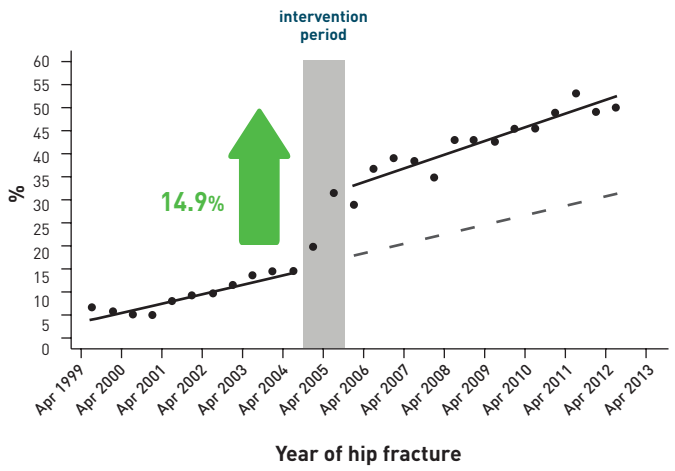
Study design[4]:
This study was based on a population-based cohort of 18,872 person, men (n = 9116) and women (n = 9756), born between 1907 and 1935 in the greater Reykjavik area; this sample represented 55% of the total Icelandic population in this age range. Fractures were documented over 510,265 person-years. An extension of Poisson regression was used to investigate the relationship between the first MOF and the second. All associations were adjusted for age and time since baseline.

MOF = major osteoporotic fracture

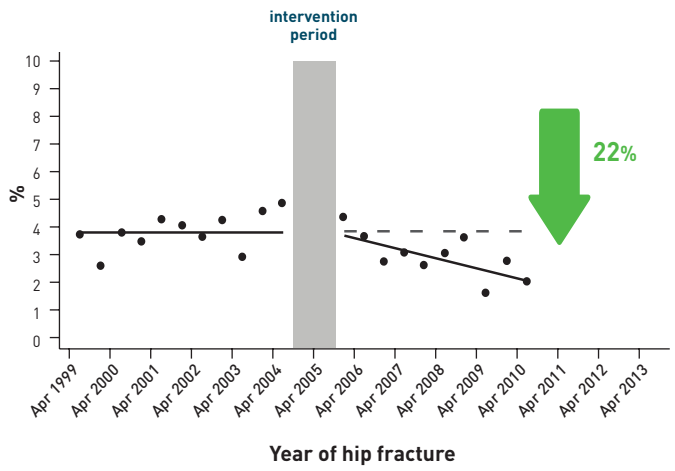
ANTI-OSTEOPOROSIS MEDICATION HELPS PREVENT SECONDARY FRACTURE

The rate of medication prescription was increased by 14.9% per 6 months and the subsequent hip fracture rate reduced 22% at 3 years after National Institute for Health and Care Excellence (NICE) announced a new guidance on the use of anti-osteoporosis medication[5]

Index hip fracture patients initiating anti-OP therapy (0-12 months)



Index hip fracture patients with subsequent hip fracture (3-year)



- observed bi-annual proportions (standardized)
- estimated pre- and post-intervention trends based on observed values
- estimated post-intervention trend based on pre-intervention trend only

Study design[5]:
The actual practical impact of events among hip fracture patients in terms of anti-osteoporosis medication prescribing and subsequent fracture incidence were estimated using primary care data (Clinical Practice Research Datalink) from 1999 to 2013. A total of 10,873 patients were included in the study. Changes in level and trend of prescribing and subsequent fracture following publication of NICE guidance and availability of generic alendronic acid were estimated using an interrupted time series analysis. Both events were considered in combination within a 1-year intervention period.

THE PRESCRIPTION RATE OF BONE HEALTH MEDICATIONS IS LOW IN HONG KONG[1]

Standard	HK (%)	UK NHFD (%)
1. Admission to orthopaedic ward within 4 hours	91.0	52
2. Surgery within 48 hours and during working hours	60.5 (exactly 48 hours)	83
3. Patients developing pressure ulcers	5.3	3.7
4. Preoperative assessment by an ortho-geriatrician	3.5	43
5. Discharged with bone protection medication	**22.9**	**69**
6. Received a falls assessment prior to discharge	98	92

Study design[1]:
Clinical data on fragility hip fracture patients admitted to six acute major hospitals in Hong Kong in 2012 were captured, including demographics, pre- and post-operative assessments, discharge details, complications, and 1-year follow-up information. Analysis was performed according to the local standards with reference to those from the British Orthopedic Association. Data were compared with a study from UK NHFD 2012, which collected from 180 hospitals across the UK with patients managed according to the UK Blue Book standards.

NHFD = National Hip Fracture Database

OSTEOPOROSIS MEDICATION RECOMMENDED BY LOCAL AND INTERNATIONAL GUIDELINES[6,7]

Prolia® is recommended as a **FIRST-LINE medication** for the treatment of postmenopausal osteoporosis:

Guidelines Recommendations

OSHK 2013[6]

Anti-osteoporosis drugs is recommended for patients at high risk for fracture:

- **Prior low-energy hip or vertebral fractures**
- BMD T-score of ⩽ -2.5 at the lumbar spine or proximal femur on DXA scan
- T-score between -1 and -2.5 if FRAX:
    1. 10-year probability of any major osteoporotic fracture is ⩾20% or;
    2. 10-year probability of hip fracture is ⩾3%

In Hong Kong, a recent local study suggests: **10-year risk threshold of 9.95% for major osteoporotic fracture** may be appropriate as an optimal cut-off point[8]

AACE/ACE 2016[7]

Strongly recommend pharmacologic therapy for patients with:

- Osteopenia or low bone mass and **history of fragility fracture of the hip or spine**
- T-score ⩽ -2.5 in the spine, femoral neck, total hip or 33% radius
- T-score between -1 and -2.5 if FRAX:
    1. 10-year probability of major osteoporotic fracture is ⩾20% in the US or;
    2. 10-year probability of hip fracture is ⩾3% in the US or;
    3. Above the country-specific threshold in other countries or regions

First-line treatment for postmenopausal women aged ⩾ 65:

- **Denosumab**
- Bisphosphonates

Initial therapy for patient at high risk of fracture:

- **Denosumab**
- Alendronate
- Risedronate
- Zoledronic acid

GOAL-DIRECTED TREATMENT FOR OSTEOPOROSIS[9]:

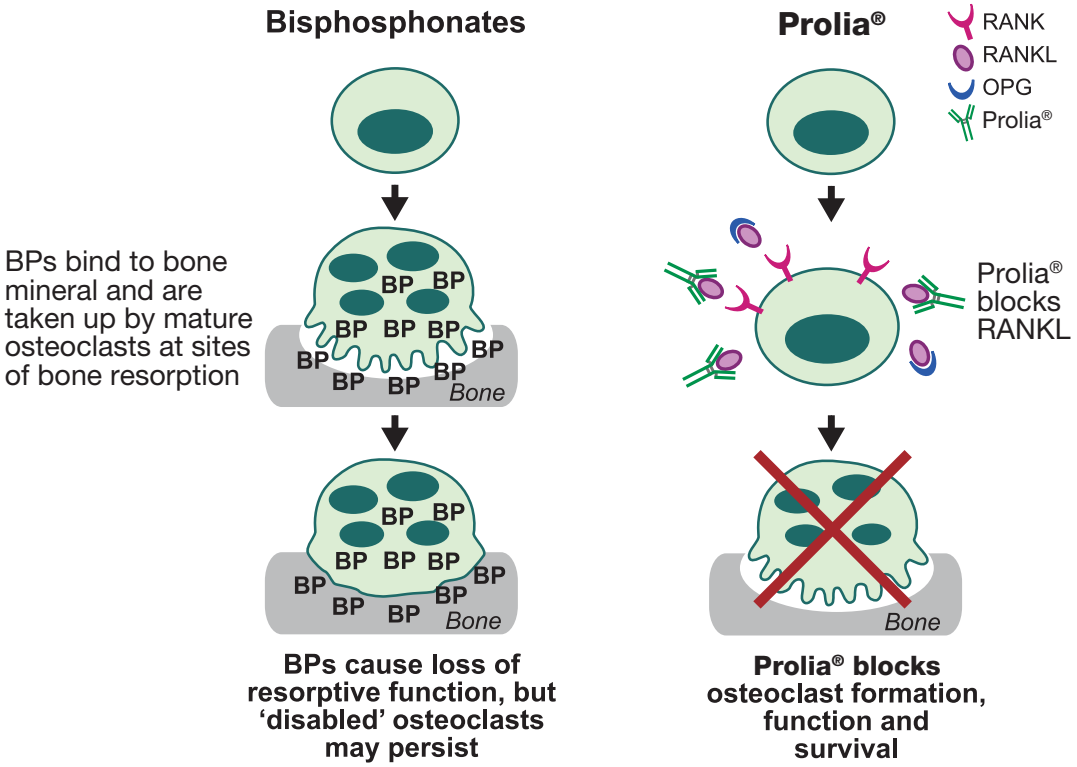
"For patients with recent fractures, it is critical to prevent fractures during the next several years, when the risk of another fracture is substantially elevated. Therapeutic agents that reduce fracture risk rapidly are desirable for these patients."[9] (Cummings SR, et al. J Bone Miner Res. 2017; 32; 3-10.)

Study design[9]:
A report published by a working group formed by The American Society for Bone and Mineral Research (ASBMR) and the United States National Osteoporosis Foundation (NOF). The group developed principles of goal-directed treatment and identified gaps that need to be filled to implement this approach.

AACE/ACE = American Association of Clinical Endocrinologists and American College of Endocrinology; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FRAX = Fracture Risk Assessment Tool; OSHK = The Osteoporosis Society of Hong Kong

PROLIA®: INHIBITS OSTEOCLASTS BEFORE THEY REACH THE BONE

Prolia® is an antibody that **inhibits osteoclast formation, function and survival** by binding to RANK ligands and prevents RANKL/RANK interaction[10,11*]



	Bisphosphonates	Prolia®
Chemistry	Chemical agent	Monoclonal antibody
Targets	Selective uptake by hydroxyapatite, inhibition of FPP synthase	Selectively binds RANKL
Distribution	Bone mineral surface	Circulating in blood and extracellular fluid
Major bone target cells	Mature osteoclasts, possible effects on osteoclast precursors and osteocytes	Osteoclast precursors and mature osteoclasts
Mechanism of action	Inhibits osteoclast resorptive function and survival by disrupting intracellular signaling pathways	Prevents the formation, function, and survival of osteoclasts

Licensed Indications in Hong Kong and Macau[10]

- **Postmenopausal Osteoporosis in Women at High Risk of Fracture**
- **Osteoporosis in Men at High Risk of Fracture**
- **Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer**
- **Treatment of Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer**

*Illustration adapted from Baron R., et al[11]

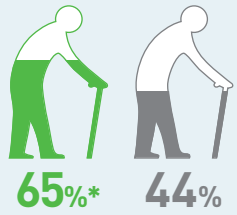
BP = bisphosphates; FPP = farnesyl pyrophosphate; OPG = osteoprotegerin; RANK/RANKL = receptor activator of nuclear factor kappa B/ receptor activator of nuclear factor kappa B ligand

ROBUST BMD GAIN WITH PROLIA® VS BISPHOSPHONATES AT MONTH 12[12-16]

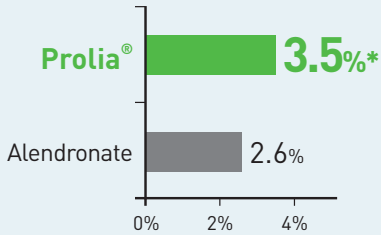
Treatment naïve patients[12]:

Total Hip

Patients achieved meaningful BMD improvement (%)§

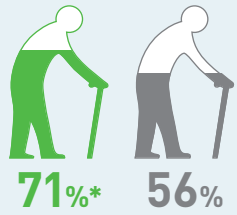


BMD change from baseline (%)

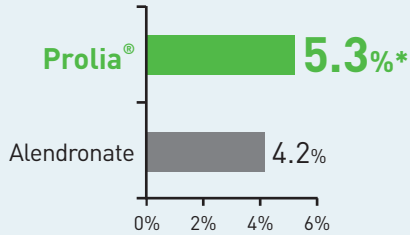


Lumbar Spine

Patients achieved meaningful BMD improvement (%)§



BMD change from baseline (%)

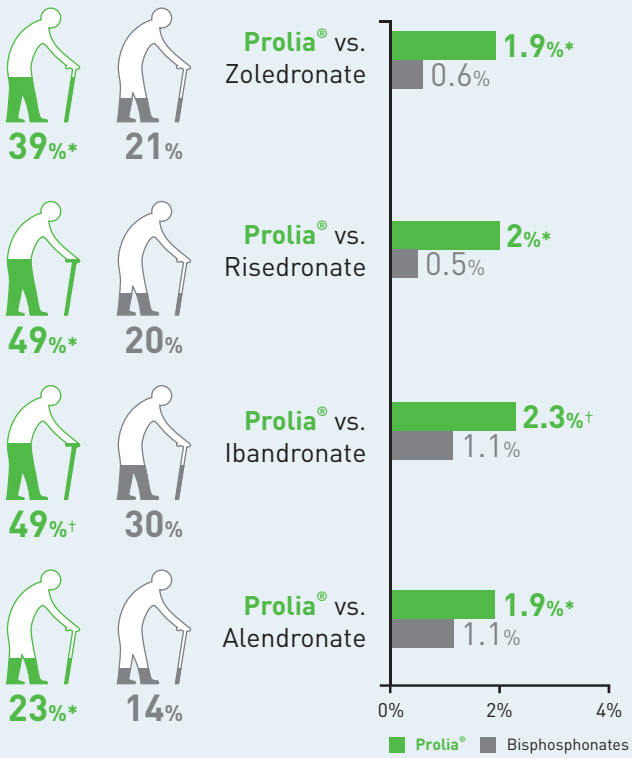


Patients previously treated with oral bisphosphonate[13-16]:

Total Hip

Patients achieved meaningful BMD improvement (%)§

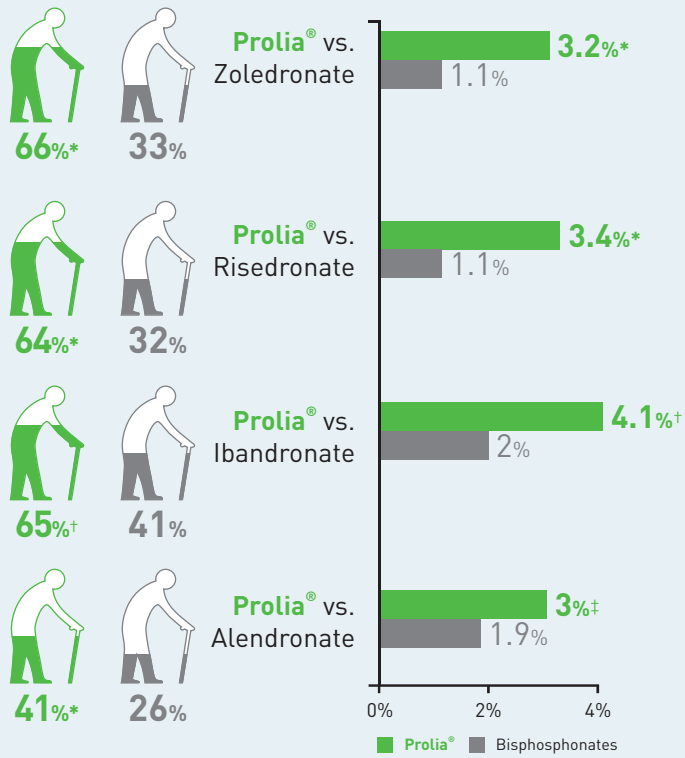
BMD change from baseline (%)



Lumbar Spine

Patients achieved meaningful BMD improvement (%)§

BMD change from baseline (%)



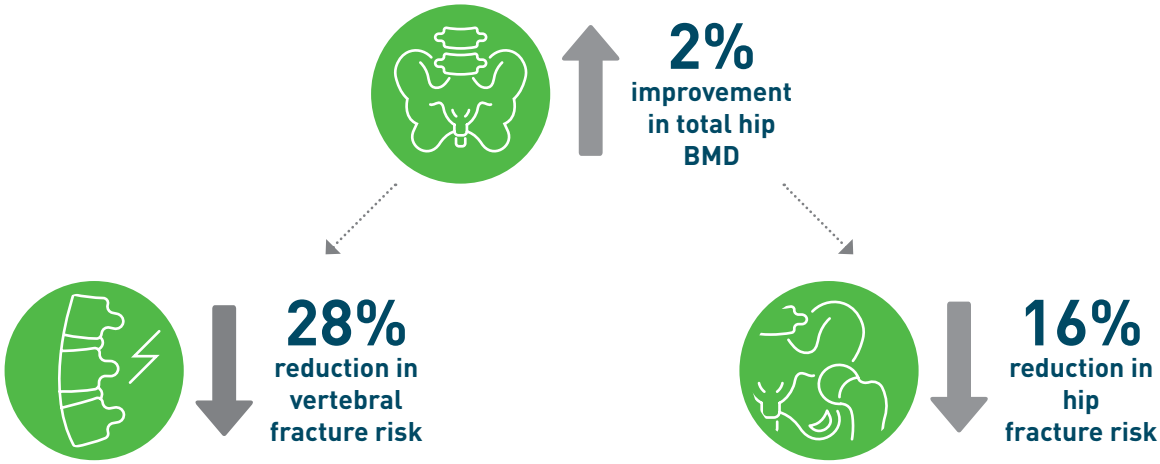
*P < 0.0001; †P <0.001; ‡P <0.01. § Meaningful BMD improvement is defined as achieving BMD gains that were beyond least significant changes (LSC). LSC reflects the smallest change in BMD that, when equaled or exceeded, allows the physician to conclude whether or not there has been a statistically significant change in the measurement.

Study design:
Ref 12: A total of 1189 postmenopausal women with a T-score ≤ –2.0 at the lumbar spine or total hip were randomized 1:1 to receive subcutaneous Prolia® injections (60 mg q6m) plus oral placebo weekly (n = 594) or oral alendronate weekly (70 mg) plus subcutaneous placebo injections q6m (n = 595). Changes in BMD were assessed at the total hip, femoral neck, trochanter, lumbar spine, and one-third radius at 6 and 12 months and in bone turnover markers at months 1, 3, 6, 9, and 12.
Ref 13: An international, multicenter, randomized double-blind trial compared the effect of transitioning from oral bisphosphonates to Prolia® or zoledronic acid (ZOL) on BMD and bone turnover. A total of 643 postmenopausal women with osteoporosis previously treated with oral bisphosphonates participated in the study. Subjects were randomized 1:1 to Prolia® 60 mg q6m plus iv placebo once or ZOL 5 mg iv once plus sc placebo q6m for 12 months. Changes in BMD and bone turnover markers were measured.
Ref 14: A randomized, open-label study, postmenopausal women aged ≥ 55 years received Prolia® 60 mg subcutaneously q6m (n= 435) or risedronate 150 mg orally every month (n = 435) for 12 months. Endpoints included percentage change from baseline in total hip BMD (primary endpoint), femoral neck, and lumbar spine BMD at month 12, and percentage change from baseline in sCTX-1 at months 1 and 6.
Ref 15: In a randomized, open-label study, postmenopausal women received 60 mg denosumab subcutaneously q6m (n = 5417) or 150 mg ibandronate orally every month (n = 5416) for 12 months. Endpoints included percentage change from baseline in total hip, femoral neck, and lumbar spine BMD at month 12 and percentage change from baseline in serum C-telopeptide at months 1 and 6 in a substudy.
Ref 16: A multicenter, international, randomized, double-blind, double-dummy study inculded 504 postmenopausal women ≥ 55 years of age with a BMD T-score of -2.0 or less and -4.0 or more who had been receiving alendronate therapy for at least 6 months. Subjects received open-label branded alendronate 70 mg once weekly for 1 month and then were randomly assigned to either continued weekly alendronate therapy (n = 251) or subcutaneous Prolia® 60 mg q6m (n = 253) and were followed for 12 months. Changes in BMD and biochemical markers of bone turnover were evaluated.

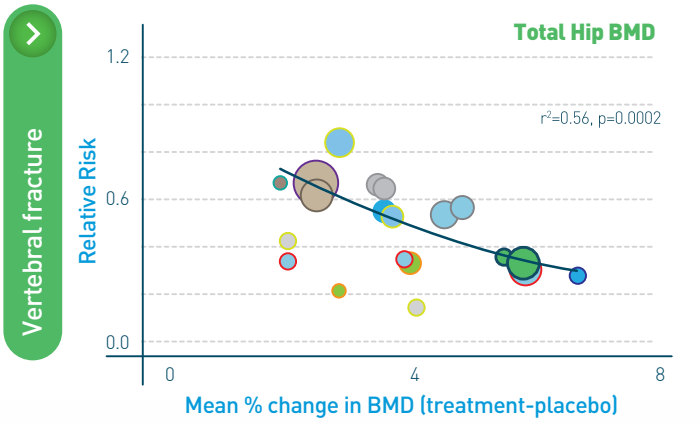
BMD = bone mineral density; iv = intravenous; sc = subcutaneous; q6m = every 6 months

CHANGE IN BMD IS ASSOCIATED WITH REDUCTION IN FRACTURES[17]

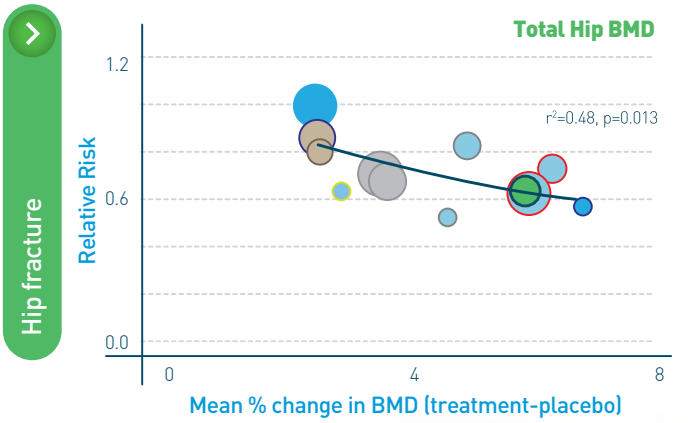
A meta-analysis of 38 placebo-controlled trials of 19 different osteoporosis therapeutic agents showed that greater improvements in BMD was strongly associated with greater reductions in fracture rate[17]:



Association of the risk of vertebral fracture and total hip BMD changes*



Association of the risk of hip fracture and total hip BMD changes*



PROLIA® · Abaloparatide · Alendronate · Arzoxifene · Bazedoxifene · Calcitonin · Clodronate · Estrogens±Prog · Etidronate · Zoledronic Acid
Ibandronate · Lasofoxifene · Odanacatib · PTH 1-34 · PTH 1-84 · Raloxifene · Risedronate · Romosozumab · Tibolone

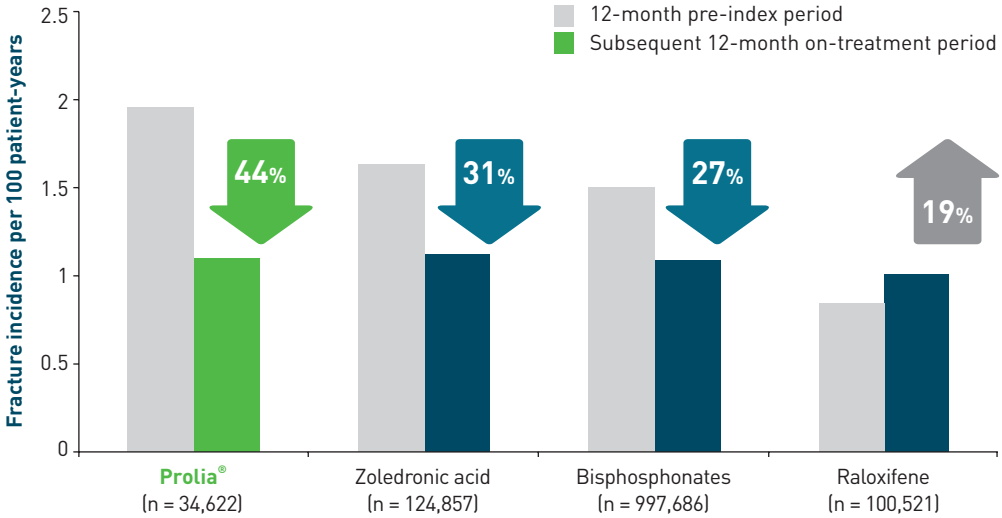
*All figures adapted from Bouxsein M.L., et al[17]

Study design[17]:
Data obtained from a meta-analysis of 38 randomized, placebo-controlled trials of 19 different therapies, including: bisphosphonates (n = 20), SERMs (n = 5), calcitonin (n = 1), estrogen compounds (n = 2), tibolone (n = 1), anti-RANK Ligand antibody (n = 2), PTH (n = 1), PTH analogs (n = 4), anti-sclerostin (n = 1) and cathepsin K inhibitor (n = 1). The associations between improvements in BMD and reductions in fracture risk were analysed by meta-regression.

BMD = bone mineral density; PTH = parathyroid hormone; SERM = selective estrogen receptor modulator

REAL-WORLD DATA: PROLIA® SHOWS A GOOD REDUCTION RATE IN FRACTURE IN 12 MONTHS[18,19]

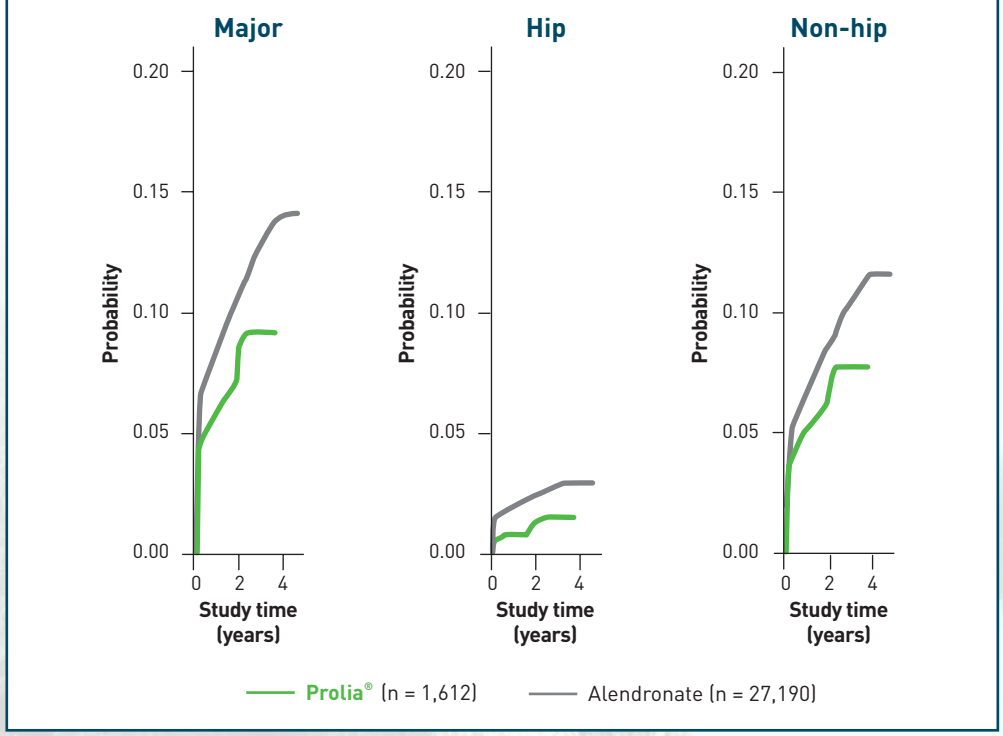
Incidence of hip fracture (women aged ≥ 65)[18]



Study design[18]:
A total of 1,278,296 women age ≥ 65 years treated with Prolia®, zoledronic acid, oral bisphosphonates, or raloxifene were identified. Fracture risk reductions in older, post-menopausal women treated with osteoporosis therapies were assessed, Fracture incidence rates before and after treatment initiation were described to understand patients' fracture risk profile, and fracture reduction effectiveness of each therapy was evaluated as a longitudinal change in incidence rates.

The use of Prolia® was associated with 35% to 50% risk reduction of hip fractures compared to alendronate amongst real-world users[19]:

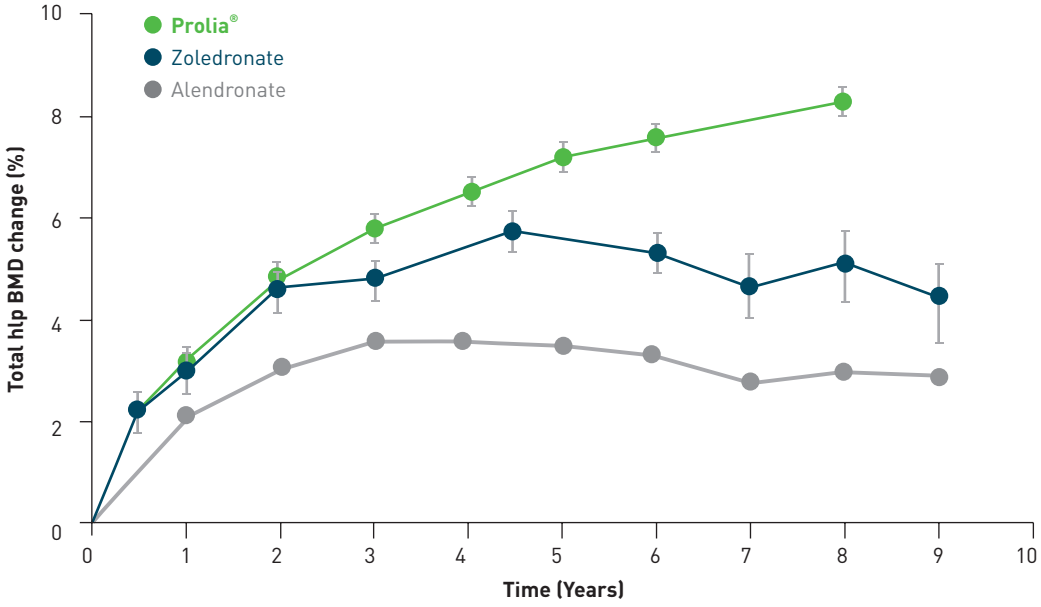
Probability of hip and osteoporotic fractures among treatment naïve users of Prolia® and alendronate[19]



Study design[19]:
Data was extracted from primary care computerized records linked to pharmacy dispensation data. All treatment naïve, incident users of Prolia® 60 mg or weekly alendronic acid between October/2010 and end/2014 were eligible. Patients were followed up from first prescription until the earliest of: first fracture, switching, treatment cessation, death, migration, or end of study. Primary and secondary outcomes were hip and all osteoporotic (any but skull/face/digits) fractures respectively.

LONG-TERM EFFICACY: PROLIA® PROVIDES SUSTAINED BMD IMPROVEMENT[20]

Long-term effects of osteoporosis treatments on total hip BMD[20]



Study design[20]:
Data derived from long-term follow-up studies of the FLEX trial (alendronate, 5–10 mg per day), the HORIZON trial (zoledronate, 5 mg per year) and the FREEDOM trial (Prolia®, 60 mg subcutaneous injection every 6 months). As data are derived from separate studies, formal comparisons between changes in BMD have not been made.

PROLIA® IS WELL TOLERATED WITH CONSISTENTLY LOW RATES OF AEs UP TO 10 YEARS[21]

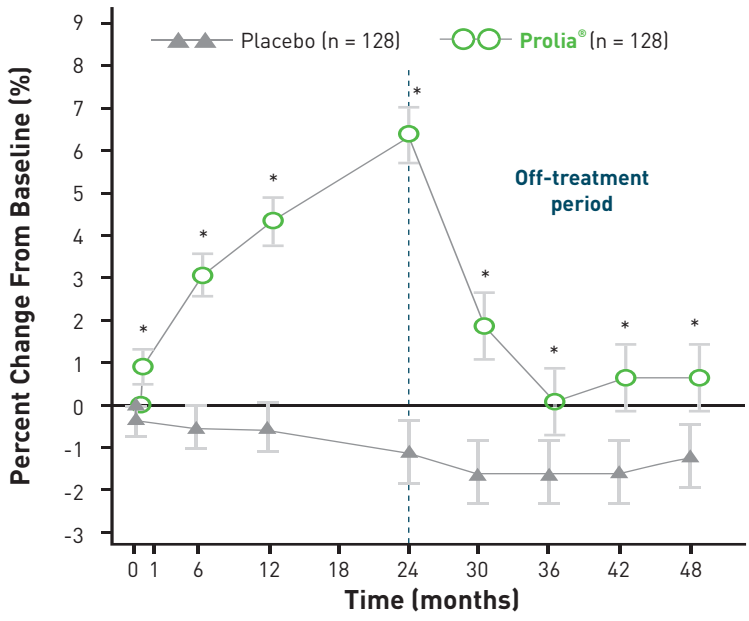
	Placebo			Combined Prolia® group									
Exposure	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**	**Year 9**	**Year 10**
Number of participants	**3,833**	**3,687**	**3,454**	**6,085**	**5,787**	**5,452**	**4,099**	**3,890**	**3,582**	**3,261**	**1,743**	**1,585**	**1,451**
All AEs	**189.5**	**156.3**	**132.8**	**165.3**	**137.8**	**124.6**	**129.9**	**110.9**	**110.0**	**108.4**	**107.6**	**109.5**	**95.9**
Infections	38.6	33.9	31.7	35.1	30.3	29.5	29.1	26.0	27.2	26.5	27.0	27.0	23.0
Malignancies	1.8	1.6	1.5	1.9	1.5	2.2	2.3	2.4	2.2	2.7	1.7	2.6	1.6
Eczema	0.8	0.5	0.6	1.4	1.1	1.0	1.1	1.2	0.9	0.7	0.8	0.9	1.3
Hypocalcaemia	<0.1	0	<0.1	<0.1	<0.1	0	<0.1	0.1	0	<0.1	<0.1	0	0.1
Pancreatitis	<0.1	<0.1	0	<0.1	<0.1	<0.1	0	<0.1	0.1	<0.1	0.1	<0.1	0
Serious AEs	**11.7**	**11.9**	**10.8**	**12.0**	**11.5**	**12.3**	**11.5**	**12.9**	**12.6**	**14.4**	**11.5**	**13.1**	**12.3**
Infections	1.1	1.4	1.4	1.5	1.6	1.4	1.4	1.3	1.9	2.3	1.2	1.5	2.6
Cellulitis or erysipelas	0	0	<0.1	<0.1	<0.1	0.2	<0.1	<0.1	0.1	<0.1	0.2	<0.1	<0.1
Fatal AEs	**0.8**	**0.8**	**1.0**	**0.7**	**0.6**	**0.7**	**0.5**	**0.8**	**0.9**	**1.5**	**0.7**	**1.0**	**0.9**
ONJ	**0**	**0**	**0**	**0**	**<0.1**	**0**	**<0.1**	**0**	**0.2**	**<0.1**	**0**	**<0.1**	**<0.1**
AFF	**0**	**0**	**0**	**0**	**0**	**<0.1**	**0**	**0**	**0**	**<0.1**	**0**	**0**	**0**

Study design[21]:
Data from a multicenter, randomized, double-blind, placebo-controlled, phase 3 FREEDOM trial. Postmenopausal women aged 60–90 years with osteoporosis enrolled from 214 centers (n = 7808) were randomly assigned (1:1) to receive 60 mg subcutaneous Prolia® or placebo q6m for 3 years. All participants who completed the FREEDOM trial without discontinuation or missing more than one dose were eligible to enrol in the open-label, 7-year extension, in which all participants received Prolia®. The primary outcome was safety monitoring, comprising assessments of adverse event and serious adverse event incidence, changes in safety laboratory analytes and participant incidence of denosumab antibody formation.

AE = adverse event; AFF = atypical femur fracture; ONJ = osteonecrosis of the jaw

THE EFFECT OF PROLIA® IS REVERSIBLE UPON TREATMENT DISCONTINUATION[22]

Changes in BMD (Lumbar Spine)[22]



*p ⩽ 0.0071

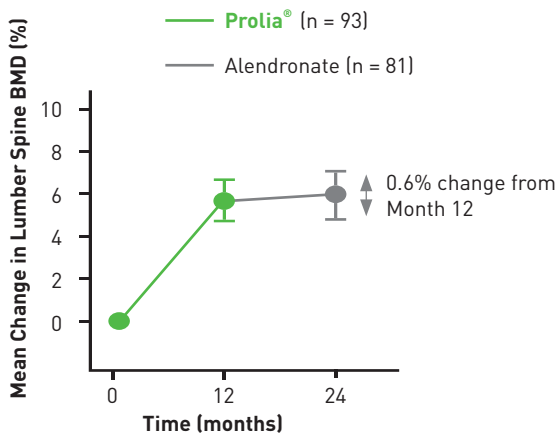
Study design[22]:
Date extracted from a phase 3, randomized, double-blinded parallel-group study. A total of 256 postmenopausal women with mean age of 59 years and mean lumbar spine T-score -1.61 were randomized to receive placebo (n = 128) and Prolia® 60 mg every 6 months (n = 128) for 24 months, followed by 24 months off-treatment. The last dose of investigated product was on the 18th month. Outcome measures included the percentage change in BMD and BTM, and AEs safety profile. Percentage change from baseline BMD is presented as least squares means.

BMD CHANGE MAINTAINED WITH BISPHOSPHONATE AFTER PROLIA® DISCONTINUATION

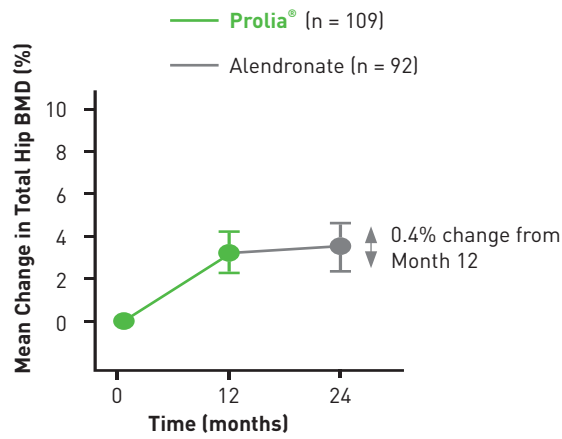
Bisphosphonate is recommended as an alternative treatment after Prolia® discontinuation by international guidelines[23]

BMD remained stable when patients received alendronate after 1-year Prolia® treatment[24]:

BMD change in Lumber Spine



BMD change in Total Hip



Study design[24]:
Postmenopausal women at 25 centers in the USA and Canada with BMD T-scores -4.0 to -2.0 and no prior bisphosphonate use were enrolled (n = 250). They were randomized to receive alendronate then denosumab, or denosumab then alendronate over successive 12-month periods. BMD was assessed at baseline and 12-month visits of each year.

AE = adverse event; BMD = bone mineral density; BTM = bone turnover markers

IMPROVE PATIENT CARE: SETTING UP FRACTURE LIAISON SERVICE[23]

- **Fracture Liaison Service (FLS)** is an osteoporosis coordinator programme
- FLS provides **routine assessment and management** for postmenopausal women and patients who have sustained a fragility fracture

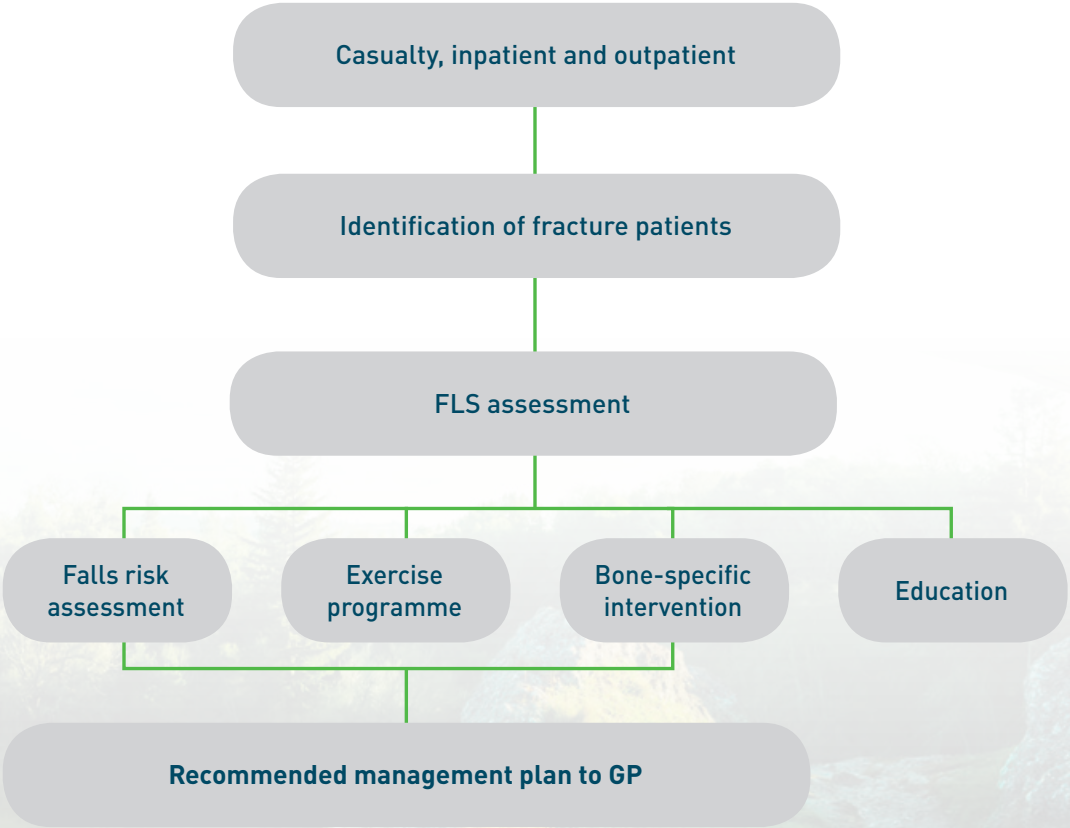
In UK, FLS has:

Increased the use of anti-osteoporosis treatment by **15%**[23]

Significantly reduced 2nd fracture rate[23]

Reduced 20% and **16%** of 30-day and 1-year mortality rates respectively[25]

Example of structure of Fracture Liaison Service[23]



Study design[25]:
The study evaluated FLS models of post-hip fracture care in terms of the impact on mortality (30 days and 1 year) and second hip fracture. Information of hip fracture hospital admissions was obtained from the UK hospital episode statistics database. Mortality records of patients aged over 60 years admitted for a primary hip fracture from 2003-2013 for 11 acute hospitals in UK (n = 33,152) were analysed. The primary outcome was time to second hip fracture within 2 years of a primary hip fracture. Secondary outcomes were time to death a) within 30 days and b) within 1 year, following a primary hip fracture admission

GP = general practitioner.

PREVENTING FUTURE FRACTURES: HELP HER MOVE FORWARD WITH THE RELENTLESS PROTECTION OF PROLIA®

- Fragility fracture is a major healthcare burden in Hong Kong[1]
- Osteoporosis medication could reduce future fractures[5]
- **Prolia®**, the first-line medication for postmenopausal osteoporosis[6,7], protects your patients from future fractures by providing:
  - ✓ Robust BMD improvement in 1 year versus bisphosphonates[12-16]
  - ✓ Real-world evidence of fracture reduction in 12 months[18]
  - ✓ Relentless improvement in BMD in all measured skeletal sites continuously throughout 10 years[12-16,20]
  - ✓ Reliable long-term safety profile up to 10 years[21]

BMD = bone mineral density

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Prolia® (Denosumab) Abbreviated Prescribing Information

Prolia® (denosumab) Solution for Injection in Pre-filled Syringe 60 mg/mL **INDICATIONS** Prolia is indicated for: i) treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy; ii) treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy; iii) treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures; iv) treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. **DOSAGE AND ADMINISTRATION** The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. Administer Prolia via subcutaneous injection in the upper arm, the upper thigh, or the abdomen. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily. CONTRAINDICATIONS Hypocalcemia and pregnancy, as well as hypersensitivity to any component of the product. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** *Hypersensitivity*: Clinically significant hypersensitivity including anaphylaxis has been reported with Prolia. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritis, and urticaria. *Hypocalcemia and Mineral Metabolism*: Hypocalcemia may be exacerbated by the use of Prolia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia. Hypocalcemia following Prolia administration is a significant risk in patients with severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis. Adequately supplement all patients with calcium and vitamin D. *Osteonecrosis of the Jaw (ONJ)*: ONJ has been reported in patients receiving Prolia. The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Prolia in patients with concomitant risk factors. All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Prolia. While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to Prolia treatment. *Atypical Subtrochanteric and Diaphyseal Femoral Fractures*: Atypical low-energy or low trauma fractures of the shaft have been reported in patients receiving Prolia. Patients should be advised to report new or unusual thigh, hip, or groin pain. *Multiple Vertebral Fractures (MVF) Following Discontinuation of Prolia Treatment*: Following discontinuation of Prolia treatment, fracture risk increases, including the risk of multiple vertebral fractures. If Prolia treatment is discontinued, consider transitioning to an alternative antiresorptive therapy. *Serious Infections*: Serious infections leading to hospitalization were reported in clinical trial. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis. *Dermatologic Adverse Reactions*: Dermatitis, eczema, and rashes. Most of these events were not specific to the injection site. Consider discontinuing Prolia if severe symptoms develop. *Musculoskeletal Pain*: Severe and occasionally incapacitating bone, joint, and/or muscle pain. Consider discontinuing use if severe symptoms develop. *Suppression of Bone Turnover*: In clinical trials treatment with Prolia resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. *Osteonecrosis of the external auditory canal*: Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors include steroid use and chemotherapy and/or local risk factors such as infection or trauma. **INTERACTIONS** In subjects with postmenopausal osteoporosis, Prolia (60 mg subcutaneous injection) did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4), indicating that it should not affect the pharmacokinetics of drugs metabolized by this enzyme in this population. **PREGNANCY AND LACTATION** *Pregnancy*: Category X. *Breast-feeding*: It is not known whether Prolia is excreted into human milk. **PEDIATRIC, GERIATRIC AND RENAL IMPAIRMENT** *Pediatric*: Prolia is not recommended in pediatric patients. *Geriatric*: No overall differences in safety or efficacy were observed in clinical studies between elderly patients and younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. *Renal Impairment*: No dose adjustment is necessary in patients with renal impairment. **UNDESIRABLE EFFECTS** The most common adverse reactions reported with Prolia in patients with postmenopausal osteoporosis are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. The most common adverse reactions reported with Prolia in men with osteoporosis are back pain, arthralgia, and nasopharyngitis. The most common (per patient incidence ≥ 10%) adverse reactions reported with Prolia in patients with bone loss receiving androgen deprivation therapy for prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer are arthralgia and back pain. Pain in extremity and musculoskeletal pain have also been reported in clinical trials. The most common adverse reactions leading to discontinuation of Prolia in patients with postmenopausal osteoporosis are back pain and constipation. **OVERDOSE** There is no experience with overdosage with Prolia. Abbreviated Prescribing Information Version: HKPROPI01 Please read the full prescribing information prior to administration and full prescribing information is available on request.

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